Radosav Vidaković

POLYVASCULAR ATHEROSCLEROSIS

DIAGNOSTIC AND PROGNOSTIC BURDEN

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Polyvascular Atherosclerosis – Diagnostic and Prognostic Burden

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INTRODUCTION AND OVERVIEW OF THE THESIS

ATHEROSCLEROSIS is a progressive disease process of the large and medium sized arteries that involves the gradual accumulation of lipids, inflammatory cells, and fibrous elements in plaques located in the vessel walls. Its pathogenesis is multifactorial, involving numerous, well known risk factors, and genetic predisposition. Some of those risk factors are modifiable (i.e., cigarette smoking, obesity, physical inactivity, elevated LDL cholesterol, reduced HDL cholesterol, hypertension, and diabetes mellitus), but some of them are not (i.e., age, gender, family history). Intensive research during the past decades has shown that atherosclerosis is a systemic disease that affects different vascular territories simultaneously (polyvascular disease, PVD). Therefore, individuals with one manifestation of atherosclerosis are more likely to have concomitant disease in other vascular territories. The process of atherosclerotic plaque formation begins early in the life, and it continuous to progress causing clinical manifestations decades later. Studies have shown that a substantial number of patients were asymptomatic prior to the acute atherosclerotic event, which itself caries a large portion of mortality and morbidity burden of atherosclerotic disease. Indeed, cardiovascular disease is the leading cause of death around the world, accounting for 50% of all mortality in developed countries, up to 85% in low and middle income countries.

In clinical settings, atherosclerosis can be manifested in directionally opposite manners by causing either occlusive or aneurismal changes, with considerable overlap between coronary (CAD), cerebral (CVD), or peripheral arterial disease (PAD). This overlap is especially present in patients who initially present with PAD, either occlusive or aneurysmal. It is well known that those patients more often suffer from myocardial infarction (MI) and stroke than the patients with other forms of atherosclerotic disease, especially if they undergo surgery. Because of that, it is of great importance to evaluate patients with PAD for the presence of CAD and CVD.

The prevalence of coexistent atherosclerotic disease depends mainly on the sensitivity of the diagnostic tool used in its identification. The majority of studies have shown that screening for atherosclerotic disease in different vascular territories by means of Doppler ultrasonography has a high sensitivity and specificity, and concordance with conventional angiography. Therefore, in **Chapter 1** this noninvasive approach was used to objectively assess the presence and prevalence of polyvascular disease in patients presented with symptomatic PAD. A large body of literature supports the idea that inflammation plays a pivotal role in all phases of atherosclerosis, from the fatty streak lesion formation to the acute coronary event due to vulnerable plaque rupture. Indeed, mediators involved in the inflammatory process have been widely studied both as surrogate biomarkers and as causal agents in the pathophysiologic network of atherogenesis and plaque vulnerability. Highsensitivity C-reactive protein (hs-CRP), a simple downstream marker of inflammation, is the most extensively studied molecule for its association with the risk of atherosclerotic events in general populations and a predictive value even in terms of secondary prevention. Therefore, in this chapter we also tested if the level of systemic inflammation reflected by the levels of circulatory hs-CRP correlates with the number of affected vascular territories.

Coronary artery disease appears to be the most prevalent atherosclerotic co-morbidity with high impact on early and late outcome. Since it can remain silent and undiagnosed for years, it is of paramount importance to diagnose and treat CAD on time. This is especially important in patients who are candidates for different surgical interventions, because postoperatively CAD is the main cause of death in these patients. **Chapters 2** and **3** give the insight in this problem, suggesting strategies in CAD identification, preoperative risk stratification and modification in specific subgroup of patients with abdominal aortic aneurysm (AAA), as well as in general surgical population.

Despite tremendous improvements in preoperative risk stratification and modification, as well as in surgical techniques, cardiovascular morbidity and mortality still remains high in perioperative period. Special problem in term of prognosis presents unrecognized MI or silent myocardial ischemia. **Chapter 4** evaluates this problem in group of vascular surgery patients. Incidence of perioperative cardiac events and outcome between surgical and endovascular repair in AAA patients is presented in **Chapter 5**.

Optimal preoperative risk stratification and perioperative risk reduction strategy accompanies accurate risk assessment by identifying potential risk factors, and their modification. Diabetes mellitus (defined as fasting glucose ≥ 7.0, random glucose ≥ 11.1 mmol/l, and glucose ≥ 11.1 mmol/l after oral glucose tolerance test) is recognized as an independent risk factor for worse postoperative outcome. The impact of impaired glucose regulation (defined as fasting glucose between 5.6–7.0 mmol/l, random glucose between 5.6 – 11.1 mmol/l, or glucose between 5.6 – 11.1 mmol/l after oral glucose tolerance test) and bad glycemic regulation in diabetic patients (those with the levels of circulating glycated hemoglobin-A_{1c} ≥ 7.0 mmol/l) on postoperative outcome is less clear. **Chapter 6** evaluates the significance of impaired glucose regulation and glycemic control on postoperative cardiac events in both diabetic and non-diabetic vascular surgery patients.

It is well known that natriuretic peptides (NPs), especially B-type (BNP) and its amino terminal cleavage equivalent (NT-proBNP), are excellent markers of left ventricular dysfunction, and predictors of outcome in heart failure (HF) patients. Beside HF, NPs have been found out to be connected with other settings, such as CAD and heart valve diseases, probably due to increased myocardial wall stress in those conditions. Also, there are a lot of evidence that supports correlation between the incidence of cardiac disrhythmias and elevated BNP/NT-proBNP levels. All those observations emerged NPs as accurate tool for preoperative risk assessment. The relation between preoperative NT-proBNP levels and postoperative extent of myocardial ischemia, circulating troponin T levels, and hart rate variability is evaluated in **Chapter 7.**

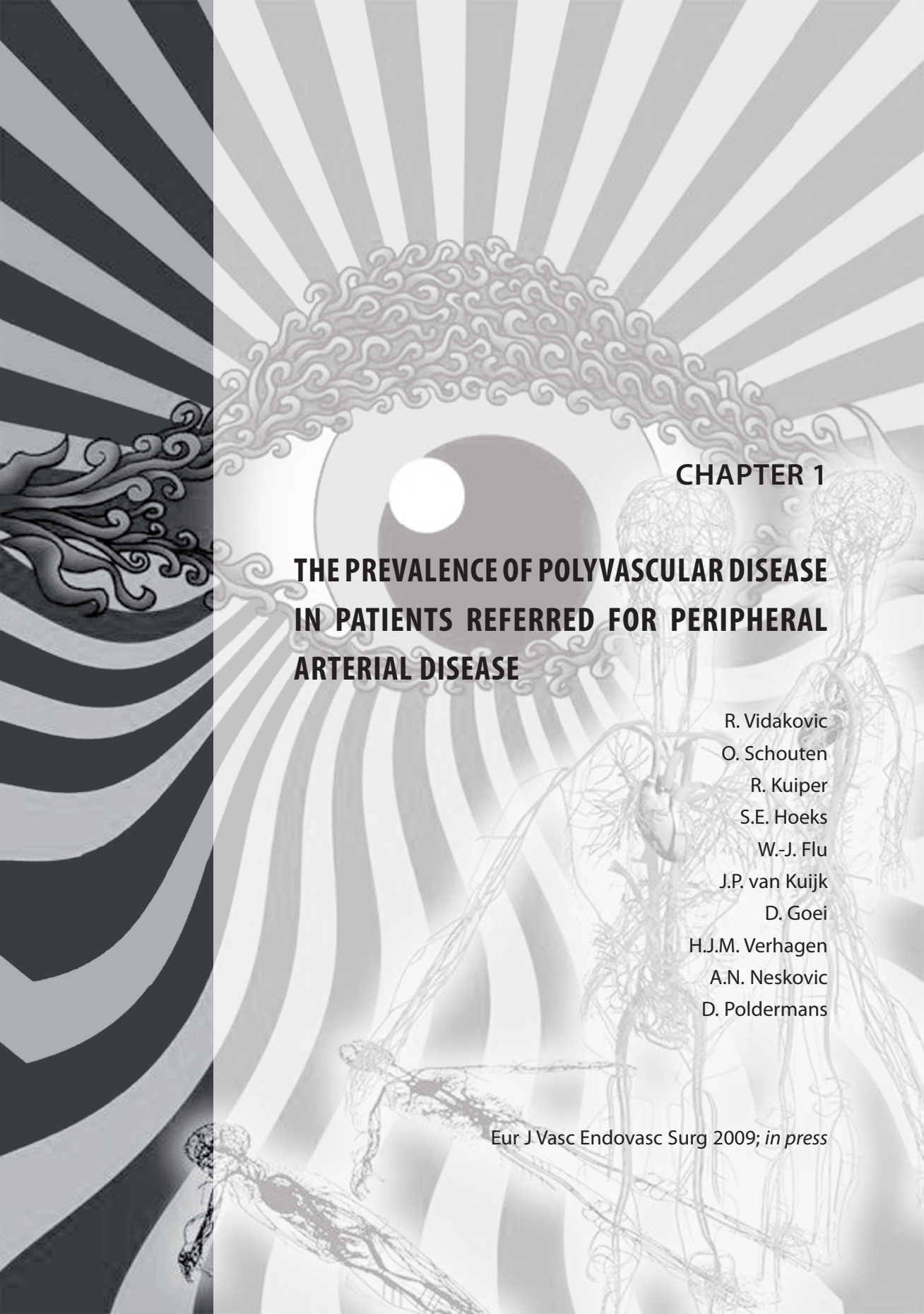
Non-invasive testing by dobutamine stress echocardiography (DSE) is common tool in identifying patients at increased risk for postoperative cardiac events. This kind of testing is mainly reserved for those patients with multiple clinical predictors of risk or other modifying factors. Since patients with left ventricular dysfunction (LVD) have

decreased short- and long-term survival after surgery, they present a challenging entity for additional preoperative DSE testing in purpose of adequate risk stratification, and possible changes in management strategy. In **Chapter 8** is presented a quantitative risk model for patients with LVD using myocardial viability profile during DSE.

The benefit of coronary revascularization in high-risk non-cardiac surgery patients is controversial. Evidence that supports this potentially cardioprotective procedure is based on the results of registries, which showed improved outcome in non-cardiac surgical patients who had coronary artery bypass grafting (CABG) or percutaneous coronary intervention with stent placement two to four years before non-cardiac surgical procedure. Whether or not prophylactic coronary revascularization is beneficial in high-risk patients immediately prior to the non-cardiac surgery is the topic of **Chapter 9**.

Finally, the last two **Chapters 10** and **11** are focused on screening of AAA. Since effective screening programs are not established yet, diagnosis of AAA is still frequently made at the time of rupture, which is related to increased postoperative mortality and morbidity. Diagnostic techniques used for AAA detection in everyday clinical practice, such as standard ultrasonography or computerized tomography, are not suitable for simple and easy screening purposes. Therefore, the diagnostic potential and accuracy of AAA detection by two new hand-held ultrasound devices are evaluated in those chapters.

Since atherosclerosis carries a large morbidity and mortality burden, its early detection, timely treatment and modification by various medical and surgical strategies are essential for improving the outcome of the patients. Maybe the results of this thesis will contribute in fulfillment of this important task.



CHAPTER 1

THE PREVALENCE OF POLYVASCULAR DISEASE IN PATIENTS REFERRED FOR PERIPHERAL ARTERIAL DISEASE

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ABSTRACT

Objective: To objectively assess the presence of polyvascular disease in patients with peripheral arterial disease and its relation to inflammation and clinical risk factors. *Methods:* A total of 431 vascular surgery patients (mean age 68 years, men 77%) with atherosclerotic disease were enrolled. The presence of atherosclerosis was assessed using ultrasonography. Affected territories were defined as: (1) carotid, stenosis of common or internal carotid artery of > 50%, (2) cardiac, left ventricular wall motion abnormalities, (3) abdominal aorta, diameter > 30 mm and (4) lower limb, ankle–brachial pressure index < 0.9. Cardiovascular risk factors and high-sensitivity C-reactive protein (hs-CRP) levels were noted in all. *Results:* One vascular territory was affected in 29% of the patients, whereas polyvascular disease was found in 71%: two affected territories in 45%, three in 23% and four in 3% of patients. Levels of hs-CRP increased with the number of affected vascular territories ($p < 0.001$). Multivariable logistic regression analysis showed age > 70 years, male gender, body mass index (BMI) > 25 kg m^{-2}, and hs-CRP to be independently associated with polyvascular disease. *Conclusion:* Polyvascular disease is a common condition in patients who have undergone vascular surgery. The level of systemic inflammation, reflected by hs-CRP levels, is moderately associated with the extent of polyvascular disease.

INTRODUCTION

Atherosclerosis is a chronic inflammatory disease that can affect different vascular territories focally. However, the presence of atherosclerosis in one vascular territory generally denotes the presence of the disease in other vascular territories, giving it a character of systemic and generalised disease. Coincidence of atherosclerotic disease in different vascular territories depends not only on the population in question but also on the criteria and methods used to assess the diagnosis. Recently published results of Reduction of Atherothrombosis for Continued Health (REACH) registry showed that patients with atherosclerotic disease in more than one vascular territory have worse long-term outcome.[1] However, the definition of poly-vascular disease (PVD) was based on relatively subjective criteria.

Ultrasonography is a highly effective and reliable modality for the detection of atherosclerotic disease.[2] Ultrasound can measure both anatomy and function, and provides well-validated surrogate markers for atherosclerosis, such as carotid intima-media complex thickness, ankle-brachial pressure index (ABI), left ventricular wall motion abnormalities and diameter of blood vessels. The role of inflammation in the pathogenesis of atherosclerosis raised the interest in identifying inflammatory markers related to the progress and extent of atherosclerotic disease. It has been shown that levels of C-reactive protein (CRP) increase in patients with coronary artery disease (CAD) and peripheral arterial disease.[3–6]

The current study aims to determine objectively the prevalence of PVD atherosclerosis in patients who have undergone vascular surgery, using ultrasonography and to determine whether there are differences in inflammatory activity related to the presence and extent of (a)symp-tomatic PVD.

METHODS

Study population

The study population composed of 431 patients with known peripheral arterial disease who were referred to the department of vascular surgery of the Erasmus Medical Centre, Rotterdam, the Netherlands, in the period between March 2006 and September 2007. Patients with (1) a symptomatic carotid artery stenosis or (2) intermittent claudication (including those with rest or night pain) or (3) patients referred because of a recently discovered abdominal aortic aneurysm were eligible for the study. The hospital's ethics committee approved the study and all patients gave informed consent.

Cardiovascular risk factors

Patients were screened for the following cardiovascular risk factors: age, gender, hypertension (previously diagnosed or blood pressure ≥ 140/90 mm Hg measured on the day of first visit) or anti-hypertensive therapy, renal failure (serum creatinine > 2mg dl^{-1}), diabetes mellitus (fasting glucose level of ≥ 7.0 mmol l^{-1}, or treatment with oral medications or insulin), hypercholesterolaemia (total cholesterol > 200 mg dl^{-1} and/or low-density lipoprotein (LDL) > 100 mg dl^{-1} and/or current statin therapy) and current or former smoking. In addition, established CAD (angina pec-toris, myocardial infarction (Ml), heart failure and previous coronary revascularization) was noted. Additionally, in all patients, serum level of high-sensitivity (hs)-CRP was determined by a nephelometric assay on a Beckman-lmmage analyzer (Beckman-Coulter, Fullerton, California, USA).

ESTABLISHMENT OF NUMBER OF AFFECTED ARTERIAL TERRITORIES

For the identification of asymptomatic atherosclerotic lesions (i.e., atherosclerotic lesion which was not suspected or diagnosed previously), we performed a duplex scan of the carotid arteries, echocardiography, ultrasono-graphic measurement of infrarenal abdominal aortic diameter and we measured the ABI. The examinations were performed and reviewed by two physicians, both skilled and experienced in ultrasonography. They were unaware of the referral diagnosis and previous medical history.

Carotid ultrasound imaging

Ultrasound images of the common, bifurcation and internal segments of each carotid artery were acquired in every patient. The common carotid artery segment was defined as the distal 1 cm of the common carotid artery, immediately before the origin of the bulb. The bifurcation segment was defined as the distal 1 cm of the bulb, where the flow divider between internal and external carotid artery is present. The internal carotid artery segment was defined as the proximal 1 cm of the internal carotid artery, starting immediately beyond the flow divider. Carotid ultrasound imaging was directed to the measurement of carotid intima-media complex thickness (CIMT) and identification of the atherosclerotic plaques in each of the six observed carotid segments. Atherosclerotic plaques were defined as an echogenic thickening of intimal reflection that encroaches on the arterial lumen, with a minimal CIMT ≥ 1.2 mm.[7] The plaque was considered significant if it causes the narrowing of common or internal

carotid artery by >50%, according to Doppler US criteria proposed by the Society of Radiologists in Ultrasound Consensus Conference.[8] Examinations were performed with a portable device, Acuson Cypress (Acuson, Mountain View, CA), using 5.4–6.6-MHz linear transducer.

Cardiac ultrasound imaging

CAD was diagnosed previously in 166 patients: in 93 (56%) by coronary angiography, in 46 (28%) by dobutamine stress echocardiography (DSE) and in 27 (16%) by radionuclide myocardial perfusion scanning. In another 265 (61%) patients without previous diagnosis, but with high probability for presence of CAD, we performed echocardiography by the protocol described elsewhere.[9] Appearance of left ventricular wall motion abnormalities during the test was considered suggestive for the presence of CAD.

Abdominal aortic ultrasound imaging

Using the portable Acuson Cypress (Acuson, Mountain View, CA) with 1.8-3.6-MHz curve-linear transducer, the ultrasound examination was focussed on the identification of the infrarenal aorta. The measurement of its maximal diameter was obtained using on-screen callipers between the two edges of the aortic wall, including intraluminal thrombus, if present. The probe was maintained perpendicular to the aortic blood flow determined by the colour Doppler to yield orthogonal sections of the aorta. Measurements were taken from the lowest renal artery to the aortic bifurcation. The maximal obtained diameter in any direction, expressed in millimetres, was used for analysis. A measured diameter of > 30 mm was considered as abnormal.

ABI measurement

The ABI in the right and left leg was calculated by dividing the right and the left ankle pressure by the brachial pressure after obtaining systolic blood pressures in the right and left brachial artery, right and left dorsalis pedis artery and right and left posterior tibia I artery. The higher of the two systolic brachial blood pressures, as well as the higher of the systolic blood pressures in the dorsalis pedis and posterior tibial artery was used for calculating the ABI. The ABI was measured after the participants had been resting in the supine position for at least 10 min. Of the ABI values obtained in each leg, the lower was used in all the analyses. An ABI of < 0.90 was considered abnormal. ABIs were measured using Doppler ultrasonic instrument Imexdop CT+ (Miami Medical, Glen Allen, VA, USA) with 8-MHz vascular probe.

STATISTICAL ANALYSIS

Continuous data are expressed as mean (±SD) or median (range) and compared using the student's t-test, one-way analysis of variance (ANOVA) or Mann-Whitney U-test when appropriate. Categorical data are presented as percent frequencies and differences between proportions were compared using the chi-square test. Receiver-operating characteristic curve analysis was used to determine the optimal cut-off value of the hs-CRP consistent with the presence of atherosclerotic changes in > 1 vascular territory. Applied multivariable logistic regression analysis was used in two models to calculate the likelihood of the presence of PVD. The variables included in the first model were: age > 70 years, gender, BMI > 25 kgm^{-2}, hypertension, dyslipidaemia, diabetes mellitus, renal failure and smoking. In the second model, we added hs-CRP to the other variables included in the first model. The performances of both models were studied with respect to discrimination and calibration. Discrimination refers to the ability to distinguish patients with and without PVD; it was quantified by C-statistic. Calibration refers to whether the predicted probabi lity of PVD is in agreement with the observed probability and was measured with the Hosmer-Lemeshow goodness-of-fit test. All statistical analyses were performed using SPSS 14.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 431 patients were included in the study. Their mean age was 68 years and 77% were male. Symptomatic carotid artery disease was the referral diagnosis in 103/431 (24%) patients, an abdominal aortic aneurysm in 170/431 (39%) and symptomatic lower extremity arterial disease in 158/431 (37%). The clinical baseline characteristics of these patients are listed in Table 1.

PREVALENCE OF PVD

A total of 213/431 patients with peripheral arterial disease were known to have PVD, that is, multiple affected arterial territories, based on clinical history and indication for referral to only a vascular surgery outpatient clinic. The routine screening of the other vascular territories using ultrasound revealed an additional 91 patients with previously unknown PVD. Importantly, in patients with already-known multiple affected arterial territories, there was an underestimation of the true number of affected territories; of 170 patients with two clinically apparent affected territories, there were 43 (25%) and

Table 1 *Baseline characteristics of study population*

	Total	Index territory			p-Value
	n = 431	Carotid	AAA	LEAD	
		n = 103	*n* = 170	*n* = 158	
Age (years; SD)	68 ±10	68 ±10	71 ±8	65 ±11	< 0.001
Men	332 (77%)	68 (66%)	152 (89%)	112 (71%)	< 0.001
BMI (kg m^{-2}; SD)	26 ±4	26 ±4	25 ±4	26 ±4	NS
History of cerebrovascular disease	155 (36%)	103 (100%)	27 (16%)	25 (16%)	<0.001
History of coronary artery disease	172 (40%)	31 (30%)	83 (49%)	58 (37%)	0.006
Heart failure	42 (10%)	4 (4%)	29 (17%)	9 (6%)	<0.001
Hypertension	335 (78%)	87 (85%)	132 (78%)	116 (73%)	NS
Diabetes mellitus	96 (22%)	26 (25%)	27 (16%)	43 (27%)	0.034
Dyslipidaemia	326 (76%)	78 (76%)	129 (76%)	119 (76%)	NS
Renal failure	71 (17%)	8 (8%)	39 (23%)	24(15%)	0.004
Current or former smoking	274 (64%)	60 (58%)	113 (67%)	101 (64%)	NS

7 (4%) with three or four affected territories, respectively, when standard ultrasound screening was used.

Based on the ultrasound measurements, 127/431 (29%) patients had only one affected arterial territory, 193/431 (45%) had two affected territories, 99/431 (23%) had three affected arterial territories and 12/431 (3%) had four affected arterial territories.

Asymptomatic atherosclerotic disease in at least one vascular territory other than the referral territory was present in 30/103 (29%) patients initially presented with symptomatic carotid artery disease, in 65/170 (38%) patients with an abdominal aortic aneurysm and in 62/158 (39%) patients with symptomatic lower extremity arterial disease.

The most prevalent asymptomatic site was the coronary artery tree as this was found to be asymptomatically present in 82/431 (19%) patients. Asymptomatic carotid artery disease, abdominal aortic aneurysm and asymptomatic lower extremity peripheral arterial disease were present in 14 (3%), 33 (8%) and 38 (9%) patients, respectively. The prevalence of concomitant atherosclerotic lesions, both symptomatic and asymptomatic, among patients with different referral diagnoses is shown in Fig. 1.

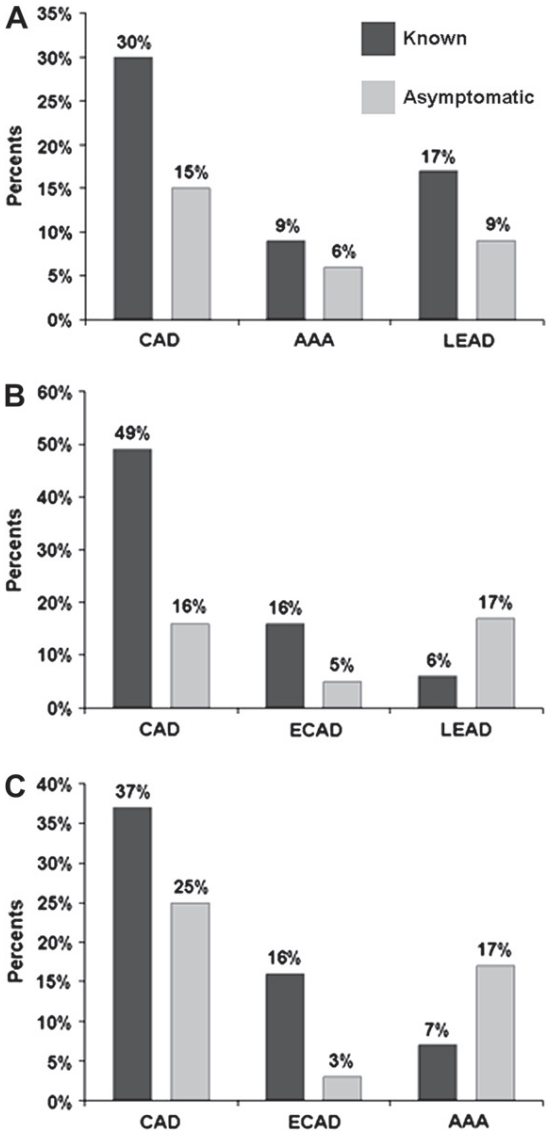


Figure 1 *Prevalence of previously known and asymptomatic atherosclerotic lesions in patients initially presented with ECAD (A), AAA (B), and LEAD (C). ECAD – extra-cranial arterial disease; AAA – abdominal aortic aneurysm; LEAD – lower extremity arterial disease; CAD – coronary artery disease.*

PVD AND CARDIOVASCULAR RISK FACTORS AND INFLAMMATION

As is shown in Table 2, when all cardiovascular risk factors were evaluated in a logistic regression analysis only age > 70 years, renal failure, male gender and BMI > 25 kgm^{-2}, were independently associated with the presence of PVD. As is shown in Fig. 2, the median values of hs-CRP differed among the patients with respect to the number of vascular territories affected by atherosclerosis. Using receiver-operating characteristic curve analysis, the optimal cut-off value of the hs-CRP levels to predict the presence of PVD was 3.60 mg l^{-1} (area under the curve 0.68). When hs-CRP is added as a dichotomous variable (i.e., below or above 3.60 mg l^{-1}) to clinical cardiovascular risk factors, it appears to be a strong predictor for the presence of PVD (OR 3.81, 95% Cl 2.39-6.09; Table 2).

DISCUSSION

This study assessed the prevalence of PVD and its relationship with cardiovascular risk factors and hs-CRP. In patients with one symptomatic arterial territory,

atherosclerotic disease in other arterial territories was common, with over two-thirds of these patients having more than one affected site. Importantly, when relying only on clinical history, 35% of patients would have been misclassified as having only one affected arterial territory. Furthermore, hs-CRP showed a close relationship with the number of affected vascular territories and increased gradually with every additional vascular territory affected.

Atherosclerosis is a complex and progressive disease that affects medium- and large-sized arteries diffusely, and involves gradual accumulation of lipids, inflammatory cells and fibrous elements in the vessel walls.[10] Besides, atherosclerosis is caused by the same pathological processes regardless of the vascular territory involved and it displays heterogeneity in space and time. Atherosclerosis affects certain sites in the arterial tree preferentially, particularly areas exposed to low shear stress, oscillatory or turbulent blood flow, like points of branching and curvatures.[11] Importantly, atherosclerosis in each vascular territory is predisposed by the same cardiovascular risk factors, such

Table 2 *Association between cardiovascular risk factors + high-sensitivity CRP and polyvascular disease*

	Univariate analysis		Model 1		Model 2		Model 3	
	OR	95% Cl	OR	95% Cl	OR	95% Cl	OR	95% Cl
Age ≥ 70 years	1.59	1.05-2.42	1.80	1.14-2.85	1.77	1.10-2.85	1.77	1.10-2.85
Male gender	3.04	1.89-4.81	2.68	1.63-4.41	2.61	1.54-4.41	2.60	1.54-4.41
BMI ≥ 25 kg m^{-2}	2.85	1.86-4.37	2.69	1.70-4.24	2.39	1.49-3.85	2.40	1.50-3.85
Hypertension	1.34	0.83-2.18	1.06	0.62-1.81	1.11	0.63-1.95	1.11	0.63-1.95
Diabetes mellitus	1.65	0.97-2.83	1.35	0.76-2.42	1.34	0.73-2.45	1.34	0.73-2.45
Dyslipidaemia	1.43	0.89-2.28	1.22	0.73-2.04	1.10	0.64-1.88	1.10	0.64-1.88
Renal failure	2.07	1.09-3.93	1.53	0.77-3.05	1.58	0.77-3.24	1.58	0.77-3.24
Current or former smoking	1.31	0.86-2.01	1.27	0.79-2.03	1.27	0.78-2.07	1.27	0.78-2.07
hs-CRP (continuous)*	1.25	1.15-1.37	–	–	1.24	1.13-1.36	–	–
Hs-CRP ≥ 3.60 mg l^{-1}	4.22	2.71-6.56	-	-	-		3.81	2.39-6.09
C-index			0.72		0.77		0.78	

BMI = body mass index; hs-CRP = high-sensitivity C-reactive protein; OR = odds ratio; Cl = confidence interval. Model 1 included risk factors only, model 2 risk factors and hs-CRP as continuous variable (as increment of 1 mg l^{-1}), and model 3 risk factors and hs-CRP as binary variable (lower or higher than the cut-off value of 3.60 mg l^{-1}).

* As increment of 1 mg l^{-1}.

as dyslipidaemia, diabetes mellitus, obesity, hypertension or smoking.[12] Interaction between them is always present, and usually it is additive. In our study, older age, male gender and BMI > 25 kg m^{-2} were strongly associated with the presence of PVD.

It has been suggested that inflammation plays a pivotal role in atherosclerosis. High-sensitivity C-reactive protein is a non-specific biomarker of inflammation. Recent large-scale population-based studies have shown that elevated levels of hs-CRP are associated with an increased risk for future cardiovascular events in both patients with or without manifest atherosclerotic disease.[13] As was recently shown in the Rotterdam study, CRP is associated with both extent and progression of atherosclerotic disease in different vascular territories.[14–15] These findings were confirmed in the present study. Whether the increased inflammatory activity in patients with poly-vascular disease is the causative mechanism for the development of polyvascular disease, or that it is merely caused by the increased number of affected vessels, remains unknown.

The concomitant occurrence in different vascular territories is a characteristic feature of atherosclerotic disease.

The generalised nature of atherosclerosis was well shown in several previously published studies. Of almost 20000 patients with peripheral, carotid and coronary atherosclerotic disease included in the Clopidogrel Versus Aspirin in Patients at Risk for Ischemic Events (CAPRIE) trial, about 23% had symptomatic disease in two, and 3% in all three vascular territories.[16] Symptomatic PVD was also common in the REACH registry, which includes more than 67000 patients from 44 countries around the world.[17] One of six patients with either coronary, cerebrovascular or peripheral arterial disease had symptomatic involvement of one or two other arterial beds, giving the overall prevalence of PVD to be almost 16%. The 1-year major event rates (cardiovascular death, Ml, or stroke

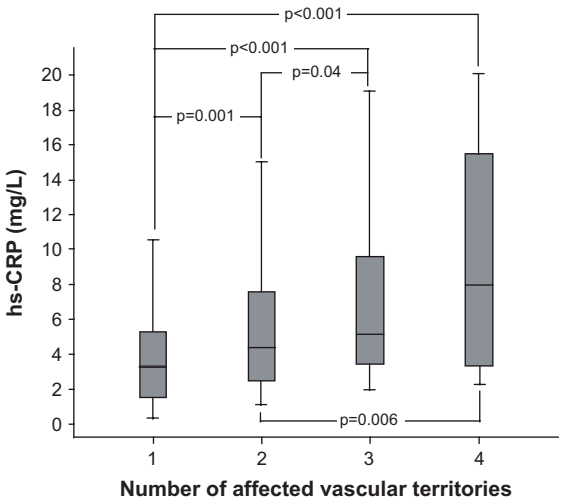


Figure 2 *Relationship between the levels of hs-CRP and number of affected vascular beds. Middle horizontal line, median; box, ±1 standard deviation; brackets, 95% confidence interval. hs-CRP = high-sensitivity C-reactive protein.*

or hospitalisation for atherothrombotic events) among the REACH registry patients increased markedly with the number of symptomatic arterial disease locations, ranging from 12.58% for patients with one to 21.14% with two and 26.27% for patients with three symptomatic arterial disease locations ($p < 0.001$ for trend).[1] The REACH registry investigators pointed out that those results might in fact underestimate the impact of peripheral arterial disease because the degree of overlap in the involvement of the different arterial territories would be even greater if the degree of asymptomatic disease were examined. In the current study, we performed extensive non-invasive screening for atherosclerotic disease in four vascular territories, in patients with at least one symptomatic territory. Indeed, using this extensive work, we found a much higher prevalence of PVD compared to the REACH registry data.

In conclusion, the prevalence of PVD in patients with symptomatic peripheral arterial disease is high. Systematical screening of patients with peripheral arterial disease using ultrasound modalities significantly increases the number of patients with PVD. Based on the outcome of the REACH registry, these patients might deserve a more aggressive medical treatment regimen since their risk for future cardiovascular events is high.

REFERENCES

1 Steg PG, Bhatt DL, Wilson PW, D'Agostino Sr R, Ohman EM, Rother J, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA* 2007;297:1197-206.

2 Olin JW, Kaufman JA, Bluemke DA, Bonow RO, Gerhard MD, Jaff MR, et al. Atherosclerotic vascular disease conference writing group IV: imaging. *Circulation* 2004; 109:2626-33.

3 Rosenson RS, Koenig W. High-sensitivity C-reactive protein and cardiovascular risk in patients with coronary heart disease. *Curr Opin Cardiol* 2002; 17:325-31.

4 McDermott MM, Green D, Greenland P, Liu K, Criqui MH, Chan C, et al. Relation of levels of hemostatic and inflammatory markers to the ankle brachial index. *Am J Cardiol* 2003;92(2): 194-9.

5 Yasojima K, Schwab C, McGeer PL. Generation of C-reactive protein and complement components in atherosclerotic plaques. *AmJPathol* 2001; 158:1039-51.

6 Vainas T, Lubbers T, Stassen FR, Herngreen SB, van Dieijen-Visser MP, Bruggeman CA, et al. Serum C-reactive protein level is associated with abdominal aortic aneurysm size and may be produced by aneurysmal tissue. *Circulation* 2003; 107(8): 1103-5.

7 Zweibel WJ. *Introduction to vascular sonography.* 4th ed. Philadelphia, PA: WB Sounders; 2000. p. 125.

8 Grant EG, Benson CB, Moneta GL, Alexandrov AV, Baker JD, Bluth El, et al. Carotid artery stenosis: gray-scale Doppler ultrasound diagnosis – Society of Radiologists in Ultrasound consensus conference. *Radiology* 2003;229:340-6.

9 Karagiannis SE, ElhendyA, Feringa HH, van Domburg R, Bax JJ, Vidakovic R, et al. The long prognostic value of wall motion abnormalities during the recovery phase of dobutamine stress echocardiography after receiving acute beta-blockade. *Coron Artery Dis* 2007; 18(3): 187-92.

10 Libby P, Rideker PM. Inflammation and atherothrombosis – from population biology and bench research to clinical practice. *J Am Coll Cardiol* 2006;48:A33-46.

11 van der Laan PA, Reardon CA, Godfrey GS. Site specificity of atherosclerosis - site-selective responses to atherosclerotic modulators. *Arterioscler Thromb Vasc Biol* 2004;24(1):12-22.

12 Ridker PM, Libby P. Risk factors for atherothrombotic disease. In: Zipes DP, Libby P, Bonow RO, Braunwald E, editors. *Braunwald's heart disease: textbook of cardiovascular medicine.* 7th ed. Philadelphia, PA: Elsevier Sounders; 2005. p. 939-58.

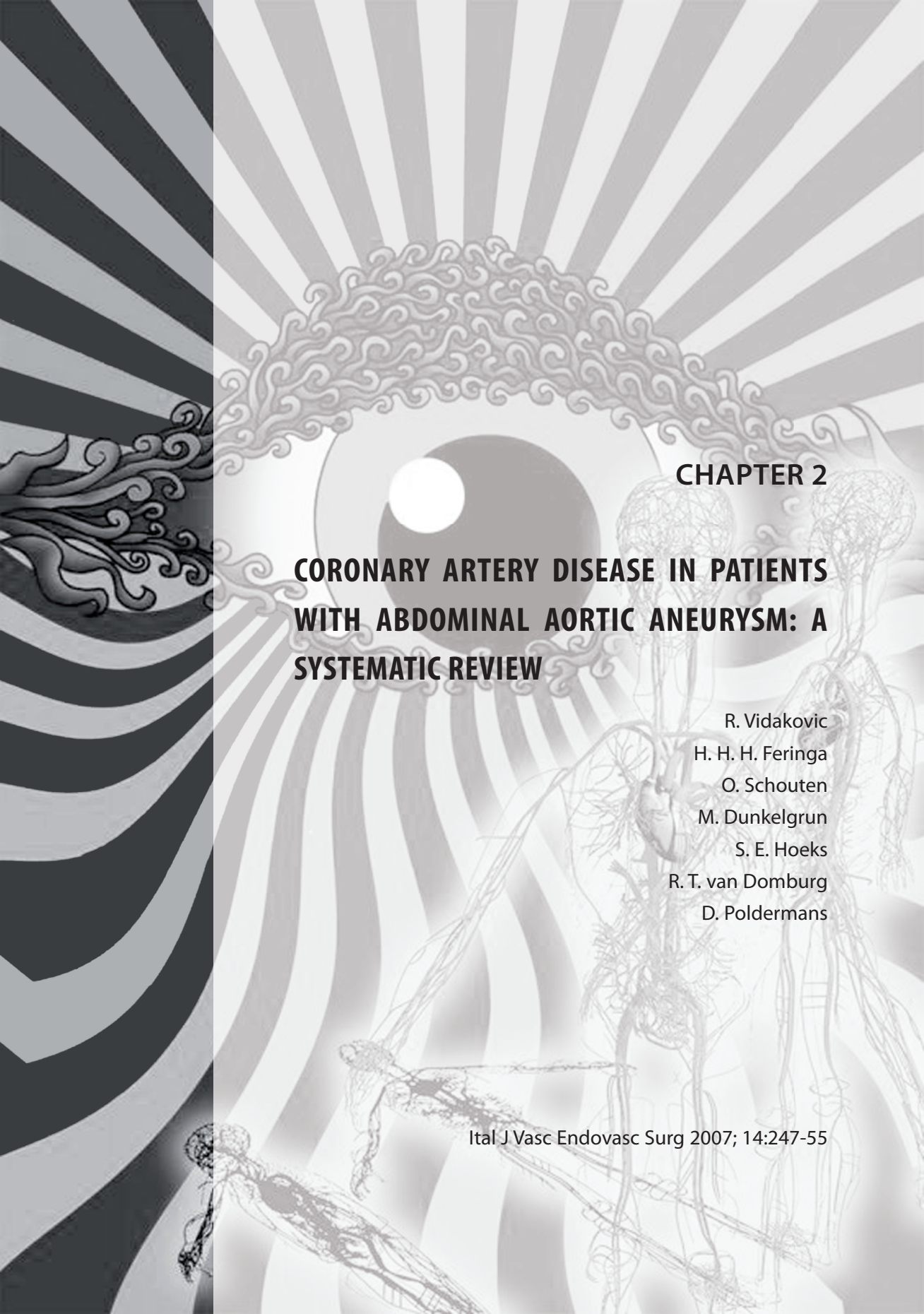
13 Ridker PM. C-reactive protein and the prediction of cardiovascular events among those at intermediate risk: moving an inflammatory hypothesis toward consensus. *J Am Coll Cardiol* 2007 May 29;49 (21):2129-38.

14 Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon 3rd RO, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Center for Disease Control and Prevention and the American Heart Association. *Circulation* 2003; 107(3):499-511.

15 Elias-Smale SE, Kardys I, Oudkerk M, Hofman A, Witteman JC. C-reactive protein is related to extent and progression of coronary and extra-coronary atherosclerosis; results from the Rotterdam study. *Atherosclerosis* 2007; 195(2):e195-202.

16 OurielK. Peripheral arterial disease. *Lancet* 2001;358:1257-64.

17 Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006;295:180-9.



CHAPTER 2

CORONARY ARTERY DISEASE IN PATIENTS WITH ABDOMINAL AORTIC ANEURYSM: A SYSTEMATIC REVIEW

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ABSTRACT

Coronary artery disease (CAD) is a frequent co-morbidity in patients with abdominal aortic aneurysm (AAA), and a leading cause of early and late morbidity and mortality after elective repair. In some patients, CAD can be asymptomatic because of reduced exercise capacity or due to pre-existing non-cardiac conditions. The preoperative identification of patients with underlying CAD is important to initiate appropriate treatment strategies to reduce the risk of perioperative complications. This review will provide current approach in preoperative evaluation of patients with CAD undergoing AAA repair. The use of clinical cardiac risk factors, noninvasive cardiac testing, novel biochemical markers, pharmacological and interventional strategies in stratification and modification of perioperative risk will be discussed.

Key words: Coronary artery disease - Aortic aneurysms, abdominal - Risk assessment - Prognosis - Perioperative care.

INTRODUCTION

Abdominal aortic aneurysm (AAA) is a common vascular disorder with potential life threatening outcome. An asymptomatic AAA can be detected in 5-8% of men and in 1% of women above 65 years of age.[1–4] Patients with AAA have frequently generalized atherosclerosis, suggesting that aneurysmal disease might be associated with the larger spectrum of polyvascular disease.[5–6]

Among all potential atherosclerotic co-morbidities in patients with AAA, coronary artery disease (CAD) attracted the most attention. Already 30 years ago, CAD was recognized as the leading cause of early and late mortality after elective AAA repair. The incidence of perioperative mortality in selected series varies from 2.7% to 5.5%, and increases up to 9% in population-based studies.[7–9] Initially, coronary angiography (CAG) was considered to be the screening tool of choice for CAD. Using CAG, the reported prevalence of severe CAD (visually assessed stenosis > 70%) in patients with AAA in Western countries was high, varying from 36% to 86%.[6, 10–13] Because CAG is not technically feasible in all patients prior to AAA repair, its own procedural related risk and the impossibility to assess functional coronary abnormalities, it was subsequently replaced by radionuclide myocardial perfusion scanning (RMPS) or stress echocardiography (SE). Beside that RMPS and SE are noninvasive and highly accurate in diagnosing CAD, both techniques showed remarkable potential of predicting early and late postoperative events in vascular surgery patients.[14–16]

Treatment strategies for AAA are open surgical or endovascular repair. Endovascular repair has the advantage of reduced short-term mortality, because of a decreased cardiac stress compared to open surgical repair. However, the long-term benefit has not been proven yet. In addition, careful monitoring on the inserted device using repeated radiographic imaging during long-term follow-up is associated with increased costs. Consequently, a substantial amount of attention was devoted to refinements of patient selection and the modification of underlying risk factors, such as CAD. This would identify the optimal therapeutic strategy for the patient at risk and improve late survival.

This review will provide current approach in preoperative evaluation of patients with CAD undergoing AAA repair. The use of clinical cardiac risk factors, noninvasive cardiac testing, novel biochemical markers, pharmacological and interventional strategies in stratification and modification of perioperative risk will be discussed (Figure 1).

PREOPERATIVE CARDIAC RISK ESTIMATION: HOW AND WHEN

Identification of clinical risk factors, which can predict postoperative cardiac complications, was of a great interest for the past 30 years. For that purpose, several risk indices were developed, such as Goldman cardiac risk index, the Detsky modified multifactorial risk index, Eagle's risk score, American Society of Anesthesiologist index, and Canadian Cardiovascular Society index.[18–22] In direct comparison of Goldman's, Detsky's, American Society of Anesthesiologist's, and Canadian Cardiovascular Society risk indices in 2035 patients, who underwent elective or urgent noncardiac surgery, Gilbert *et al.* showed that they all performed better than chance.[23] However, no index was significantly superior to the other. The recently published revision of the Goldman risk index by Lee *et al.,* named revised cardiac risk index, substantially improved its predictive value.[24]

By identifying 6 predictors of major postoperative cardiac complications (ischemic heart disease, congestive heart failure, cerebrovascular disease, diabetes mellitus treated with insulin, renal failure, and high risk surgery), this risk index stratifies patients in 4 categories: with 0, 1, 2, and > 3 risk factors. The estimated rates for postoperative

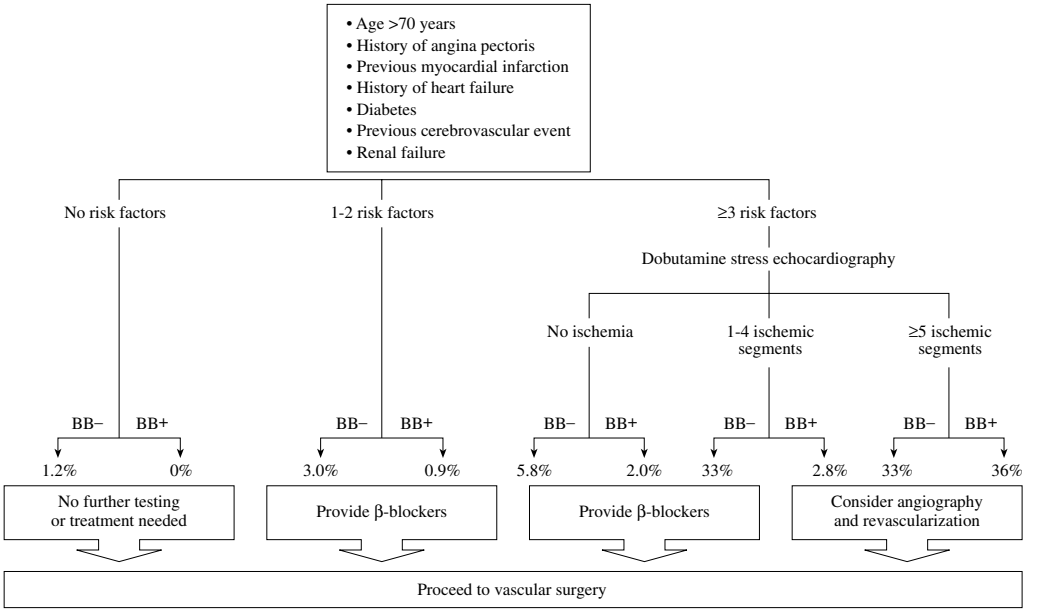


Figure 1 *Algorithm for preoperative cardiac evaluation in non-cardiac surgery. The proportions are the incidence of cardiac death or myocardial infarction. BB: β-blockers. From Boevsma et al.[11].*

major cardiac complications in each group are 0.4%, 0.9%, 7%, and 11%, respectively. The limitation of these findings for assessing patients undergoing vascular surgery was that only 110 of 2 893 patients (3.8%) had abdominal aortic surgery. Boersma *et al.* validated the Lee risk index in a large cohort of 108 593 patients who underwent all types of noncardiac surgical procedures, including vascular surgical procedures, and demonstrated a substantial improvement by adding the surgical risk of the various procedures.[25]

As it is stated in American College of Cardiology/ American Heart Association guidelines for perioper-ative cardiovascular evaluation for noncardiac surgery, patients scheduled for AAA repair should be further evaluated by noninvasive testing, if they have intermediate clinical predictors (mild angina, prior infarction, treated heart failure, or diabetes) or minor clinical predictors combined with limited exercise tolerance.[26] Among all available noninvasive testing modalities (*i.e.,* exercise electrocardiography, RMPS, SE) SE has potential advantages, although prospective studies comparing modalities prior to surgery are lacking.[14, 27–29] The test evaluates both resting left ventricular dysfunction and inducible myocardial ischemia. Both are known predictors of postoperative ischemic complications and late cardiac death.[30] Experience with dobutamine SE indicates that this test has very high negative predictive value (between 90% and 100%), which indicates that a negative test allows a safe surgical procedure.[30] The positive predictive value of dobutamine SE is lower (between 23% and 45%), but higher than in RMPS.[29]

Beside that preoperative noninvasive testing increases cost of treatment of vascular surgery patients, it also might delay surgery and run the risk of aneurys-mal rupture. Although there is no doubt that high-risk patients (> 3 risk factors) should be further evaluated by noninvasive testing, the question whether or not it can be omitted in intermediate-risk patients (1 or 2 risk factors) remains open. Recently published Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo II (DECREASE II) study tried to resolve this dilemma.[31] Of 1 476 screened vascular surgery patients treated with (β-blockers, 770 were identified to be of intermediate-risk for postoperative major cardiac events. These patients were randomly assigned to cardiac stress-testing (n = 386) or no testing. Test results were used to optimize perioperative cardiac care, including optimal heart rate (HR) control in patients with ischemia below the ischemic HR threshold, and coronary revascularization was considered in those with extensive ischemia on test (> 5 left ventricular segments). All patients proceeded to planned vascular surgery with (β-blocker therapy aiming at a HR of 60 to 65 beats per minute. Study results showed that

patients assigned for no testing had the same incidence of primary endpoints (cardiac death or nonfatal myocardial infarction) as those assigned for testing (1.8% *vs* 2.3%; P = 0.62), and waited for the vascular surgery intervention almost 3 weeks less.

Blood serum markers, such as serum creatinine and serum glucose levels, have recently emerged as promising tools in both preoperative risk score refinement and postoperative management guidance.[32-33] Of the other blood serum markers, natriuretic peptides, particularly B-type natriuretic peptide (BNP) and N-ter-minal portion of its precursor (NT-proBNP), were intensively investigated as prognostic markers in vascular surgery patients. Besides their well-defined diagnostic and prognostic value in heart failure patients, recent studies indicated that BNP and NT-proBNP levels have an incremental value in the diagnosis and management of myocardial ischemia in patients with stable CAD.[34–38] Indeed, myocardial ischemia or hypoxia might directly influence natriuretic peptide release, independent of changes in left ventricular function.[39] Two recently published studies by Feringa *et al.* have demonstrated that elevated NT-proBNP values strongly predict short- and long-term adverse cardiac events in patients undergoing elective surgery for AAA or leg bypass.[40–41] Optimal cut-off values of NT-proBNP to predict short- and long-term adverse cardiac events, determined by receiver operated curve characteristics analysis, differed in those two studies *(i.e.,* 533 ng/L for prediction of short-term, and 315 ng/L for prediction of long-term outcome). Taking into account objectiveness, relatively low cost and availability of natriuretic peptides, establishing of a universal cut-off value through the future studies can make them a first-line tool in preoperative risk assessment.

BETA-BLOCKERS AND STATINS: EASY WAY TO MODIFY THE PERIOPERATIVE RISK AND IMPROVE OUTCOME

Beta-blockers

Stress response to major surgery is characterized by increased sympathetic activity, which can provoke rupture of atherosclerotic plaques in coronary arteries, coronary arterial vasospasm, and myocardial oxygen supply/demand mismatch. All those might lead to postoperative myocardial infarction, with a potential fatal outcome. Cardioprotective effect of β-blockers is based on the fact that they can diminish the effects of increased sympathetic activity in surgical patients.

The first evidence supporting the use of β-blockers in surgical patients was published by Mangano *et al.* more than 10 years ago.[42] Two hundred patients with

known or suspected CAD undergoing high-risk non-cardiac surgery were randomized to receive atenolol or placebo. Atenolol was given intravenously before and immediately after surgery (bolus of 5 mg) and orally thereafter (50-100 mg) for the duration of hospital-ization up to a maximum of 7 days. Atenolol therapy was not associated with reduced in-hospital incidence of cardiac death or myocardial infarction, although myocardial ischemia assessed by continuous Holter monitoring was significantly reduced. Importantly, overall mortality after discharge from the hospital was significantly lower among the atenolol-treated patients than among those who were given placebo over the 6 months following hospital discharge (0% *vs* 8%; P < 0.001), over the first year (3% *vs* 14%; P = 0.005), and over 2 years (10% *vs* 21%; P = 0.019).

In DECREASE I trial, 112 selected vascular surgery patients with evidence of myocardial ischemia on pre-operative dobutamine SE were randomized to receive placebo or bisoprolol (5-10 mg).[43] Treatment with bisoprolol was started at least 7 days before surgery. Perioperative bisoprolol use resulted in 10-fold reduction in the incidence of cardiac death and myocardial infarction (3.4% *vs* 34%; P < 0.001).

Maximum benefit of β-blocker therapy in vascular surgery patients with CAD can be achieved only if a tight HR control is established. That was proved in a recently published study on 272 vascular surgery patients on chronic β-blocker therapy.[44] Higher doses of β-blockers and lower HR were associated with reduced perioperative ischemia detected on ECG Holter monitoring (HR: 2.49; 95% confidence interval [CI]: 1.79-3.48) and troponine T release (HR: 1.53; 95% CI: 1.16-2.03) (Figure 2).

Statins

Statins are potent inhibitors of cholesterol biosynthesis. In clinical trials, statins are beneficial in the primary and secondary prevention of coronary heart disease. However, the overall benefits observed with statins appear to be greater than what might be expected from changes in lipid levels alone, suggesting

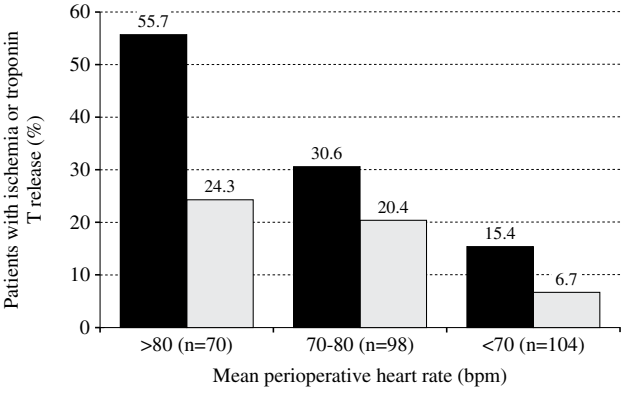


Figure 2 *Correlation of perioperative heart rate and myocardial ischemia during 12-lead electrocardiographic monitoring and troponin T release. [From Feringa et al.[44]].*

effects beyond cholesterol lowering. Indeed, recent studies indicate that some of the cholesterol-independent or "pleiotrop-ic" effects of statins involve improving endothelial function, enhancing the stability of atherosclerotic plaques, decreasing oxidative stress and inflammation, and inhibiting the thrombogenic response.[45]

As a result of their proven benefit in reduction of cardiovascular events in patients with atherosclerosis, statins are increasingly used in AAA patients. A number of pleiotropic effects of statins would be expected to slow an AAA growth. Indeed, recently published results of ultrasound surveillance study in patients with small AAA are in line with this assumption.[46] During a follow-up period of 3 years, patients who were on statin therapy had lower mean aneurysmal growth of 1.6 mm/year in comparison with non-users.

To evaluate the association between statin use and perioperative mortality, Poldermans *et al.* performed a case-controlled study among patients who underwent major vascular surgery (86% AAA surgery).[47] A cardiovascular complication during the perioperative phase was the primary cause of death in 104 (65%) case subjects. Statin therapy was significantly less common in cases than in controls (8% *vs* 25%; P < 0.001). The risk of perioperative mortality among statin users was reduced 4.5 times compared with nonusers (adjusted odds ratio for perioperative mortality among statin users as compared with nonusers was 0.22 [95% CI: 0.1 to 0.47]).

Kertai *et al.* investigated the effect of statin therapy on long-term outcome after successful AAA surgery.[48] Of the 510 patients who survived surgery beyond 30 days for AAAs, 154 (30%) were treated with statins. At 4.7-year follow-up, 27 of 154 patients (18%) treated with statins and 178 of 356 patients (50%) not treated with statins had died (P < 0.001) (Figure 3).

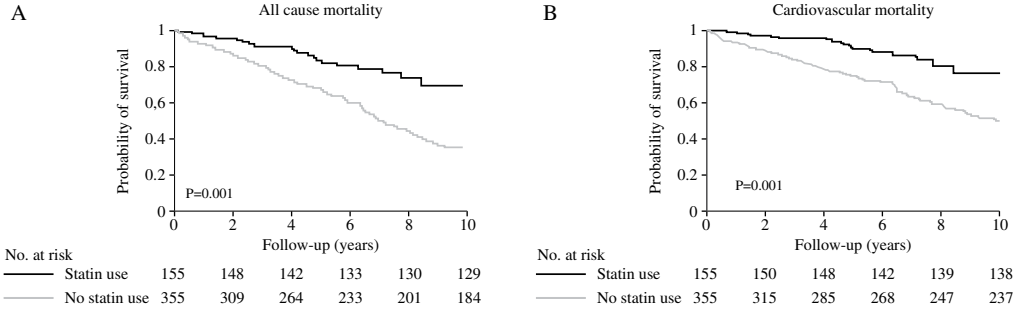


Figure 3 *All-cause (A) and cardiovascular (B) mortality in patients after abdominal aortic aneurysm surgery in relation to use of statins. [From Kertai et al[48]].*

However, no randomized clinical trial of statins has focused on cardiovascular events in patients with AAA, and they are needed before routine statin use in all AAA patients is recommended. The results of ongoing DECREASE III trial will provide insight in the effect of statins on perioperative inflammatory response and whether a reduced inflammatory response is associated with improved cardiovascular outcome.

CORONARY REVASCULARIZATION PRIOR TO ABDOMINAL AORTIC ANEURYSM REPAIR: IS IT JUSTIFIED TO POSTPONE SURGERY?

Percutaneous coronary interventions

There have been several studies evaluating the clinical utility of percutaneous coronary intervention (PCI) in high-risk patients undergoing major noncardiac surgery, including vascular surgery. In studies of Elmore *et al.* and Gottlieb *et al.,* retrospective data were collected of patients who underwent PCI prior to surgery.[49, 50] These patients were referred for PCI because of the need to relieve symptomatic angina or to treat myocardial ischemia identified by noninvasive testing. The findings of these studies indicated that the incidence of perioperative cardiac death and myocardial infarction was low, but the investigators in these studies failed to use a comparison group of patients with CAD not treated with PCI. The apparent limitations of these studies prompted Posner *et al.* to conduct an investigation to compare cardiac outcomes after noncardiac surgery in patients with prior PCI, patients with non-revascularized CAD and normal controls.[51] The results showed that patients treated with PCI within 90 days of noncardiac surgery had a similar incidence of perioperative events to matched patients with CAD who had not been revascularized. Patients who underwent noncardiac surgery more than 90 days after PCI had a lower risk of cardiac events than non-revascularized patients, but not as low as normal controls. However, the effect of revascularization was limited to a reduction in the incidence of angina pectoris and congestive heart failure, and there was no reduction in the incidence of death and nonfatal myocardial infarction. Apart from these findings, it is also important to note that if PCI procedure and coronary stent placement are performed < 6 weeks before major noncardiac surgery, the risk of perioperative coronary thrombosis or major bleeding complications may be substantially increased.[52–53] Two separate small-scale studies reported an increased rate of serious bleeding complications if antithrombot-ic therapy was continued until the time of surgery, and

in patients in whom antiplatelet drugs were discontinued 1 or 2 days before surgery an increased rate of fatal events was observed due to stent thrombosis.[52–53] The risk of these complications persisted for 6 weeks after coronary stent placement. Patients who underwent surgery > 6 weeks after coronary stent placement experienced no adverse cardiac events.

However, these reports were on patients with bare-metal stents. In the current era of drug-eluting stents which require dual antiplatelet therapy with aspirin and clopidogrel, the question remains whether or not there is the difference between them and bare-metal stents in the incidence of serious adverse cardiac and bleeding events after non-cardiac surgery. Recently published study by Schouten *et al.* addressed this topic.[54] A total of 192 noncardiac surgery patients (99 with drug-eluting and 93 with bare-metal stents) were divided in two groups: 1) early-surgery group (defined as noncardiac surgery during which clopidogrel was required during the pivotal trials that led to approval of those devices and according to their labels: bare-metal stents 1 month, sirolimus-eluting stents 3 months, and paclitaxel-eluting stents 6 months), and 2) late-surgery group. According to this classification, 30 patients underwent early and 162 late surgery. During the first 30 postoperative days, 5 fatal myocardial infarctions occurred (4 in early- and 1 in late-surgery group), all in patients in whom antiplatelet therapy was discontinued preoperatively. There was no difference in the incidence of serious adverse events between patients with bare-metal and those with drug-eluting stents (2.2% *vs* 3%; P = 0.7). Also, there was no difference in need for blood transfusions between patients who continued and patients who discontinued antiplatelet therapy (24% *vs* 20%; P = 0.5). The authors concluded that early noncardiac surgery after coronary artery stenting is associated with increased rate of perioperative adverse cardiac events. The major cause of that was discontinuation of antiplatelet therapy, but not the type of stent *{i.e.,* bare-metal or drug-eluting).

Coronary artery bypass grafting

The results of the largest retrospective study to date indicated that coronary artery bypass grafting (CABG) had a protective effect prior to noncardiac surgery.[55] Data for 3 368 patients analyzed from the Coronary Artery Surgery Study (CASS) registry showed that patients who underwent CABG before abdominal, vascular, thoracic, or head and neck surgery had a lower incidence of perioperative mortality (3.3% *vs* 1.7%) and myocardial infarction (2.7% vs 0.8%) compared with medically treated patients.

The largest reduction in perioperative mortality was observed in patients with a history of advanced angina pectoris and in patients with multivessel CAD. However, if the mortality rates of the revascularization procedures were considered the combined mortality of the revascularized patients was similar to the medically treated patients. Hassan *et al.,* using data from the Bypass Angioplasty Revascularization Investigation (BARI), showed there was no difference in the incidence of cardiac death and myocardial infarction between patients who underwent PCI or CABG and subsequent noncardiac surgery (PCI group: 1.6% *vs.* CABG group: 1.6%).[56] Recently published prospective randomized Coronary Artery Revascularization Prophylaxis (CARP) trial comprised 510 patients who where scheduled for elective AAA repair (n = 169; 33%) or lower extremity revascularization, and were selected for preoperative CAG if a cardiology consultant considered that there was an increased risk for a perioperative cardiac complications.[57] Provided that their CAG revealed at least 70% stenosis of one or more major coronary arteries, patients were randomized to receive either preliminary coronary revascularization (PCI: n = 141; CABG: n = 99) plus medical management or medical management alone in conjunction with their elective vascular procedure. The findings of this study indicated that patients undergoing coronary revascularization prior to vascular surgery had a 3.1% mortality rate within 30 days after surgery compared to a 3.4% rate for those treated medically (P = 0.87). The rate of perioperative nonfatal myocardial infarction as detected by troponin elevation was also similar in coronary revascularization patients and patients not undergoing coronary revascularization (11.6% *vs* 14.3%; P = 0.37). Additionally, the late survival rates at median follow-up of 2.7 years did not differ significantly between the patients who were assigned to have preliminary coronary intervention and those who were not (78% *vs* 77%). Furthermore, the results of this trial also indicated that coronary revascularization prior to vascular surgery was associated with delay or cancellation of the required vascular operation. However, it should be realized that the vast majority of patients included in the CARP trial had single- or two-vessel disease with a preserved left ventricular function, and sufficient cardio-protection by medical therapy (β-blockers in 85% of all patients, aspirin in 72%, and statins in 53%), which may explain the CARP trial findings. Hence, if a beneficial effect of the invasive strategy of prophylactic revascularization is to be expected, then at least patients with extensive CAD should benefit from this strategy. This hypothesis was evaluated in recently published DECREASE-V Pilot study.[58] The total of 101 patients scheduled

for elective vascular surgery (AAA repair in 50 [50%] patients), with extensive stress-induced ischemia on dobutamine SE (> 5 ischemic of 17 segments) or RMPS (> 3 ischemic walls), were randomized either to prophylactic myocardial revascularization (49 patients) or medical therapy (52 patients). A reduced left ventricular ejection fraction (< 35%) was observed in 43 (43%) patients. Among the patients allocated to preoperative coronary revascularization, CAG revealed three-vessel disease in 33 (67%) patients and left main disease in 4 (8%). A PCI was performed in 32 patients and CABG in 17. The 30-day outcome was not improved by myocardial revascularization; the incidence of all-cause mortality or nonfatal myocardial infarction for patients with preoperative revascularization or medical treatment only was 43% *vs* 33%, respectively (P = 0.3). The same was observed for the incidence of one-year composite end points (revascularization group: 49% *vs* medical therapy group: 44%; P = 0.48).

Based on the results of CARP and DECREASE-V Pilot trials, high-risk patients randomized to coronary revascularization prior to vascular surgery had no better short- and long-term postoperative outcomes than medically treated patients. Therefore, in the light of these findings, a decision whether or not to proceed with coronary revascularization should be made independent of the need for major vascular surgery.[26]

According to this, we can expect less serious cardiac events in patients who undergo EVAR. Indeed, that was proven by the two recently published studies comparing EVAR and open repair.

In the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial, 30-day operative mortality rate was 4.6% in open repair and 1.2% in EVAR patients.[59] Similarly, Endovascular Aneurysm Repair (EVAR-1) trial also showed a significantly lower 30-day mortality rate for EVAR (1.7%) compared to open repair (4.7%).[60] Despite a clear perioperative benefit for patients treated endovascularly in EVAR-1 and DREAM, both trials failed to show a benefit in overall survival after a median follow-up of respectively 2.9 and 1.8 years.[60-61] Approximately 30-40% of late mortality in both trials was attributed to cardiovascular causes.

It has to be pointed out that less than a half of patients in the DREAM and EVAR-1 trials had a history of cardiac disease (44% and 43%, respectively). To evaluate if EVAR is beneficial on short-term outcome in high-risk patients with AAA in comparison with open repair, Schouten *et al.* conducted a study on 77 patients (39 treated endovascularly) who had >3 risk factors and documented CAD by dobutamine

SE.[62] The incidence of perioperative myocardial infarction or cardiovascular death was significantly lower in patients' receiving endovascular repair in comparison to patients receiving open repair (0% *vs* 13%; P = 0.02). As it was pointed by the authors, the main limitations of this study are that it was not randomized, and that patients were selected for open or endovascular repair on the basis of surgeon's preference and anatomical features. Therefore, despite a clear evidence of improved perioperative outcome, future randomized studies have to clarify advantage of EVAR on long-term outcome in high-risk patients with AAA.

Open or endovascular aneurysm repair: can we modify cardiac risk by the type of intervention?

Initially, endovascular aneurysm repair (EVAR) was developed as the alternative to open repair in patients considered not fit enough to withstand open surgery. As the technology improved, EVAR has been used increasingly in patients judged fit for open repair. In comparison to the open surgery, in patients undergoing EVAR no aortic clamping and declamping are performed, the procedure is done under loco-regional anesthesia, and in combination with reduced blood loss a more hemodynamic stable condition is achieved.

Practical guidelines for perioperative management in abdominal aortic aneurysm patients

Due to the surgical risk, AAA patients are by definition never classified as low-risk patients. Clinical cardiac risk markers stated in Revised Cardiac Risk Index, in combination with ECG and laboratory markers, can truly stratify patients in intermediate- and high-risk population. Intermediate-risk patients can probably be operated without any additional non-invasive screening, and should be treated with β-blockers (aiming HR 60-65/min) and statins. In addition to intensive medical therapy with β-blockers and statins, high-risk patients should be screened non-invasively for the extent of underlying CAD. According to the results of non-invasive screening, patients will be further referred for CAG if they have extensive ischemia and considered as potential candidates for coronary revascularization, or they can proceed to the planned surgery if they have mild to moderate ischemia.[17]

Although coronary revascularization did not show significant advantages compared to the medical therapy in high-risk patients, it has to be considered in patients with unstable CAD. In patients in whom coronary revascularization was done

by PCI with stents, antiplatelet therapy should only be discontinued perioperatively if bleeding risks with increased mortality or sequels are comparable with the observed cardiovascular risks after its withdrawal. Endovascular AAA repair is an reasonable alternative to open repair in high-risk patients, because it results in reduced rates of perioperative cardiac morbidity and mortality, a shorter initial hospital stay, and shorter recovery time, but it is limited only to anatomically suitable patients with infrarenal AAA and it is still not proved to increase long-term survival.

REFERENCES

1. Scott RA, Vardulaki KA, Walker NM, Day NE, Duffy SW, Ashton HA. The long-term benefits of a single scan for abdominal aortic aneurysm (AAA) at age 65. Eur J Vasc Endovasc Surg 2001;21:535-40.
2. The Multicentre Aneurysm Screening Study Group Participants. Multicentre Aneurysm Screening Study Group: the Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. Lancet 2002;360:1531-9.
3. Lederle FA, Johnson GR, Wilson SE. Abdominal aortic aneurysm in women. J Vasc Surg 2001;34:122-6.
4. Scott RA, Bridgewater SG, Ashton HA. Randomized clinical trial of screening for abdominal aortic aneurysm in women. Br J Surg 2002;89:283-5.
5. Reed D, Reed C, Stemmermann G, Hayashi T. Are aortic aneurysms caused by atherosclerosis? Circulation 1992;85:205-ll.
6. SukhijaR, AronowWS,Yalamanchili K, SinhaN, Babu S. Prevalence of coronary artery disease, lower extremity peripheral atrial disease, and cerebrovascular disease in 110 men with an abdominal aortic aneurysm. Am J Cardiol 2004;94:1358-9.
7. Lederle FA, Wilson SE, Johnson GR, Reinke DB, Littooy FN, Archer CW *et al.* Immediate repair compared with surveillance of small abdominal aortic aneurysms. N Engl J Med 2002;346:1437-44.
8. Brady AR, Fowkes FG, Greenhalgh RM, Powell JT, Ruckley CV, Thompson SG. Risk factors for postoperative death following elective surgical repair of abdominal aortic aneurysm: results ofrom the UK Small Aneurysm Trial. On behalf of of the UK Small Aneurysm Trial participants. Br J Surg 2000,87:742-9.
9. Kertai MD, Boersma E, Poldermans D. Small abdominal aortic aneurysms. N Engl J Med 2002;347:1112-5.
10. Hertzer NR, Beven EG, Young JR, O'Hara PJ, Ruschhaupt WF III, Graor RA *et al.* Coronary artery disease in peripheral vascular patients. A classification on 1000 coronary angiograms and results of surgical management. Ann Surg 1984;199:223-33.
11. Yeager RA, Weigel RM, Murphy ES, McConnell DB, Sasaki TM, Vetto RM. Application of clinically valid cardiac factors to aortic aneurysm surgery. Arch Surg 1986;121:278-81.

12. Acinapura AJ, Rose DM, Kramer MD, Jacobowitz IJ, Cunningham JN Jr. Role of coronary angiography and coronary artery bypass surgery prior to abdominal aortic aneurysm. J Cardiovasc Surg (Torino) 1987;28:552-7.
13. Perry MO, Calcagno D. Abdominal aortic aneurysm surgery: the basic evaluation of cardiac risk. Ann Surg 1988;208:738-42.
14. Shaw LJ, Eagle KA, Gersh BJ, Miller DD. Meta-analysis of intravenous dipyridamole-thallium 201 imaging (1985 to 1994) and dobu-tamine echocardiography (1991 to 1994) for risk stratification before vascular surgery. J Am Coll Cardiol 1996;27:787-98.
15. Davila-Roman VG, Waggoner AD, Sicard GA, Geltman EM, Schechtman KB, Perez JE. Dobutamine stress echocardiography predicts surgical outcome in patients with an aortic aneurysm and peripheral vascular disease. J Am Coll Cardiol 1993;21:957-63.
16. Poldermans D, Arnese M, Fioretti PM, Boersma E, Thomson IR, Rambaldi R *et al.* Sustained prognostic value of dobutamine stress echocardiography for late cardiac events after major noncardiac vascular surgery. Circulation 1997;95:53-8.
17. Boersma E, Poldermans D, Bax JJ, Steyerberg EW, Thomson IR, Banga JD *et al.* Predictors of cardiac events after major vascular surgery: role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. JAMA 2001 ;285:1865-73.
18. Goldman L, Caldera DL, Nussbaum SR, Southwick FS, Krogstad D, Murrey B *et al.* Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med 1977;297:845-50.
19. Detsky AS, Abrams HB, McLaughlin JR, Drucker DJ, Sasson Z, Johnston N *et al.* Predicting cardiac complications in patients undergoing noncardiac surgery. J Gen Intern Med 1986;l:211-9.
20. Eagle KA, Coley CM, Newell JB, Brewster DC, Darling RC, Strauss HW *et al.* Combining clinical and thallium data optimizes preopera-tive assessment of cardiac risk before major vascular surgery. Ann Intern Med 1989;110:859-66.
21. American Society of Anesthesiologists. New classification of physical status. Anesthesiology 1963;24:111.
22. Campeau L. Letter: Grading of angina pectoris. Circulation 1976;54:522-3.
23. Gilbert K, Larocque BJ, Patrick LT. Prospective evaluation of cardiac risk indices for patients undergoing noncardiac surgery. Ann Intern Med 2000;133:356-9.
24. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF *et al.* Derivation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999;100:1043-9.
25. Boersma E, Kertai MD, Schouten O, Bax JJ, Noordzij P, Steyerberg EW *et al.* Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee cardiac risk index. Am J Med 2005;l 18:1134-41.
26. Eagle KA, Berger PB, Calkinis H, Chaitman BR, Ewy GA, Fleischmann KE *et al.* ACC/AHA gudelines for perioperative cardiovascular evaluation for non cardiac surgery. Circulation 2002;105;1257-67.
27. Mantha S, Roizen MF, Barnard J, Thisted RA, EUis JE, Foss J. Relative effectiveness of four preoperative tests for predicting adverse cardiac outcomes after vascular surgery: a meta-analysis. Anesth Analg 1994;79:422-33.

28. Kertai MD, Boersma E, Bax JJ, Heijenbrok-Kal MH, Hunink MG, LTtalien GJ *et al.* A meta-analysis comparing the prognostic accuracy of six diagnostic tests for predicting perioperative cardiac risk in patients undergoing major vascular surgery. Heart 2003;89:1327-34.

29. Kertai MD, Boersma E, Sicari R, LTtalien GJ, Bax JJ, Roelandt JR *et al.* Which stress test is superior for perioperative cardiac risk stratification in patients undergoing major vascular surgery? Eur J Vasc Endovasc Surg 2002;24:222-9.

30. Poldermans D, Fioretti PM, Foster M, Thomson IR, Boersma E, el-Said M et al. Dobutamine stress echocardiography for assessment of perioperative risk in patients undergoing major vascular surgery. Circulation 1993;87:1506-12.

31. Poldermans D, Bax JJ, Schouten O, Neskovic AN, Paelinck B, Rocci G *et al.* Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo Study Group. Should major vascular surgery be delayed because of preoperative cardiac testing in intermediate risk patients receiving beta-blocker therapy with tight heart rate control? J Am Coll Cardiol 2006;48:964-9.

32. Kertai MD, Boersma E, Bax JJ, van den Meiracker AH, van Urk H, Roelandt JR *et al.* Comparison between serum creatinine and creati-nine clearance for the prediction of postoperative mortality in patients undergoing major vascular surgery. Clin Nephrol 2003;59:17-23.

33. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M *et al.* Intensive insulin therapy in the critically ill patients. N Engl J Med 2001 ;345:1359-67.

34. Tsutamoto T, Wada A, Maeda K, Hisanaga T, Maeda Y, Fukai D *et al.* Attenuation of compensation of endogenous cardiac natriuretic pep-tide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. Circulation 1997;96:509-16.

35. Hartmann F, Packer M, Coats AJ, Fowler MB, Krum H, Mohacsi P *et al.* Prognostic impact of plasma N-terminal pro-brain natriuretic peptide in severe chronic congestive heart failure: a substudy of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial. Circulation 2004;110:1780-6.

36. Weber M, Dill T, Arnold R, Rau M, Ekinci O, MuUer KD *et al.* N terminal B-type natriuretic peptide predicts extent of coronary artery disease and ischemia in patients with stable angina pectoris. Am Heart J2004;148:612-20.

37. Ndrepepa G, Braun S, Mehilli J, von Beckerath N, Vogt W, Schomig A *et al.* Plasma levels of N-terminal pro-brain natriuretic peptide in patients with coronary artery disease and relation to clinical presentation, angiographic severity, and left ventricular ejection fraction. Am J Cardiol 2005;95:553-7.

38. Bibbins-Domingo K, Ansari M, Schiller NB, Massie B, Whooley MA. Is B-type natriuretic peptide a useful screening test for systolic or diastolic dysfunction in patients with coronary disease? Data from the Heart and Soul Study. Am J Med 2004;l 16:509-16.

39. Sabatine MS, Morrow DA, de Lemos JA, Omland T, Desai MY, Tanasijevic M *et al.* Acute changes in circulating natriuretic peptide levels in relation to myocardial ischemia. J Am Coll Cardiol 2004;44:1988-95.

40. Feringa HH, Bax JJ, Elhendy A, de Jonge R, Lindemans J, Schouten O *et al.* Association of plasma N-terminal pro-B-type natriuretic peptide with postoperative cardiac events in patients undergoing surgery for abdominal aortic aneurysm or leg bypass. Am J Cardiol 2006;98:111-5.

41. Feringa HH, Schouten O, Dunkelgrun M, Bax JJ, Boersma E, Elhendy A *et al.* Plasma N-terminal pro-B-type natriuretic peptide as long-term prognostic marker after major vascular surgery. Heart 2006;93:226-31.

42. Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. N Engl JMedl996;335:1713-20.

43. Poldermans D, Boersma E, Bax JJ, Thomson IR, van de Ven LLM, Blankensteijn JD *et al.* The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. N Engl J Med 1999;341:1789-94.

44. Feringa HH, Bax JJ, Boersma E, Kertai MD, Meij SH, Galal W *et al.* High dose of beta-blockers and tight heart rate control reduce myocardial ischemia and troponin T release in vascular surgery patients. Circulation 2006;114(l Suppl):I344-9.

45. Moreno PR, Fuster V. The year in atherothrombosis. J Am Coll Cardiol 2004 ;44:2099-110.

46. Schouten O, van Laanen JJH, Boersma E, Vidakovic R, Feringa HHH, Dunkelgrun M *et al.* Statins are associated with a reduced infrarenal abdominal aortic aneurysm growth. Eur J Vasc Endovasc Surg 2006;32:21-6.

47. Poldermans D, Bax JJ, Kertai MD, Krenning B, Westerhout CM, Schinkel AFL *et al.* Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. Circulation 2003;107:1848-51.

48. Kertai MD, Boersma E, Westerhout CM, van Domburg RT, Klein J, Bax JJ *et al.* Association between long-term statin use and mortality after successful abdominal aortic aneurysm surgery. Am J Med 2004;116:96-103.

49. Elmore JR, HaUett JW, Gibbons RJ, Naessens JM, Bower TC, Cherry KJ *et al.* Myocardial revascularization before abdominal aortic aneurys-morrhaphy: effect of coronary angioplasty. Mayo Clin Proc 1993; 68: 637-41.

50. Gottlieb A, Banoub M, Sprung J, Levy PJ, Beven M, Mascha EJ. Perioperative cardiovascular morbidity in patients with coronary artery disease undergoing vascular surgery after percutaneous transluminal coronary angioplasty. J Cardiothorac Vasc Anesth 1998;12:501-6.

51. Posner KL, van Norman GA, Chan V Adverse cardiac outcomes after noncardiac surgery in patients with prior percutaneous transluminal coronary angioplasty. Anesth Analg 1999;89:553-60.

52. Kaluza GL, Joseph J, Lee JR, Raizner AE. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. J Am Coll Cardiol 2000;35:1288-94.

53. Wilson SH, Fasseas P, Orford JL, Lennon RJ, Horlocker T, Charnoff NE *et al.* Clinical outcome of patients undergoing non-cardiac surgery in two months following coronary stenting. J Am Coll Cardiol 2003;42:234-40.

54. Schouten O, van Domburg RT, Bax JJ, de Jaegere PJ, Dunkelgrun M, Hoeks SE *et al.* Noncardiac surgery after coronary stenting: early surgery and interruption of antiplatelet therapy are associated with an increase in major adverse cardiac events. J Am Coll Cardiol 2007;49:122-4.

55. Eagle KA, Rihal CS, Mickel MC, Holmes DR, Foster ED, Gersh BJ. Cardiac risk of noncardiac surgery: influence of coronary disease and type of surgery in 3368 operations. CASS Investigators and University of Michigan Heart Care Program. Coronary Artery Surgery Study. Circulation 1997;96:1882-7.

56. Hassan SA, HlatkyMA, BoothroydDB,WinstonC, MarkDB, Brooks MM *et al.* Outcomes of noncardiac surgery after coronary bypass surgery or coronary angioplasty in the Bypass Angioplasty Revascularization Investigation (BARI). Am J Med 2001; 110:260-6.

57. McFalls EO, Ward HB, MoritzTE, Goldman S, Krupski WC, Littooy F *et al.* Coronary artery revascularization before elective major vascular surgery. N Engl J Med 2004;351:2795-804.

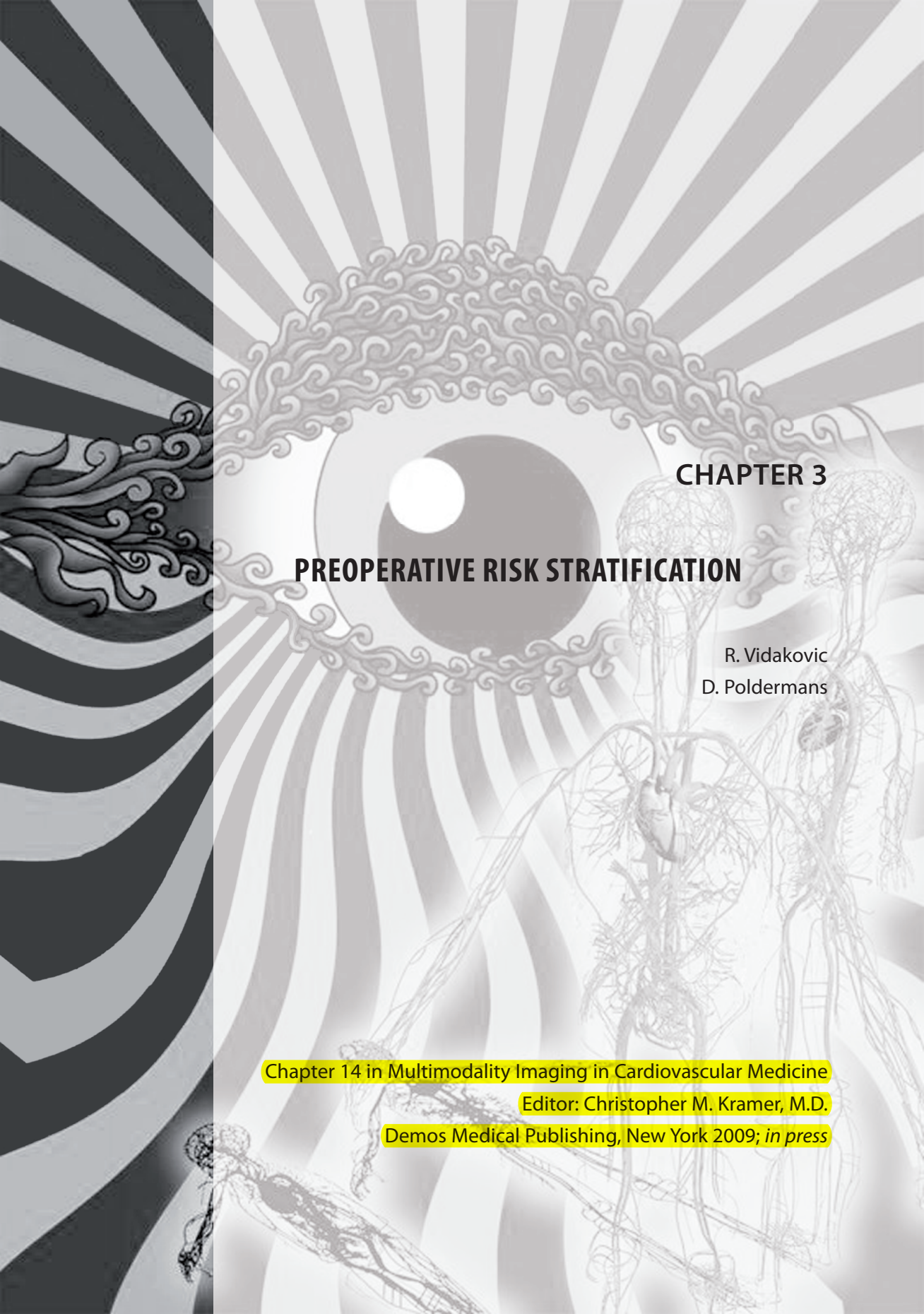
58. Poldermans D, Schouten O, Vidakovic R, Bax JJ, Thomson IR, Hoeks SE *et al.* A clinical randomized trial to evaluate the safety of a non-invasive approach in high-risk patients undergoing major vascular surgery: the DECREASE-V Pilot Study. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. J Am Coll Cardioll 2007;49:1763-9.

59. Prinssen M, Verhoeven ELG, Buth J, Cuypers PWM, van Sambeek MRHM, Blam R *et al.* A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. Dutch Randomized Endovascular Aneurysm Management (DREAM) Trial Group. N Eng JMed2004;351:1607-18.

60. EVAR Trial participants. Endovascular aneurysm repair *versus* open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial. Lancet 2005;365:2179-86.

61. Blankensteijn JD, de Jong SE, Prinssen M, van der Ham AC, Buth J, van Sterkenburg SM *et al.* Two-year outcomes after conventional or endovascular repair of abdominal aortic aneurysms. Dutch Randomized Endovascular Aneurysm Management (DREAM) Trial Group. N Engl J Med 2005;352:2398-405.

62. Schouten O, Dunkelgrun M, Feringa HHH, Kok NFM, Vidakovic R, Bax JJ *et al.* Myocardial damage in high-risk patients undergoing elective endovascular or open infrarenal abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg 2007;33:544-9.



CHAPTER 3

PREOPERATIVE RISK STRATIFICATION

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INTRODUCTION

Early or late perioperative cardiovascular morbidity and mortality are among the major problems in patients undergoing non-cardiac surgery. It is estimated that of almost 40 million annually performed surgical procedures in Europe, cardiovascular mortality occurs in 0,3%, and postoperative myocardial infarction (MI) in 1%. In a pooled analysis of unselected non-cardiac surgery patients over the age of 40 years, a 30-day incidence of postoperative cardiac events (MI and cardiac death) was 2,5%. [1] The rate of these events is even higher in vascular surgery patients (6,2%). [2] The true event rate of postoperative cardiac complications can be even higher, since most of them occurs asymptomatically, and depends on the type of postoperative surveillance. [3, 4][Fig. l4-l]

The majority of postoperative cardiac complications are caused by sudden or prolonged myocardial ischemia due to a primary coronary event (such as plaque erosion and/or rupture, fissuring, or dissection) or due to either increased oxygen demand or decreased supply (such as coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension). [5, 6] Other major determinants of adverse postoperative outcome are aortic stenosis and left ventricular dysfunction. [7-9] The pathophysiology of cardiac events in those two conditions is related to an interaction of developing hypotension and low cardiac output during surgery, and possible underlying coronary artery disease (CAD).

To reduce postoperative cardiac morbidity and mortality, preoperative screening is of paramount importance. This screening involves identification of potential risk factors, as well as different noninvasive imaging modalities. In this chapter we will describe the current status of preoperative risk stratification for patients undergoing non-cardiac surgery.

ESTIMATION OF CARDIAC RISK

Identification of clinical risk factors, which can predict postoperative cardiac complications, was of a great interest for the past 30 years. For that purpose, several risk indices were developed, such as Goldman cardiac risk index, the Detsky modified multifactorial risk index, Eagle's risk score, American Society of Anesthesiologist index, and Canadian Cardiovascular Society index. [10-14] In direct comparison of Goldman's, Detsky's, American Society of Anesthesiologist's, and Canadian Cardiovascular Society risk indices in 2035 patients, who underwent elective or urgent noncardiac surgery,

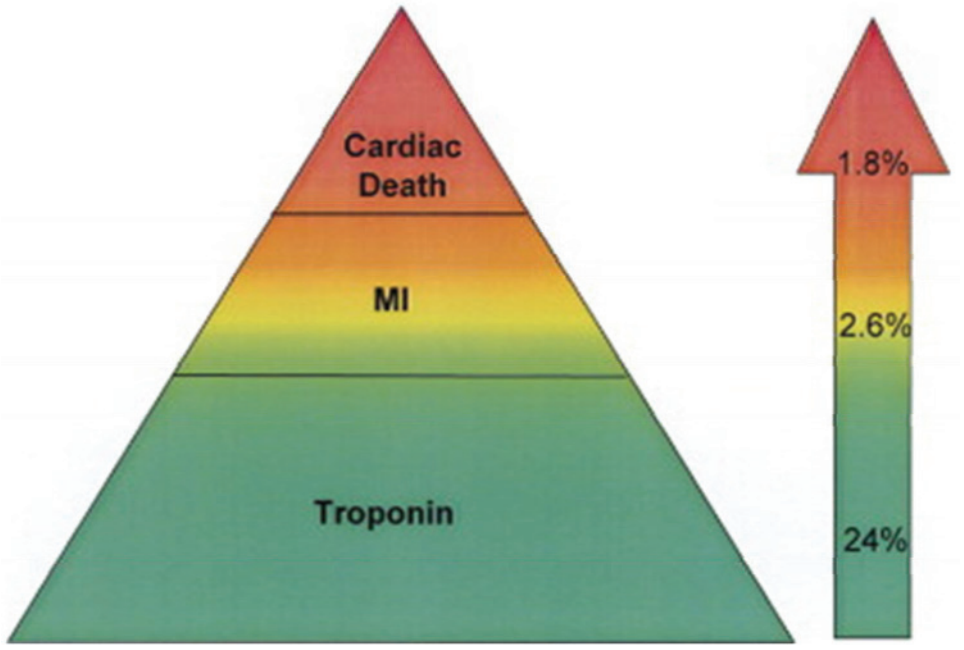


Figure 14-1 *The incidence of peri operative cardiac events in non-cardiac surgery. [4]*

Gilbert *et al.* showed that they all performed better than chance. [15] However, no index was significantly superior to the other. The recently published revision of the Goldman's risk index by Lee *et al,* named Revised Cardiac Risk Index, substantially improved its predictive value. [16] By identifying 6 predictors of major postoperative cardiac complications (ischemic heart disease, congestive heart failure, cerebrovascular disease, diabetes mellitus treated with insulin, renal failure, and high risk surgery), this risk index stratifies patients in 4 categories: with 0, 1,2, and > 3 risk factors. The estimated rates for postoperative major cardiac complications in each group are 0.4%, 0.9%, 7%, and 11%, respectively. Boersma *et al.* validated the Lee risk index in a large cohort of 108.593 patients who underwent all types of non-cardiac surgical procedures, including vascular surgical procedures, and demonstrated a substantial improvement by adding the surgical risk of the various procedures. [17]

The American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines on perioperative cardiovascular evaluation and care for non-cardiac surgery provide the stepwise algorithm to preoperative cardiac assessment. [18] This algorithm uses the urgency of non-cardiac surgery, clinical risk factors, and patients' functional capacity in prediction of postoperative cardiac events. Clinical risk

factors are divided in three categories: major, intermediate, and minor risk factors. [Table 14-1] In difference to the previous edition of these guidelines, the category of intermediate risk factors is substituted by the risk factors included in Revised Cardiac Risk Index, with the exclusion of the type of surgery, which is incorporated elsewhere in the algorithm. The first step in this algorithm is to determine the urgency of non-cardiac surgery. Patients needing emergency non-cardiac surgery should proceed to surgery without the delay of additional cardiac evaluation, with the instructions for postoperative surveillance and risk factor management. The next steps refer to the patients considered for elective non-cardiac surgery:

a) In the presence of active cardiac conditions the surgery should be canceled or delayed until the cardiac problem has been clarified and treated appropriately.

b) Patients scheduled for the low risk surgery (reported cardiac risk generally < 1%) and good functional capacity, or diminished functional capacity but no risk factors, should proceed with planned surgery.

c) Patients scheduled for intermediate risk surgery (reported cardiac risk generally 1-5%) or high risk surgery (reported cardiac risk generally > 5%), with poor

Table 14-1 *Clinical predictor of increased perioperative cardiovascular risk [18]*

Major predictors – active cardiac conditions

- Unstable coronary syndromes
  - Unstable or severe angina
  - Recent MI
- Decompensated heart failure
- Significant arrhythmias
- Severe valvular disease

Intermediate predictors*

- History of heart disease
- History of compensated or prior heart failure
- History of cerebrovascular disease
- Diabetes mellitus
- Renal insufficiency

Minor predictors

- Advanced age (> 70 years)
- Abnormal ECG (left ventricular hypertrophy, left bundle-branch block, ST-T abnormalities
- Rhythm other than sinus
- Severe valvular disease

*Clinical risk factors from the Revised Cardiac Risk Index, except type of surgery

or unknown functional capacity and 1-2 clinical risk factors, should proceed with the planned surgery with tight heart rate control using beta-blockers, or to preoperative testing if that will change management; the same refer to the patients scheduled for intermediate risk surgery, poor or unknown functional capacity, and > 3 risk factors.

d) Patients scheduled for high risk surgery (reported cardiac risk generally > 5%), poor or unknown functional capacity, and > 3 risk factors should be considered for preoperative testing if it will change management.

ADDITIONAL TESTING

Further cardiac testing is warranted only if the test results will change perioperative management. Beside that preoperative noninvasive testing increases cost of treatment of non-cardiac surgery patients, it also might delay surgery and run the risk of. Although there is no doubt that high-risk patients (> 3 risk factors and poor functional capacity) should be further evaluated by noninvasive testing, the question whether or not it can be omitted in intermediate-risk patients (1 or 2 risk factors) remains open. Recently published Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo II (DECREASE II) study tried to resolve this dilemma. [3] Of 1.476 screened vascular surgery patients treated with beta-blockers, 770 were identified to be of intermediate-risk for postoperative major cardiac events. These patients were randomly assigned to cardiac stress-testing (n = 386) or no testing. Test results were used to optimize perioperative cardiac care, including optimal heart rate (HR) control in patients with ischemia below the ischemic HR threshold, and coronary revascularization was considered in those with extensive ischemia on test (> 5 left ventricular segments). All patients proceeded to planned vascular surgery with P-blocker therapy aiming at a HR of 60 to 65 beats per minute. Study results showed that patients assigned for no testing had the same incidence of primary endpoints (cardiac death or nonfatal MI) as those assigned for testing (1.8% *vs.* 2.3%; P = 0.62), and waited for the vascular surgery intervention almost 3 weeks less.

Several imaging modalities can be used for the additional preoperative testing, such as stress echocardiography (SE), myocardial perfusion scintigraphy (MPS), cardiac computed tomography (CCT), and cardiac magnetic resonance (CMR).

Stress echocardiography

This diagnostic method is based on the enhancement of myocardial oxygen demand and subsequent ischemia by infusion of incremental doses of dobutamine,

which increases myocardial contractility and heart rate. Commenced contractile dysfunction in ischemic myocardial segments is assessed by echocardiography as wall motion abnormalities. [Figure 14-2] Numerous studies showed stress echocardiography as predictive for short- and long-term perioperative cardiac events, with a high negative and moderate positive predictive value. [19-26] The most useful prognostic data obtained during stress echocardiography are ischemic threshold (i.e., the cardiac workload necessary to induce myocardial ischemia), extent and severity of wall motion abnormalities. The test results are limited in patients on β-blocker therapy (diminished HR response), and in those with bad image quality.

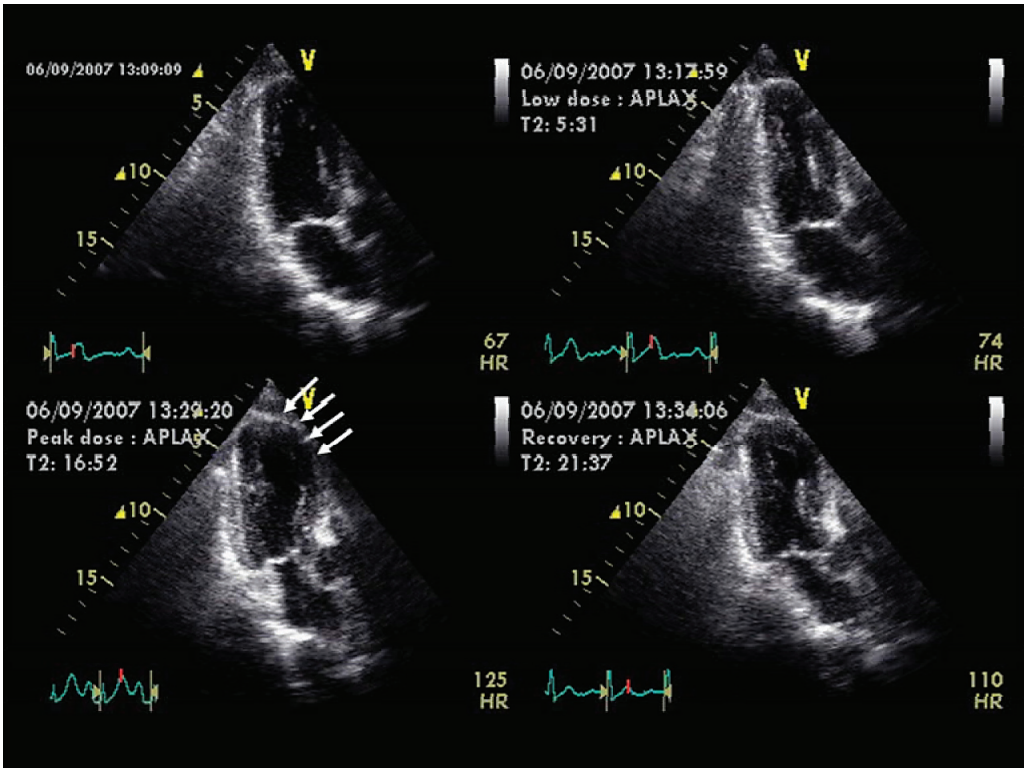


Figure 14-2 *Dobutamine stress echocardiography. Quad-screen format of apical 3-chamber view, end-systolic frames at baseline (upper left), low dose (upper right), peak dose (lower left) and recovery (lower right). At low dose, there is increased systolic wall thickening in all segments indicating improvement in contractility. At peak dose, akinesis of distal septum and apex can be noted; arrows indicate region with absent wall thickening, consistent with ischemic response.*

(Image courtesy Aleksandar N. Neskovic, MD, Department of Cardiology, Clinical Hospital Center "Zemun", Belgrade, Serbia)

Myocardial perfusion scintigraphy

Diminished blood flow through the stenotic coronary arteries can be diagnosed using of small amounts of intravenously administered radioactive tracers such as thallium-201 or technetium 99-m. Perfusion defects are more obvious if recorded during exercise or pharmacologic stress, and can be classified as reversible (ischemia) or fixed (scar). [Figure 14-3] This diagnostic technique has been extensively studied in the setting of preoperative risk assessment, showing its high sensitivity but low specificity in predicting postoperative cardiac complications. [27-30] The likelihood of peri operative complications is higher with reversible perfusion defects, and increases with its extent. [31]

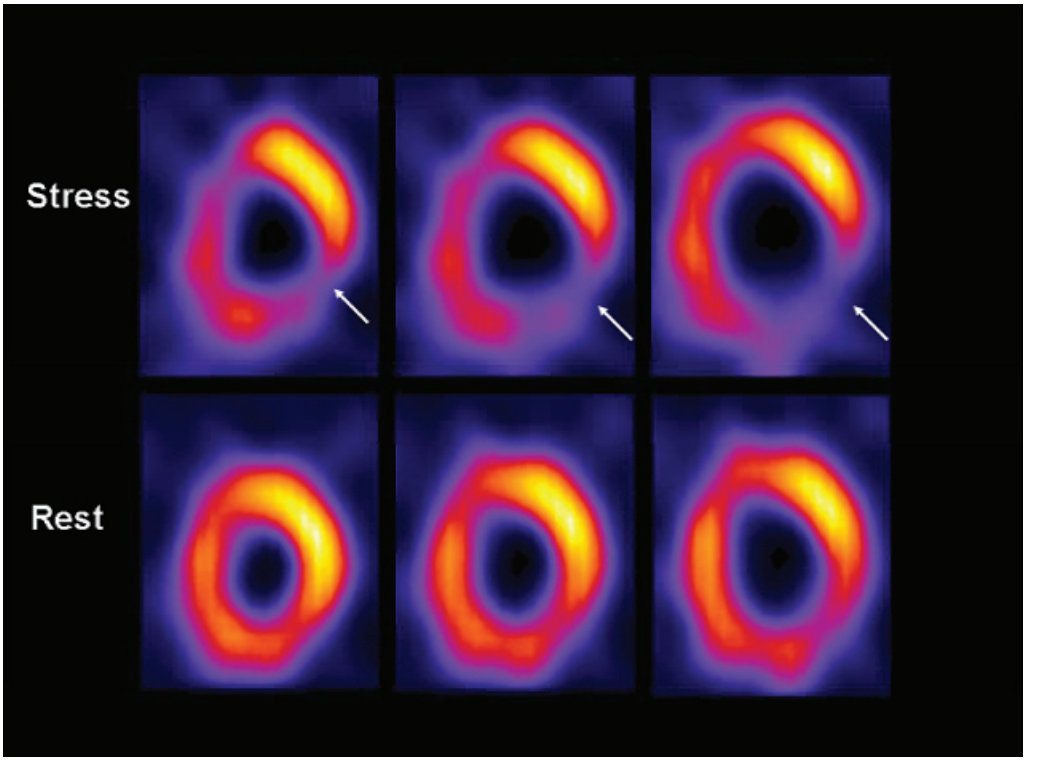


Figure 14-3 *Dipyridamole thallium-201 myocardial perfusion scintigraphy. Lower images are taken at rest, and upper images during dipyridamole stress. The arrows indicate the presence of reversible perfusion defect in the lateral wall.*

(Images courtesy Jeroen J. Bax, MD, Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands.)

Cardiac computed tomography

In the past decade, cardiac computed tomography (CCT) emerged as reliable diagnostic method for the assessment of CAD, coronary artery anatomy, and cardiac function. [Figures 14-4 and 14-5] Constant technological improvements in the field of CCT (introduction of dual-source and 256-slice CTs) impose it as excellent alternative to standard coronary angiography in selected group of patients. Studies investigating the accuracy of CCT in detection of obstructive CAD report its sensitivity, specificity, positive and negative predictive value to be 94-99%, 95-97%, 76-97%, and 93-99%, respectively. [32, 33] In regard to high specificity of CCT reported, it appears as an excellent diagnostic modality for excluding CAD. In difference to conventional coronary angiography, CCT allows the assessing of atherosclerotic plaque morphology

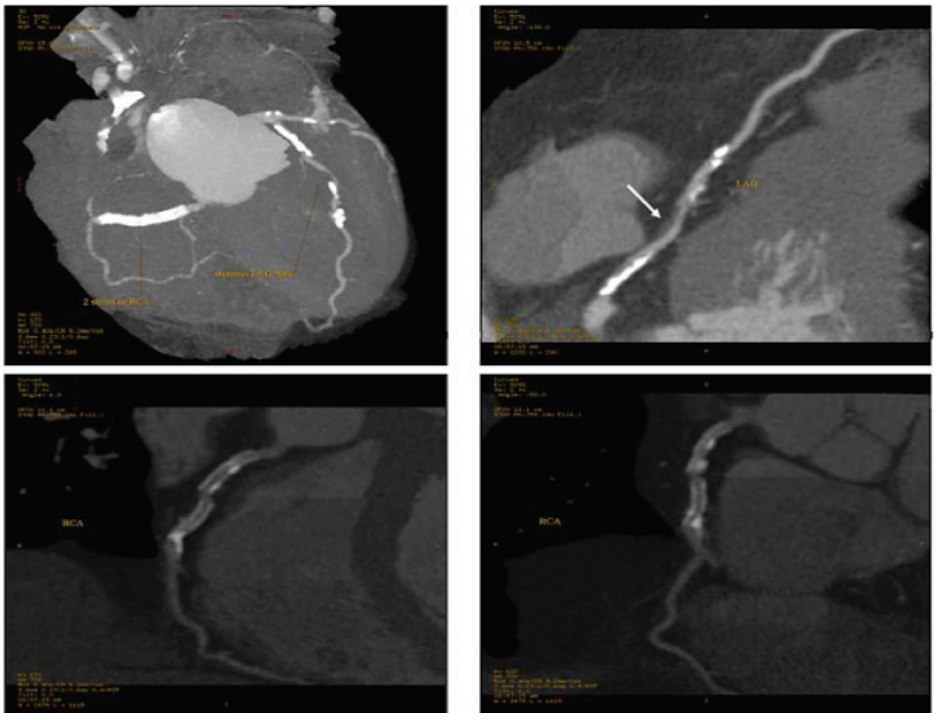


Figure 14-4 *Cardiac computerized tomography. Coronary angiography in patient with bilateral aorto-illiacal stenosis and previously performed percutaneous coronary intervention with placement of two stents in right coronary arery. Both stents are of good patency (lower left and right panels). Stenosis of the left descending coronary artery of 50% is indicated by the arrow (upper right panel).*
(Image courtesy Dragan Sagic, MD, Department of Cardiology, Dedinje Cardiovascular Institute, Belgrade, Serbia)

and identifying unstable plaques. [34, 35] The assessment of plaque morphology may have an important role in identifying patients who are at greater perioperative risk for adverse cardiac events. Cardiac computed tomography also showed high accuracy in assessing coronary artery graft and stent patency. [36-39] Nevertheless, there are certain limitations to the use of CCT in those settings which can lead to the diminished quality of the images of the grafts and implanted stents (i.e., presence of surgical clips, calcifications, and metallic artifacts). Although two-dimensional echocardiography will remain the preferred tool in preoperative assessment of global left ventricular function and wall motion, CCT showed as accurate tool for this purposes. [40]

There are certain limitations of CCT that can not be ignored. Image acquisition is highly dependent on heart rhythm and rate (motion artifacts), amount of coronary calcium, and it requires exposing of patients to relatively high radiation dose. Above all, the cost of the CCT equipment is higher in comparison to other easily available noninvasive imaging modalities, i.e. echocardiography. In the light of these limitations remains the question who is the candidate for preoperative testing with CCT. To our opinion, the most reasonable will be to use CCT in defining of peri operative risk in patients who have positive or equivocal non-invasive cardiac stress tests, i.e. dobutamine SE or MPS.

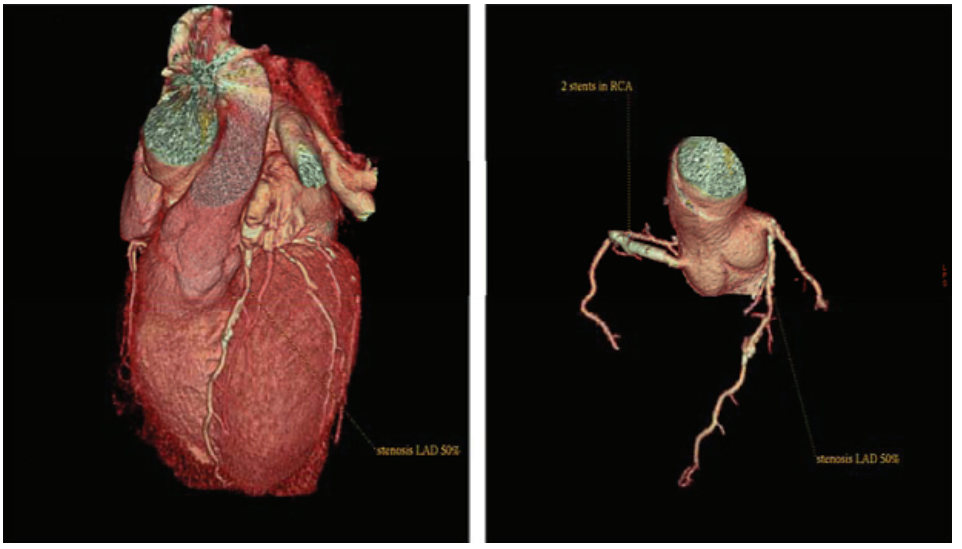


Figure 14-5 *Cardiac computed tomography. 3-D reconstruction of coronary angiography in the same patient.*
(Image courtesy Dragan Sagic, MD, Department of Cardiology, Dedinje Cardiovascular Institute, Belgrade, Serbia)

Cardiac magnetic resonance

The particular interest for cardiac magnetic resonance (CMR) in the settings of preoperative risk stratification is based on its' excellent possibilities in assessment of ventricular function, myocardial perfusion, and coronary artery anatomy. [41-44] In patients who are not suitable for SE (i.e., bad images because of suboptimal acoustic window), stress CMR using dobutamine appears as a good alternative. The protocol for administration of dobutamine and image analysis in stress CMR is similar to dobutamine SE. [Figure 14-5] Studies have shown high accuracy and reproducibility of stress CMR in detection of wall motion abnormalities. [45, 46] In the study of Hundley et al., CMR showed excellent performance in predicting of future cardiac events in patients with inducible ischemia (hazard ratio 3.3, CI 1.1 to 9.7). [47] The same group analyzed the accuracy of stress CMR for preoperative risk assessment. [48] Of the 102 patients referred for non-cardiac surgery (29 vascular, and 73 nonvascular), myocardial ischemia occurred in 25 patients during dobutamine stress CMR. Postoperative cardiac events (death, nonfatal MI, and congestive heart failure) developed in 5 of those patients, presenting a sensitivity and specificity of CMR for the prediction of peri operative cardiac complications of 84 % and 78%, respectively.

Because of its noninvasive nature, superb image quality, absence of radiation and application of contrast media, CMR appears to be excellent cardiovascular imaging modality. The main limitations are complexity of the technique, its cost, and high dependency on the operator expertise.

HOW THE TEST RESULTS CAN INFLUENCE THE MANAGEMENT?

Patients with estimated intermediate – or high-risk for perioperative cardiac complications, with normal tests and no stress-induced myocardial ischemia should proceed with the planed surgery. The situation is more complex if the test results are positive and final decision whether to operate with the use of optimal cardioprotective therapy or to perform preoperative cardiac revascularization depends mainly on the extent and severity of stress-induced myocardial ischemia.

Cardioprotective medical therapy – β-blockers and statins

Cardioprotective effect of β-blockers is based on the fact that they can diminish the effects of increased sympathetic activity in surgical patients.

In DECREASE I trial, 112 selected vascular surgery patients with evidence of myocardial ischemia on preoperative dobutamine SE were randomized to receive placebo or bisoprolol (5-10 mg). [49] Treatment with bisoprolol was started at least 7 days before surgery. Peri operative bisoprolol use resulted in 10-fold reduction in the incidence of cardiac death and myocardial infarction (3.4% vs. 34%; $P < 0.001$).

Maximum benefit of β-blocker therapy in vascular surgery patients with CAD can be achieved only if a tight HR control is established. That was proved in a recently published study on 272 vascular surgery patients on chronic β-blocker therapy. [50] Higher doses of β-blockers and lower HR were associated with reduced peri operative

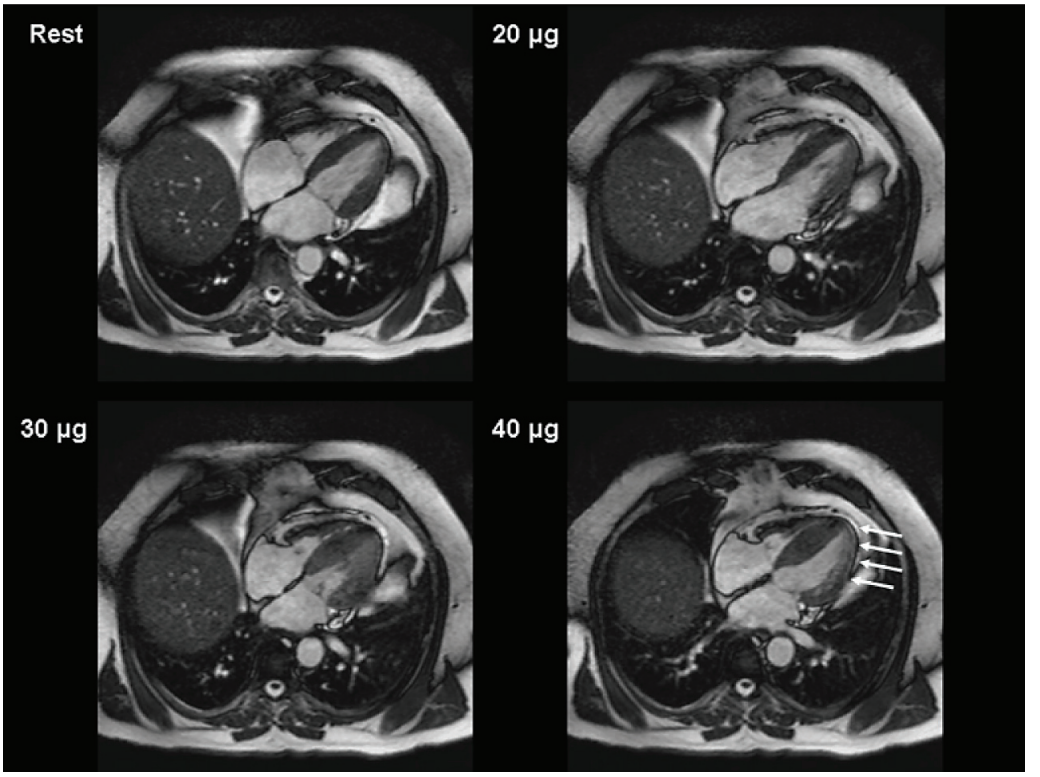


Figure 14-6 *Dobutamine stress cardiac magnetic resonance test. Quad-screen format of 4-chamber view, end-systolic frames at baseline (upper left), 20 µg/kg/min dose (upper right), 30 µg/kg/min dose (lower left) and 40 µg/kg/min (lower right) of dobutamine. At lower doses, there is increased systolic wall thickening in all segments indicating improvement in contractility. At 40 µg/kg/min dose, akinesis of apex and lateral wall can be noted; arrows indicate region with absent wall thickening, consistent with ischemic response.*

ischemia detected on ECGHolter monitoring (hazard ratio: 2.49; 95% confidence interval [CI]: 1.79-3.48) andtroponine T release (hazaed ratio: 1.53; 95% CI: 1.16-2.03).

The beneficial cardioprotective effect of β-blockers in non-cardiac surgery was questioned by the recently published PeriOperative ISchemic Evaluation (POISE) trial. [51] In the trial, 8.351 patients were randomly assigned to either controlled-release oral metoprolol-succinate or placebo. Fewer patients in the metoprolol group than in the placebo group had a myocardial infarction (4,2% vs. 5,7% patients; hazard ratio 0,73; CI = 0,60-0,89; p = 0,0017). Nevertheless, the incidence of deaths and stroke in the metoprolol group was higher than in the placebo group (3,1% vs. 2,3% patients; hazard ratio 1,33; CI = l,03-l,74; p = 0,0317 for all-cause mortality; 1,0% vs. 0,5% patients; hazard ratio 2,17, CI = l,26-3,74; p = 0,0053 for stroke). The different outcomes in the POISE trail in comparison to those previously mentioned can be explained by difference in β-blockers dosing regimes. Unusually high starting dose of metoprolol-succinate in the POISE trial, and short initiation time of therapy before surgery, might have caused an unfavorable hemodynamic condition that ultimately resulted in higher incidence of all-cause mortality and stroke.

Regardless to the POISE trial results, current ACC/AHA guidelines recommend the use of peri operative β-blocker therapy, preferably long-acting agents started days to weeks before elective surgery.

Cardioprotective effect of statins is based on their so called "pleiotropic" properties (i.e., improving endothelial function, enhancing the stability of atherosclerotic plaques, decreasing oxidative stress and inflammation, and inhibiting the thrombogenic response).

To evaluate the association between statin use and perioperative mortality, Poldermans et al. performed a case-controlled study among patients who underwent major vascular surgery. [52] A cardiovascular complication during the perioperative phase was the primary cause of death in 104 (65%) case subjects. Statin therapy was significantly less common in cases than in controls (8% *vs* 25%; P < 0.001). The risk of perioperative mortality among statin users was reduced 4.5 times compared with nonusers (adjusted odds ratio for perioperative mortality among statin users as compared with nonusers was 0.22 [95% CI: 0.1 to 0.47]).

Prospective, double-blinded placebo-controlled trial by Durazzo et al., randomized 100 patients referred for vascular surgery to either 20 mg atorvastatin or placebo for 45 days. [53] After 6 months of follow-up, the incidence of cardiovascular events (death,

nonfatal MI, stroke, or unstable angina pectoris) was 3 times lower with atorvastatin then with placebo (8% vs. 26%; p = 0,031).

Coronary revascularization prior to non-cardiac surgery

Both percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are evaluated in purpose of risk reduction in non-cardiac surgery patients.

Study of Posner et al. compared cardiac outcomes after non-cardiac surgery in patients with prior percutaneous coronary intervention (PCI), patients with non-revascularized CAD and normal controls. [54] The results showed that patients treated with PCI within 90 days of non-cardiac surgery had a similar incidence of peri operative events to matched patients with CAD who had not been revascularized. Patients who underwent non-cardiac surgery more than 90 days after PCI had a lower risk of cardiac events than non-revascularized patients, but not as low as normal controls. However, the effect of revascularization was limited to a reduction in the incidence of angina pectoris and congestive heart failure, and there was no reduction in the incidence of death and nonfatal MI. Apart from these findings, it is also important to note that if PCI procedure and coronary stent placement are performed < 6 weeks before major non-cardiac surgery, the risk of peri operative coronary thrombosis or major bleeding complications may be substantially increased. [55, 56]

Recently published prospective randomized Coronary Artery Revascularization Prophylaxis (CARP) trial comprised 510 patients who where scheduled for elective major vascular surgery, and were selected for preoperative CAG if a cardiology consultant considered that there was an increased risk for a perioperative cardiac complications. [57] Patients with at least 70% stenosis of one or more major coronary arteries were randomized to receive either preliminary coronary revascularization (PCI: n = 141;

CABG: n = 99) plus medical management or medical management alone in conjunction with their elective vascular procedure. The study did not find difference in 30-days mortality rate between patients who had coronary revascularization prior to vascular surgery and those who were treated medically (3.1% vs. 3.4%; p = 0.87). The rate of perioperative nonfatal myocardial infarction as detected by troponin elevation also did not differ in coronary revascularization patients and patients treated medicaly (11.6% vs 14.3%; p = 0.37). Additionally, the late survival rates at median follow-up of 2.7 years did not differ significantly between the patients who were assigned to have

preliminary coronary intervention and those who were not (78% vs 77%). Furthermore, the results of this trial also indicated that coronary revascularization prior to vascular surgery was associated with delay or cancellation of the required vascular operation.

However, CARP trial findings may be explained by the fact that the vast majority of included patients had single- or two-vessel disease with a preserved left ventricular function, and sufficient cardio-protection by medical therapy β-blockers in 85% of all patients, aspirin in 72%, and statins in 53%). Hence, if a beneficial effect of the invasive strategy of prophylactic revascularization is to be expected, then at least patients with extensive CAD should benefit from this strategy. This hypothesis was evaluated in recently published DECREASE-V Pilot study. [58] The total of 101 patients scheduled for elective vascular surgery, with extensive stress-induced ischemia on dobutamine SE (≥ 5 ischemic of 17 segments) or MPS (≥ 3 ischemic walls), were randomized either to prophylactic myocardial revascularization (49 patients) or medical therapy (52 patients). A reduced left ventricular ejection fraction (< 35%) was observed in 43 (43%) patients. Among the patients allocated to preoperative coronary revascularization, CAG revealed three-vessel disease in 33 (67%) patients and left main disease in 4 (8%). A PCI was performed in 32 patients and CABG in 17. The 30-day outcome was not improved by myocardial revascularization; the incidence of all-cause mortality or nonfatal MI for patients with preoperative revascularization or medical treatment

Table 14-2 *Surgery-specific risk of peri operative cardiac events in noncardiac surgery [18]*

Estimated risk	Type of surgery
High (> 5%)	• Aortic and other type of major vascular surgery
	• Any other surgical procedure associated with large fluid shifts and/or blood loss
Intermediate (1-5%)	• Carotid endarterectomy
	• Head and neck surgery
	• Orthopedic surgery
	• Prostate surgery
Low (< 1%)	• Endoscopic procedures
	• Superficial procedures
	• Cataract surgery
	• Breast surgery
	• Ambulatory surgery

only was 43% vs. 33%, respectively (p = 0.3). The same was observed for the incidence of one-year composite end points (revascularization group: 49% vs medical therapy group: 44%; p = 0.48).

Potentially harmful effect of coronary revascularization in high-risk non-cardiac surgery patients might arise from two reasons: a) the delaying of planed non-cardiac surgery, and b) higher cumulative risk of both coronary revascularization and non-cardiac surgery then non-cardiac surgery alone. Current ACC/AHA guidelines recommend prophylactic coronary revascularization in non-cardiac surgery patients only for cardiac unstable patients.

CONCLUSION

Clinical cardiac risk markers, together with the type and urgency of planed surgery, can truly stratify patients in intermediate- and high-risk population. Intermediate-risk patients can probably be operated without any additional noninvasive screening, and should be treated with β-blockers (aiming HR 60-65/min) and statins. In addition to intensive medical therapy with P-blockers and statins, high-risk patients should be screened noninvasively for the extent of underlying CAD if that will change treatment management. The choice of the test should be based on the centers' experience and short-term availability. Although coronary revascularization did not show significant advantages compared to the medical therapy in high-risk patients, it has to be considered in patients with unstable CAD. In patients in whom coronary revascularization was done by PCI with stents, antiplatelet therapy should only be discontinued perioperatively if bleeding risks with increased mortality or sequels are comparable with the observed cardiovascular risks after its withdrawal.

REFERENCES

1. Mangano DT. Perioperative cardiac morbidity. Anesthesiology, 1990; 72(1): 153-184.
2. Mackey WC, Fleisher LA, Haider S, at al. Perioperative myocardial ischemic injury in high-risk vascular surgery patients: Incidence and clinical significance in a prospective clinical trial. J Vasc Surg 2006; 43(3): 533-538.
3. Poldermans D, Bax JJ, Schouten O, et al. Should major vascular surgery be delayed because of preoperative cardiac testing in intermediate risk patients receiving beta-blocker therapy with tight heart rate control? J Am Coll Cardiol 2006; 48: 964-969.

4. Feringa HH, Karagiannis SE, Vidakovic R, et al. The prevalence and prognosis of unrecognized myocardial infarction and silent myocardial ischemia in patients undergoing major vascular surgery. Coron Artery Dis 2007 Nov; 18(7):571-6.
5. Dawood MM, Gupta DK, Southern J, et al. Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. IntJ Cardiol 1996; 57:37-44.
6. Warltier DC, Pagel PS, Kersten JR, et al. Approaches to the prevention of perioperative myocardial ischemia. Anesthesiology 2000; 92: 253-259.
7. Kertai M, Bountioukos M, Boersma E, et al. Aortic stenosis: An underestimated risk factor for perioperative complications in patients undergoing noncardiac surgery. Am JMed2004; 116(1): 8-13.
8. Christ M, Sharkova Y, Geldner G, et al. Preoperative and perioperative care for patients with suspected or established aortic stenosis facing noncardiac surgery. Chest 2005; 128: 2944-2953.
9. Kazmers A, Cerqueira MD, Zierler DE , et al. Perioperative and late outcome in patients with left ventricular ejection fraction of 35% or less who require major vascular surgery. J Vasc Surg 1988; 8(3): 307-315.
10. Goldman L, Caldera DL, Nussbaum SR, Southwick FS, Krogstad D, Murrey B *et al.* Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl JMed 1977;297:845-50.
11. Detsky AS, Abrams HB, McLaughlin JR, Drucker DJ, Sasson Z, Johnston N *et al.* Predicting cardiac complications in patients undergoing noncardiac surgery. J Gen Intern Med 1986; 1:211-9.
12. Eagle KA, Coley CM, Newell JB, Brewster DC, Darling RC, Strauss HW *et al.* Combining clinical and thallium data optimizes preoperative assessment of cardiac risk before major vascular surgery. Ann Intern Med 1989; 110:859-66.
13. American Society of Anesthesiologists. New classification of physical status. Anesthesiology 1963;24:111.
14. Campeau L. Letter: Grading of angina pectoris. Circulation 1976;54:522-3.
15. Gilbert K, Larocque BJ, Patrick LT. Prospective evaluation of cardiac risk indices for patients undergoing noncardiac surgery. Ann Intern Med 2000;133:356-9.
16. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF *etal.* Derivation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999; 100:1043-9.
17. Boersma E, Kertai MD, Schouten O, Bax JJ, Noordzij P, Steyerberg EW *et al.* Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee cardiac risk index. Am JMed 2005;118: 1134-41.
18. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (writing committee to revise the 2002 guidelines on perioperative cardiovascular evaluation for noncardiac surgery). J Am Coll Cardiol 2007; 50(17): el59-e241.
19. Poldermans D, Fioretti PM, Forster T, et al. Dobutamine stress echocardiography for assessment of perioperative cardiac risk in patients undergoing major vascular surgery. Circulation 1993; 87: 1506-12.

20. Poldermans D, Fioretti PM, Forster T, et al. Dobutamine-atropine stress echocardiography for assessment of perioperative and late cardiac risk in patients undergoing major vascular surgery. Eur J Vasc Surg 1994; 8: 286-93.
21. Poldermans D, Arnese M, Fioretti PM, et al. Improved cardiac risk stratification in major vascular surgery with dobutamine-atropine stress echocardiography. J Am Coll Cardiol 1995; 26: 648-53.
22. Ballal RS, Kapadia S, Secknus MA, et al. Prognosis of patients with vascular disease after clinical evaluation and dobutamine stress echocardiography. Am Heart J 1999; 137:469-75.
23. Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery: Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. N Engl J Med 1999; 341: 1789-94.
24. Das MK, Pellikka PM, Mahoney DW, et al. Assessment of cardiac risk before nonvascular surgery: Dobutamine stress echocardiography in 530 patients. J Am Coll Cardiol 2000; 35: 1647-53.
25. Boersma E, Poldermans D, Bax JJ, et al. Predictors of cardiac events after major vascular surgery: Role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. JAMA 2001; 285: 1865-73.
26. Karagiannis SE, Elhendy A, Feringa HH, et al. The long prognostic value of wall motion abnormalities during the recovery phase of dobutamine stress echocardiography after receiving acute beta-blockade. Coron Artery Dis 2007; 18: 187-92.
27. Boucher CA, Brewster DC, Darling RC, et al. Determination of cardiac risk by dipyridamol-thallium imaging before peripheral vascular surgery. N Engl J Med 1985; 312: 389-94.
28. Cutler BS, Leppo JA. Dipyridamole thallium 201 scintigraphy to detect coronary artery disease before abdominal aortic surgery. J Vasc Surg 1987; 5: 91-100.
29. Mangano DT, London MJ, Tubau JF, et al. Study of Preopeartive Ischemia Research Group. Dipyridamole thallium-201 scintigraphy as a preoperative screening test: a re-examination of its predictive potential. Circulation 1991; 84: 493-502.
30. Baron JF, Mundler O, Bertrand M, et al. Dipyridamole-thallium scintigraphy and gated radionuclide angiography to assess cardiac risk before abdominal aortic surgery. N Engl J Med 1994; 330: 663-9.
31. Etchells E, Meade M, Tomlinson G, Cook D. Semiquantitative dipyridamole myocardial stress perfusion imaging for cardiac risk assessment before noncardiac vascular surgery: a meta-analysis. J Vasc Surg 2002; 36: 534-40.
32. MolletNR, Cademartiri F, van Mieghem CA, et al. High-resolution spiral computed tomography coronary angiography in patients referred for diagnostic conventional coronary angiography. Circulation 2005; 112: 2318-2323.
33. Schijuf JD, Pundziute D, Jukema JW, et al. Diagnostic accuracy of 64-slice multislice computed tomography in the non-invasive evaluation of significant coronary artery disease. Am J Cardiol 2006; 98:145-148.
34. Bamberg F, Dannemann N, Shapiro MD, et al. Association between cardiovascular risk profiles and the presence and extent of different types of coronary atherosclerotic plaque as detected by multidetector computed tomography. Arterioscler Thromb VascBiol. 2008; 28(3): 568-574.

35. Rasouli ML, Shavelle DM, French WJ, et al. Assessment of coronary plaque morphology by contrast-enhanced computed tomographic angiography: comparison with intravascular ultrasound. Coron Artery Dis. 2006; 17(4): 359-364.

36. Malagutti P, Nieman K, Meijeboom WB, et al. Use of 64-slice CT in symptomatic patients after coronary bypass surgery: evaluation of grafts and coronary arteries. Eur Heart J 2007; 28: 1879-1885.

37. Soon KH, Kelly Am, Cox, et al. Non-invasive multislice computed tomography coronary angiography for imaging coronary arteries, stents, and bypass grafts. Intern Med J 2006; 36: 43-50.

38. Oncel D, Oncel G, Karaca M. Coronary stent patency and in-stent restenosis: determination with 64-section multidetector CT coronary angiography–initial experience. Radiology 2007; 242: 403-409.

39. Cademartiri F, Schujif JD, Pugliese F, et al. Usefulness of 64-slice multislice computed tomography coronary angiography to assess in-stent restenosis. J Am Coll Cardiol 2007; 49: 2204-2210.

40. Henneman MM, Schuijf JD, Jukema JW, et al. Assessment of global and regional left ventricular function and volumes with 64-slice MSCT: a comparison with 2D echocardiography. JNucl Cardiol 2006; 13(4): 480-487.

41. Bellenger NG, Burgess M, Ray SG, et al. Comparison of left ventricular ejection fraction and volumes in heart failure by two-dimensional echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance: Are they interchangeable? Eur Heart J 2000; 21:1387-1396.

42. Giang TH, Nanz D, Coulden R, et al: Detection of coronary artery disease by magnetic resonance myocardial perfusion imaging with various contrast medium doses: First European multi-centre experience. Eur Heart J 2004; 25:1657-1665.

43. Sakuma H, SuzawaN, Ichikawa Y, et al: Diagnostic accuracy of stress first-pass contrast-enhanced myocardial perfusion MRI compared with stress myocardial perfusion scintigraphy. AJR Am J Roentgenol 2005; 185: 95-102.

44. Kim WY, Danias PG, Stuber M, et al: Coronary magnetic resonance angiography for the detection of coronary stenosis. N Engl J Med 2001; 345: 1863-1869.

45. Syed MA, Paterson DI, Ingkanisorn WP, et al: Reproducibility and inter-observer variability of dobutamine stress CMR in patients with severe coronary disease:implications for clinical research. J Cardiovasc Magn Reson 2005; 7: 763-768.

46. Paetsch I, Jahnke C, Ferrari VA, et al: Determination of interobserver variability for identifying inducible left ventricular wall motion abnormalities during dobutamine stress magnetic resonance imaging. Eur Heart J 2006; 27: 1459-1464.

47. Hundley WG, Morgan TM, Neagle CM, et al. Magnetic resonance imaging determination of cardiac prognosis. Circulation 2002; 106(18): 2328-2333.

48. Rerkpattanapipat P, Morgan TM, Neagle CM, et al.. Assessment of preoperative cardiac risk with magnetic resonance imaging. Am J Cardiol. 2002;90(4):416-

49. Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. N Engl J Med 1999; 341: 1789-1794.

50. Feringa HH, Bax JJ, Boersma E, et al. High dose of beta-blockers and tight heart rate control reduce myocardial ischemia and troponin T release in vascular surgery patients. Circulation 2006; 114(1 Suppl): 1344-349.

51. Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. POISE Study Group. Lancet 2008; 371(9627): 1839-1847.

52. Poldermans D, Bax JJ, Kertai MD, et al. Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. Circulation 2003; 107: 1848-1851.

53. Durazzo AE, Machado FS, Ikeoka DT, et al. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. J Vasc Surg 2004;39(5):967-975.

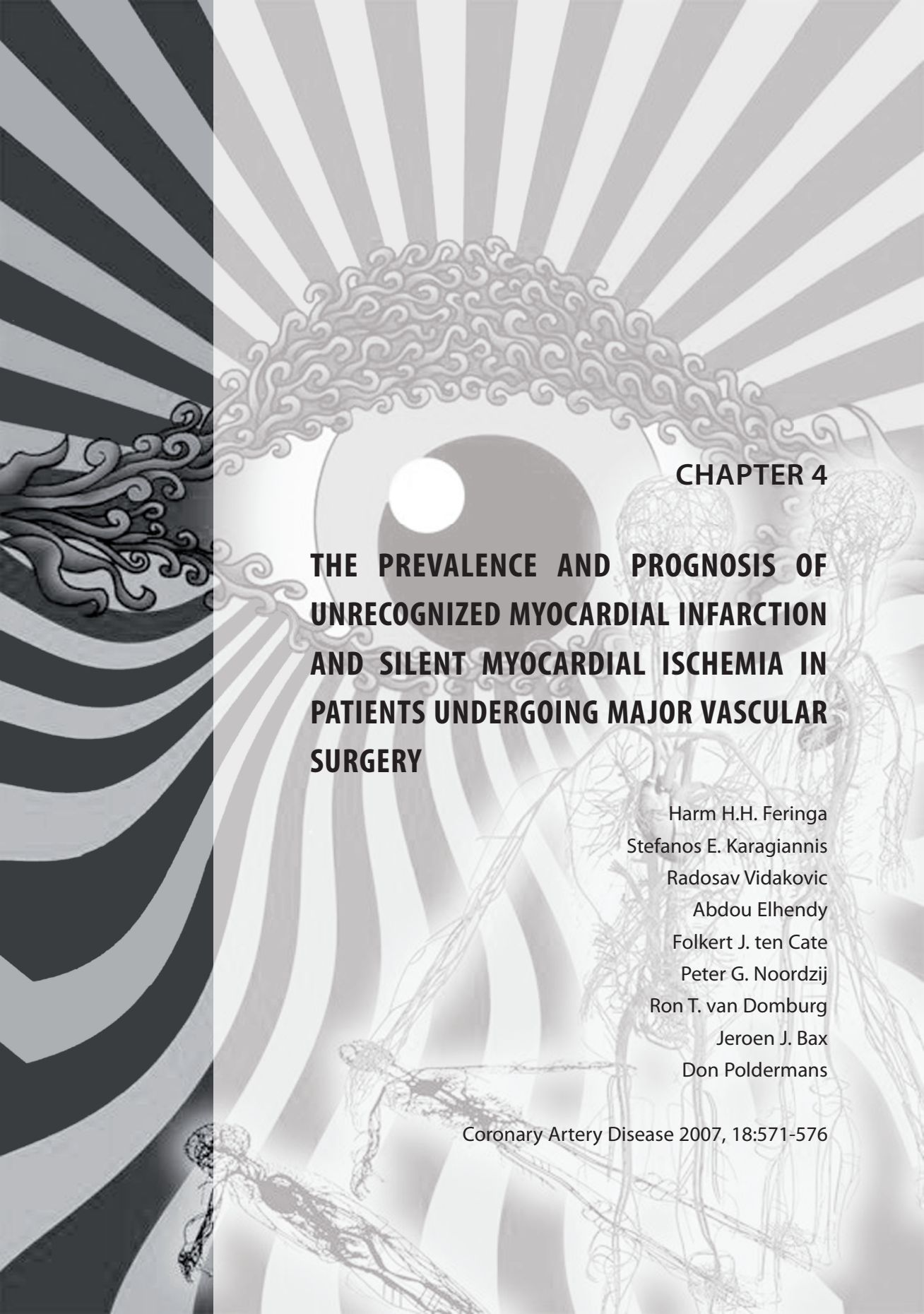
54. Posner KL, van Norman GA, Chan V. Adverse cardiac outcomes after noncardiac surgery in patients with prior percutaneous transluminal coronary angioplasty. Anesth Analg 1999; 89: 553-560.

55. Kaluza GL, Joseph J, Lee JR, Raizner AE. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. J Am Coll Cardiol 2000; 35: 1288-1294.

56. Wilson SH, Fasseas P, Orford JL, et al. Clinical outcome of patients undergoing non-cardiac surgery in two months following coronary stenting. J Am Coll Cardiol 2003; 42: 234-240.

57. McFalls EO,Ward HB, Moritz TE, et al. Coronary artery revascularization before elective major vascular surgery. N Engl J Med 2004; 351: 2795-2804.

58. Poldermans D, Schouten O,Vidakovic R, et al. A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery: the DECREASE-V Pilot Study. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. J Am Coll Cardioll 2007; 49: 1763-1769.



CHAPTER 4

THE PREVALENCE AND PROGNOSIS OF UNRECOGNIZED MYOCARDIAL INFARCTION AND SILENT MYOCARDIAL ISCHEMIA IN PATIENTS UNDERGOING MAJOR VASCULAR SURGERY

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ABSTRACT

Objective The aim of this study is to determine the prevalence and prognosis of unrecognized myocardial infarction (Ml) and silent myocardial ischemia in vascular surgery patients.

Methods In a cohort of 1092 patients undergoing preoperative dobutamine stress echocardiography and noncardiac vascular surgery, unrecognized Ml was determined by rest wall motion abnormalities in the absence of a history of Ml. Silent myocardial ischemia was determined by stress-induced wall motion abnormalities in the absence of angina pectoris. Beta blockers and statins were noted at baseline. During follow-up (mean: 6±4 years), all-cause mortality and major cardiac events (cardiac death or nonfatal Ml) were noted.

Results The prevalence of unrecognized Ml and silent myocardial ischemia was 23 and 28%, respectively. Both diabetes and heart failure were important predictors of unrecognized Ml and silent myocardial ischemia. During follow-up, all-cause mortality occurred in 45% and major cardiac events in 23% of patients. In multivariate analysis, unrecognized Ml and silent myocardial ischemia were significantly associated with increased risk of mortality [hazard ratio (HR), 1.86; 95% confidence interval (CD, 1.53-2.25 and HR, 1.74; 95% Cl, 1.46-2.06, respectively] and major cardiac events (HR, 2.15; 95% Cl, 1.59-2.92 and HR, 1.86; 95% Cl, 1.43-2.41, respectively). In patients with unrecognized Ml, p-blockers and statins were significantly associated with improved survival. Statins improved survival in patients with silent myocardial ischemia.

Conclusions In patients undergoing major vascular surgery, unrecognized Ml and silent myocardial ischemia are highly prevalent (23 and 28%) and associated with increased long-term mortality and major cardiac events. *Coron Artery Dis* 18:571 -576

Key words: asymptomatic coronary artery disease, noninvasive stress testing, prevalence, prognosis, vascular surgery

INTRODUCTION

Since 1919, cardiovascular disease has been the single leading cause of death in the United States and is the underlying or contributing cause of death in about 58% of all cases [1]. Cardiac complications also remain the leading cause of morbidity and mortality in patients undergoing major vascular surgery. Perioperative cardiac complication rates in vascular surgery patients have been reported to range from 2.2 to 19.0% [2]. The high frequency of perioperative cardiac complications reflects the high prevalence of underlying coronary artery disease. Indeed, coronary angiographic abnormalities have been reported in up to 92% of patients [3]. Patients with coronary artery disease, however, may not always present with a history of myocardial infarction (MI) or with symptoms of angina pectoris [4,5]. Unfortunately, the prevalence and prognosis of these patients with asymptomatic coronary artery disease is not well known. In view of the many major vascular surgery procedures performed annually, routine screening for asymptomatic coronary artery disease may be recommended to identify high-risk patients who may benefit from medical treatment.

Dobutamine stress echocardiography is a widely used noninvasive technique for the detection of coronary artery disease. Regional wall motion abnormalities during rest signify infarcted myocardial tissue and wall motion abnormalities during stress testing signify myocardial ischemia. This study reports the prevalence and long-term prognosis of unrecognized MI and silent myocardial ischemia in 1092 patients who underwent preoperative dobutamine stress echocardiography and major vascular surgery. In addition, the effect of chronic β-blocker and statin therapy on survival in patients with asymptomatic coronary artery disease was evaluated.

METHODS

Patient population

A total of 1092 patients who underwent major none-mergent noncardiac vascular surgery at the Erasmus Medical Center in Rotterdam, The Netherlands, were enrolled in this study from April 1990 to January 2004. In all patients, a preoperative dobutamine stress echocardio-graphy was performed to detect the presence and extent of coronary artery disease. The study protocol was approved by the Hospital's Ethics Committee and all patients gave informed consent. Before surgery, patients were screened for the following cardiac risk factors: age over 70 years, angina pectoris, prior MI on the basis

of history or a finding of pathologic Q waves on electro-cardiography, compensated congestive heart failure or a history of congestive heart failure, drug therapy for diabetes mellitus, renal dysfunction and prior stroke or transient ischemic attack. The use of cardiac medication was recorded and chronic use was ascertained if medication was documented at least 1 month before surgery and at hospital discharge.

Dobutamine stress echocardiography

Patients underwent a resting two-dimensional precordial echocardiographic examination and standard apical and parasternal views were recorded on videotape. Dobutamine hydrochloride was administered intravenously with an infusion pump with incremental doses of 10 (μg/kg/min every 3 min to a maximum of 40 (μg/kg/min (stage 4) and continued for 6 min. The dobutamine infusion was stopped if a target heart rate was achieved [85% of a theoretic maximal heart rate; men: (220-age) x 85%; women: (200-age) x 85%]. If the target heart rate was not achieved and patients had no symptoms or signs of ischemia, atropine sulfate (starting with 0.25 mg and increased to a cumulative maximum of 2.0 mg) was given intravenously at the end of stage 4 whereas the dobutamine administration was continued. During the test, a 12-lead electrocardiogram was recorded at baseline and every minute. Blood pressure was measured by sphygmomanometry every 3 min. Metoprolol was administered (1.0-5.0 mg intravenously) to reverse the side effects of the administration of dobutamine or the dobutamine–atropine combination if the side effects did not revert spontaneously and quickly. Atropine was administered as an antidote if bradycardia and hypotension occurred. The criteria for stopping the test were: (i) severe new echocardiographic wall motion abnormalities in multiple locations, (ii) horizontal or downsloping electrocardiographic ST depression of ≥ 0.2 mV measured 80 ms after the J point, or ST-segment elevation of ≥ 0.2 mV in the absence of Q waves, (iii) symptomatic decline in systolic blood pressure of more than 40 mmHg from the resting value, or a systolic blood pressure of less than 100 mmHg, (iv) hypertension (blood pressure > 240/140 mmHg), (v) the occurrence of cardiac arrhythmias, (vi) severe angina pectoris and (vii) intolerable adverse side effects, considered to be the result of dobutamine or atropine.

Assessment of echocardiographic images

Off-line assessment of echocardiographic images was performed by two experienced investigators without knowledge of the patient's clinical data but with knowledge of the doses of dobutamine and atropine used. From 1990 to 1993, the left

ventricle was divided into 14 segments and wall motion was scored on a 4-point ordinal scale [6]. After 1993 a 16-segment 5-point score was used [7]. MI was considered in the presence of rest wall abnormalities. Myocardial ischemia was considered if new wall motion abnormalities occurred (i.e. if wall motion in any segment worsened by ≥ 1 grade(s) during the test, with the exception of akinesis becoming dyskinesis). For each patient, a wall motion score index (total score divided by the number of assessable segments) was calculated at rest and during peak stress. The extent of ischemia was defined as the number of segments exhibiting deteriorating wall motion during stress. When there was disagreement between the two assessors, a third investigator viewed the images without knowledge of the previous assessments and a majority decision was reached. Unrecognized MI was defined as rest wall motion abnormalities in the absence of a history of MI. Silent myocardial ischemia was defined as stress-induced wall motion abnormalities in the absence of a history of angina pectoris or complaints during stress test.

Follow-up

Study endpoints were death and cardiac events (composite of cardiac death and nonfatal MI) during long-term follow-up after successful vascular surgery. Information on mortality and cause was obtained by contacting the referring physician or by approaching the municipal civil registry to determine survival status. In patients who died, death certificates and autopsy reports were reviewed and general practitioners were approached to ascertain the cause of death. Cardiac death was defined as death caused by acute MI, cardiac arrhythmias, congestive heart failure or sudden death. Nonfatal MI was diagnosed when at least the following were present: elevated cardiac enzyme levels, development of new Q waves (> l mm or > 30 ms), and typical symptoms of angina pectoris. No patients were lost to follow-up.

Data analysis

Continuous data were expressed as mean (± SD) and compared using the Student's *t*-test. Categorical data were compared using the χ^2 test. A final set of independent and significant predictors of asymptomatic coronary artery disease was obtained by multivariate logistic regression analysis with stepwise deletion of the least significant variable. Only variables with a *P* value ≤ 0.10 were retained in the model. The Kaplan-Meier method with the log-rank test was used to assess differences in survival between patient groups. Cox proportional hazard regression analysis was used to evaluate the

long-term prognostic value of asymptomatic coronary artery disease. In multivariate analysis, adjustments were made for age, sex, diabetes, heart failure, cerebrovascular disease, hypertension and cardiovascular medication. The risk associated with a given variable was expressed by a hazard ratio (HR) with corresponding 95% confidence interval (CI). For all tests, a *P* value less than 0.05 (two-sided) was considered significant. All analyses were performed using SPSS statistical software (Chicago, Illinois, USA).

RESULTS

Baseline characteristics of the study population are presented in Table 1. A total of 371 patients (34%) presented with a history of MI, 178 patients (16%) had angina

Table 1 *Baseline characteristics of patients undergoing major vascular surgery*

	n = 1092
Age (years)	64±15
Sex (male)	848 (78%)
Length (cm)	171 ±9
Body mass index (kg/m^2)	25±4
History of angina pectoris	1 78 (16%)
History of myocardial infarction	371 (34%)
Coronary artery disease	446 (41%)
History of congestive heart failure	65 (6%)
Hypertension	491 (45%)
Smoking	331 (30%)
Hypercholesterolemia	205 (19%)
Diabetes mellitus	124 (11%)
Chronic obstructive pulmonary disease	202 (18%)
Renal insufficiency	73 (7%)
Angiotensin converting enzyme inhibitor	296 (27%)
Aspirin	270 (25%)
Beta blockers	289 (35%)
Calcium antagonist	296 (36%)
Coumarin	21 2 (19%)
Digitalis	41 (4%)
Diuretic	1 69 (15%)
Nitrates	241 (22%)
Statins	286 (26%)

Values are expressed as mean ±SD or number and percentage.

pectoris and 446 patients (41%) presented with symptomatic coronary artery disease. During stress echocardiography, the maximum dobutamine dose was 36 μg/kg/min and atropine was administered in 30%. The test was terminated for the following reasons: achievement of the target heart rate in 89%, maximal dobuta-mine/atropine dose in 3%, ST-segment changes in 3%, abnormal blood pressure in 1%, arrhythmias in 1%, severe angina in 1% and for other symptoms in 2%. No fatal complications were observed. Rest wall motion abnormalities were observed in 533 patients (49%) and new wall motion abnormalities in 399 (37%).

Prevalence and predictors of asymptomatic coronary artery disease

Unrecognized MI and silent myocardial ischemia were detected in 255 (23%) and 309 (28%) patients, respectively. The incidence of unrecognized MI and silent myocardial ischemia was significantly higher in patients with diabetes (34 and 41%, respectively) (Fig. 1). The rest wall motion score index in patients with unrecognized MI was comparable with the rest wall motion score index in patients with a recognized MI (1.52 vs. 1.48, respectively, P = 0.4). The wall motion score index at peak stress between patients with silent and symptomatic myocardial ischemia was comparable (1.52 vs. 1.61, respectively, P = 0.1). The extent of ischemia between patients with silent and symptomatic myocardial ischemia was also comparable (4.9 vs. 4.8 segments, respectively, P = 0.7). As demonstrated in Table 2, a history of heart

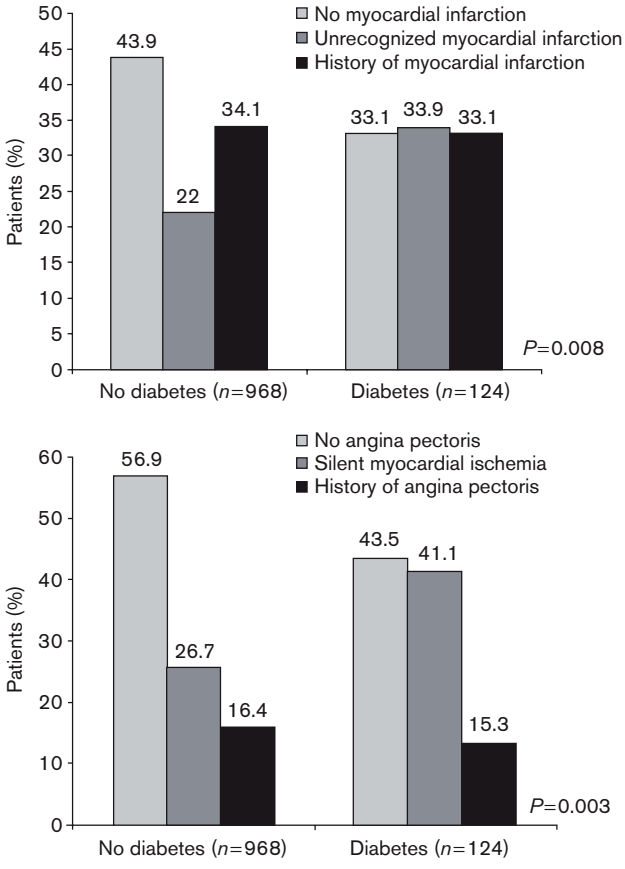


Figure 1

Table 2 *Independent predictors of unrecognized myocardial infarction (a) and silent myocardial ischemia (b) in patients undergoing major vascular surgery*

	Odds ratio	95% Confidence interval	*P* value
(a) Unrecognized myocardial infarction (n = 255)			
History of heart failure	7.88	2.16-28.74	0.002
Diabetes mellitus	2.28	1.34-3.88	0.002
C-index			< 0.001
(b) Silent myocardial ischemia (n = 397)			
Renal failure	1.88	1.09-3.23	0.02
History of heart failure	4.40	2.18-8.87	< 0.001
Diabetes mellitus	1.83	1.20-2.79	0.005
C-index			< 0.001

failure and diabetes were strong predictors of unrecognized MI and silent myocardial ischemia.

Prognosis of asymptomatic coronary artery disease

During a mean follow-up of 6 ± 4 years, all-cause mortality and cardiac events occurred in 491 patients (45%) and 253 patients (23%), respectively. Kaplan-Meier analysis showed that patients with unrecognized MI *(P* < 0.001) and silent myocardial ischemia *(P* < 0.001) had a worse survival compared with patients with no symptoms or signs of coronary artery disease. In multivariate analysis, unrecognized MI and silent myocardial ischemia remained significantly associated with increased all-cause mortality and cardiac events (Table 3).

Prognostic value of stress echocardiography in symptomatic coronary artery disease

Multivariate analysis revealed that rest wall motion abnormalities were associated with increased all-cause mortality (HR, 1.52; 95% CI, 1.16-1.99) and cardiac events (HR, 1.56; 95% CI, 1.09-2.23) in patients with a history of MI. Stress-induced wall motion abnormalities were associated with increased all-cause mortality (HR, 1.83; 95% CI, 1.35-2.49) and cardiac events (HR, 1.90; 95% CI, 1.27-2.83) in patients with a history of angina pectoris. Either rest or new wall motion abnormalities were associated with increased all-cause mortality (HR, 1.43; 95% CI, 1.16-1.76) and cardiac events (HR, 1.44; 95% CI, 1.08-1.88) in patients with a history of MI or angina pectoris.

Chronic beta blocker and statin therapy

Multivariate analysis showed that β-blockers were significantly associated with a lower mortality rate in subgroups of patients with unrecognized MI, compared with patients with no β-blockers (Table 4). Statins were associated with a lower mortality rate in subgroups of patients with unrecognized MI and silent myocardial ischemia, compared with patients with no statins (Table 4).

Table 3 *Prognostic value of unrecognized myocardial infarction and silent myocardial ischemia in patients undergoing major vascular surgery*

	Long-term mortality (n = 491)	Long-term cardiac events (n = 253)
No myocardial infarction (reference)	1.0	1.0
Unrecognized myocardial infarction	1.86 (1.53-2.25)	2.15 (1.59-2.92)
Recognized myocardial infarction	1.99 (1.70-2.33)	3.08 (2.42-3.92)
No myocardial ischemia (reference)	1.0	1.0
Silent myocardial ischemia	1.74 (1.46-2.06)	1.86 (1.43-2.41)
Symptomatic myocardial ischemia	1.42 (1.17-1.75)	1.80 (1.35-2.40)

Values are expressed as hazard ratio with 95% confidence interval. All associations were entered in multivariate analysis with adjustment for baseline clinical risk factors and chronic medication use.

Table 4 *Association between p-blockers and long-term mortality among patients with unrecognized myocardial infarction and silent myocardial ischemia*

	Chronic β-blocker therapy (%)	Beta blockers and long-term mortality (n = 491)	Chronic statin therapy (%)	Statins and long-term mortality (n = 491)
No myocardial infarction (reference)	22	0.80 (0.45-1.41)	23	0.43 (0.26-0.71)
Unrecognized myocardial infarction	43	0.46 (0.27-0.81)	28	0.44 (0.23-0.85)
Recognized myocardial infarction	47	0.59 (0.39-0.91)	28	0.26 (0.16-0.45)
No myocardial ischemia (reference)	22	0.70 (0.47-1.06)	24	0.42 (0.27-0.64)
Silent myocardial ischemia	52	0.59 (0.33-1.05)	29	0.32 (0.19-0.54)
Symptomatic myocardial ischemia	43	0.52 (0.24-1.09)	28	0.30 (0.11-0.86)

Values are expressed as hazard ratio with 95°/o confidence interval. All associations were entered in multivariate analysis with adjustment for baseline clinical risk factors.

DISCUSSION

Prevalence

We found that vascular surgery patients with asymptomatic coronary artery disease are an underestimated risk group. Unrecognized MI and silent myocardial ischemia was detected in 23 and 28% of patients, respectively. The prevalence of unrecognized MI and silent myocardial ischemia was considerably higher in patients with diabetes (34 and 41%, respectively). This suggests a later clinical manifestation of coronary artery disease in patients with diabetes, compared with patients with no diabetes. Interestingly, abnormalities during cardiac testing were comparable between patients with and without symptomatic disease. Thus, the absence of symptoms does not imply less coronary artery disease severity. A high prevalence of asymptomatic coronary artery disease is not uncommon in the general population. Among participants in the Framingham Study with MIs, around 25% presented with electrocardiographic abnormalities suggestive of MI without recollection of any relevant discomfort or symptoms compatible with infarction [4]. Among asymptomatic type 2 diabetic patients, 22% presented with silent myocardial ischemia as detected by cardiac stress testing [8].

Prognosis

Unrecognized MI and silent myocardial ischemia have now been recognized as clinical syndromes within the spectrum of coronary artery disease. Our results showed that the prognosis of asymptomatic coronary artery disease was as poor as the prognosis of patients with symptomatic coronary artery disease. The ultimate goal of surgery in patients with vascular disease is to improve symptoms and prognosis. Many studies have focused on the reduction of mortality and morbidity during hospital stay and their findings have resulted in helpful recommendations on perioperative care [9]. Unfortunately, guidelines on clinical management after successful hospital discharge are limited, although many patients remain at increased risk of adverse late events. Screening for asymptomatic coronary artery disease is still controversial. Stress testing may influence patient management and long-term outcome. When optimal medical therapy is, however, provided routine noninvasive testing may not influence patient management [9]. The COURAGE trial, for example, demonstrated that in patients with stable coronary artery disease, percutaneous coronary intervention did not reduce the risk of death, MI or other major cardiovascular events when added to optimal medical therapy [10].

Stress echocardiography in symptomatic coronary artery disease

Stress echocardiography has been demonstrated to be a useful method for prognostic risk assessment in patients undergoing major vascular surgery. Patients with symptomatic coronary artery disease have a high pretest probability of coronary artery disease. According to the Bayes theorem, a normal stress test result in these patients only modestly reduces the posttest probability of coronary artery disease [11]. In this study, dobutamine stress echocardiography added independent prognostic information in patients with a history of angina or MI and with a high pretest probability of coronary artery disease. Symptomatic patients with stress-induced myocardial ischemia had a higher risk of death and hard cardiac events, whereas in patients with a normal dobutamine stress echocardiography the incidence of events was substantially lower. These findings indicate that symptomatic patients with negative dobutamine stress echocardiography findings can be exempted from further (invasive) evaluation unless a change in clinical status occurs. Those with positive findings may benefit from further cardiac evaluation with appropriate management.

Medical treatment

As patients with asymptomatic coronary artery disease are at similar mortality risk as symptomatic patients, cardioprotective strategies should be considered in all asymptomatic patients who successfully underwent major vascular surgery. Previous studies have demonstrated that statins reduce cardiovascular events during perioperative and long-term follow-up [12,13]. Beta blockers have been demonstrated to effectively protect against the life-threatening complications of coronary artery disease in postinfarct patients [14] and in those with heart failure [15]. In this study, a protective effect of statins was observed in both symptomatic and asymptomatic disease patients. Beta blockers were significantly protective in patients with unrecognized or recognized MI, and nonsignificantly in patients with silent myocardial ischemia. It should be noted that no decisive evidence has been published in literature which demonstrates that β-blockers improve survival in patients with angina, except for its effect on symptomatic relief and blood pressure reduction [16].

Study limitations

No angiography was performed in this study. Therefore, the prevalence and prognosis of asymptomatic angio-graphic coronary artery stenosis cannot be described. Second, although physicians can be confident about the interpretation of

the echocardiographic images, misinterpretation of wall motion abnormalities can still occur. Excellent technical performance and diagnostic accuracy of dobutamine stress echocardiography for coronary artery disease have, however, been reported previously [17]. Finally, the data apply to patients referred to a tertiary referral center in Western Europe. These patients may have a different cardiovascular risk profile compared with patients referred to primary or secondary referral centers.

SUMMARY

The prevalence of unrecognized MI and silent myocardial ischemia in patients undergoing major vascular surgery was 23 and 28%, respectively. Both diabetes and heart failure were important predictors of asymptomatic coronary artery disease. Abnormalities during cardiac testing were comparable between symptomatic and asymptomatic patients. The prognosis of patients with asymptomatic disease was similar to the prognosis of patients with symptomatic disease and was distinctively worse than that of patients without coronary artery disease. Not only symptomatic patients, but also patients with asymptomatic coronary artery disease may benefit from cardiovascular medication.

REFERENCES

1 Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, *et al.* American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics: 2006 update. *Circulation* 2006; 113:85-151.

2 Mangano DT, Goldman L. Preoperative assessment of patients with known or suspected coronary disease. *N Engl J Med* 1 995; 333:1 750-1 756.

3 Hertzer NR, Beven EG, Young JR, O'Hara PJ, Ruschhaupt WF III, Graor RA, *et al.* Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. *Ann Surg* 1984; 199:223-233.

4 Kannel WB, Abbott RD. Incidence and prognosis of unrecognized myocardial infarction. An update on the Framingham study. *N Engl J Med* 1984; 311:1144-1147.

5 Nabel EG, Rocco MB, Barry J, Campbell S, Selwyn AP. Asymptomatic ischemia in patients with coronary artery disease. *JAMA* 1987; 257:1923-1928.

6 Edwards WD, Tajik AJ, Seward JB. Standardized nomenclature and anatomic basis for regional tomographic analysis of the heart. *Mayo Clin Proc* 1 981; 56:479-497.

7 Bourdillon PD, Broderick TM, Sawada SG, Armstrong WF, Ryan T, Dillon JC, *et al.* Regional wall motion index for infarct and noninfarct regions after reperfusion in acute myocardial infarction: comparison with global wall motion index. *J Am Soc Echocardiogr* 1989; 2:398-407.

8 Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, *et al.* Detection of Ischemia in Asymptomatic Diabetics Investigators. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care* 2004; 27:1954-1961.

9 Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, *et al.* ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery: executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation* 2002; 105:1257-1267.

10 Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, *et al.* COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. W *Engl J Med* 2007; 356:1503-151 6.

11 Bianchi MT, Alexander BM. Evidence based diagnosis: does the language reflect the theory? *BMJ* 2006; 333:442-445.

12 Durazzo AE, Machado FS, Ikeoka DT, De Bernoche C, Monachini MC, Puech-Leao P, *et al.* Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. *J Vasc Surg* 2004; 39:967-975.

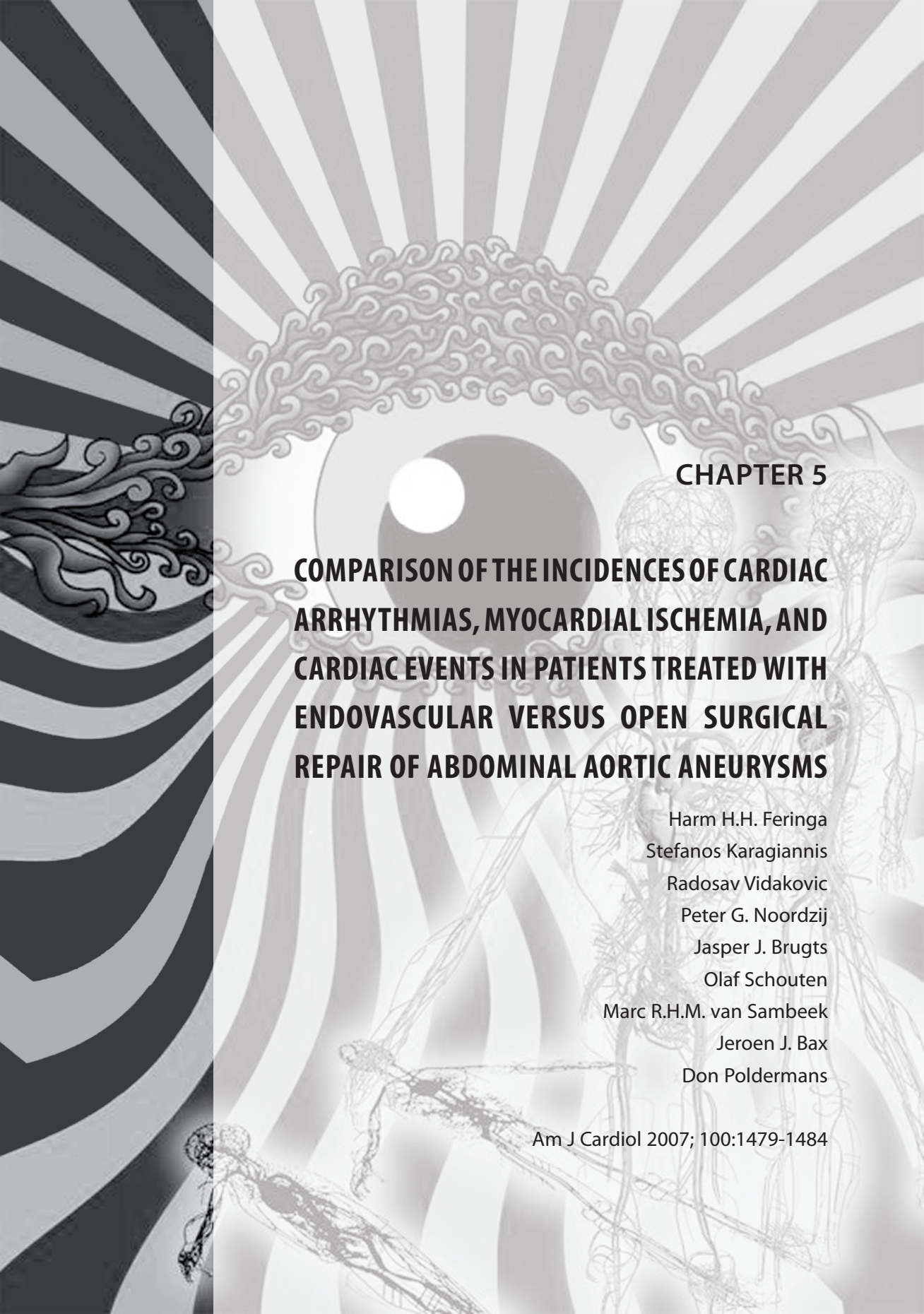
13 Kertai MD, Boersma E, Westerhout CM, van Domburg R, Klein J, Bax JJ, *et al.* Association between long-term statin use and mortality after successful abdominal aortic aneurysm surgery. *Am J Med* 2004; 116:96-103.

14 Yusuf S, Wittes J, Friedman L Overview of results of randomized clinical trials in heart disease. I. Treatments following myocardial infarction. *JAMA* 1988; 260:2088-2093.

15 Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, *et al.* Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001; 344:1651-1658.

16 Armstrong WF, Zoghbi WA. Stress echocardiography: current methodology and clinical applications. *J Am Coll Cardiol* 2005; 45:1 739-1 747.

17 Opie LH, Commerford PJ, Gersh BJ. Controversies in stable coronary artery disease. *Lancet* 2006; 367:69-78.



CHAPTER 5

COMPARISON OF THE INCIDENCES OF CARDIAC ARRHYTHMIAS, MYOCARDIAL ISCHEMIA, AND CARDIAC EVENTS IN PATIENTS TREATED WITH ENDOVASCULAR VERSUS OPEN SURGICAL REPAIR OF ABDOMINAL AORTIC ANEURYSMS

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Am J Cardiol 2007; 100:1479-1484

ABSTRACT

This study examines differences in cardiac arrhythmias, perioperative myocardial ischemia, troponin T release, and cardiovascular events between endovascular and open repair of abdominal aortic aneurysms (AAAs). Of 175 patients, 126 underwent open AAA repair and 49 underwent endovascular AAA repair. Continuous 12-lead electrocardiographic monitoring, starting 1 day before surgery and continuing through 2 days after surgery, was used for cardiac arrhythmia and myocardial ischemia detection. Troponin T was measured on postoperative days 1, 3, and 7 and before discharge. Cardiac events (cardiac death or Q-wave myocardial infarction) were noted at 30 days and at follow-up (mean 2.3 years). New-onset atrial fibrillation, nonsustained ventricular tachycardia, sustained ventricular tachycardia, and ventricular fibrillation occurred in 5%, 17%, 2%, and 1% of patients, respectively. Myocardial ischemia, troponin T release, and 30-day and long-term cardiac events occurred in 34%, 29%, 6%, and 10% of patients, respectively. Significantly higher heart rates and less heart rate variability were observed in the open AAA repair group. Cardiac arrhythmias were less prevalent in the endovascular AAA repair group (14% vs 29%, $p = 0.04$). Endovascular repair was also significantly associated with less myocardial ischemia (odds ratio 0.14, 95% confidence interval 0.05 to 0.40, $p < 0.001$) and troponin T release (odds ratio 0.10, 95% confidence interval 0.02 to 0.32, $p < 0.001$) and lower 30-day mortality (zero vs 8.7%, $p = 0.03$) and 30-day cardiac event rates (zero vs 7.9%, $p = 0.04$). Long-term mortality and cardiac event rates were not significantly lower in the endovascular AAA repair group. In conclusion, endovascular AAA repair is associated with a lower incidence of perioperative cardiac arrhythmias, myocardial ischemia, troponin T release, cardiac events, and all-cause mortality compared with open AAA repair. (Am J Cardiol 2007;100:1479-1484)

INTRODUCTION

This prospective observational study was conducted to assess whether endovascular repair of abdominal aortic aneurysms (AAAs) is associated with a lower incidence of perioperative myocardial ischemia, perioperative troponin T release, and 30-day and long-term cardiac events compared with open repair. In addition, perioperative heart rate, heart rate variability, and incidence of cardiac arrhythmias were compared between the 2 types of procedures.

METHODS

A total of 175 patients underwent elective open or endovascular repair of infrarenal AAAs at the Erasmus Medical Center in Rotterdam, The Netherlands, from 2002 through 2006. The study was performed with the informed consent of all patients and was approved by the hospital's medical ethics committee. Patients with a cardiac pacemaker, left ventricular hypertrophy, left or right bundle branch block, or atrial fibrillation were excluded. Patients who participated in clinical intervention trials in or outside the Erasmus Medical Center were also excluded. At study enrollment, a detailed cardiac history was obtained, and patients were screened for hypertension (blood pressure ≥ 140/90 mm Hg), diabetes (fasting glucose level ≥ 7.0 mmol/L or insulin therapy), renal failure (serum creatinine level ≥ 2.0 mg/dl [177 μmol/L]), smoking, and history of cerebrovascular events. Beta-blocker therapy was considered to achieve heart rates of 60 to 65 beats/min at rest.

Before surgery, patients deemed at high risk underwent dobutamine stress echocardiography for the assessment of coronary artery disease. Dobutamine stress echocardiography was performed according to established protocols. The left ventricle was divided into 17 segments, and wall motion was scored on a 5-point scale (1 = normal, 2 = mild hypokinesia, 3 = severe hypokinesia, 4 = akinesia, and 5 = dyskinesia). The results were considered positive if wall motion in any segment decreased by ≥ 1 grade during testing.

Surgery was performed by experienced surgeons and interventional physicians. Patients with an infrarenal AAA ≥ 5.5 cm in diameter on computed tomography were considered for endovascular or open aneurysm repair. Hospital guidelines recommended endovascular repair in patients at increased cardiac risk. However, the choice of procedure was left to the discretion of the vascular surgeon and was mainly

based on patient preference. Endovascular repair was carried out through the femoral route with generally available stents and protection devices. Locoregional anesthesia was used for endovascular AAA repair and a combination of locoregional and general anesthesia was used for open AAA repair. All patients received standard perioper-ative pain management. Beta-blocker therapy was continued postoperatively. In patients who were unable to take β blockers orally or by nasogastric tube, intravenous meto-prolol was administered. Beta blockers were withheld if heart rate was <50 beats/min or if systolic blood pressure was < 100 mm Hg.

Patients were continuously monitored with a 10-elec-trode, 12-lead digital electrocardiographic recorder (DR180+ Digital Recorder; NorthEast Monitoring, Maynard, Massachusetts) starting 1 day before surgery until 2 days after surgery. Recording lengths were 10 seconds every minute. The frequency response was 0.05 to 150 Hz. Electrocardiographic data were processed by a technician and analyzed by 2 experienced cardiologists blinded to the patient's clinical data. After excluding all abnormal QRS complexes, the recordings were analyzed for ST-segment deviations. A continuous ST-segment trend was generated, and all potential ischemic episodes were identified. Episodes of ischemia were defined as reversible ST-segment changes lasting >1 minute and shifting from baseline to > 0.1 mV (1 mm). The baseline ST-segment level was denned as the average ST segment during a stable period (duration of 20 minutes) preceding each ischemic episode. ST-segment change was measured 60 ms after the J point. If the J point was within the T-wave, the ST-segment change was measured 40 ms after that point. The ischemic burden was calculated by multiplying ischemia duration by ST-segment deviation.

Troponin T levels were measured on postoperative days 1, 3, and 7; before discharge; and whenever clinically indicated by electrocardiographic changes consistent with myocardial ischemia or infarction. Troponin T level was measured by an electrochemiluminescence immunoassay on the Elecsys 2010 device (Roche Diagnostics, Mannheim, Germany). For the definition of positive troponin T levels, 0.03 ng/ml was used as the cut-off value, as lower values do not meet the imprecision criteria of < 10%.

Mean heart rate was calculated before, during, and after surgery. Heart rate variability was computed using time-domain analysis of short-term 5-minute recordings. Consecutive 5-minute recordings of 2-hour periods were obtained in a standard fashion at the evening before surgery, during the first 2 hours of surgery, and the second evening after surgery. The SD of the NN intervals (SDNN) was

calculated in milliseconds. All electrocardiographic recordings were analyzed for new-onset atrial fibrillation, monomorphic or polymorphic ventricular tachycardia, and ventricular fibrillation. Nonsustained ventricular tachycardia was denned as an episode of >3 consecutive ventricular premature beats at a rate of >120 beats/min lasting < 30 seconds. Sustained ventricular tachycardia lasted >30 seconds.

During a mean follow-up of 2.3 years, outpatient visits were scheduled every 3 months after discharge. Study end-points were all-cause mortality and major cardiac events (cardiac death and nonfatal Q-wave myocardial infarction) during hospital stay and follow-up. Nonfatal Q-wave myocardial infarction was diagnosed when at least the following were present: increased cardiac enzyme levels, development of typical electrocardiographic changes (new Q waves >1 mm or >30 ms), and typical symptoms of angina pectoris. Cardiac death was denned as death caused by acute myocardial infarction, cardiac arrhythmias, congestive heart failure, or sudden death. No patients were lost to follow-up.

The study group was divided according to endovascular or open AAA repair. Continuous data were expressed as means ± SD or medians with interquartile ranges and compared using Student's *t* test or Mann-Whitney test. Categorical data were analyzed using the chi-square test. Binary logistic regression analysis and Cox proportional-hazards models were used for perioperative and long-term outcome analysis, respectively. A propensity score for surgical procedure was calculated, which was constructed using multiple logistic regression analysis.[1] Variables associated with the decision to perform endovascular AAA repair were included in the multivariate propensity score. In multivari-ate analysis, adjustments were made for age, gender, diabetes, renal failure, coronary artery disease (i.e., history of angina or myocardial infarction or stress-induced ischemia), history of cerebrovascular disease, hypertension, β blockers, statins, and propensity scores. For all tests, a p value < 0.05 (2-sided) was considered significant. All analysis was performed using SPSS statistical software (version 12.0; SPSS, Chicago, Illinois).

RESULTS

Among 175 patients, open AAA repair was performed in 126 and endovascular AAA repair in 49. No significant differences were observed between open and endovascular repair in terms of baseline clinical characteristics, dobut-amine stress

echocardiographic results, and cardiovascular medication (Table 1). Mean preoperative heart rate was similar between open and endovascular repair. However, duration of surgery and total fluid infusion were significantly higher in patients with open AAA repair than in those who underwent endovascular repair (Table 1). Propensity analysis demonstrated that patients were more likely to undergo endovascular AAA repair if they were older (p = 0.04) and if they had a history of angina pectoris (p = 0.052). Propensity scores ranged from 0.35 to 0.95.

Table 1 *Baseline characteristics of the study population*

Characteristic	AAA Repair (n = 175)		
	Endovascular (n = 49)	Open (n = 126)	p Value
Age >70 yrs	32 (65%)	65 (52%)	0.1
Men	42 (86%)	105 (83%)	0.7
Angina pectoris	12 (24%)	21 (17%)	0.2
Previous myocardial infarction	17 (35%)	54 (43%)	0.3
Previous coronary revascularization	9 (18%)	18 (14%)	0.5
Previous congestive heart failure	1 (2%)	5 (4%)	0.5
Previous cerebrovascular events	6 (12%)	20 (16%)	0.5
Renal failure	2 (4%)	5 (4%)	1.0
Diabetes mellitus	4 (8%)	19 (15%)	0.2
Hypertension	16 (33%)	50 (40%)	0.4
Hypercholesterolemia*	14 (29%)	40 (32%)	0.7
Current or past smoker	25 (51%)	81 (64%)	0.1
Aspirin	27 (55%)	53 (42%)	0.1
Angiotensin-converting enzyme inhibitors	10 (20%)	35 (28%)	0.3
β blockers	39 (80%)	93 (74%)	0.4
Calcium channel blockers	10 (20%)	35 (28%)	0.3
Statins	22 (45%)	59 (47%)	0.8
Stress-induced myocardial ischemia	13 (27%)	29 (23%)	0.8
Duration of operation (h)	3.0 ± 1.1	5.6 ± 1.4	< 0.001
Fluid infusion during operation (1)	0.4 ± 0.3	2.8 ± 1.7	< 0.001
Heart rate 1 d before surgery (beats/minute)	69 ± 11	70 ± 15	0.3

Values are expressed as means ± SD or number and percentage.

* Defined by low-density lipoprotein cholesterol level > 130 mg/dl or the use of lipid-lowering medication.

Myocardial ischemia during continuous 12-lead electro-cardiography was detected in 60 patients (34%). A total of 109 episodes of myocardial ischemia were detected. The median duration of ischemic events was 81 minutes (interquartile range 60 to 269) and the median ST-segment deviation was 1.4 mm (interquartile range 1.0 to 2.7). Myocardial ischemia was significantly lower in patients who underwent endovascular AAA repair than in those who underwent open repair (Table 2). The ischemic burden was also significantly lower in patients who underwent endovascular AAA repair (median 67 mm*min) compared with those who underwent open repair (median 209 mm*min, p = 0.003). In multivariate analysis, endovascular AAA repair remained significantly associated with lower myocardial ischemia (Table 2).

Troponin T release was detected in 51 patients (29%). The median troponin T value was 0.45 ng/ml (interquartile range 0.08 to 0.75). In univariate and multivariate analyses, endovascular AAA repair was significantly associated with lower troponin T

Table 2 *Myocardial ischemia, troponin T release, and clinical outcome in patients treated with endovascular or open repair*

Variable	AAA Repair (n = 175)			
	Endovascular (n = 49)	Open (n = 126)	Relative Risk (95% CI)†	p Value
Ischemia and troponin T				
ST-segment changes	5 (10.2%)	55 (43.7%)	0.14 (0.05-0.40)	< 0.001
Before operation	4 (8.2%)	7 (5.6%)	2.10 (0.50-8.61)	0.3
During operation	5 (10.2%)	41 (32.5%)	0.24 (0.09-0.68)	0.007
After operation	3 (6.1%)	35 (27.8%)	0.18 (0.05-0.62)	0.006
Troponin T release	3 (6.1%)	48 (38.1%)	0.10 (0.02-0.32)	< 0.001
Myocardial injury*	5 (10.2%)	64 (50.8%)	0.11 (0.03-0.26)	< 0.001
Outcome				
All-cause mortality at 30 d	0	11 (8.7%)	–	0.03‡
Cardiac events at 30 d	0 (0%)	10 (7.9%)	–	0.04‡
Long-term all-cause mortality	4 (8.2%)	17 (13.5%)	0.52 (0.17-1.63)	0.2
Long-term cardiac events	3 (6.1%)	15 (11.9%)	0.45 (0.12-1.81)	0.3

* Composite of myocardial ischemia and troponin T release.

† Adjusted for age, gender, diabetes, renal failure, coronary artery disease, history of heart failure, history of cerebrovascular disease, hypertension, β blockers, statins, and propensity score.

‡ Calculated by chi-square test. CI = confidence interval.

release (Table 2). In patients with myocardial damage, the level of troponin T release was significantly lower after endovascular AAA repair (median 0.17 ng/ml) compared with open AAA repair (0.45 ng/ml, p <0.001).

Mean preoperative heart rate and heart rate variability were comparable between open and endovascular procedures. However, during and after surgery, heart rate was significantly higher and heart rate variability was significantly lower in the open AAA repair group compared with the endovascular AAA repair group (Table 3). Interestingly, patients with myocardial ischemia after surgery had a lower degree of heart rate variability before (SDNN 32 ± 29 vs 50 ± 26, p = 0.002), during (SDNN 23 ± 19 vs 36 ± 24, p = 0.01) and after surgery (SDNN 21 ± 19 vs 46 ± 42, p = 0.008) compared with patients with no myocardial ischemia. Patients with troponin T release also had a lower degree of heart rate variability before (SDNN 49 ± 25 vs 32 ± 29, p = 0.002), during (SDNN 23 ± 21 vs 37 ± 23, p = 0.004), and after surgery (SDNN 21 ± 18 vs 47 ± 39, p < 0.001) compared with patients with no troponin T release.

New-onset atrial fibrillation, nonsustained ventricular tachycardia, sustained ventricular tachycardia, and ventricular fibrillation occurred in 9 (5%), 29 (17%), 4 (2%), and 2 (1%) patients, respectively. Patients with perioperative cardiac arrhythmias were more likely to have perioperative ischemia and troponin T release than patients without arrhythmias (Figure 1). In addition, heart rate during and after surgery was significantly higher and heart rate variability during and after surgery was significantly lower in patients with cardiac arrhythmias (Figure 2). Sustained ventricular tachycardia and ventricular fibrillation were not observed in patients treated with endovascular AAA repair but occurred in 4 (3%) and 2 patients (2%), respectively, treated with open surgical AAA repair. The incidences of atrial fibrillation and nonsustained ventricular tachycardia were also nonsignificantly lower in patients treated with endovascular AAA repair (Table 3). The cumulative incidence of cardiac arrhythmias was significantly lower in endovascular AAA repair versus open surgery (Table 3).

All-cause mortality and cardiac events occurred in 11 (6.3%) and 10 (5.7%) patients, respectively, during hospital stay. In-hospital mortality and cardiac events were not observed after endovascular AAA repair, but occurred in 11 (9%) and 10 (8%) patients, respectively, treated with open surgical repair (Table 2). During follow-up, all-cause mortality and cardiac events occurred in 21 (12%) and 18 (10%) patients, respectively. Patients treated with endovascular AAA repair were at a nonsignificantly

Table 3 *Perioperative heart rate, heart rate variability, and arrhythmias in patients treated with endovascular or open repair*

Variable	AAA Repair (n = 175)		
	Endovascular (n = 49)	Open (n = 126)	p Value
Heart rate (beats/min)	69 ± 10	75 ± 14	0.01
Before operation	69 ± 11	70 ± 15	0.3
During operation	68 ±9	74 ± 13	0.009
After operation	72 ± 13	81 ± 15	0.004
Heart rate variability (SDNN)			
Before operation (ms)	48 ±20	49 ±21	0.7
During operation (ms)	42 ±20	26 ± 18	0.001
After operation (ms)	44 ±20	28 ±21	0.004
Arrhythmias			
Any	7 (14.3%)	37 (29.3%)	0.04
Nonsustained ventricular tachycardia	6 (12.2%)	23 (18.3%)	0.3
Sustained ventricular tachycardia	0	4(3.1%)	0.2
Newly onset atrial fibrillation	1 (2.0%)	8 (6.3%)	0.2
Ventricular fibrillation	0 (0%)	2 (1.6%)	0.4

Values are expressed as mean ± SD where applicable.

lower risk of long-term mortality and cardiac events versus those treated with open AAA repair (Table 2).

DISCUSSION

Several studies have demonstrated that endovascular procedures can significantly decrease cardiovascular events in the perioperative period in comparison with open repair.[27] Long-term studies have suggested no sustained survival benefit after the first postoperative year for endovascular stent placement.[8] In a previous study, we demonstrated that endovascular stent-grafting was associated with a reduced incidence of perioperative complications, but with comparable long-term cardiac outcome.[7] In the present study, perioperative 72-hour 12-lead electrocardiographic monitoring was applied in a contemporary patient cohort. Endovascular repair was significantly associated with a lower perioperative heart rate and higher perioperative heart rate variability. Patients treated with endovascular repair also had a lower incidence of

perioperative cardiac arrhythmias, myocardial ischemia, troponin T release, mortality, and cardiac events. We confirmed that long-term mortality and cardiac event rates were nonsignificantly lower in patients treated with endovascular repair.

In previous studies, myocardial ischemia during major vascular surgery has been observed in as many as 41% of patients and has been demonstrated to be a strong predictor of subsequent clinical cardiovascular events.[9] The present study detected perioperative myocardial ischemia in 34% of patients. Myocardial ischemia in the perioperative setting may arise from increased myocardial oxygen demand or reduced supply. Factors that increase myocardial oxygen demand are mainly tachycardia and hypertension resulting from surgical stress, postoperative pain, interruption of β-blocker use, or the use of sympathomimetic drugs. In contrast, decreased supply may be the result of hypotension, vasospasm, anemia, hypoxia, or coronary artery plaque rupture. Invasive procedures have been associated with significant changes in arterial

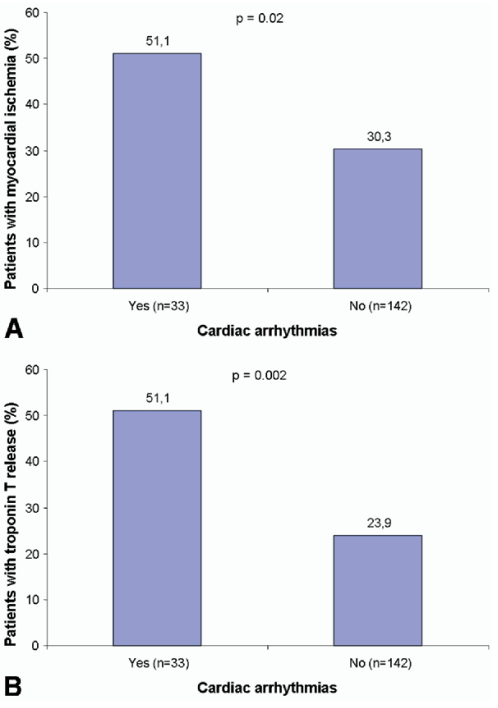


Figure 1 *Incidence of perioperative myocardial ischemia (A) and troponin T release (B) in patients with and without perioperative cardiac arrhythmias.*

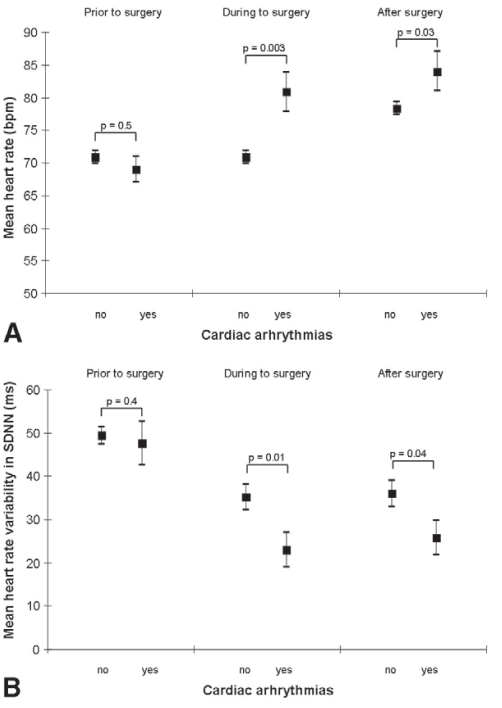


Figure 2 *Mean heart rate (A) and heart rate variability (±SEM) (B) in patients with and without perioperative cardiac arrhythmias.*

pressure, cardiac output, and increases in blood lactate, catecholamine, and arterial pH.[10–11] Therefore, the higher heart rate in patients undergoing open repair is likely the result of increased surgical stress and sympathetic tone.

Heart rate variability has been used as a measure of cardiac autonomic function and mostly reflects vagal tone. Increased anesthetic depth and sympathetic tone most likely explain the lower perioperative heart rate variability in patients with open repair compared with endovascular repair.[12] It has been suggested that decreased heart rate variability could trigger ischemic events.[13, 14] In the present study, myocardial ischemia and troponin T release was preceded by significantly lower heart rate variability. The present results therefore support the view that ischemic events predominantly occur in situations with increased sympathetic activity.

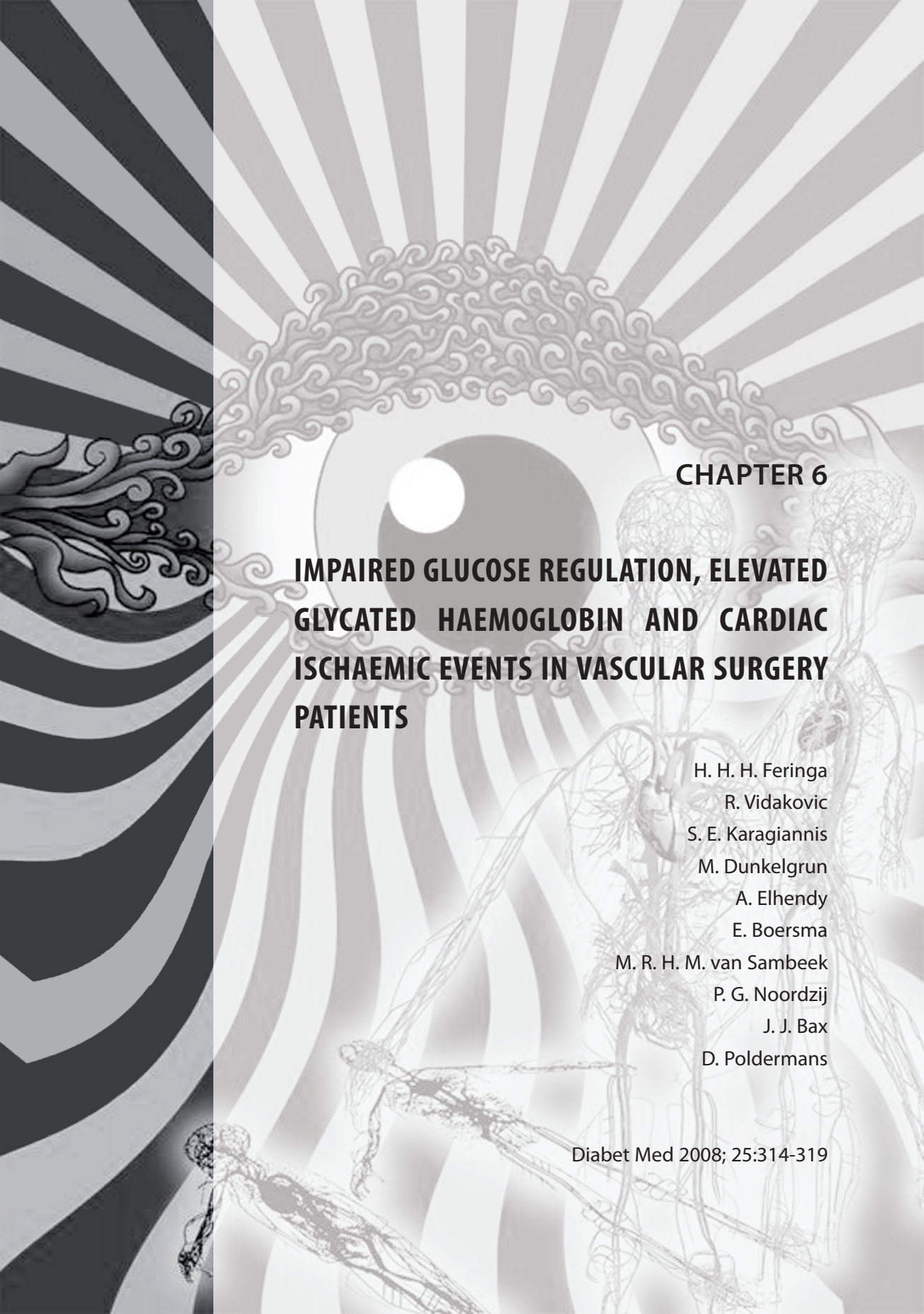
This study further revealed a higher incidence of cardiac arrhythmias in patients treated with open repair. In addition, patients with perioperative cardiac arrhythmias had a higher incidence of myocardial ischemia and troponin T release. They also had significantly higher heart rates and lower heart rate variability during and after surgery. These results therefore suggest that surgical stress, higher heart rates, and lower heart rate variability in association with myocardial oxygen supply/demand mismatch cause the higher incidence of sustained and nonsustained ventricular tachycardias, new-onset atrial fibrillation, and ventricular fibrillation in patients treated with open repair compared with endovascular repair.

Cardiac complications remain a leading cause of morbidity and mortality among patients treated with vascular surgery. As a result of the lack of long-term data, the choice between stent placement and open repair now heavily relies on surgeon experience and patient preference. Concerns have been raised about the long-term efficacy and safety of endovascular grafts. Not only have endoleaks become increasingly common as the duration of follow-up is extended, aneurysm-related deaths after successful endograft therapy have also been reported.[15]

The major limitation in this study is that the surgical procedures were not randomly assigned to the patients. However, baseline clinical characteristics were comparable and detailed cardiac assessment with dobutamine stress test echocardiography revealed no significant baseline differences between the 2 types of surgery. In addition, we used multivariate analysis and propensity analysis to adjust for known possible confounding factors. Unfortunately, no data were available regarding the incidence of repeat procedures for graft leaks in patients treated with endovascular surgery.

REFERENCES

1. Rubin DB. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med* 1997;127:757-763.
2. Katzen BT, Dake MD, MacLean AA, Wang DS. Endovascular repair of abdominal and thoracic aortic aneurysms. *Circulation* 2005;112: 1663-1675.
3. EVAR trial participants. Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomized controlled trial. *Lancet* 2004;364:843-848.
4. Dutch Randomized Endovascular Aneurysm Management (DREAM) Trial Group. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. *N Engl J Med* 2004: 351:1607-1618.
5. EVAR trial participants. Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomized controlled trial. *Lancet* 2005;365: 2179-2186.
6. EVAR trial participants. Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomized controlled trial. *Lancet* 2005;365: 2187-2192.
7. Schouten O, van Waning VH, Kertai MD, Feringa HH, Bax JJ. Boersma E, Elhendy A, Biagini E, van Sambeek MR, van Urk H, Poldermans D. Perioperative and long-term cardiovascular outcomes in patients undergoing endovascular treatment compared with open vascular surgery for abdominal aortic aneurysm or iliaco-femoro-popliteal bypass. *Am J Cardiol* 2005;96:861-866.
8. Dutch Randomized Endovascular Aneurysm Management (DREAM) Trial Group. Two-year outcomes after conventional or endovascular repair of abdominal aortic aneurysms. *N Engl J Med* 2005;352: 2398-2405.
9. The Study of Perioperative Ischemia Research Group. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. *N Engl J Med* 1990;323: 1781-1788.
10. Baxendale BR, Baker DM, Hutchinson A, Chuter TA, Wenham PW, Hopkinson BR. Haemodynamic and metabolic response to endovascular repair of infra-renal aortic aneurysms. *Br J Anaesth* 1996;77: 581-585.
11. Thompson JP, Boyle JR, Thompson MM, Strupish J, Bell PR, Smith G. Cardiovascular and catecholamine responses during endovascular and conventional abdominal aortic aneurysm repair. *Eur J Vasc En-dovasc Surg* 1999;17:326-333.
12. Kanaya N, Hirata N, Kurosawa S, Nakayama M, Namiki A. Differential effects of propofol and sevoflurane on heart rate variability. *Anesthesiology* 2003;98:34-40.
13. Kop WJ, Verdino RJ, Gottdiener JS, O'Leary ST, Bairey Merz CN, Krantz DS. Changes in heart rate and heart rate variability before ambulatory ischemic events. *J Am Coll Cardiol* 2001;38:742-749.
14. Lanza GA, Pedrotti P, Pasceri V, Lucente M, Crea F, Maseri A. Autonomic changes associated with spontaneous coronary spasm in patients with variant angina. *J Am Coll Cardiol* 1996;28: 1249-1256.
15. Elefteriades JA, Percy A. Endovascular stenting for descending aneurysms: wave of the future or the emperor's new clothes? *J Thorac Cardiovasc Surg* 2007;133:285-288.



CHAPTER 6

IMPAIRED GLUCOSE REGULATION, ELEVATED GLYCATED HAEMOGLOBIN AND CARDIAC ISCHAEMIC EVENTS IN VASCULAR SURGERY PATIENTS

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ABSTRACT

Aims Cardiac morbidity and mortality is high in patients undergoing high-risk surgery. This study investigated whether impaired glucose regulation and elevated glycated haemoglobin (HbA_{1c}) levels are associated with increased cardiac ischaemic events in vascular surgery patients.

Methods Baseline glucose and HbA_{1c} were measured in 401 vascular surgery patients. Glucose < 5.6 mmol/l was defined as normal. Fasting glucose 5.6-7.0 mmol/l or random glucose 5.6-11.1 mmol/l was defined as impaired glucose regulation. Fasting glucose ≥ 7.0 or random glucose ≥ 11.1 mmol/l was defined as diabetes. Perioperative ischaemia was identified by 72-h Holter monitoring. Troponin T was measured on days 1,3 and 7 and before discharge. Cardiac death or Q-wave myocardial infarction was noted at 30-day and longer-term follow-up (mean 2.5 years).

Results Mean (± SD) level for glucose was 6.3 ± 2.3 mmol/l and for HbA_{1c} 6.2 ± 1.3%. Ischaemia, troponin release, 30-day and long-term cardiac events occurred in 27, 22, 6 and 17%, respectively. Using subjects with normal glucose levels as the reference category, multivariate analysis revealed that patients with impaired glucose regulation and diabetes were at 2.2- and 2.6-fold increased risk of ischaemia, 3.8- and 3.9-fold for troponin release, 4.3- and 4.8-fold for 30-day cardiac events and 1.9- and 3.1-fold for long-term cardiac events. Patients with HbA_{1c} > 7.0% (n = 63, 16%) were at 2.8-fold, 2.1-fold, 5.3-fold and 5.6-fold increased risk for ischaemia, troponin release, 30-day and long-term cardiac events, respectively.

Conclusions Impaired glucose regulation and elevated HbA_{1c} are risk factors for cardiac ischaemic events in vascular surgery patients.

Diabet. Med. 25, 314-319 (2008)

Keywords glycated haemoglobin, impaired glucose tolerance, prognosis, vascular surgery

Abbreviations BNP, brain-natriuretic peptide; HbA_{1c}, glycated haemoglobin

INTRODUCTION

Annually, around 0.2% of the Dutch population undergoes major non-cardiac vascular surgery [1]. Among diabetic patients undergoing major vascular surgery, cardiac complications are the leading cause of morbidity and mortality. The incidence of perioperative cardiac events in these patients ranges from 6% to 21% [2-5]. Cardiac complications in diabetes are likely to be the result of impaired glucose metabolism leading to endothelial dysfunction, myocardial ischaemia and myocardial tissue damage [6]. Pre-diabetes represents a metabolic stage intermediate between normal glucose homeostasis and diabetes [7]. These patients have a long asymptomatic period of glucose dysregulation and are at risk of developing Type 2 diabetes [7]. Although diabetes has been recognized as an independent predictor of post-operative outcome, the prognosis of non-diabetic patients with impaired glucose regulation is not well known. In addition, poor glycaemic control in diabetic and non-diabetic patients may be associated with adverse cardiac outcome.

This study was conducted to elucidate the association between impaired glucose regulation and elevated glycated haemoglobin (HbA_{1c}) with perioperative and long-term cardiac ischaemic events in patients undergoing major vascular surgery.

PATIENTS AND METHODS

The study population consisted of 401 consecutive patients with peripheral arterial disease undergoing elective abdominal aortic aneurysm repair, peripheral artery bypass surgery or carotid artery surgery at the Erasmus Medical Center in Rotterdam, the Netherlands, during the period 2002 to 2006. This prospective study was approved by the hospital's ethical committee and performed with the informed consent of all patients. Patients with a cardiac pacemaker, left ventricular hypertrophy, left or right bundle branch block and atrial fibrillation were excluded. Patients who participated in clinical intervention trials at or outside the Erasmus Medical Center were also excluded. Patients were enrolled up to 3 months prior to surgery at the outpatient clinic. All patients underwent preoperative risk stratification, including cardiac stress testing. Preoperative cardiac revascularization based on positive preoperative stress test results was not routinely offered in our hospital. In all patients, beta-blockers were considered prior to surgery to obtain perioperative heart rates of 60-65 beats per minute. Baseline characteristics were obtained and included demographic, historical, laboratory and

electrocardiographic information. Body mass index was calculated using the formula weight/ height^2. Renal dysfunction was defined as serum creatinine > 177 μmol/l or if renal dialysis was required [8].

Baseline glucose and HbA_{1c} measurements

Baseline glucose and HbA_{1c} measurements were obtained during preoperative assessment at a central laboratory. Blood samples were obtained using venipuncture with minimal stasis. Glucose was enzymatically determined using the Hexokinase method (Boehringer, Mannheim, Germany). HbA_{1c} was determined by using an enzyme immunoassay based on microtitre plate technology. Information was obtained on history of diabetes and use of blood glucose-lowering treatment. Patients were classified into three categories. Glucose < 5.6 mmol/l was defined as normal. Fasting glucose between 5.6-7.0 mmol/l or random glucose between 5.6-11.1 mmol/l was defined as impaired glucose regulation. Fasting glucose > 7.0 or random glucose > 11.1 mmol/l, or the use of blood glucose-lowering medication was defined as diabetes [7]. Eighty-three per cent of the population had a fasting glucose and 17% a random glucose measured. Patients with impaired glucose regulation were followed closely with regular blood pressure check-ups, weight/ body mass index measurements and repeated glucose measurements. Glucose-lowering medication and insulin therapy were considered in patients meeting the criteria for diabetes mellitus. Although patients were counselled on healthy lifestyle and risk-factor reduction, no formal follow-up with glucose tolerance testing was performed.

Perioperative myocardial ischaemia

Patients were continuously monitored with a 10-electrode, 12-lead digital electrocardiograph (ECG) recorder (DR180 + Digital Recorder; NorthEast Monitoring Inc., Maynard, MA, USA), starting 1 day before surgery and continuing up to 2 days after. Recordings were performed in the continuous 12-lead mode with a recording length of 10 s every min. The frequency response was 0.05-150 Hz. Electrocardiographic data were initially processed by a technician and analysed by two experienced cardiologists who were blinded to the patient's clinical data. After excluding all abnormal QRS complexes, the ambulatory electrocardiography recordings were analysed for ST-segment deviations. A continuous ST-segment trend was generated and all potential ischaemic episodes were identified. Episodes of ischaemia were defined as reversible

ST-segment changes, lasting at least 1 min and shifting from baseline by more than 0.1 mV (1 mm). The baseline ST-segment level was defined as the average ST segment during a stable period (duration of 20 min) preceding each ischaemic episode. ST-segment change was measured 60 ms after the J point. If the J point fell within the T-wave, the ST segment change was measured 40 ms after that point. Patients who developed perioperative myocardial ischaemia were referred for further cardiovascular investigation. In these patients, it was ascertained that they received beta-blockers, statins and aspirin at hospital discharge.

Perioperative troponin T release

Troponin T levels were measured on post-operative days 1, 3 and 7, before discharge and whenever clinically indicated by ECG changes, consistent with myocardial ischaemia or infarction. Troponin T level was measured by an electrochemiluminescence immunoassay on the Elecsys 2010 (Roche Diagnostics, Mannheim, Germany). The lower limit of detection of 0.03 ng/ml was used to define positive troponin T levels as lower levels do not meet the imprecision criteria of < 10%.

Clinical cardiac outcome

Study end points were major cardiac events (cardiac death and non-fatal Q-wave myocardial infarction) during the perioperative period (30-day period after surgery) and during follow-up (mean 2.5 years). During follow-up, outpatient visits were scheduled every 3 months after discharge. Cardiac death was defined as death caused by acute myocardial infarction, cardiac arrhythmias, congestive heart failure or sudden death. Non-fatal myocardial infarction was diagnosed when at least the following criteria were present: elevated cardiac enzyme levels, development of new Q waves (> 1 mm or > 30 ms), and typical symptoms of angina pectoris. No patients were lost to follow-up.

Data analysis

Differences between groups with normal glucose, impaired glucose regulation and diabetes were assessed using one-way analysis of variance for continuous characteristics and χ^2-test for dichotomous characteristics. Patients with impaired glucose regulation and diabetes were compared with patients with normal glucose levels. Binary logistic regression analysis was used to determine the association of glucose and HbA_{1c} status with perioperative myocardial ischaemia, troponin T release and 30-day cardiac events. Cox proportional hazard analysis was used to assess the association of glucose and HbA_{1c}

status with late cardiac events. In multivariate analysis, adjustments were made for age, gender, angina pectoris, myocardial infarction, congestive heart failure, hypertension, stroke, smoking, renal dysfunction and laboratory measures. Only laboratory measures of which the values were significantly different between the three groups were included (Table 1). In addition, absolute glucose and HbA_{1c} values were assessed as continuous variables. Odds and hazard ratios are given with 95% confidence intervals. For all tests, a *P* value < 0.05 (two-sided) was considered significant. All analysis was performed using SPSS 12.0 statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

Mean (+ SD) glucose in the study population was 6.3 + 2.3 mmol/l and mean HbA_{1c} 6.2 + 1.3%. The characteristics of the patients with normal glucose levels *(n* = 220, 55%), impaired glucose regulation *(n* = 112,28 %) and diabetes *in* = 69,17%) are presented in Table 1. Patients with impaired glucose regulation had a higher prevalence of angina pectoris, myocardial infarction, coronary bypass surgery and congestive heart failure, compared with patients with normal glucose levels. Laboratory testing revealed that urea and high-sensitivity C-reactive protein were significantly higher in patients with impaired glucose regulation, compared with patients with normal glucose levels (Table 1). Haemoglobin and haematocrit were significantly lower in patients with impaired glucose regulation (Table 1).

Events

Perioperative myocardial ischaemia during 72-h 12-lead electrocardiographic monitoring occurred in 108 patients (27%). Perioperative troponin T release occurred in 90 patients (22%) and 30-day major cardiac events in 23 patients (6%). One hundred and thirty-one patients (33 %) experienced either an episode of myocardial ischaemia, troponin T release or a major cardiac event in the perioperative period. During follow-up, 85 patients (21 %) died. Cardiac death or non-fatal myocardial infarction during follow-up occurred in 69 patients (17%).

Glucose and HbA_{1c} status in relation to events

The incidence of myocardial ischaemia was 19% in patients with normal glucose levels, 35% in patients with impaired glucose regulation and 41% in diabetes (P< 0.001). Similarly, the incidence of troponin T release was 11, 36 and 38% (P< 0.001). Thirty-day

Table 1 *Characteristics of the study population (n = 401) by glucose status*

Characteristic	No diabetes (*n* = 332)		
	Normal glucose (*n* = 220)	Impaired glucose regulation (*n* = 112)	Diabetes (n = 69)
Age (years)	66 ± 11	68 ±9	66 ±11
Gender, % male	77.3	80.4	72.5
Angina pectoris, %	14.5	24.1*	20.3
Previous myocardial infarction, %	28.2	47.3*	44.9†
Previous percutaneous coronary angioplasty, %	5.9	10.7	10.1
Previous coronary artery bypass grafting, %	9.5	26.8*	17.4
History of congestive heart failure, %	0.9	9.3*	4.3
Rest wall motion abnormalities, %	29.5	33.0	27.5
Stress-induced wall motion abnormalities, %	25.0	29.5	27.5
Hypertension, %	40.0	36.6	49.3
Stroke, %	13.1	16.1	13.0
Past smoking, %	60.9	58.0	43.5†
Current smoking, %	31.4	28.6	20.3
Renal dysfunction, %	1.8	8.9	4.3
Body mass index, kg/m^2	24.9 ±3.5	25.3 ±4.0	26.8 ±3.6†
Ankle-brachial index	0.88 ±0.26	0.80 ±0.32	0.80 ±0.28
Forced expiratory volume in 1 s, 1	2.5 ±0.8	2.4 ±0.8	2.4 ±0.8
Urea (mmol/l)	6.6 ±3.7	8.3 ±3.9*	7.5 ±3.6
Creatinine (μmol/l)	97±83	101 ± 68	100 ±69
Low-density lipoprotein cholesterol (mmol/l)	3.1 ± 1.1	3.1 ± 1.1	2.8 ±1.0
High-density lipoprotein cholesterol (mmol/l)	1.3 ±0.6	1.3 ±0.5	1.2 ±0.4
Total cholesterol (mmol/l)	4.9 ±1.2	5.1 ±1.3	4.8 ±1.3
Haemoglobin (mmol/l)	8.7±0.9	8.4 ±1.2*	8.4 ±1.3†
Haematocrit	0.42 ±0.04	0.39 ±0.05*	0.40 ±0.06
High sensitivity C-reactive protein (mg/1)	9.9±13.8	46 ±77*	24±40‡
Uric acid (mmol/l)	0.34 ±0.09	0.35 ±0.1	0.38 ±0.12
N-terminal pro-BNP level, pmol/1 (median)	101	124	111
Glycated haemoglobin (%)	5.6 ±0.4	6.0 ±0.8	7.9±1.8†‡
Aspirin use at baseline, %	53.2	52.7	58.0
Beta-blocker use at baseline, %	69.1	73.2	75.4
Statin use at baseline, %	50.5	51.8	56.5

Values are presented as percentage or as mean ± standard deviation, unless otherwise stated.
*P < 0.05 impaired glucose regulation vs. normal glucose.
†P < 0.05 diabetes vs. normal glucose.
‡P < 0.05 diabetes vs. impaired glucose regulation.
BNP, brain-natriuretic peptide.

cardiac events occurred in 2, 10 and 10% (P < 0.001), respectively. These differences between patients with impaired glucose regulation and diabetes were not significant. A higher proportion of patients with normal baseline glucose levels survived, compared with patients with impaired glucose regulation or diabetes (P< 0.001) (Fig. 1). Multivariate analysis revealed that patients with impaired glucose regulation and diabetes were at 2.2- and 2.6-fold increased risk for myocardial ischaemia, 3.8- and 3.9-fold increased risk for troponin T release, 4.3- and 4.8-fold increased risk for 30-day cardiac events, 2.0- and 2.7-fold increased risk for long-term mortality and 1.9- and 3.1-fold increased risk for long-term cardiac events (Table 2). Patients with HbA_{1c} > 7.0% (*n* = 63, 16%) were at 2.8-fold, 2.1-fold, 5.3-fold, 3.6-fold and 5.6-fold increased risk for myocardial ischaemia, troponin T release, 30-day cardiac events, long-term mortality and long-term cardiac events, respectively (Table 2). When using absolute values, higher glucose and HbA_{1c} remained significantly associated with increased perioperative and long-term events (Table 2). Additional adjustment for lipids, and baseline use of aspirin, statin and beta-blockers did not change the results.

DISCUSSION

The results of this study indicate that impaired glucose regulation is common in vascular surgery patients (28 %). Moreover, higher HbA_{1c} (> 7.0 %) was present in 16% of patients. Importantly, both impaired glucose regulation and elevated HbA_{1c} were associated with an increased incidence of perioperative myocardial ischaemia, perioperative troponin T release, and 30-day and long-term cardiac events, independent of age, gender and clinical risk factors.

Insulin resistance with hyperglycaemia is believed to be the major underlying pathologic mechanism for the associated susceptibility to premature cardiovascular disease in pre-diabetic patients. Adipose tissue plays a crucial role in the pathogenesis of insulin resistance and is the main causative mechanism of Type 2 diabetes. Metabolic disturbances associated with insulin resistance beyond hyperglycaemia include dyslipidaemia, hypercoagulability and inflammation. In the current study, the highest level of the inflammation marker high-sensitivity C-reactive protein was found in patients with impaired glucose regulation. Inflammation probably links the metabolic and vascular pathologies [9]. Hyperglycaemia also exerts direct effects on the progression of atherosclerosis by the formation of reactive advanced glycation end products that

Table 2 *Multivariate association of baseline glucose and glycated haemoglobin with perioperative and long-term cardiac events*

Characteristic	Myocardial ischaemia (*n* = 108) OR(95%CI)	Troponin T release (*n* = 90) OR (95%CI)	Thirty-day cardiac events (*n* = 23) OR (95%CI)	Composite of perioperative events (*n* = 131) OR (95%CI)	Mortality during follow-up (*n* = 85) HR (95% CI)	Cardiac events during follow-up (*n* = 69) HR (95% CI)
Normal glucose levels (reference) (*n* = 220)	1.0	1.0	1.0	1.0	1.0	1.0
- Impaired glucose regulation *(n* = 112)	2.2(1.3-3.9)	3.8 (2.1-7.0)	4.3 (1.4-13.5)	2.4(1.4-4.1)	2.0(1.1-3.8)	1.9(1.0-3.7)
- Diabetes *(n = 69)*	2.6(1.4-4.9)	3.9 (2.0-7.7)	4.8 (1.4-16.6)	3.9(2.1-7.3)	2.7(1.2-5.6)	3.1 (1.5-6.4)
Absolute glucose levels, per mmol/l ↑	1.3 (1.1-1.4)	1.4(1.2-1.5)	1.2(1.0-1.3)	1.4 (1.2-1.5)	1.2 (1.1-1.3)	1.1 (1.0-1.2)
HbA_{1c}> 7.0% (*n* = 63)	2.8(1.3-6.0)	2.1 (1.1-6.5)	5.3 (1.7-16.6)	3.0(1.4-6.5)	3.6(1.2-11.1)	5.6(2.1-14.6)
Absolute HbA_{1c}, per % t	1.5 (1.2-2.0)	1.3 (1.0-1.7)	1.5(1.1-3.8)	1.5(1.1-1.9)	1.5(1.0-2.1)	1.4(1.1-1.8)

Adjusted for age, gender, angina pectoris, myocardial infarction, congestive heart failure, hypertension, stroke, smoking, renal dysfunction and the laboratory variables, which showed significant differences among the three groups as in Table 1.

CI, confidence interval; HbA_{1c}, glycated haemoglobin; HR, hazard ratio; OR, odds ratio.

mediate vascular damage [9]. In addition, hyperglycaemia can be deleterious for the heart because of hypovolaemia, modulation of nitric oxide metabolism and oxidative stress and down-regulation of ischaemic preconditioning [10].

The cardiac event rate in vascular surgery patients is high [11], reflecting the high prevalence of underlying coronary artery disease. Indeed, coronary angiographic abnormalities have been reported in up to 92% of patients [12]. In our contemporary study cohort, a relatively high incidence of perioperative cardiac complications was observed (6%). It should be noted that this study was conduced at a university hospital, which acts as a tertiary referral centre for approximately 30 affiliated hospitals. The high incidence may be related to the admission and treatment of high-risk patients, who would not have been cared for in other hospitals. The rate of myocardial ischaemia as assessed by continuous 12-lead electrocardio-graphic monitoring was more than three times higher (27%) than the incidence of perioperative cardiac events. The recognition of silent perioperative ischaemic episodes is important, as these relate directly to myocardial damage, infarction and cardiac death [6]. The incidence of myocardial ischaemia was significantly higher in patients with impaired glucose regulation (35%) and patients with diabetes (41%), compared with patients with normal glucose levels (19%).

This study demonstrated the value of glucose and HbA_{1c} in defining perioperative and long-term risk in vascular surgery patients. However, the management of these patients remains a challenge. Patients with impaired glucose regulation do not meet the criteria for diabetes, but have impaired glucose metabolism, which places them at risk for developing diabetes or cardiovascular disease. We observed that survival in patients with impaired glucose metabolism was comparable with survival in patients with diabetes. Although loss of body weight, exercise and

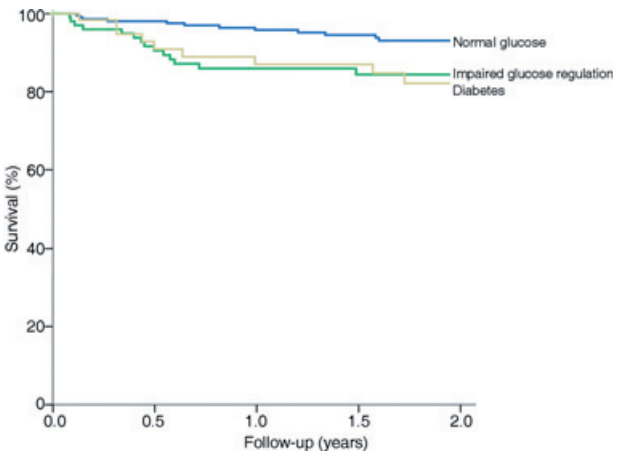


Figure 1 *Kaplan-Meier curves demonstrating survival in patients by glucose regulation status ($P < 0.001$; between-group analysis of variance).*

certain pharmacological agents can prevent the development of diabetes in patients with impaired glucose regulation, the impact on cardiovascular risk has not yet been examined. Randomized trials have demonstrated the benefit of beta-blockers and statins in the reduction of perioperative cardiac events in vascular surgery patients [13,14]. In diabetic patients, however, outcome was similar in patients randomized to either metoprolol or placebo [5]. The relatively short-term use of metoprolol in this study (from the day before surgery to a maximum of 8 days after) may explain this finding, as long-term beta-blocker treatment with slow heart rate are important factors in ischaemic event reduction. In addition to cardiovascular medication, aggressive glucose management in these patients should improve outcome. Abnormal glucose tolerance is an important predictor of long-term outcome after myocardial infarction [15]. Intensive insulin treatment to achieve normoglycaemic levels (< 6.1 mmol/l) reduced mortality in critically ill patients [16] and diabetic patients undergoing cardiac surgery [17]. However, randomized trials in major vascular surgery patients are needed to determine the role of intensified insulin therapy on cardiovascular outcome.

Several limitations should be addressed. Firstly, as a glucose challenge test was not routinely performed in this study, the number of patients with impaired glucose regulation may be underestimated in this study cohort. Secondly, we excluded patients with a cardiac pacemaker, left ventricular hypertrophy, left or right bundle branch block, atrial fibrillation and patients who participated in clinical intervention trials at or outside the Erasmus Medical Center. The exclusion of these patients may have biased the final results. Thirdly, the results of this study apply to high-risk patients with peripheral arterial disease undergoing major vascular surgery. Extrapolation to other patient groups should be carried out cautiously. However, a recent study in non-cardiac non-vascular surgery patients demonstrated comparable findings, showing that preoperative hyperglycaemia is associated with increased cardiovascular mortality [18]. Finally, patients with perioperative myocardial ischaemia were referred for further cardiovascular investigation. In these patients, it was ascertained that they received beta-blockers, statins and aspirin at hospital discharge. Symptomatic patients with perioperative myocardial ischaemia, troponin T release and newly developed Q-waves were referred for cardiac catheterization. Unfortunately, no detailed data on patients who eventually received coronary interventions were available.

In conclusion, the results of this study show that impaired glucose regulation and elevated HbA_{1c} are risk factors for cardiac ischaemic events in vascular surgery

patients. The value of screening for dysglycaemia and the benefits of aggressive glucose management in this setting require further study.

REFERENCES

1 Prismant Ziekenhuisstatistiek-Verrichtingen. 2003. Available at http://www.prismant.nl Last accessed 1 September 2007.

2 Mangano DT, Browner WS, Hollenberg M, Li J, Tateo IM. Long-term cardiac prognosis following non-cardiac surgery. The Study of Perioperative Ischemia Research Group./ *Am MedAssoc* 1992; 268: 233-239.

3 Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF *et al.* Derivation and prospective validation of a simple index for prediction of cardiac risk of major non-cardiac surgery. *Circulation 1999;* 100: 1043-1049.

4 Boersma E, Poldermans D, Bax JJ, Steyerberg EW, Thomson IR, Banga JD, DECREASE Study Group (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiogrpahy). Predictors of cardiac events after major vascular surgery: role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy./ *Am MedAssoc* 2001; 285: 1865-1873.

5 DIPOM Trial Group. Effect of peri operative beta blockade in patients with diabetes undergoing major non-cardiac surgery: randomized placebo controlled, blinded multicentre trial. *Br Med J* 2006; 332: 1482-1489.

6 Landesberg G, Luria MH, Cotev S, Eidelman LA, Anner H, Mosseri M *et al.* Importance of long-duration postoperative ST-segment depression in cardiac morbidity after vascular surgery. *Lancet* 1993; 341:715-719.

7 American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2006; 29: S43-48.

8 Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW *et al.* National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003; 139: 137-147.

9 Bansilal S, Farkouh ME, Fuster V. Role of insulin resistance and hyperglycemia in the development of atherosclerosis. *Am J Cardiol* 2007; 99: 6B-14B.

10 Devos P, Chiolero R, Van den Berghe G, Preiser JC. Glucose, insulin and myocardial ischaemia. *Curr Opin Clin Nutr Metab Care* 2006; 9: 131-139.

11 Mangano DT. Adverse outcomes after surgery in the year 2001–a continuing odyssey. *Anesthesiology* 1998; 88: 561-564.

12 Hertzer NR, Beven EG, Young JR, O'Hara PJ, Ruschhaupt WF 3rd, Graor RA *et al.* Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. *Ann Surg* 1984; 199: 223-233.

13 Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. The effect of bisoprolol on periop-erative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. *NEnglJMed* 1999; 341: 1789-1794.

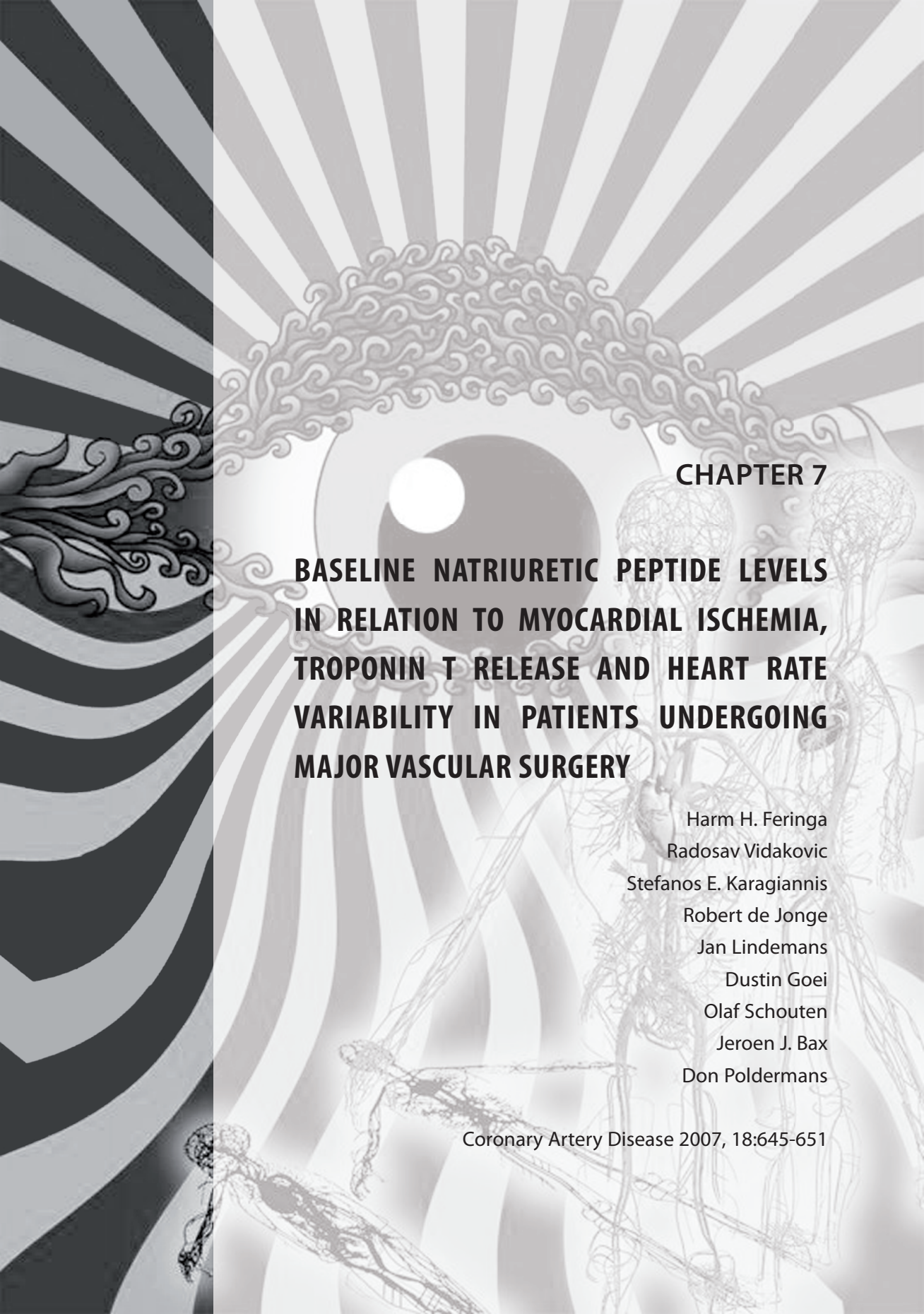
14 Durazzo AE, Machado FS, Ikeoka DT, De Bernoche C, Monachini MC, Puech-Leao P *et al.* Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. / *Vasc Surg* 2004; 39: 967-975.

15 Bartnik M, Malmberg K, Norhammar A, Tenerz A, Ohrvik J, Ryden L. Newly detected abnormal glucose tolerance: an important predictor of long-term outcome after myocardial infarction. *Eur Heart} 2004;* 25:1990-1997.

16 van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M *et al.* Intensive insulin therapy in the critically ill patients. *NEnglJMed*2001; 345: 1359-1367.

17 Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, Williams BA *et al.* Intraoperative hyperglycemia and perioperative outcomes in cardiac surgery patients. *Mayo Clin Froc* 2005; 80: 862-866.

18 Noordzij PG, Boersma E, Schreiner F, Kertai MD, Feringa HH, Dunkelgrun M *et al.* Increased preoperative glucose levels are associated with perioperative mortality in patients undergoing non-cardiac non-vascular surgery. *Eur } Endocrinol* 2007; 156: 137-142.



CHAPTER 7

BASELINE NATRIURETIC PEPTIDE LEVELS IN RELATION TO MYOCARDIAL ISCHEMIA, TROPONIN T RELEASE AND HEART RATE VARIABILITY IN PATIENTS UNDERGOING MAJOR VASCULAR SURGERY

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Coronary Artery Disease 2007, 18:645-651

ABSTRACT

Background This study was conducted to determine the association between baseline *N*-terminal pro-B-type natriuretic peptide (NT-proBNP) and myocardial ischemia, troponin T release and heart rate variability (HRV) in patients undergoing major vascular surgery.

Methods In a prospective study, 182 vascular surgery patients were evaluated by clinical risk factors, dobutamine stress echocardiography and baseline NT-proBNP levels. Myocardial ischemia was detected by continuous 12-lead electrocardiographic monitoring starting 1 day before to 2 days after surgery. Troponin T (>0.03ng/ml) was measured on day 1, 3 and 7 postoperatively and before discharge. HRV was measured at the day prior to surgery.

Results The median NT-proBNP level was 184 ng/l (interquartile range: 79-483 ng/l). Myocardial ischemia was detected in 21% and troponin T release in 17% of patients. After adjustment for clinical risk factors and stress echocardiography results, higher NT-proBNP levels (per 1 ng/l increase in the natural logarithm of NT-proBNP) were associated with a higher incidence of myocardial ischemia (odds ratio: 1.59, 95% confidence interval: 1.21-2.08, $P < 0.001$) and troponin T release (odds ratio: 1.76, 95% confidence interval: 1.33-2.34, $P < 0.001$). The optimal cutoff value of NT-proBNP to predict ischemia and/or troponin T release was 270 ng/l (area under the curve: 0.70). Higher baseline NT-proBNP levels were also associated with a larger ischemic burden at electrocardiographic monitoring ($r = 0.22$, P=0.03). No significant correlation, however, was found between NT-proBNP and preoperative HRV ($r = -0.024$, $P = 0.78$).

Conclusion Elevated baseline NT-proBNP levels are significantly associated with perioperative myocardial ischemia and troponin T release, but not with preoperative HRV in patients undergoing major vascular surgery. *Coron Artery Dis* 18:645-651 © 2007 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Key words: heart rate variability, myocardial ischemia, natriuretic peptides, troponin T

INTRODUCTION

Natriuretic peptides are endogenous cardiac hormones that include atrial natriuretic peptide (A-type), brain natriuretic peptide (B-type or BNP) and its aminoterm-inal portion *N*-terminal pro-B-type natriuretic peptide (NT-proBNP) [1,2]. NT-proBNP is synthesized in the ventricular myocardium and released in response to ventricular wall stress [3,4]. NT-proBNP has been demonstrated to be an important diagnostic and prognostic marker in patients with heart failure [5,6]. The diagnostic and prognostic value of elevated levels of NT-proBNP has more recently been shown in patients with acute coronary syndromes and stable coronary artery disease [7,8]. In the search for safe, inexpensive and accurate preoperative screening, natriuretic peptides have emerged as promising preoperative risk measures.

Three studies published last year have consistently demonstrated that elevated natriuretic peptide levels predict short-term adverse cardiovascular events in patients undergoing elective noncardiac surgery [9–11]. The prognostic value of preoperative natriuretic peptides was also sustained for long-term events, as demonstrated in a study involving 335 patients who were followed for a mean duration of 14 months [12].

Patients who experience perioperative myocardial ischemia detected during continuous 12-lead electrocardiographic monitoring or who have troponin T release are considered to be at increased risk for adverse postoperative cardiac events [13,14]. In addition, reduced heart rate variability has also been associated with a worse prognosis in patients with myocardial infarction, congestive heart failure, or in patients undergoing major surgery [15,16]. A positive association of elevated baseline natriuretic peptides with increased perioperative myocardial ischemia and decreased preoperative heart rate variability may strengthen the evidence that natriuretic peptides can be used as a preoperative risk marker. The primary objective of this study was to determine whether baseline NT-proBNP levels are associated with myocardial ischemia as assessed by continuous 12-lead electrocardiographic monitoring and troponin T release in patients undergoing major vascular surgery. The secondary objective was to assess the association between baseline NT-proBNP levels and preoperative heart rate variability.

METHODS

Study population

Patients scheduled for elective abdominal aortic aneur-ysm repair, lower extremity bypass surgery or carotid artery surgery at the Erasmus University Medical Center in Rotterdam, The Netherlands, were prospectively included in the study from January 2004 to December 2006 after giving informed consent. Patients with severe valvular heart disease or hypertrophic or dilated cardio-myopathy were excluded. Patients who participated in clinical intervention trials at or outside the Erasmus Medical Center were also excluded (i.e. the DECREASE III trial). All patients agreed on participation in the study and the Institutional Review Board approved the protocol. Baseline clinical data were collected by structured interviews with the patients and by reviewing the medical records. On the basis of the Revised Cardiac Risk Index by Lee *et al.* [17], patients were screened for each of the following cardiac risk factors: history of coronary artery disease, congestive heart failure, cerebro-vascular accident or transient ischemic attack, diabetes mellitus (fasting glucose level ≥ 7.0 mmol/l or treatment with insulin) and renal dysfunction [preoperative serum creatinine level > 2.0 mg/dl (177 μmol/l) or treatment with renal dialysis]. Coronary artery disease was defined as patients presented with current stable or unstable angina pectoris or if patients had a history of myocardial infarction. A preoperative electrocardiogram was obtained and evaluated. Patients were also screened for hypertension (blood pressure ≥ 140/90 mmHg or antihyper-tensive drugs), hypercholesterolemia (plasma cholesterol level ≥ 5.5 mmol/l or treatment with cholesterol lowering drugs), smoking and cardiac medication use, including statins, β-blockers, aspirin, angiotensin-converting enzyme inhibitors and calcium channel blocking agents.

Measurement of baseline *N*-terminal pro-B-type natriuretic peptide

The mean time of venous blood sampling prior to surgery was 22 ±11 days and all samples were collected before dobutamine stress echocardiography. The samples were centrifuged and plasma was frozen at – 80°C until assay. NT-proBNP was measured with an electrochemiluminescence immunoassay kit (Elecsys 2010, Roche GmbH, Mannheim, Germany). This 'sandwich'-type quantitative immunoassay is based on polyclonal antibodies against epitopes in the *N*-terminal part of proBNP. The lower detection limit was 5 ng/ 1. Intra-assay coefficients of variance at 271 and 6436 ng/l were 1.9 and 0.9%, respectively.

Dobutamine stress echocardiography

Dobutamine stress echocardiography was performed prior to surgery. Patients underwent a resting two-dimensional precordial echocardiographic examination and standard apical and parasternal views were recorded on videotape. Dobutamine hydrochloride was then administered intravenously by infusion pump, starting at 10 μ/kg/min for 3 min (5 μg/kg/min for 5 min, followed by 10 μg/kg/min for 5 min in patients with resting wall motion abnormalities), and increased by 10 μg/kg/min every 3 min to a maximum of 40 μg/kg/min. The dobutamine infusion was stopped if a target heart rate (85% of a theoretic maximal heart rate) was achieved. If the target heart rate was not achieved and patients had no symptoms or signs of ischemia, atropine sulfate (starting with 0.25 mg, increased to a maximum of 2.0 mg) was given intravenously whereas the administration of dobutamine was continued. Metoprolol was administered (1.0–5.0 mg intravenously) to reverse the side effects of the administration of dobutamine or the dobutamine–atropine combination if the side effects did not revert spontaneously and quickly. Two experienced investigators performed off-line assessment of echocardiographic images. The left ventricle was divided into 17 segments, and wall motion was scored on a 5-point scale (1 = normal, 2 = mild hypokinesis, 3 = severe hypokinesis, 4 = akinesis and 5 = dyskinesis). Ischemia was defined as new or worsening wall motion abnormalities (compared with resting images of the same test) as indicated by an increase of regional wall motion score ≥ 1 grade(s) with stress. Akinesis becoming dyskinesis was not considered an ischemic response.

Myocardial ischemia during 12-lead electrocardiography

Patients were continuously monitored with a 10-elec-trode, 12-lead digital ECG recorder (DR180 + Digital Recorder, NorthEast Monitoring Inc., Massachusetts, USA), starting 1 day before surgery up to 2 days after. Recordings were performed in the continuous 12-lead mode with a recording length of 10 s every minute. The frequency response was 0.05–150 Hz. Electrocardiographic data were initially processed by a technician and analyzed by two experienced investigators, who were blinded to the patient's clinical data. After excluding all abnormal QRS complexes, the ambulatory ECG recordings were analyzed for ST-segment deviations. A continuous ST-segment trend was generated and all potential ischemic episodes were identified. Episodes of ischemia were defined as reversible ST-segment changes, lasting at least one minute and shifting from baseline to more than 0.1 mV (lmm). The baseline ST-segment level

was defined as the average ST segment during a stable period (duration of 20 min) preceding each ischemic episode. ST-segment change was measured 60 ms after the J point. If the J point fell within the T-wave, the ST-segment change was measured 40 ms after that point. The ischemic burden (mm*min) was defined as maximum ST-segment deviation multiplied by ischemia duration.

Troponin T measurement

In all patients, troponin T levels were measured on postoperative day 1, 3, 7, before hospital discharge and whenever clinically indicated by ECG changes, consistent with myocardial ischemia or infarction. Troponin T level was measured using a whole blood rapid test (TropT version 2, Roche Diagnostics, Mannheim, Germany). A value of greater than 0.03 ng/ml was used to define positive troponin T levels.

Heart rate variability

Heart rate variability was computed for each participant using time-domain analysis of short-term 5-min recordings in the preoperative period. Consecutive 5-min recordings of 2-h periods were standardly obtained at the evening before surgery. The average heart rate variability of the 5-min recordings during the 2-h period was calculated. We used standard time-domain measures including the standard deviation of the normal-to-normal (NN) intervals (SDNN) and the square root of the mean squared differences of successive NN intervals (rMSSD).

Perioperative management

Prior to surgery, patients with β-blockers were asked about medication adherence. Beta-blockers were withheld if patients presented with a systolic blood pressure < 100 mmHg or with a heart rate < 50 bpm. Beta-blockers were administered orally. In patients not able to take their medication orally, β-blockers were administered by naso-gastric tube or by intravenous line. All patients received standard perioperative pain management. Surgical procedures were classified as abdominal aortic aneurysm repair (91 patients, 50%), lower extremity revascularization (57 patients, 31%) and carotid artery surgery (34 patients, 19%).

Follow-up

Study endpoints were hard cardiac events (cardiac death and nonfatal myocardial infarction) during follow-up. Outpatient visits were scheduled every 3 months after discharge. Cardiac death was defined as any death with a cardiovascular cause, including

those deaths following a cardiac procedure, cardiac arrest, myocardial infarction, pulmonary embolus, stroke, hemorrhage or sudden deaths owing to unknown causes. Nonfatal myocardial infarction was diagnosed when at least two of the following were present: elevated cardiac enzyme levels (troponin T > 0.1 ng/ml), development of typical electrocardiographic changes (new Q waves > 1 mm or > 30 ms), and typical symptoms of angina pectoris. No patients were lost to follow-up.

Statistical analysis

Continuous data are expressed as mean (± SD) and compared by using the Student *t*-test. Categorical data are presented as percentages and analyzed using the % test with Yates' correction. Baseline natriuretic peptide levels were abnormally distributed and converted to its natural logarithm. Binary logistic regression analysis was used to study the association between natriuretic peptides and myocardial ischemia and troponin Trelease. Receiver operating curve characteristic analysis was used to assess the optimal cutoff value of NT-proBNP in predicting the composite of myocardial ischemia and troponin T release. Cox regression analysis was used to study the association between natriuretic peptides and long-term events. The Pearson coefficient was used to estimate the correlation between baseline natriuretic peptides and preoperative heart rate variability. In multivariate analysis, adjustments were made for age, sex, cardiac risk factors according to the Revised Cardiac Risk Index (coronary artery disease, history of congestive heart failure, cerebrovascular disease, diabetes mellitus and renal failure), dobutamine stress test results, hypertension and cardiovascular medication. Odds and hazard ratios are given with 95% confidence intervals. For all tests, a P value < 0.05 (two-sided) was considered significant. All analysis was performed using SPSS 12.0 statistical software (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Baseline characteristics

Inclusion criteria were fulfilled in 182 patients. Baseline characteristics are presented in Table 1. The mean age of the study population was 66 ±11 years and 81% were male. The distribution of baseline NT-proBNP levels and its natural logarithm are presented in Fig. 1. The median NT-proBNP level was 184ng/l (interquartile range: 79-483 ng/l). Dobutamine stress echocardiography showed rest wall motion

Table 1 *Baseline characteristics of the study population*

	n = 182
Age (years)	66± 11
Male	147 (81%)
Current stable angina pectoris	34 (1 9%)
History of myocardial infarction	52 (29%)
Previous coronary artery revascularization	23 (13%)
History of congestive heart failure	11 (65%)
History of cerebrovascular event	50 (28%)
Renal failure	9 (5%)
Diabetes mellitus	28 (15%)
Hypertension	76 (42%)
Hypercholesterolemia	70 (39%)
Current or past smoking	91 (50%)
Aspirin	101 (56%)
Angiotensin-converting enzyme inhibitors	46 (25%)
Beta-bloc kers	152 (84%)
Calcium channel blockers	37 (20%)
Digoxin	2 (1 %)
Statins	109 (60%)
Preoperative heart rate	67±10
Rest wall motion abnormalities	45 (25%)
Stress induced new wall motion abnormalities	31 (17%)
Abdominal aortic aneurysm repair	91 (50%)
Lower extremity revascularization	57 (31%)
Carotid artery surgery	34 (1 9%)

Values are given in number (%), or in mean ± standard deviation.

abnormalities in 25% and stress-induced wall motion abnormalities in 17% of the patients. No fatal complications occurred during or immediately after the stress test.

N-terminal pro-B-type natriuretic peptide in relation to myocardial ischemia and troponin T release

Myocardial ischemia during continuous 12-lead electrocardiographic registration was assessed in 38 participants (21%). A total of 77 periods of myocardial ischemia were detected. The number of ischemic events per patient ranged from 1 to 5. The

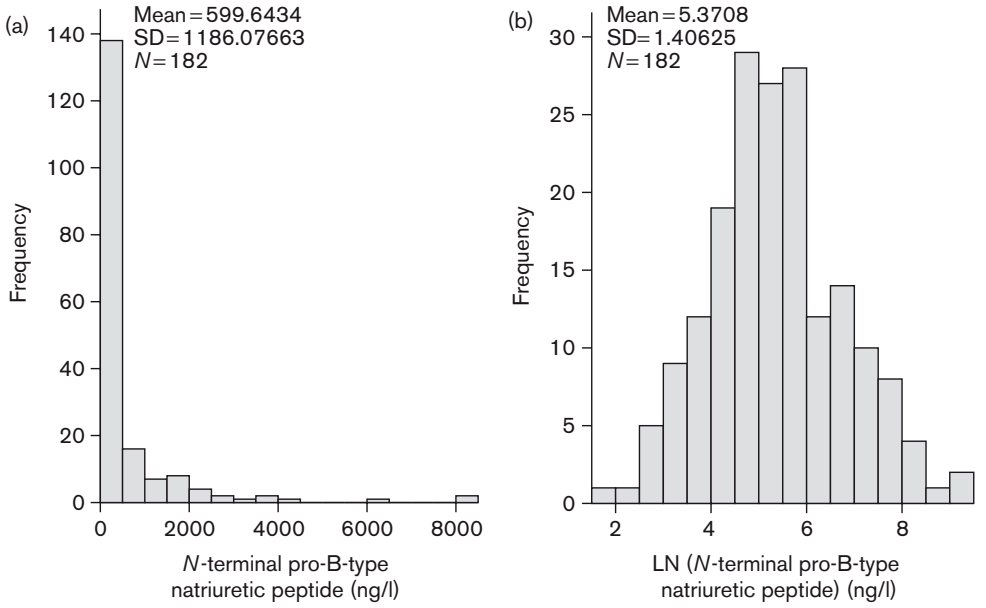


Figure 1 *A histogram showing the distribution of N-terminal pro-B-type natriuretic peptide levels in the study population.*

median duration of ischemic events was 43 min (range: 5-1130 min) and the median ST-segment deviation was 1.5 mm (range: 1.0-5.6mm). In patients with ischemia, median ischemic burden was 72mm*min (range: 7-5508 mm*min). Troponin T levels greater than 0.03ng/ml were measured in 31 patients (17%). Troponin T values ranged from 0.03 to 8.2ng/ml. Figure 2 demonstrates the median NT-proBNP level in patients with myocardial ischemia, troponin T release and late cardiac events.

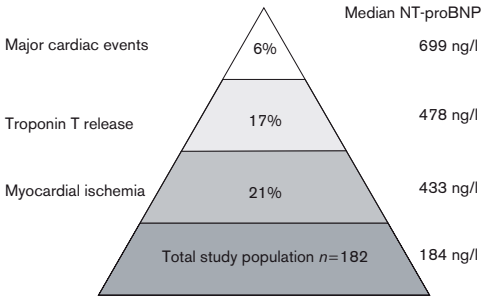
As demonstrated in Fig. 3, higher baseline NT-proBNP levels were associated with an increased incidence of myocardial ischemia and troponin T release. The optimal cutoff value to predict the composite of myocardial ischemia and troponin T release as determined by receiver operating characteristic analysis was 270 ng/1 (area under the curve: 0.70) (Fig. 4). Interestingly, in the 38 patients with myocardial ischemia, higher NT-proBNP levels correlated significantly with a larger ischemic burden at 12-lead ECG monitoring (r = 0.22, P= 0.03). In multivariate analysis, higher baseline NT-proBNP levels remained significantly associated with a higher incidence of myocardial ischemia and troponin T release (Table 2).

During follow-up, hard cardiac events occurred in 11 patients (6%). Higher baseline NT-proBNP levels were significantly associated with a higher incidence of hard

cardiac events, irrespective of clinical variables and dobutamine stress echocardiography results (Table 2).

N-terminal pro-B-type natriuretic peptide and preopera-tive heart rate variability

Mean SDNN and rMSSD prior to surgery was 47 ± 26 and 37 ± 34 ms, respectively. No correlation was found between baseline NT-proBNP levels and preoperative



The incidence of myocardial ischemia, troponin T release and late hard cardiac events and the median *N*-terminal pro-B-type natriuretic peptide level.

Figure 2 *The incidence of myocardial ischemia, troponin T release and late hard cardiac events and the median N-terminal pro-B-type natriuretic peptide level.*

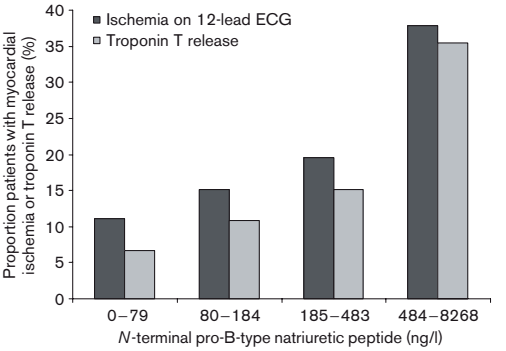


Figure 3 *The proportion of patients with perioperative myocardial ischemia detected by continuous 1 2-lead electrocardiographic monitoring and troponin T release in relation to baseline N-terminal pro-B-type natriuretic peptide levels, according to the quartiles.*

Table 2 *Univariate and multivariate analysis of the association between baseline N-terminal pro-B-type natriuretic peptide and perioperative myocardial ischemia as detected by continuous 12-lead electrocardiographic monitoring, troponin T release and early and late hard cardiac events*

		Odds/Hazard ratio per 1 ng/l increase in the natural logarithm of baseline NT-proBNP (95% Cl)	
	Number of events	Univariate	Multivariate[1]*
Perioperative myocardial ischemia	38 (21%)	1.59 (1.21-2.08)	1.49 (1.12-1.98)
Troponin T release	31 (1 7%)	1.76 (1.33-2.34)	1.63 (1.22-2.19)
Hard cardiac events during follow-up	11 (6%)	1.68 (1.10-2.55)	1.59 (1.03-2.50)

[a]Adjusted for age, sex, coronary artery disease, history of congestive heart failure, history of cerebrovascular events, diabetes mellitus, renal failure, hypertension, dobutamine stress echocardiography results and cardiovascular medication. Cl, confidence interval; NT-proBNP, W-terminal pro-B-type natriuretic peptide.

SDNN (r = -0.024, P =0.78) and rMSSD (r = 0.14, P = 0.1) (Fig. 5). Furthermore in a subgroup of patients without rest wall motion abnormalities and new wall motion abnormalities *(n* = 130), no correlation was found between baseline NT-proBNP levels and preoperative SDNN (r = -0.009, P = 0.9) and rMSSD (r = 0.12, *P = 0.08).*

DISCUSSION

In this study of patients undergoing major vascular surgery, we found that increased levels of preoperative NT-proBNP significantly correlated with an increased incidence of perioperative myocardial ischemia during continuous 12-lead electrocardiographic monitoring and with increased troponin T release. This association was independent of baseline clinical variables and independent of preoperative dobutamine stress echocardiography results. No association was observed between baseline NT-proBNP levels and preoperative heart rate variability.

N-terminal pro-B-type natriuretic peptide and perioperative myocardial ischemia

Natriuretic peptides are released from the ventricle and play a valuable role in the regulation of body fluid and blood pressure. Ventricular wall stress causes synthesis and release of natriuretic peptides and explains the elevated levels in patients with left ventricular dysfunction. The reason for elevated natriuretic peptides in patients with ischemic heart disease has not been completely understood. In an experimental rat model of acute myocardial infarction, ventricular

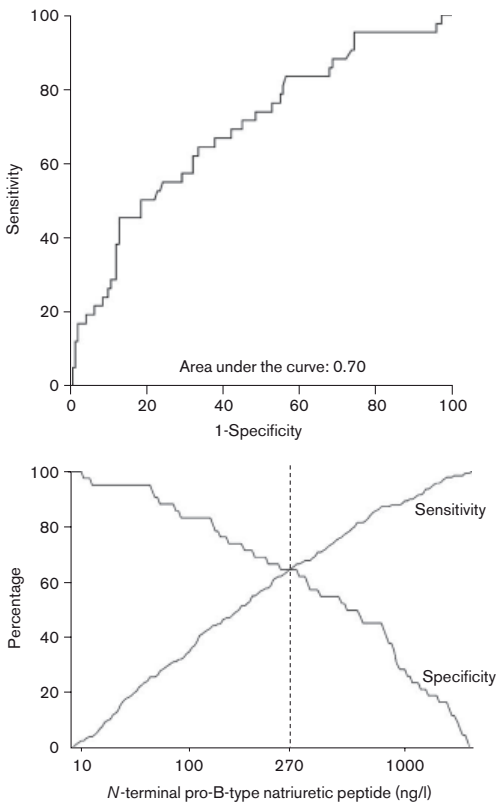


Figure 4 *Receiver operating curve analysis demonstrating the optimal cutoff value of plasma N-terminal pro-B-type natriuretic peptide levels for predicting the composite of perioperative myocardial ischemia and troponin T release.*

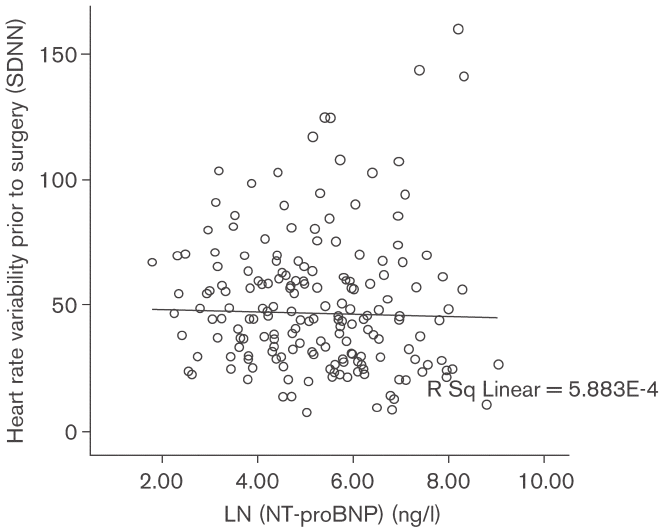


Figure 5 *A scatter plot demonstrating the correlation between the natural logarithm of baseline plasma N-terminal pro-B-type natriuretic peptide level and preoperative heart rate variability (SDNN).*

BNP mRNA expression and tissue concentrations of BNP were increased both in the noninfarcted as well as in the infarcted region [18]. Another study obtained myocardial biopsies from patients with coronary artery disease and demonstrated an association between BNP mRNA expression in ischemic myocardium and plasma BNP levels, even in the absence of left ventricular dysfunction as evaluated by ventriculography [19]. Ndrepepa and colleagues [20] found a positive association between the level of NT-proBNP and the severity of angiographic coronary artery disease in patients with angina pectoris and acute myocardial infarction. It has been hypothesized that ventricular wall stress secondary to chronic or repetitive ischemia triggers the synthesis and release of natriuretic peptides. Sabatine and colleagues [21] measured NT-proBNP levels before and after exercise testing with nuclear perfusion imaging, and showed that NT-proBNP levels rose immediately in patients with exercise-induced transient myocardial ischemia and that the magnitude of NT-proBNP rise was associated with the severity of ischemia. This study supports the notion that natriuretic peptide levels are associated with myocardial ischemia, irrespective of baseline rest wall motion abnormalities, and that elevations in natriuretic peptides may reflect early silent or symptomatic ischemic heart disease.

N-terminal pro-B-type natriuretic peptide and heart rate variability

Heart rate variability, a commonly used measure of cardiac autonomic dysfunction, mostly reflects vagal tone. Reduced heart rate variability in patients following a myocardial infarction or congestive heart failure has consistently been shown to be predictive of sudden, arrhythmic, cardiovascular and noncardiovascular

mortality. Furthermore in patients undergoing major noncardiac surgery at high risk of coronary artery disease, depressed heart rate variability before induction of anesthesia has been found to be an independent predictor of 1-year mortality [16]. It has been hypothesized that natriuretic peptides are released as an early response to cardiac autonomic dysfunction, before the onset of clinically detectable cardiac dysfunction. In an histological study of a dissected bovine heart, BNP and ANP immunoreactiv-ities frequently occur in the atrioventricular bundle and are colocalized in Purkinje fibers, suggesting that natriuretic peptides may act in an autocrine and/or paracrine way in the conduction system [22]. It also has been reported that exogenous administration of BNP in a rat model can modulate autonomic nervous activity [23]. The relation between NT-proBNP and the severity of autonomic dysfunction, however, remains poorly understood. A previously published study found in 32 consecutive patients with type 2 diabetes that increased levels of plasma BNP correlated with cardiac reflex parasympathetic dysfunction [24]. A significant association between BNP and heart rate variability could not be established, which may have been due to the small sample size. In this study involving 182 patients, an association between NT-proBNP and heart rate variability could also not be established in the total population as well as in the population of patients without resting and stress-induced echocardiographic abnormalities. Therefore, in our opinion, it seems not likely that decreased heart rate variability contributes significantly to the synthesis and release of NT-proBNP.

Clinical implications

Risk stratification identifies patients at risk for perioperative and long-term mortality who benefit from primary and secondary prevention strategies, such as risk factor reduction, life-style modification and optimal medical treatment with β-blockers and statins. Natriuretic peptides are promising markers for risk assessment in patients undergoing major vascular surgery. Currently, preoperative risk stratification is based on a set of clinical risk factors that allows an estimate of the weighted risk of perioperative cardiac complications. According to the American College of Cardiology/American Heart Association guidelines, preoperative cardiac exercise or pharmacological stress testing is recommended in all patients at increased cardiac risk on the basis of clinical risk profile, functional capacity and type of surgery [25]. Extensive screening increases costs and delays surgery. The optimal algorithm that includes NT-proBNP for preoperative risk stratification still has to be developed. Although this

study was not designed to elucidate the biological mechanism between elevated NT-proBNP levels and cardiovascular events, the results showed that NT-proBNP levels are associated with important correlates of adverse cardiovascular outcome. Ultimately, the utility of NT-proBNP lies in its ability to guide and improve perioperative medical management.

Study limitations

Several limitations should be noted when interpreting the results of the study. The results apply to patients undergoing major vascular surgery, and our findings may not be generalized to patients undergoing general or low-risk surgery. For troponin Trelease, we used a lower cutoff level of 0.03 ng/ml to define positive troponin T levels. Lower troponin T levels were not used, as they do not meet the imprecision criteria (coefficient of variation) of < 10%. Therefore, the results may have been biased to the detection of higher troponin T release.

Conclusion

On the basis of this observational study, increased preoperative NT-proBNP levels in patients scheduled for major vascular surgery are associated with an increased incidence of perioperative myocardial ischemia during 12-lead electrocardiographic monitoring and increased troponin T release, independent of clinical risk factors and dobutamine stress echocardiography results. These findings support the evidence that natriuretic peptides can be used as prognostic marker in patients undergoing major vascular surgery. Although it has been hypothesized that NT-proBNP may be elevated in patients with cardiac autonomic dysfunction, this study could not establish an association between baseline NT-proBNP levels and preoperative heart rate variability.

REFERENCES

1 Levin ER, Gardner DG, Samson WK. Natriuretic peptides. W *Engl J Med* 1998; 339:321-328.

2 Hall C. Essential biochemistry and physiology of (NT-pro)BNR *Eur J Heart Fail* 2004; 6:257-260.

3 Yoshimura M, Yasue H, Okumura K, Ogawa H, Jougasaki M, Mukoyama M, *et al.* Different secretion patterns of atrial natriuretic peptide and brain natriuretic peptide in patients with congestive heart failure. *Circulation* 1993; 87:464-469.

4 Yasue H, Yoshimura M, Sumida H, Kikuta K, Kugiyama K, Jougasaki M, *et al.* Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. *Circulation* 1 994; 90:1 95-203.

5 Lainchbury JG, Campbell E, Frampton CM, Yandle TG, Nicholls MG, Richards AM. Brain natriuretic peptide and n-terminal brain natriuretic peptide in the diagnosis of heart failure in patients with acute shortness of breath. *J Am Coll Cardiol* 2003; 42:728-735.

6 Bettencourt P, Azevedo A, Pimenta J, Frioes F, Ferreira S, Ferreira A. W-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. *Circulation* 2004; 110:2168-2174.

7 AtheroGene Investigators. Analysis of W-terminal-pro-brain natriuretic peptide and C-reactive protein for risk stratification in stable and unstable coronary artery disease: results from the AtheroGene study. *Eur Heart J* 2005; 26:241-249.

8 Kragelund C, Gronning B, Kober L, Hildebrandt P, Steffensen R. W-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. W *Engl J Med* 2005; 352:666-675.

9 Yeh HM, Lau HP, Lin JM, Sun WZ, Wang MJ, Lai LR Preoperative plasma W-terminal pro-brain natriuretic peptide as a marker of cardiac risk in patients undergoing elective non-cardiac surgery. *Br J Surg* 2005; 92:1041-1045.

10 Feringa HH, Bax JJ, Elhendy A, de Jonge R, Lindemans J, Schouten O, *et al.* Association of plasma W-terminal pro-B-type natriuretic peptide with postoperative cardiac events in patients undergoing surgery for abdominal aortic aneurysm or leg bypass. *Am J Cardiol* 2006; 98:111-115.

11 Dernellis J, Panaretou M. Assessment of cardiac risk before non-cardiac surgery: brain natriuretic peptide in 1590 patients. *Heart* 2006; 92: 1645-1650.

12 Feringa HH, Schouten O, Dunkelgrun M, Bax JJ, Boersma E, Elhendy A, *et al.* Plasma W-terminal pro-B-type natriuretic peptide as long-term prognostic marker after major vascular surgery. *Heart* 2007; 93:226-231.

13 The Study of Perioperative Ischemia Research Group. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing non-cardiac surgery. W *Engl J Med* 1990; 323: 1781-1788.

14 Lopez-Jimenez F, Goldman L, Sacks DB, Thomas EJ, Johnson PA, Cook EF, *et al.* Prognostic value of cardiac troponin T after noncardiac surgery: 6-month follow-up data. *J Am Coll Cardiol* 1997; 29:1241-1245.

15 Bilchick KC, Berger RD. Heart rate variability. *J Cardiovasc Electrophysiol* 2006; 17:691-694.

16 Filipovic M, Jeger R, Probst C, Girard T, Pfisterer M, Gurke L, *etal.* Heart rate variability and cardiac troponin I are incremental and independent predictors of one-year all-cause mortality after major noncardiac surgery in patients at risk of coronary artery disease. *J Am Coll Cardiol* 2003; 42:1 767-1 776.

17 Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, *et al.* Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1 999; 100:1043-1049.

18 Hama N, Itoh H, Shirakami G, Nakagawa O, Suga S, Ogawa Y, *et al.* Rapid ventricular induction of brain natriuretic peptide gene expression in experimental acute myocardial infarction. *Circulation* 1 995; 92:1558-1564.

19 Goetze JP, Christoffersen C, Perko M, Arendrup H, Rehfeld JF, Kastrup J, *etal.* Increased cardiac BNP expression associated with myocardial ischemia. *FASEB J* 2003; 17:1105-1107.

20 Ndrepepa G, Braun S, Mehilli J, von Beckerath N, Vogt W, Schomig A, *etal.* Plasma levels of W-terminal pro-brain natriuretic peptide in patients with coronary artery disease and relation to clinical presentation, angiographic severity, and left ventricular ejection fraction. *Am J Cardiol* 2005; 95:553-557.

21 Sabatine MS, Morrow DA, de Lemos JA, Omland T, Desai MY, Tanasijevic M, *etal.* Acute changes in circulating natriuretic peptide levels in relation to myocardial ischemia. *J Am Coll Cardiol* 2004; 44:1 988-1 995.

22 Hansson M, Forsgren S. Immunoreactive atrial and brain natriuretic peptides are co-localized in Purkinje fibres but not in the innervation of the bovine heart conduction system. *Histochem J* 1 995; 27:222-230.

23 Thomas CJ, Head GA, Woods RL. Similar baroreflex bradycardic actions of atrial natriuretic peptide and B and C types of natriuretic peptides in conscious rats. *J Hypertens* 1999; 17:801-806.

24 Yufu K, Takahashi N, Nakagawa M, Hara M, Saikawa T, Yoshimatsu H. Brain natriuretic peptide and cardiac autonomic function in type 2 diabetic patients. *Diabetes Res Clin Pract* 2006; 72:12-19.

25 Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, *etal.* ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery: executive summary report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation* 2002; 105:1257-1267.

CHAPTER 8

VALUE OF MYOCARDIAL VIABILITY ESTIMATION USING DOBUTAMINE STRESS ECHOCARDIOGRAPHY IN ASSESSING RISK PREOPERATIVELY BEFORE NONCARDIAC VASCULAR SURGERY IN PATIENTS WITH LEFT VENTRICULAR EJECTION FRACTION < 35%

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ABSTRACT

Patients with heart failure (HF) scheduled for vascular surgery have an increased risk of adverse postoperative outcome, and stratification usually depends on dichotomous risk factors. A quantitative prognostic model for patients with HF was developed using wall motion patterns during dobutamine stress echocardiography (DSE). A total of 295 consecutive patients (mean age 67 ± 12 years) with ejection fraction < 35% were studied. During DSE, wall motion patterns of dysfunctional segments were scored as scar, ischemia, or sustained improvement. Cardiac death and myocardial infarction were noted periopera-tively and during 5 years of follow-up. Of 4,572 dysfunctional segments; 1,783 (39%) had ischemia, 1,280 (28%) had sustained improvement, and 1,509 (33%) had scar. In 212 patients, si ischemic segment was present; 83 had only sustained improvement. Periop-erative and late cardiac event rates were 20% and 30%, respectively. Using multivariate analysis, number of ischemic segments was associated with perioperative cardiac events (odds ratio per segment 1.6, 95% confidence interval 1.05 to 1.8), whereas number of segments with sustained improvement was associated with improved outcome (odds ratio per segment 0.2, 95% confidence interval 0.04 to 0.7). Multivariate independent predictors of late cardiac events were age and ischemia. Sustained improvement was associated with improved survival. In conclusion, DSE provides accurate risk stratification of patients with HF undergoing vascular surgery.
 (Am J Cardiol 2007;99:1555-1559)

INTRODUCTION

Preoperative cardiac risk assessment for patients undergoing major vascular surgery is a challenging entity. Patients are mainly stratified according to the number of dichotomous cardiac risk factors.[1, 2] At present, risk stratification of patients with heart failure (HF) scheduled for vascular surgery mainly depends on left ventricular (LV) function at rest because patients with LV dysfunction have decreased long-term survival after major vascular surgery.[3–5] However, the presence of myocardial viability, in other words, dysfunctional segments that improve after inotropic stimulation, might enhance preoperative risk stratification. Quantification of dobutamine stress echocardiography (DSE) results would help in this aspect. We tried according to the Bayes-ian principle to change the before-test probability in more precise after-test quantification of risk and therefore stratify patients with HF more accurately. The aim of our study is to assess prognostic implications of ischemia or sustained improvement as the 2 main patterns of response of viable tissue to DSE in patients with known LV ejection fraction ≤ 35% undergoing major vascular surgery.

METHODS

The study population included 295 consecutive patients with known LV ejection fraction ≤ 35% who were referred to the Erasmus MC (Rotterdam, The Netherlands) for major vascular noncardiac surgery from June 1999 to June 2001. All patients underwent DSE for evaluation of viability. Diabetes mellitus is denned as fasting plasma glucose ≥ 126 mg/dl on ≥ 2 occasions and/or requirement for insulin or oral hypoglycemic agents according to criteria of the American Diabetes Association.[6] Hypercholesterolemia is defined as total cholesterol of 200 mg/dl or use of a cholesterol-lowering agent. Hypertension is denned as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of antihypertensive medication. The local medical ethics committee approved the study protocol. Patients gave informed consent for the study.

The DSE protocol was approved by the Hospital Ethical Committee and performed in accordance with well-established protocols.[7, 8] Studies were performed using a Sonos 5500 imaging system (Phillips Medical Systems, Eindhoven, The Netherlands). Patients underwent a 2-dimen-sional echocardiographic examination at rest using the standard apical and parasternal views. Images were recorded on videotape and also digitized for comparison of different stages. Dobutamine was administered intravenously using an infusion pump, starting at 5 μg/kg/min followed by 10 μg/kg/min for 5 minutes,

increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min (stage 5), and continued for 6 minutes. The dobutamine infusion was stopped if a target heart rate (85% of a theoretical maximal heart rate [men: (220 - age) X 85%; women: (200 - age) X 85%] was achieved. If the target heart rate was not achieved and patients had no symptoms or signs of ischemia, atropine (starting with 0.25 mg, increased to a maximum of 2.0 mg) was given intravenously at the end of stage 5 while dobutamine administration was continued. During the test, a 12-lead electrocardiogram was recorded every minute. Blood pressure was measured every 3 minutes. Metoprolol was administered (1.0 to 5.0 mg) intravenously according to heart rate response and systolic blood pressure, and after peak stress, images were acquired to achieve a recovery phase, denned as heart rate within 10% range of heart rate at rest. Criteria for stopping the test were (1) achievement of target heart rate, (2) severe and extensive new wall motion abnormalities, (3) horizontal or downsloping ST depression ≥ 0.2 mV measured 80 ms after the J point or ST-segment elevation ≥ 0.2 mV in the absence of Q waves, (4) symptomatic decrease in systolic blood pressure > 40 mm Hg or systolic blood pressure ≤ 90 mm Hg, (5) hypertension (blood pressure ≥ 240/140 mm Hg), (6) occurrence of sustained cardiac arrhythmias, (7) severe angina pectoris, and (8) intolerable adverse effects considered to be the result of dobutamine or atropine. Two experienced investigators performed off-line assessment of echocardiographic images without knowledge of the patient's clinical and coronary angiographic data, but with knowledge of dobutamine and atropine doses used. Inter- and intraobserver agreement for analysis of DSE studies were reported previously (92% and 94%, respectively).[9] Regional function was scored according to a 16-segment 5-point scoring model as 1 = normal, 2 = mildly hypokinetic, 3 = severely hypokinetic, 4 = akinetic, and 5 = dyskinetic. Wall-motion score index (total score divided by number of segments scored) was calculated at rest, at low dose, and during peak stress. Myocardial viability was assessed in severely dysfunctional segments. The 4 types of wall motion responses observed were (1) biphasic pattern (ischemia): improvement in wall motion at dobutamine 5, 10, or 20 mg/kg/min with worsening at higher dosages; (2) worsening only (ischemia); (3) sustained improvement; and (4) no change or scar. Severely dysfunctional segments showing a biphasic, sustained, or worsening response were considered viable, whereas segments with unchanged wall motion were considered scarred.

Evaluated end points were all-cause mortality, cardiac death, and nonfatal myocardial infarction. Cardiac death was denned using clinical data of acute myocardial

infarction and/or significant cardiac arrhythmias and/or refractory congestive heart failure, together with electrocardiographic and autopsy studies when available. Increases in cardiac isoenzymes and the development of new electrocardiographic changes denned a nonfatal myocardial infarction. In patients with > 1 cardiac event, the worst event was chosen of documented cardiac death (worst) and nonfatal infarction (less worst). Perioperative cardiac events were considered events that occurred within 30 days after surgery. Follow-up data were obtained in 2006. Mean long-term follow-up was 60 ± 24 months after DSE. Physicians who were unaware of patients' stress test results assessed events. The present status was determined by contacting the patient's general physician and/or review of hospital records. The date of the last interview or review was used to calculate follow-up time.

The *t* test was used for continuous variables, and chi-square test was used for categorical variables. Characteristics were summarized as percentages for categorical variables and mean ± SD for continuous variables. Univariate and multivariate analysis of clinical and echocardiographic variables with the end points were assessed using logistic regression analysis for the 30-day after-surgery period and using a Cox proportional hazards model for long-term follow-up. All clinical and representative DSE variables were considered in the model regardless of their univariate significance. Variables were selected in a stepwise forward selection manner with entry and retention set at a significance level of 0.05. The fitted model included age only for the purpose of adjustment. All other models were based on variables selected in the stepwise algorithm, which were replaced by dichotomous versions to facilitate ease of clinical use. Risk of a variable is expressed as hazard ratio (HR) or odds ratio (OR) with a 95% confidence interval (CI). The probability of cardiac death-free survival was calculated using the Kaplan-Meier method, and the resulting curves were compared using log-rank test.[10]

RESULTS

Patient demographic and clinical characteristics are listed in Table 1. Patients' medications were continued during the study.

During DSE, heart rates increased significantly from rest to peak stress. Rate-pressure product values at rest, low, and peak were 8,694 ± 286, 13,910 ± 546, and 17,028 ± 351, respectively. In 91% of patients, target heart rate was reached. Atropine was added at peak stress in 97 patients because the majority was on long-term β-blocker therapy. Mean maximal dobutamine dose was 38 ± 8 μg/kg/min. Side effects

included hemodynamically stable sustained ventricular tachycardia (> 10 complexes) in 4 patients (1%), nonsustained ventricular tachycardia (< 10 complexes) in 14 (5%), atrial fibrillation in 4 (1%), and severe hypotension (systolic blood pressure decrease > 40 mmHg) in 4 (1%). No myocardial infarction or ventricular fibrillation was recorded during or attributed to DSE. Wall motion score index at rest was 2.08 ± 0.50; at low dose, 1.39 ± 0.44; and at peak dose, 1.89 ± 0.55. Of 4,572 dysfunctional segments, 1,783 (39%) showed an ischemic response, 1,280 (28%) had sustained improvement, and in 1,509 (33%), motion patterns were unchanged during DSE and therefore defined as scar. As expected, all patients with LV dysfunction of ischemic cause had several degrees of scar tissue. Two hundred twelve patients had ≥1 ischemic segment, whereas 83 patients experienced only a sustained improvement during DSE. In 26 patients with severe ischemia during DSE and symptomatic angina not relieved by medication, the cardiac revascularization procedure preceded noncardiac surgery.

Table 1 *Study population characteristics (n = 295)*

Men	234 (79%)
Women	61 (21%)
Age (yrs)	67 ± 12
Hypertension	87 (29%)
Diabetes mellitus	53 (18%)
Previous myocardial infarction	158 (54%)
Cholesterol >200 mg/dl	77 (26%)
Smoking	114(39%)
Angina	27 (9%)
Previous percutaneous coronary intervention	21 (7%)
Previous coronary artery bypass grafting	56 (19%)
Cardiac medications	
Angiotensin-converting enzyme inhibitors	100 (34%)
Aspirin	23 (8%)
Statins	18 (6%)
/3 Blockers	99 (34%)
Calcium channel blockers	79 (27%)
Nitrates	71 (24%)
Diuretics	59 (20%)
Digoxin	28 (9%)

During the early perioperative period, that is, within 30 days after surgery, 6 patients died, 34 patients experienced a nonfatal acute myocardial infarction, and 54 patients experienced an ischemic cardiac event (increased isoen-zymes). Of these 54 patients, 47 (87%) had shown ischemia during DSE and 7 (13%) showed sustained improvement ($p < 0.001$). Of 34 patients with acute myocardial infarction, these numbers were 29 (83%) and 5 (15%, $p < 0.001$). Four of 26 patients (15%) who underwent coronary revascularization before vascular surgery experienced a nonfatal myocardial infarction.

Univariate significant predictors of perioperative cardiac events were cholesterol > 200 mg/dl (OR 1.71, 95% CI 1.03 to 2.85, $p = 0.04$) and ischemia during DSE (OR 2.77, 95% CI 1.15 to 6.64, $p = 0.001$).

Multivariate analysis showed that an increased number of segments with sustained improvement during DSE compared with the number of ischemic segments was associated with improved postoperative outcome. The only multivariable independent predictors of early perioperative cardiac events were previous myocardial infarction (OR 1.5, 95% CI 1.05 to 2.3), ischemia (OR 1.6, 95% CI 1.05 to 2.8), and sustained improvement during DSE (OR 0.2, 95% CI 0.04 to 0.7, Figure 1). For perioperative all-cause mortality, the only independent predictor in multivariate analysis was age (OR 1.03, 95% CI 1.05 to 1.1).

Long-term follow-up was successful for all patients. The all-cause mortality rate was 43% (128 patients), and 70% (89 patients) of that was attributed to cardiac causes. Thirteen patients (4%) experienced a nonfatal myocardial infarction. Overall, 102 patients (35%) experienced >1 hard cardiac event. Of 128 patients who died from all causes, only 21 had sustained improvement during DSE. Furthermore, only 11 patients with sustained improvement during DSE died from cardiac causes, and another 3 experienced a nonfatal myocardial infarction. Of 26 patients who underwent

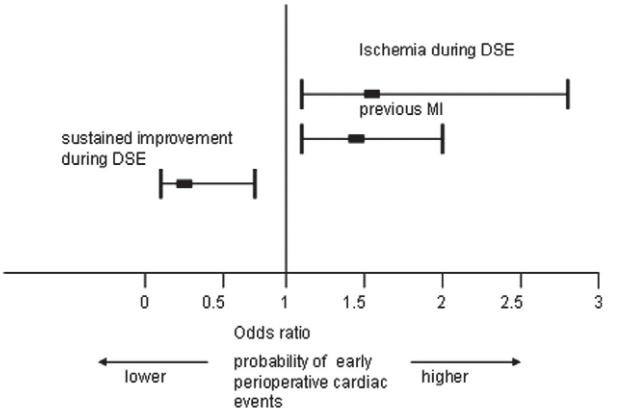

Figure 1 *Independent multivariate predictors of cardiac events within 30 days after major vascular surgery in patients with LV ejection fraction < 35%. MI = myocardial infarction.*

coronary revascularization before vas-cular surgery, 6 died from all causes and 7 experienced late cardiac events, 4 of which were fatal myocardial infarctions.

Univariate analysis for all-cause mortality showed that β-blocker use was associated with improved outcome (HR 0.61, 95% CI 0.42 to 0.89, p = 0.006). Sustained improvement (HR 0.71, 95% CI 0.49 to 1.01, p = 0.09) and ischemia (HR 1.21, 95% CI 0.83 to 1.76, p = 0.30) during DSE were not significant univariable predictors. However, in a multivariate model of clinical and echocardiographic parameters, the only independent predictors of all-cause mortality were age (HR 1.05, 95% CI 1.02 to 1.07) and ischemia (HR 1.06, 95% CI 1.02 to 1.12) during DSE.

Univariable predictors of cardiac events are listed in Table 2. Angina was not a significant univariate predictor for any event (HR 1.0, 95% CI 0.56 to 1.68, p = 0.55). In the multivariate model, age (HR 1.05, 95% CI 1.02 to 1.08) and ischemia during DSE (HR 1.9, 95% CI 1.1 to 4.0) were independent predictors of cardiac events, whereas sustained improvement (HR 0.5, 95% CI 0.3 to 0.9) proved to be protective.

Kaplan-Meier curves for the end point of cardiac events in patients with sustained improvement versus ischemia during DSE are shown in Figure 2.

DISCUSSION

This study shows the independent prognostic value of wall motion patterns during DSE in patients with LV dysfunction undergoing major vascular surgery for the

Table 2 *Uniavariate predictors of cardiac events (cardiac death and myocardial infarction) in patients with heart failure undergoing major vascular surgery*

Univariable Predictors	HR	95% CI	p Value
Previous myocardial infarction	1.51	1.00-2.31	0.05
Hypertension	1.15	0.75-1.78	0.51
Smoking	1.05	0.70-1.57	0.84
Age	1.00	0.59-1.71	0.99
Diabetes mellitus	1.00	0.60-1.70	0.99
β Blockers	0.62	0.38-0.95	0.04
Statins	0.62	0.35-1.09	0.07
Ischemia during low-high DSE	1.65	0.93-2.92	0.06
Sustained improvement during low-high	0.72	0.43-1.22	0.25
DSE			

prediction of cardiac events within 30 days after surgery and for all-cause mortality and hard cardiac events during a long-term mean follow-up of 5 years.

Our results show that sustained improvement during DSE provides a protective effect in both the early periop-erative period and for long-term cardiac events. Conversely, ischemia proved to be hazardous in both early and long-term follow-up periods. When patients with sustained improvement were compared with patients with ischemia during DSE, they experienced significantly fewer events in the early perioperative period ($p < 0.001$). Moreover, the difference in survival during long-term follow-up regarding cardiac events between the 2 different viability responses during DSE was significant ($p = 0.02$; Figure 2).

Ischemia during DSE also predicted decreased survival in all-cause mortality.

Furthermore, the beneficial effect that β blockers exert in patient survival[11] was reconfirmed in our study for both all-cause mortality and late cardiac events.

It is extensively reported that cardiovascular complications are the leading cause of death after noncardiac surgery.[12–14] That was also the case in our study. We found that 70% of total mortality was attributed to cardiac causes. Furthermore, patients with LV dysfunction at rest had greatly decreased long-term survival after noncardiac surgery.[14–18] Regarding early perioperative outcome, this was not clearly shown, maybe because of the inability of LV ejection fraction at rest to provide information regarding severe underlying coronary artery disease.[14] Therefore, using DSE, we further stratified patients with LV dysfunction at rest according to viability profile. Viable patients with sustained improvement experienced much fewer cardiac events during the first 30 days after surgery compared with patients with an ischemic response in low-high DSE.

This is in accordance with a previous study by Landesberg et al.[19] Although these investigators used thallium scan and not DSE, they similarly

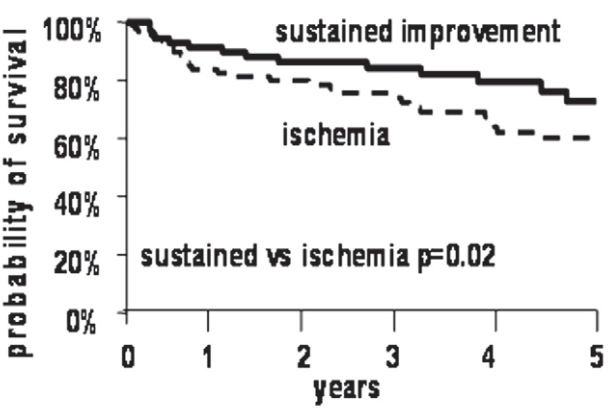

Figure 2 *Kaplan-Meier curves show survival from cardiac events in patients with LV ejection fraction (LVEF) < 35% who underwent major vascular surgery with sustained improvement versus ischemia during low-high DSE.*

found that ischemia was associated with an increased incidence of troponin increase during the early perioperative period.[19, 20] Also, in a previous study from our group, the presence of new wall motion abnormalities during DSE was a powerful determinant of increased risk of perioperative events.[14, 21] Other studies also showed similar results.[22–24] However, the present study is the only 1 to our knowledge that shows a clear benefit for patients with LV dysfunction and sustained improvement during DSE regarding early perioperative outcome. Especially patients with predominantly sustained improvement are at lower risk and might respond favorably to low-dose inotropic stimulation during surgery. However, in patients with a predominantly ischemic response, β blockers or revascularization could be considered. Previous studies evaluated the role of extended ischemia detection in stress echocardiography with either dobutamine.[11, 14, 25] or dipyridamole[26] and its correlation with late cardiac events in patients undergoing noncardiac surgery. Furthermore, the extent of fixed and reversible perfusion defects on dipyridamole thallium scintigraphy was a significant indicator of late cardiac risk.[23, 27] We also found similar results regarding the probability of all-cause mortality and long-term cardiac events. However, our study population was more homogenous because it consisted of only patients with known LV dysfunction of ischemic origin. Moreover, we tried to investigate further possible stratification of these patients according to viability response during DSE. Using an extensive Internet search of medical libraries, we concluded that our study is the first to our knowledge showing a beneficial effect of a sustained improvement response during DSE for viability estimation in this group of patients for the end point of long-term cardiac death.

A possible limitation of our study is that as an observational one, it relied mainly upon medical records and administrative data, meaning that effects of some cardiac risk factors could be biased. Nevertheless, most predictive values that we found are in concordance with previous studies from both our and other institutions. Another possible limitation could be that we did not investigate the impact of response to dobutamine according to type of surgery. However, the aim of our study is to provide a more accurate stratification of risk of patients with LV dysfunction irrespective of type of scheduled surgery.

REFERENCES

1. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major non-cardiac surgery. *Circulation* 1999; 100: 1043-1049.
2. Hernandez AF, Newby LK, O'Connor CM. Preoperative evaluation for major noncardiac surgery focusing on heart failure. *Arch Intern* Med 2004;164:1729-1736.
3. Halm EA, Browner WS, Tubau JF, Mangano DT. Study of perioperative ischemia research group. Echocardiography for assessing cardiac risk in patients having non-cardiac surgery. *Ann Intern Med* 1996;125: 433-441.
4. Rohde LE, Polanczyk CA, Goldman L, Cook EF, Lee RT, Lee TH. Usefulness of transthoracic echocardiography as a tool for risk stratification of patients undergoing major non-cardiac surgery. *Am J Cardiol* 2001; 87:505-509.
5. Andris Kazmers, Kohler TR. Very late survival after vascular surgery. *Surg Res* 2002;105:109-114.
6. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997;20:1183-1197.
7. American Society of Echocardiography Committee on Standards. Subcommittee on Quantitation of Two-Dimensional Echocardiograms. Recommendations for quantification of the left ventricle by two-dimensional echocardiography. *J Am Soc Echocardiogr* 1989;2:358-367.
8. Armstrong WF, Pellikka PA, Ryan T, Crouse L, Zoghbi WA. Stress echocardiography: recommendations for performance and interpretation of stress echocardiography. Stress Echocardiography Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* 1998;11:97–104.
9. Arnese M, Cornel JH, Salustri A, Maat A, Elhendy A, Reijs AE, Ten Cate FJ, Keane D, Balk AH, Roelandt JR. Prediction of improvement of regional left ventricular function after surgical revascularization: a comparison of low dose dobutamine echocardiography with 201T1 single-photon emission computed tomography. *Circulation* 1995;91: 2748-2752.
10. Cox DR. Regression models and life-tables. *J Royal Stat Soc B* 1972: 34:187-202.
11. Boersma E, Poldermans D, Bax JJ, Steyerberg EW, Thomson IR, Banga JD, van De Ven LL, van Urk H, Roelandt JR, for the DECREASE Study Group (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiogrpahy). Predictors of cardiac events after major vascular surgery: role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. *JAMA* 2001; 285:1865-1873.
12. Mangano DT. Perioperative cardiac morbidity. *Anesthesiology* 1990: 72:153-184.
13. Sicari R. Perioperative risk stratification in non cardiac surgery: role of pharmacological stress echocardiography. *Cardiovasc Ultrasound* 2004;2:4.
14. Poldermans D, Bax JJ, Thomson IR, Boersma E, van der Meer P, Fioretti PM, Elhendy A, van de Ven LMM, Roelandt JRTC, van Urk H. Role of dobutamine stress echocardiography for preoperative cardiac risk assessment before major cardiac surgery: a diagnostic tool comes of age. *Echocardiography* 2000;17:79-91.

15. Kazmers A, Cerqueira MD, Zierler RE. Perioperative and late outcome in patients with left ventricular ejection fraction of 35% or less who require major vascular surgery. *J Vasc Surg* 1988;8:307-315.
16. Back MR, Leo F, Cuthbertson D, Johnson BL, Shames ML, Bandyk DF. Long-term survival after vascular surgery: specific influence of cardiac factors and implications for preoperative evaluation. *J Vasc Surg* 2004;40:752-760.
17. Papaioannou GI, Heller GV. Risk assessment by myocardial perfusion imaging for coronary revascularization, medical therapy, and noncar-diac surgery. *Cardiol Rev* 2003;ll:60-72.
18. De Bels D, Coriat P, Puybasset L. What pre-operative explorations should be performed in a cardiac patient scheduled for non cardiolog-ical surgery? *Presse Med* 2003;32:553-560.
19. Landesberg G, Mosseri M, Shatz V, Akopnik I, Bocher M, Mayer M, Anner H, Berlatzky Y, Weissman C. Cardiac troponin after major vascular surgery: the role of perioperative ischemia, preoperative thallium scanning and coronary revascularization. *J Am Coll Cardiol* 2004;44:569-575.
20. Mukherjee D, Eagle KA. Perioperative cardiac assessment for noncar-diac surgery: eight steps to the best possible outcome. *Circulation* 2003;107:2771-2774.
21. Poldermans D, Arnese M, Fioretti PM, Salustri A, Boersma E, Thomson IR, Roelandt JR, van Urk H. Improved cardiac risk stratification in major vascular surgery with dobutamine-atropine stress echocardiography. *J Am Coll Cardiol* 1995;26:648-653.
22. Mackey WC, Fleisher LA, Haider S, Sheikh S, Cappelleri JC, Lee WC, Wang Q, Stephens JM. Perioperative myocardial ischemic injury in high-risk vascular surgery patients: incidence and clinical significance in a prospective clinical trial. *J Vasc Surg* 2006;43:533-538.
23. Stratmann HG, Younis LT, Wittry MD, Amato M, Miller DD. Dipy-ridamole technetium-99m sestamibi myocardial tomography in patients evaluated for elective vascular surgery: prognostic value for perioperative and late cardiac events. *Am Heart J* 1996; 131:923-929.
24. Kertai MD, Boersma E, Klein J, van Urk H, Poldermans D. Optimizing the prediction of perioperative mortality in vascular surgery by using a customized probability model. *Arch Intern Med* 2005;165: 898-904.
25. Poldermans D, Rambaldi R, Fioretti PM, Boersma E, Thomson IR, van Sambeek MR, van Urk H. Prognostic value of dobutamine-atropine stress echocardiography for peri-operative and late cardiac events in patients scheduled for vascular surgery. *Eur Heart J* 1997;18(suppl D): SD86-SD96.
26. Rossi E, Citterio F, Vescio MF, Pennestri F, Lombardo A, Loperfido F, Maseri A. Risk stratification of patients undergoing peripheral vascular revascularization by combined resting and dipyridamole echocardiography. *Am J Cardiol* 1998;82:306-310.
27. Eagle KA, Singer DE, Brewster DC, Darling RC, Mulley AG, Boucher CA. Dipyridamole-thailium scanning in patients undergoing vascular surgery. Optimizing preoperative evaluation of cardiac risk. *JAMA* 1987;257:2185-2189.

CHAPTER 9

A CLINICAL RANDOMIZED TRIAL TO EVALUATE THE SAFETY OF A NONINVASIVE APPROACH IN HIGH-RISK PATIENTS UNDERGOING MAJOR VASCULAR SURGERY THE DECREASE-V PILOT STUDY

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ABSTRACT

Objectives The purpose of this research was to perform a feasibility study of prophylactic coronary revascularization in patients with preoperative extensive stress-induced ischemia.

Background Prophylactic coronary revascularization in vascular surgery patients with coronary artery disease does not improve postoperative outcome. If a beneficial effect is to be expected, then at least those with extensive coronary artery disease should benefit from this strategy.

Methods One thousand eight hundred eighty patients were screened, and those with 3 risk factors underwent cardiac testing using dobutamine echocardiography (17-segment model) or stress nuclear imaging (6-wall model). Those with extensive stress-induced ischemia (> 5 segments or > 3 walls) were randomly assigned for additional revascularization. All received beta-blockers aiming at a heart rate of 60 to 65 beats/min, and antiplatelet therapy was continued during surgery. The end points were the composite of all-cause death or myocardial infarction at 30 days and during 1-year follow-up.

Results Of 430 high-risk patients, 101 (23%) showed extensive ischemia and were randomly assigned to revascularization (n = 49) or no revascularization. Coronary angiography showed 2-vessel disease in 12 (24%), 3-vessel disease in 33 (67%), and left main in 4 (8%). Two patients died after revascularization, but before operation, because of a ruptured aneurysm. Revascularization did not improve 30-day outcome; the incidence of the composite end point was 43% versus 33% (odds ratio 1.4, 95% confidence interval 0.7 to 2.8; p = 0.30). Also, no benefit during 1-year follow-up was observed after coronary revascularization (49% vs. 44%, odds ratio 1.2, 95% confidence interval 0.7 to 2.3; p = 0.48).

Conclusions In this randomized pilot study, designed to obtain efficacy and safety estimates, preoperative coronary revascularization in high-risk patients was not associated with an improved outcome. (J Am Coll Cardiol 2007;49: 1763-9) © 2007 by the American College of Cardiology Foundation

Abbreviations and Acronyms: ACC = American College of Cardiology; AHA = American Heart Association; CABG = coronary artery bypass graft; Cl = confidence interval; LVEF = left ventricular ejection fraction; OR = odds ratio; PCI = percutaneous coronary intervention

INTRODUCTION

Patients with multiple cardiac risk factors scheduled for major vascular surgery are at increased risk of perioperative cardiac complications. According to the guidelines of the American College of Cardiology/American Heart Association (ACC/AHA), it is highly recommended to refer these patients for noninvasive cardiac stress testing before surgery (1). The guidelines also recommend coronary angiography for patients with high-risk noninvasive test results, and myo-cardial revascularization in patients with prognostic high-risk anatomy in whom long-term outcome is likely to be improved. However, noninvasive testing may delay surgery and run the risk of aortic aneurismal rupture or exacerbation of critical limb ischemia. Furthermore, coronary revascularization is commonly performed by percutaneous coronary intervention (PCI) with stent placement instead of bypass surgery (CABG). Although this approach prevents further delay of the index surgical procedure, it necessitates the prolonged use of extensive antiplatelet therapy, which may aggravate the risk of perioperative bleeding complications. But temporary discontinuation of antiplatelet therapy is potentially harmful, as it may lead to in-stent thrombosis (2,3).

The current ACC/AHA recommendations are based on small observational, noncontrolled studies and expert opinion (4,5). The usefulness of the strategy of prophylactic revascularization was not confirmed by the recently completed CARP (Coronary Artery Revascularization Prophylaxis) randomized trial (6). In this trial, the incidence of perioperative myocardial infarction was similar in patients allocated to prophylactic revascularization versus those allocated to optimal medical therapy (12% vs. 14% events). There was also no beneficial effect observed during long-term follow-up. However, it should be realized that the vast majority of patients included in the CARP trial had single-or 2-vessel disease with a preserved left ventricular function. Indeed, based on previous research from our group, sufficient cardioprotection by medical therapy can be expected in these patients, which may explain the CARP trial findings (7). In contrast, patients with multiple cardiac risk factors and extensive stress-induced myocardial ischemia are insufficiently protected (7).

Hence, if a beneficial effect of the invasive strategy of prophylactic revascularization is to be expected, then at least patients with extensive coronary artery disease should benefit from this strategy. We therefore undertook the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo)-V pilot study to

assess the feasibility and to obtain initial efficacy and safety estimates for the design of an adequately powered randomized controlled clinical trial in these patients.

METHODS

Patients

This study was conducted during 2000 to 2005 in 6 hospitals in Belgium (until 2001), Brazil (until 2001), the Netherlands, Italy, Serbia, and Montenegro. The early cessation in participation to the study of 2 centers was due to logistic reasons. A total of 1,880 consecutive patients undergoing elective open abdominal aortic or infrainguinal arterial reconstruction were screened for the prevalence of cardiac risk factors (Fig. 1).

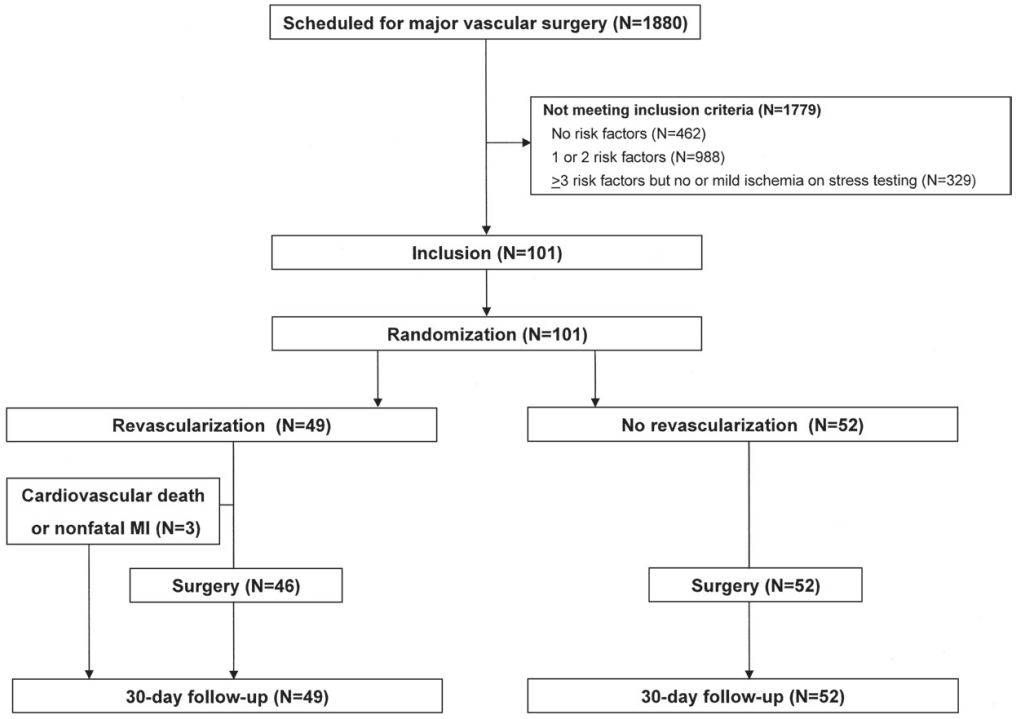

Figure 1 Flowchart of the Study *Cardiac – risk factors included age over 70 years, angina pectoris, prior myocardial infarction (Ml) on the basis of history or a finding of pathologic Q waves on electrocardi-ography, compensated congestive heart failure or a history of congestive heart failure, current treatment for diabetes mellitus, renal dysfunction (serum creatinine >160 /µmol/l), and prior stroke or transient ischemic attack. Patients with > 3 risk factors and extensive ischemia were randomly (1:1) assigned to coronary revascularization.*

These included age over 70 years, angina pectoris, prior myocardial infarction on the basis of history or a finding of pathologic Q_waves on electrocardiography, compensated congestive heart failure or a history of congestive heart failure, drug therapy for diabetes mellitus, renal dysfunction (serum creatinine > 160 μmol/l), and prior stroke or transient ischemic attack (7). Patients with at least 3 risk factors underwent cardiac stress testing before surgery. All patients who experienced extensive stress-induced ischemia were enrolled in the DECREASE-V pilot study.

All patients provided informed consent, and the study was approved by the Erasmus Medical Center Medical Ethics Committee and local research ethics committees.

Cardiac testing

Left ventricular ejection fraction (LVEF) was measured from resting echocardiographic images using the biplane Simpson's rule. Cardiac stress testing was performed by dobutamine echocardiography or dobutamine or dipyridamole perfusion scintigraphy, as previously described (8,9). Test results were scored by the extent of stress-induced ischemia using a 17-segment model in dobutamine echocardiography and a 6-wall model in stress perfusion scintigraphy. Limited ischemia was defined by the presence of 1 to 4 ischemic segments or 1 to 2 ischemic walls, whereas extensive ischemia was defined by ≥ 5 ischemic segments or ≥ 3 ischemic walls.

Allocated treatment

Perioperative beta-blocker therapy was installed in all patients at the screening visit, regardless of test results. A computer algorithm was used at each center to assign patients with extensive stress-induced ischemia randomly, in a 1:1 ratio, to 1 of the 2 strategies. The sealed envelope method was used to conceal treatment allocation, and it was assured that envelopes were opened in consecutive order. Patients were randomized to either an invasive approach followed by revascularization or a noninvasive approach. Quantitative analysis of all coronary an-giographies was reviewed centrally at Erasmus Medical Center, Rotterdam, the Netherlands, by 2 experienced cardiologists. They assessed independently the number of affected vessels. The mode of revascularization, CABG or PCI with stenting, was decided by the treating physicians, based on coronary anatomy and the possible delay of the index surgical procedure. Patients allocated to the medical-only strategy were referred for surgery without further delay.

Beta-blocker therapy

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

Perioperative management

Anesthetic management, monitoring, and other aspects of perioperative management were at the discretion of the attending physician. Results of preoperative testing and coronary revascularization were discussed with the attending physicians, and hemodynamic management was implemented accordingly. Anticoagulant and antiplatelet therapy was continued after PCI and during the index surgical procedure. Intraoperative ischemia was treated at the discretion of attending physicians, and additional beta-blockers were permitted.

End point definition

All patients were monitored for cardiac events after screening. Twelve-lead electrocardiogram (ECG) and serum troponin-T level were systematically determined 1, 3, 7, and 30 days after surgery. Outpatient follow-up was performed at 30 days if a patient had been discharged from the hospital. At the outpatient clinic, all patients were screened at 3-month intervals for cardiac events by clinical history and 12-lead ECG. All data were collected by the participating centers and evaluated in a blinded fashion by members of the adverse-events committee. The primary end point was the composite of all-cause death and nonfatal myocardial infarction that occurred between screening and 30-days after the index surgical procedure. Patients were followed-up

during at least 1 year after surgery, and the composite of all-cause death and nonfatal myocardial infarction during this period was considered as secondary end point. Myocardial infarction within 48 h after CABG was defined as a creatine kinase (CK)-MB rise above 5X the local upper limit of normal. Myocardial infarction within 48 h after PCI was defined as a CK-MB rise above 3X the upper limit of normal.

Myocardial infarction within 30 days after the index surgical procedure was defined as a positive troponin-T level in combination with new Qjwaves on the ECG lasting more than 0.03 s. In all other situations, myocardial infarctions were defined by new Qjwaves lasting more than 0.03 s.

Sample size

The purpose of this pilot study was to assess the feasibility of prophylactic revascularization in high-risk patients scheduled for major vascular surgery, and to obtain initial efficacy and safety estimates needed for the design of an adequately powered randomized controlled clinical trial. We aimed for the enrollment of 100 patients, 50 in each strategy. Based on the DECREASE-I study (7), an incidence of 33% of the primary end point was expected in the patients allocated to optimal medical therapy only. It was recognized a priori that a modest, but clinically relevant, risk reduction by prophylactic revascularization would not be detectable given this sample size. However, if the beneficial effect of revascularization was similar to the observations in the CASS (Coronary Artery Surgery Study) registry (85% risk reduction associated with prior CABG in vascular surgery), then our study has 93% power (type II error of 7%), based on a 2-sided test with a type I error of 5%.

Statistical analysis

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

RESULTS

Characteristics of patients

A total of 1,880 vascular surgery patients were enrolled and screened for cardiac risk factors (Fig. 1), and 430 (23%) were classified as high risk, who were referred for cardiac testing. Testing showed extensive ischemia in 101 (22%). Dobutamine echocardiog-raphy was performed in 88 (88%), and stress scanning in 13 (13%). No serious side effects occurred during stress testing. Of 101 patients with extensive stress-induced ischemia, 49 patients were randomized for coronary revascularization. A reduced LVEF (< 35%) was observed in 43 (43%) patients. No patient had significant valve disease such as aortic stenosis or mitral valve regurgitance. Coronary angiography, performed in patients allocated to the invasive strategy, showed 2-vessel disease in 12 (24%), 3-vessel disease in 33 (67%), and left main disease in 4 (8%). A PCI was performed in 32 patients, using a drug-eluting stent in 30 and a bare-metal stent in 2, and bypass surgery in 17. There were no differences in the presence of ischemic heart disease (i.e., previous myocardial infarction and angina pectoris) or other baseline characteristics between the randomized groups (Table 1). Complete revascularization was achieved in 42 (86%). Incomplete revascularization occurred in 7 (15%) patients initially scheduled for a percutaneous intervention. Bypass surgery was considered not feasible in these patients as the index procedure could not be further delayed. The median duration of revascularization to operation was 29 (13 to 65) days in the 17 patients undergoing bypass surgery and 31 (19 to 39) days in the 32 patients undergoing a percutaneous intervention.

Antiplatelet therapy, using aspirin and clopidogrel, was continued during surgery in all patients who underwent a PCI. The median perioperative blood transfusion requirement in patients with and without antiplatelet therapy was similar: 2 versus 3 U (p value = 0.25).

Perioperative cardiac events

Two patients died before vascular surgery because of a ruptured aneurysm after successful bypass surgery. Their aortic diameters were, respectively, 62 and 73 mm. In 1 patient, a myocardial infarction occurred after an incomplete coronary revascularization. This precluded the proceeding of the scheduled vascular surgery. Revascularization did not improve 30-day outcome after vascular surgery. Troponin elevation was found in 38.8% in the noninvasive group versus 34.7% in the invasive

group. The incidence of all-cause death or nonfatal myocardial infarction for patients with preoperative revasculanzation or medical treatment only was 43% versus 33%, respectively (odds ratio [OR] 1.4, 95% confidence interval [Cl] 0.7 to 2.8; p = 0.30) (Table 2). Also, no difference was observed in the incidence of perioperative cardiac events between patients treated by prophylactic bypass surgery or percutaneous intervention (41.1% vs. 43.8%, respectively).

Table 1 *Baseline Characteristics*

	Revascularizatior	No Revascularization
Number of patients	49	52
Age (yrs)	71 (64, 74)	70 (63, 75)
Men	42 (86%)	47 (90%)
History of diabetes	18 (37%)	15 (29%)
Current angina pectoris	25 (51%)	22 (42%)
History of myocardial infarction	49 (100%)	50 (96%)
History of congestive heart failure	23 (47%)	24 (46%)
History of cerebrovascular accident	20 (41%)	13 (25%)
History of renal failure	9 (18%)	11 (21%)
Aspirin use	37 (76%)	30 (58%)
Beta-blocker use	34 (70%)	36 (69%)
ACE inhibitor use	28 (57%)	22 (42%)
Statin use	34 (69%)	30 (58%)
Type of surgery		
Thoraco-abdominal	5 (10%)	5 (10%)
Tube graft	11 (22%)	14 (27%)
Bifurcated graft	10 (20%)	15 (29%)
Femoro-popliteal	23 (47%)	18 (35%)
Right coronary artery disease	39 (80%)	-
Left artery descending	46 (94%)	-
Left circumflex artery	37 (76%)	-
Number of diseased vessels		–
1	0	–
2	12 (24%)	–
3	33 (67%)	–
Left main disease (%)	4 (8%)	–

ACE = angiotensin-converting enzyme.

Late cardiac events

The incidence of the 1-year end point all-cause death or nonfatal myocardial infarction in high-risk patients was 47%. In high-risk patients, no long-term benefit was observed after coronary revascularization; respectively, 49% versus 44% of patients with preoperative revascularization or medical treatment only died or experienced a nonfatal myocardial infarction (OR 1.2, 95% Cl 0.7 to 2.3; p = 0.48) (Fig. 2). No patients initially randomized for medical therapy underwent revascularization within 1 year of follow-up. One patient randomized to the invasive strategy underwent a redo PCI because of myocardial infarction in the first year of follow-up.

Implications for a study design

Assuming that the event rates in the 101 studied patients are representative of what would occur in the planned study, the required sample size for a randomized study to establish definitively that coronary revascularization is superior to medical therapy to improve postoperative outcome in high-risk patients by 20% (relative risk) compared to optimal medical therapy would be over 300 patients per arm. This would require a sample size of 9,000 major vascular surgery patients, of which 2,000 patients have 3 or more cardiac risk factors at screening.

Table 2 *Patient Outcome*

	Revasculanzation n (%)	No Revasculanzation n (%)	HR (95% Cl)	p Value
Number of patients	49	52		
Events before surgery				
All-cause mortality	2 (4.1)	0	-	0.23
Myocardial infarction	1 (2.1)	0	-	
Composite	3 (6.1)	0	–	0.11
Events up to 30 days after surgery				
All-cause mortality	11 (22.5)	6(11.5)	2.2 (0.74-6.6)	0.14
Myocardial infarction	17 (34.7)	16 (30.8)	–	
Composite	21 (42.9)	17 (32.7)	1.4 (0.73-2.8)	0.30
Events up to 365 days after surgery				
All-cause mortality	13 (26.5)	12 (23.1)	1.3 (0.55-2.9)	0.58
Myocardial infarction	18 (36.7)	19 (36.5)		
Composite	24 (49.0)	23 (44.2)	1.2 (0.68-2.3)	0.48

Cl = confidence interval; HR = hazard ratio.

DISCUSSION

The concept of a beneficial effect of prophylactic coronary revascularization before major vascular surgery is based on the assumption that perioperative myocardial infarctions arise at locations in coronary arteries with hemodynamically critical stenosis, elicited by the stress of surgery. Preopera-tive coronary revascularization might prevent this devastating event and, in addition, improve long-term outcome. This hypothesis was supported by the CASS study that showed a reduced incidence of nonfatal myocardial infarctions after previous bypass surgery among vascular surgery patients compared with those treated medically (8.5% vs. 0.6%, p = 0.001) (4). More recently, the data from the BARI (Bypass Angioplasty Revascularization Investigation) trial showed that bypass surgery and PCI had similar low rates of postoperative cardiac events in noncardiac surgery (5). However, these studies were not designed to assign the optimal strategy in severely ill patients with extensive coronary artery disease immediately before major vascular surgery. In addition, these studies could not address the concern of delaying the vascular surgical procedure because of testing, revascularization, and initiation of antiplatelet therapy since the time between revascularization and non-cardiac surgery in these studies was, respectively, 4.1 and 2.4 years.

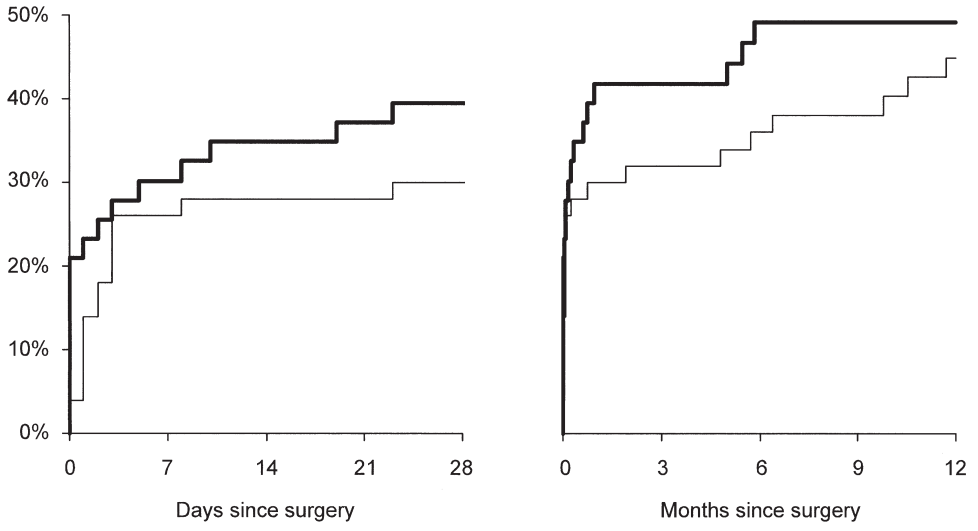

Figure 2 Patient Outcome *– Incidence of All-Cause Death or Myocardial Infarction During 1-Year Follow-Up According to the Allocated Strategy in Patients With 3 or More Cardiac Risk Factors With Extensive Stress-Induced Ischemia*

Light line = best medical treatment only;
dark line = best medical treatment and prophylactic revascularization.

The randomized CARP trial was the first study that addressed the strategy of prophylactic revascularization compared with optimal medical therapy in patients with clinically stable coronary artery disease who were scheduled for major vascular surgery (6). This trial showed that prophylactic revascularization was safe but did not improve perioperative or long-term outcome. The long-term mortality was 22% in patients allocated to prophylactic coronary revascularization, compared with 23% in the medical only strategy ($p = 0.92$). Also, the incidence of perioperative nonfatal myocardial infarction was similar, respectively, 12% and 14% ($p = 0.37$). In the present study, the effect of prophylactic revascularization was comparable to the effect reported by McFalls et al. (6), although the study population is different. The current study population consisted of 12% women, 43% of the patients had a reduced left ventricular function (LVEF < 35%), and the vast majority of patients, 75%, had 3-vessel or left main disease compared with 33% in the CARP trial. In a subgroup of 37 comparable patients of the CARP trial (i.e., 3 or more cardiac risk factors and extensive stress-induced ischemia assessed by noninvasive testing), prophylactic coronary revascularization was associated with a favorable, nonsignificant trend for long-term survival (OR 4.0, 95% CI 0.8 to 19). If a beneficial effect of revascularization was to be expected, this should have occurred in the selected population with high-risk anatomy. However, this was not observed, although the current study was not powered to test this strategy. A study to establish the effect of coronary revascularization would require, based on the findings of this pilot study, a screening population of 9,000 patients, of which 2,000 would have 3 or more risk factors, and of these 600 would have extensive stress-induced ischemia during cardiac testing and be eligible for randomization to revascularization. Our findings support the current guidelines of the ACC/AHA on perioperative management in high-risk patients to reserve revascularization only for cardiac unstable patients. After successful vascular surgery, these patients should be regularly screened for the presence of ischemic complaints, and aggressive anti-ischemic therapy, both medical and invasive, should be considered. As shown in Figure 2, a trend was observed for a "catch up" of late cardiac events in patients treated medically. In these patients at high risk scheduled for major vascular surgery, prophylactic revascularization might be switched to late revascularization, preventing the delay of surgery.

The apparent lack of benefit of coronary revascularization of the present study is not fully understood. Most likely, patients with stress-induced ischemia not only suffer

from a blood flow-limiting coronary lesion but also from (multiple) nonsignificant lesions that are vulnerable to rupture due to the stress of surgery (10). The perioperative stress response, which includes a cytokine response, catecholamine surge with associated hemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation, and consequent hy-percoagulability, triggers coronary plaque rupture, leading to thrombus formation and subsequent vessel occlusion (11,12). Autopsy results have shown that this mechanism is responsible for at least half of all perioperative infarctions (10,12). These findings are in line with dobutamine echo-cardiography results that show a correlation between the assessment of the preoperative culprit coronary lesion and the location of the perioperative myocardial infarction in only half of all cases (13). Surgical or percutaneous treatment of the culprit coronary lesion(s) apparently provides insufficient protection for rupture of these instable lesions.

The optimal perioperative evaluation and management of patients with multiple risk factors and extensive stress-induced ischemia remains controversial. Success will depend on careful collaboration between cardiologists, anesthesiologists, and surgeons. In patients with aortic aneurysms, a surgical repair is performed to reduce the chance of aneurysm-related death. It might be hypothesized that abdominal aortic aneurysm repair should not be performed in this high-risk group. As the current trial shows, open repair poses an unacceptable 30-day cardiac event rate of approximately 30%, whereas the chance of aneurysm rupture is around 9 per 100 person-years. Endovascular treatment modalities may be an alternative for these high-risk patients. Although the EVAR (Endovascular Aneurysm Repair)-2 trial showed no benefit of elective endovascular repair in patients deemed unfit for open repair because of comorbidities (14), these findings were not confirmed in the recently conducted study by the Society for Vascular Surgery Outcomes Committee. In a group of 565 high-risk patients, matched for the EVAR-2 inclusion criteria, undergoing endovascular repair, perioperative mortality was 2.9%. These promising results need to be confirmed in a large study population. Importantly, in all cases, an individualized strategy should be performed, weighing the chances of future aneurysms rupture or limb salvage instead of amputation and short-term perioperative events.

CONCLUSIONS

In this small randomized pilot study, designed to obtain initial efficacy and safety estimates for the design of an adequately powered randomized controlled clinical trial,

preoperative coronary revascularization in high-risk vascular surgery patients with extensive stress-induced ischemia was not associated with an improved postoperative and long-term outcome.

REFERENCES

1. Eagle KA, Berger PB, Calkins H, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery: executive summary: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardio-vascular Evaluation for Noncardiac Surgery). Circulation 2002;105: 1257-67.
2. Kaluza GL, Joseph J, Lee JR, Raizner ME, Raizner AE. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. J Am Coll Cardiol 2000;35:1288-94.
3. Wilson SH, Fasseas P, Orford JL, et al. Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting. J Am Coll Cardiol 2003;42:234-40.
4. Eagle KA, Rihal CS, Mickel MC, Holmes DR, Foster ED, Gersh BJ. Cardiac risk of noncardiac surgery: influence of coronary disease and type of surgery in 3368 operations. CASS Investigators and University of Michigan Heart Care Program. Coronary Artery Surgery Study. Circulation 1997;96:1882-7.
5. Hassan SA, Hlatky MA, Boothroyd DB, et al. Outcomes of noncardiac surgery after coronary bypass surgery or coronary angioplasty in the Bypass Angioplasty Revascularization Investigation (BARI). Am J Med 2001;110:260-6.
6. McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. N Engl J Med 2004;351:2795-804.
7. Boersma E, Poldermans D, Bax JJ, et al. Predictors of cardiac events after major vascular surgery: role of clinical characteristics, dobutamme echocardiography, and beta-blocker therapy. JAMA 2001;285: 1865-73.
8. Poldermans D, Arnese M, Fioretti PM, et al. Improved cardiac risk stratification in major vascular surgery with dobutamine-atropme stress echocardiography. J Am Coll Cardiol 1995;26:648-53.
9. Schinkel AF, Bax JJ, Elhendy A, et al. Long-term prognostic value of dobutamine stress echocardiography compared with myocardial per-fusion scanning in patients unable to perform exercise tests. Am J Med 2004;117:l-9.
10. Dawood MM, Gutpa DK, Southern J, Walia A, Atkinson JB, Eagle KA. Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. Int J Cardiol 1996; 57:37-44.
11. Mangano DT. Perioperative cardiac morbidity. Anesthesiology 1990; 72:153-84.
12. Cohen MC, AretzTH. Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. Cardiovasc Pathol 1999; 8:133-9.

13. Poldermans D, Boersma E, Bax JJ, et al. Correlation of location of acute myocardial mfarct after noncardiac vascular surgery with preoperative dobutamine echocardiographic findings. Am J Cardiol 2001; 88:1413-4.
14. EVAR Trial Participants. Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomised controlled trial. Lancet 2005;365:2187-92.

CHAPTER 10

ABDOMINAL AORTIC ANEURYSM SCREENING USING NON-IMAGING HAND-HELD ULTRASOUND VOLUME SCANNER: A PILOT STUDY

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ABSTRACT

Background. Screening for abdominal aortic aneurysms (AAA) is cost-effective and timely repair improves outcome. Using standard ultrasound (US) an AAA can be accurately diagnosed or ruled-out. However, this requires training and bulk equipment.

Aim. To evaluate the diagnostic potential of a new hand-held ultrasound bladder volume indicator (BVI) in the setting of AAA screening.

Methods. In total, 94 patients (66 ± 14 years, 67 men) referred for atherosclerotic disease were screened for the presence of AAA (diameter > 30 mm using US). All patients underwent both examinations, with US and BVI. Using the BVI, aortic volume was measured at 6 pre-defined points. Maximal diameters (US) and volumes (BVI) were used for analyses.

Results. In 54 (57%) patients an AAA was diagnosed using US. The aortic diameter by US correlated closely with aortic volume by BVI ($r = 0.87$, $p < 0.0001$). Using a cut-off value of ≥ 50 ml for the presence of AAA by BVI, sensitivity, specificity, positive and negative predictive value of BVI in detection of AAA were 94%, 82%, 88% and. 92%, respectively. The agreement between the two methods was 89%, kappa 0.78.

Conclusion. The bladder volume indicator is a promising tool in screening patients for AAA.

Keywords: Abdominal aortic aneurysm; Screening; Ultrasound; Volume.

INTRODUCTION

Abdominal aortic aneurysm (AAA) requires both early detection and timely repair to reduce aneurysm-related mortality and improve outcome. The prevalence of AAA is strongly influenced by age and gender and can be detected in 5–8% of men and in 1% of women over the age of 65 years.[1–4] Since effective screening programs are not established yet, diagnosis of an AAA is still frequently made at the time of rupture or impending rupture, which leads to a dramatic increase of postoperative mortality and morbidity.[5]

Cost-effectiveness of screening for AAA is highly dependent on the selection of the patient population.

Several diagnostic techniques, including ultrasound and computerized tomography, can be used for the detection of AAA. However, these techniques are expensive and usually require bulky equipment with a trained staff, which prevails the widespread use for screening purposes. Considering the increased incidence of AAA in the near future, a simple and inexpensive screening device that can also be used outside the hospital setting in the general population is useful.

This prospective study sought to evaluate the diagnostic potential and accuracy in AAA screening of a low cost hand-held ultrasound scanner for the three-dimensional measurement, originally intended as an automatic bladder volume indicator (BVI). As a reference, a standard ultrasound device (US) was used. The study was designed to test the hypothesis that BVI would be helpful in detection of AAA in a high-risk patient population.

METHODS

Study population

The study population consisted of 94 patients referred because of atherosclerotic disease to the outpatient clinic of the Erasmus University Medical Center, Rotterdam, the Netherlands. Patients were screened for cardiovascular risk factors, including: age, hypertension, angina pectoris, previous myocardial infarction, heart failure, stroke, renal failure (serum creatinine > 2 mg/dl), smoking, diabetes mellitus, hypertension, and hypercholesterolemia. Medical therapy was noted in all.

After informed consent was obtained, all patients underwent both examinations, with US and BVI. The examinations were performed by a physician skilled and experienced in abdominal ultrasono-graphic practice. Examinations with BVI were re-

peated by a second physician similarly skilled and experienced. Physicians were blinded for the previous findings. An abdominal aortic aneurysm was defined as an abdominal aorta of > 30 mm.

Hand-held US scanner for the three-dimensional assessment of volumes (BVI)

The Mobile Bladderscan BVI 6400 (Diagnostic Ultrasound, Bothell, WA, USA) is a non-imaging volumetric ultrasound device that is designed for automatic measurement of bladder volume (Fig. 1a). It measures ultrasonic (3.7 MHz) reflections within the patient's body on 12 rotational planes within a 120 degree sector, detects fluid-tissue borders, creates a 3-dimensional shape of the organ, and calculates the fluid volume.[6] Transducer is slightly focused, with focus at 6–8 cm.

When imaging on the lower abdomen, a penetration depth of 14–16 cm is possible. An aiming icon on the instrument's LCD screen guides the user to optimal positioning of the scan-head, to ensure accuracy of measurement. After pressing the scan button, the volume is reported on the LCD screen within 5 seconds (Fig. 1b). With the BVI, the aortic volume in milliliters was measured in every patient lying in supine position with elevated knees at six pre-defined symmetrical topographic points around the abdominal midline until the level of umbilicus. Maximal measured volume was used for the analysis.

Standard two dimensional duplex US device

The standard US device Sonos 5500 (Hewlett Packard, Andover, Massachussets, USA) was used for examination of abdominal aorta. All ultrasound examinations were

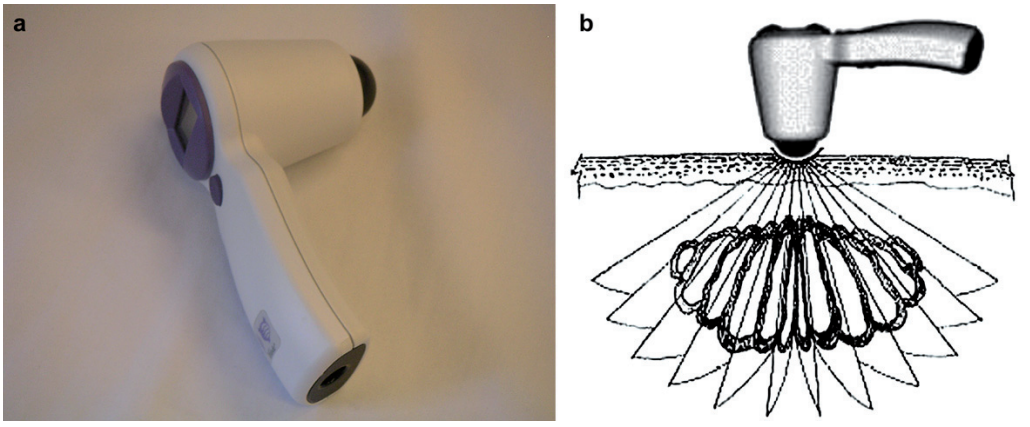

Figure 1 *Bladder volume indicator (a) and principle of acquirement of measurements (b).*

focused on the identification of the infrarenal aorta and assessment of its diameter in transverse (anterior–posterior) and sagittal (left-to-right) dimension at four levels. All diameters were measured from edge to edge of the aortic wall, including intraluminal thrombus, when present. The values of obtained measurements were expressed in centimeters, and maximal measured diameter was used for the analysis.

Statistical analysis

Descriptive statistics were reported as means (±SD) for normal distributions or as median (range) in case of a skewed distribution. A comparison of results between the groups obtained by both US and BVI was analyzed using the Student *t* test; the test results were considered significant at a *p* value of less than .05. BVI and US produce measures that cannot be compared directly (volumes and diameters, respectively). Therefore, correlation of results obtained by US and BVI was assessed by Spearman's coefficient of rank correlation. The diagnostic accuracy and predictive value of BVI was compared with US, which was considered the standard tool for assessment of AAA diameter. The agreement for the measurements between the two examination techniques was assessed by 2 x 2 tables using weight kappa statistics. Kappa values < 0.4,0.4–0.75, and > 0.75 were considered to represent poor, fair to good, and excellent agreement respectively, based on Fleiss's classification.[7] All analysis was performed using the statistical software SPSS for Windows 12.0.1 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Patient's characteristics of the study population are shown in Table 1. As shown patients presenting with an AAA were predominantly males. Patients with an aortic aneurysm also were older and more frequently had a history of myocardial infarction as compared to those without an aortic aneurysm. The US and BVI examinations were feasible in all patients. The median maximal aortic diameter in the total study population using US was 39 mm (range 14–85). A total of 54 (57%) patients had a abdominal aortic diameter > 30 mm. The median maximal aortic volume measured by BVI was 71 ml (range 14–210 ml).

Maximal aortic diameter assessed by US correlated closely with the maximal aortic volume by BVI (r = 0.87, p < .0001, 95% CI = 0.81-0.91, Fig. 2). Using a cut-off value of >50 ml for the presence of AAA by BVI, sensitivity, specificity, positive and negative predictive value of the BVI in detection of AAA were 94%, 82%, 88% and

Table 1. Characteristics of study population

Characteristic	All patients (*n* = 94)	Patients with AAA (n = 54)	Patients without AAA (*n* = 40)	P-value
Age, years (SD)	66 ±14	70 ±11	62 ±17	.009
Males (%)	67 (71)	45 (83)	22 (55)	.003
BMI (kg/m^2)	25 ±4	25 ±4	25 ±4	ns
Myocardial infarction (%)	20 (21)	16 (29)	4(10)	0.04
Angina pectoris (%)	18 (19)	9(16)	9(23)	ns
Heart failure (%)	5(5)	4(7)	1(3)	ns
Renal failure (%)	5(5)	5(9)	0	ns
Diabetes mellitus (%)	12 (13)	7(13)	5(13)	ns
Hypertension (%)	50 (53)	30 (56)	20 (50)	ns
Cerebrovascular disease (%)	15 (16)	7(13)	8(20)	ns
Current or former smoking (%)	76 (81)	47 (86)	29 (73)	ns
Hypercholesterolaemia (%)	43 (46)	21 (39)	22 (55)	ns
Aortic diameter by US, mm (SD)	39 ±19	52 ±16	21 ±4	.001
Aortic volume by BVI, ml (SD)	71 ±47	96 ±48	37 ±14	.001

AAA = abdominal aortic aneurysm; BMI = body mass index; US = standard ultrasound device; BVI = bladder volume indicator, ns = not significant (i.e. $p > 0.05$).

92%, respectively. The agreement between US and BVI in detecting an AAA was 89%, kappa 0.78 (Table 2). Inter- and intraobserver variability of BVI measurements were 93% and 94%.

DISCUSSION

The prognosis for ruptured AAAs is poor. Therefore, screening of patients at risk and timely elective repair improves outcome. The preferred screening method is ultrasound imaging. It is cheaper than other imaging modalities and non-invasive. Ultrasonography can measure the size of AAA with accuracy of 2–3 mm, with sensitivity and specificity approaching 99%.[8–10] With ultrasonography it is poss-ible to diagnose or rule-out the AAA rapidly and accurately.[10, 11] At present, ultrasound screening with standard US devices requires training and bulky equipment. We hypothesized that the BVI can be used for the screening of AAA.

This study shows that BVI can be effectively used for the detection of AAA in high-risk individuals. To our knowledge this device has never been utilized for this

purpose before. The sensitivity, specificity and accuracy for the detection of AAA are very similar to those of US. There is a good correlation between diameter obtained by US and volume obtained by BVI. Considering its low cost (about €8.000 for the BVI 6400), steep learning curve and potential widespread availability, screening for AAA using this device is promising.

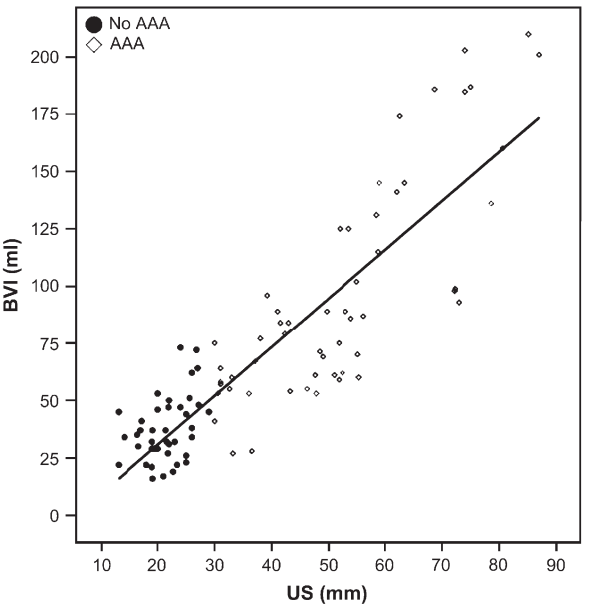

Figure 2 *Correlation between maximal diameter of aorta measured by standard ultrasound device (US) and maximal volume of aorta measured by bladder volume indicator (BVI).*

Bladder volume indicator (BVI), presented for the first time in 1988, was originally designed for the estimation of postvoid residual volumes. The device is inexpensive and can effectively be used after a short training. Since now, several generations of BVIs were widely applied in clinical practice, and they proved to be a very useful tool in diagnosing and management of voiding dysfunction. A measurement method of bladder volume is different between BVI and US. Several reports in urological literature found that the BVI is as reliable and accurate as the standard US to measure postvoid residual urine.[12, 13]

Recently, it has been shown that portable US devices can also be successful in screening patients with risk-factors for AAA.[2, 14, 15] Compared to the portable US

Table 2 *Agreement of diameter measured by ultrasound device (US) and volume measured by bladder volume indicator (BVI). Number of patients: 94. Values of > 30 mm for US and > 50 ml for BVI were considered suggestive for the presence of AAA*

		US	
		< 30 mm	> 30 mm
BVI	< 50ml ≥ 50ml	33 7	3 51

Agreement 89%; Kappa = 0.78.

devices, the BVI is simpler for use, requires a shorter training period, and is roughly four times cheaper. Because of this, it is presumable that BVI could be adopted in near future for the large screening programs for AAA, and that the examination could be performed by a nurse or a technician.

The BVI uses a three-dimensional ultrasound technique detecting volumes, in contrast to conventional ultrasound techniques measuring anterior–posterior or sagittal diameter. There are few publications regarding the volume measurements for detection and follow-up of aneurysmal disease of the aorta, and according to them the volumetric assessment has potential advantages. Being that a three dimensional change is reflected by a much smaller change in two dimensions, it might be concluded that volume measurements are more accurate than the measurements of diameter, because they will encounter changes in aneurysm size earlier.[16] Currently, volumetric measurement using CT is suggested as diagnostic method of choice in follow-up of patients after endovascular AAA repair (EVAR), but this is time-consuming and requires specific and expensive hardware and software for acquiring data.[17–19] We hypothize that the BVI may play a role in the follow-up of patients after EVAR.

There are several factors influencing BVI results. The BVI has a 120 degrees angle of view for every of 12 rotational planes, and interpolates between planes creating a 3-dimensional reconstruction of differently shaped cavities for the volume measurement. In the case of tube-like cavity with open ends, such as the abdominal aorta, the BVI takes one sample (part) of that cavity, and calculates its volume. The size of that sample primarily depends on the depth at which the abdominal aorta lies and on the penetration depth of the US beam. This means that when the AAA is close to the anterior abdominal wall the sample taken by the BVI for the volume measurement will be smaller than the sample of the same AAA which is positioned deeper in the abdomen (Fig. 3). Taking into consideration technical characteristics of the BVI 6400, we have estimated that the volume of 50 ml corresponds with the AAA which diameter is 30 mm (by the definition, the lower diameter considered for the AAA), and which is positioned close to the anterior abdominal wall. For this reason, we have decided to use this value as the cut-off point for the presence of the AAA. Also, sampling at several different points (in our study at six symmetrical predefined points) diminishes the chance to skip aneurysmaticaly changed part of the abdominal aorta.

Other possible problems, which could influence the BVI results, might be: extracted edges between aortic wall and blood, thickened aortic wall, irregular aortic

wall, and confusing inferior vena cava or bowel for abdominal aorta. The later might be overcome by the addition of a Doppler measurement, identifying blood flow coming from the heart compared to veneous return. Operator depending factors include the angle between BVI and the abdominal wall and compatibility between abdominal wall and ultrasound probe.

At present the BVI can not be used as a diagnostic tool. The results of this pilot study imply that a secondary examination by the standard US is recommended in patients with measured volumes larger than 50 ml.

Future directions. This study showed the potential of a hand-held automatic US bladder device to detect AAA in a high-risk patient population. It is interesting to determine its potential role in screening of medium-risk population, in follow-up of patients with known AAA, especially after EVAR (potential presence of endovascular leak), and in screening of first-degree relatives of patients with AAA. Future studies are needed to clarify these issues.

REFERENCES

1 Scott RA, Vardulaki KA, Walker NM, Day NE, Duffy SW, Ashton HA *et al.* The long-term benefits of a single scan for abdominal aortic aneurysm (AAA) at age 65. *Eur J Vasc Endovasc Surg* 2001;21:535-540.

2 Ashton HA, Buxton MJ, Day NE, Kim LG, Marteau TM, Scott RA *et al.* Multicentre Aneurysm Screening Study Group: the Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. *Lancet* 2002;360:1531-1539.

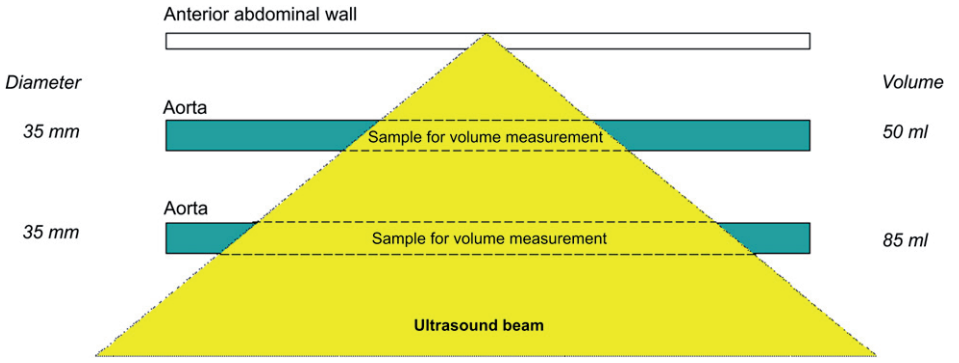

Figure 3 *Relation between the volumes measured by the BVI and position of the aorta to the anterior abdominal wall. Detailed explanation in the text.*

3 Lederle FA, Johnson GR, Wilson SE. Abdominal aortic aneurysm in women. / *Vasc Surg* 2001;34: 122-126.

4 Scott RA, Bridgewater SG, Ashton HA. Randomized clinical trial of screening for abdominal aortic aneurysm in women. *Br J Surg* 2002;89:283-285.

5 Daly KJ, Torella F, Ashleigh R, McCollum CN. Screening, diagnosis and advances in aortic aneurysm surgery. *Gerontology* 2004; 50:349-359.

6 Marks LS, Dorey FJ, Luz Macarian M, Park C, de Kernion JB. Three-dimensional ultrasound device for rapid determination of bladder volume. *Urology* 1997;50:341-348.

7 Fleiss JL. Statistical Methods for Rates and Proportions. 2nd ed. New York, NY: Wiley; 1981.

8 Lederle FA, Walker JM, Reineke DB. Selective screening for abdominal aortic aneurysms with physical examination and ultrasound. *Arch Intern Med* 1988;148:1753-1756.

9 Quill DS, Colgan MP, Sumner DS. Ultrasonic screening for the detection of abdominal aortic aneurysms. *Surg Clin North Am* 1989;69:713-720.

10 Giaconi S, Lattanzi F, Orsfni E, Prosperi R, Tartarini G. Feasibility and accuracy of a rapid evaluation of the abdominal aorta during routine transthoracic echocardiography. *Ital Heart J Suppl* 2003;4(4):332-336.

11 Kuhn M, Bonnin RL, Davey MJ, Rowland JL, Langlois SL. Emergency department ultrasound scanning for abdominal aortic aneurysm: accessible, accurate, and advantageous. *Ann Emerg Med* 2000;36(3):219-223.

12 Yucel S, Kocak H, Sanli A, Tosun O, Tuncer M, Ersoy F *et al.* How accurate is measuring postvoid residual volume by portable abdominal ultrasound eqipment in peritoneal dialysis patient? *Neurourol Urodyn* 2005;24:358-361.

13 Byun SS, Kim HH, Paick JS, Kamg W, Oh SJ. Accuracy of bladder volume determinations by ultrasonography: are they accurate over entire bladder volume range? *Urology* 2003;62:656–660.

14 Vourvouri EC, Poldermans D, Schinkel AF, Sozzi FB, Bax JJ, Van Urk H *et al.* Abdominal aortic aneurysm screening using a handheld ultrasound device. *"A* pilot study. *Eur J Vasc Endovasc Surg* 2001;22(4):352-354.

15 Lin PH, Bush RL, McCoy SA, Felkai D, Pasnelli TK, Nelson JC *et al. A* prospective study of a hand-held ultrasound device in abdominal aortic aneurysm evaluation. *Am J Surg* 2003;186(5): 455-459.

16 Wever JJ, Blankensteitn JD, Th M Mali WP, Eikelboom BC. Maximal aneurysm diameter follow-up is inadequte after endovascular abdominal aortic aneurysm repair. *Eur J Vasc Endovasc Surg* 2000;20:177-182.

17 Wever JJ, Blankensteijn JD, van Rijn JC, Broeder IA, Eikelboom BC, Mali WP. Inter- and intraobserver variability of CT measurements obtained after endovascular repair of abdominal aortic aneurysms. *AJR Am J Roentgenol* 2000 Nov;175(5): 1279-1282.

18 Rubfn GD. Helical CT angiography of the thoracic aorta. / *Thorac Imaging* 1997;12:128-149.

19 Armon MP, Yusuf SW, Whitaker SC, Gregson RH, Wenham PW, Hopkinson BR. Thrombus distribution and changes in aneurysm size following endovascular aortic aneurysm repair. *Eur J Vasc Endovasc Surg* 1998;16:472-476.

CHAPTER 11

COMPARISON WITH COMPUTED TOMOGRAPHY OF TWO ULTRASOUND DEVICES FOR DIAGNOSIS OF ABDOMINAL AORTIC ANEURYSM

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ABSTRACT

Screening for abdominal aortic aneurysms (AAAs) in patients at risk will become more cost effective if a simple, inexpensive, and reliable ultrasound device is available. The aim of this study was to compare a 2-dimensional, handheld ultrasound device and a newly developed ultrasound volume scanner (based on bladder scan technology) with computed tomography (CT) for diagnosing AAA. A total of 146 patients (mean age 69 ± 10 years; 127 men) were screened for the presence of AAAs (diameter > 3 cm) using CT. All patients were examined with the handheld ultrasound device and the volume scanner. Maximal diameters and volumes were used for the analyses. AAAs were diagnosed by CT in 116 patients (80%). The absolute difference of aortic diameter between ultrasound and CT was < 5 mm in 88% of patients. Limits of agreement between ultrasound and CT (-6.6 to 9.4 mm) exceeded the limits of clinical acceptability (±5 mm). An excellent correlation between ultrasound and CT was observed (r = 0.98). The correlation coefficient between the volume scanner and CT was 0.86, with agreement of 90% and κ value of 0.73. Using an optimal cut-off value of > 56 ml, denned by receiver-operating characteristic curve analysis, sensitivity, specificity, and the positive and negative predictive values of the volume scanner for detecting AAA were 90%, 90%, 97%, and 71%, respectively. In conclusion, this study shows that a 2-dimensional, handheld ultrasound device and a newly developed ultrasound volume scanner can effectively identify patients with AAAs confirmed by CT. (Am J Cardiol 2007;100:1786-1791)

INTRODUCTION

In this prospective study, we evaluated the diagnostic potential and accuracy of abdominal aortic aneurysm (AAA) detection using 2 different ultrasound devices. The first was a 2-dimensional, duplex, handheld ultrasound device (USHH). The second was a newly developed, low-cost, handheld ultrasound volume scanner for 3-dimensional measurements, originally intended as an automatic bladder volume indicator (BVI). Axial computed tomo-graphic measurements of aortic diameter were used as a reference.

METHODS

The study population consisted of 146 consecutive patients referred to the Department of Vascular Surgery of the Erasmus Medical Center (Rotterdam, The Netherlands) for surgical treatment of peripheral arterial disease. The hospital's ethics committee approved the study, and all patients gave informed consent. Patients were screened for the following cardiovascular risk factors: age, angina pectoris, previous myocardial infarction, hypertension, heart failure, stroke, renal failure (serum creatinine > 2 mg/dl), smoking, diabetes mellitus, and hypercholesterolemia (total cholesterol ≥ 200 mg/dl, low-density lipoprotein cholesterol ≥ 100 mg/ dl, or receiving statin therapy). Medical therapy was noted in all patients at enrollment. All patients underwent examinations with USHH and the BVI in random order. The examinations were performed and reviewed by 2 physicians, both skilled and experienced in abdominal ultra-sonography. Each physician was blinded to the computed tomographic measurements.

Axial computed tomographic examinations were performed with the Siemens Somatom Sensation 16 machine (Siemens AG, Munich, Germany). The examinations were performed with 4-mm slice thickness and 4-mm increments, with 100 ml of nonionic contrast medium. Results were reported as the maximal diameter of the infrarenal aorta in any direction. An AAA was defined as an abdominal aorta ≥ 30 mm in diameter by computed tomography (CT).

The handheld ultrasound device SonoSite Titan (SonoSite Inc., Bothell, Washington) is a small unit with a 2- to 5-MHz probe (Figure 1). The ultrasound examination was focused on the identification of the infrarenal aorta. The measurement of its maximal diameter was obtained using on-screen calipers from edge to edge of the aortic wall, including the intraluminal thrombus if present. The probe was maintained perpendicular to the aortic blood flow determined by color Doppler to yield orthogonal sections of the aorta. Measurements were taken from the lowest renal artery to the

aortic bifurcation. The maximal obtained diameter in any direction, expressed in millimeters, was used for analysis.

The Mobile Bladderscan BVI 6400 (Diagnostic Ultrasound, Bothell, Washington) is a nonimaging volumetric ultrasound device designed for the automatic measurement of bladder volume (Figure 1). It measures ultrasonic (3.7 MHz) reflections within a 120° sector, detects fluid-tissue borders, creates a 3-dimensional shape of the organ, and calculates the fluid volume.[1] The transducer is slightly focused, with focus at 6 to 8 cm. When imaging on the lower abdomen, a penetration depth of 14 to 16 cm is possible. An aiming icon on the instrument's liquid crystal display guides the user to optimal positioning of the scan head to ensure the accuracy of measurement. After pressing the scan button, the volume is reported on the liquid crystal display within 5 seconds. With the BVI, aortic volume (in milliliters) was measured at 6 predefined symmetrical topographic points around the abdominal midline until the level of the umbilicus in every patient lying in the supine position with elevated knees. The maximal measured volume was used for analysis.

Descriptive statistics are reported as mean ± SD for those normally distributed or as medians and ranges in case of skewed distribution. Measurements among the CT,

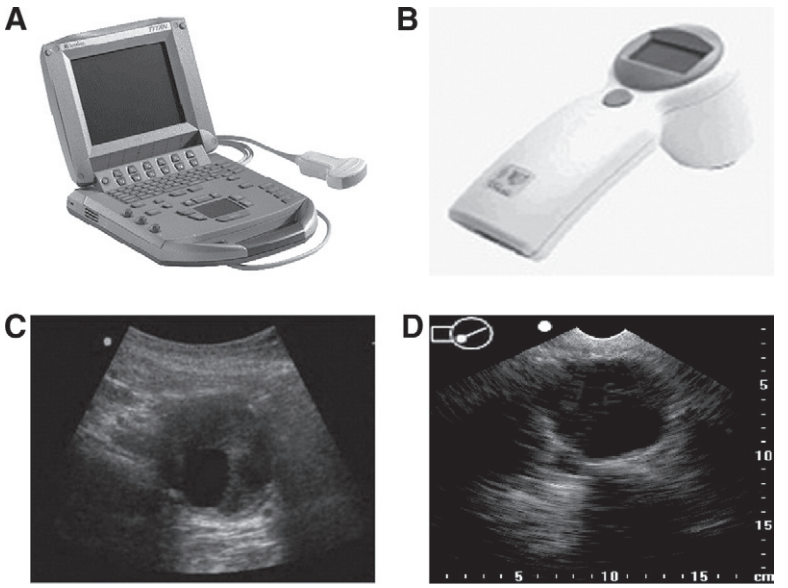

Figure 1 *SonoSite Titan (SonoSite Inc., Bothell, Washington) (A) and Mobile Bladderscan BVI 6400 (Diagnostic Ultrasound, Bothell, Washington) (B). (C, D) Images of an AAA obtained by these 2 devices.*

USHH, and BVI groups were analyzed using the paired Student's *t* test. A p value < 0.05 was considered significant. Correlations among CT, USHH, and BVI were assessed using Spearman's coefficient of rank correlation. The variability between CT and USHH was calculated according to the method described by Bland and Altman and is reported as 95% limits of agreement (LOAs; mean difference ± 2 SD), also adding the limits of ≤ 2 mm and ≥ 5 mm and the concept of the "clinically acceptable difference."[24] These limits express the proportion of observed differences within each limit. The clinically acceptable LOAs were denned as -5 to 5 mm.[5] Bland-Altman analysis could not be performed between CT and BVI, because these 2 methods assess different metric units (millimeters and milliliters, respectively). The diagnostic accuracy and predictive value of the BVI were compared with those of CT, which was considered the reference tool for the assessment of maximal aortic diameter. The 2X2 tables using weight κ statistics assessed the agreement between BVI and computed tomo-graphic measurements. Kappa values < 0.4, 0.4 to 0.75, and > 0.75 were considered to represent poor, fair to good, and excellent agreement, respectively, on the basis of Fleiss et al's[6] classification. Receiver-operating characteristic curve analysis was used to determine the optimal cut-off value of the volumes obtained by the BVI to predict AAA. All analysis was performed using SPSS version 12.0.1 for Windows (SPSS, Inc., Chicago, Illinois).

RESULTS

The characteristics of the study population are listed in Table 1. Patients with AAAs were predominately men and were older compared with patients without AAAs. USHH and BVI measurements were feasible in all patients. In 116 patients (79%), the diameter of the infrarenal aorta was >30 mm on CT; the diameter was 30 to 50 mm in 32 patients and >50 mm in 84 patients. The average difference between computed tomographic and USHH measurements for the whole group was 1.4 ± 4 mm; the differences were 0.5 ± 2.7 mm in patients with aortic diameters <30 mm, 0.5 ± 3.7 mm in patients with aortic diameters of 30 to 50 mm, and 2.0 ± 4.4 mm in patients with aortic diameters >50 mm. Computed tomographic measurements were larger than USHH measurements in 78 patients (53%), smaller in 51 (35%), and equal in 17 (12%). The difference between the 2 measurements was < 2 mm in 54 patients (37%) and > 5 mm in 18 patients (12%). The clinically acceptable difference between computed tomographic and USHH measurements of < 5 mm was present in 128 patients (88%). The mean

Table 1 *Baseline characteristics of the study population*

Variable		AAA		
	All Patients (n = 146)	Present (n = 116)	Absent (n = 30)	*p* Value
Age (yrs)	69 ± 10	71 ± 8	61 ± 13	0.003
Men	127 (87%)	105 (91%)	22(71%)	0.006
Body mass index (kg/m^2)	26 ± 4	26 ± 4	28 ± 6	NS
Myocardial infarction	57 (39%)	49 (43%)	8 (26%)	NS
Angina pectoris	41 (28%)	33 (29%)	8 (26%)	NS
Heart failure	19 (13%)	17 (15%)	2 (7%)	NS
Hypertension	77 (53%)	63 (55%)	14 (45%)	NS
Renal failure	32 (22%)	28 (24%)	4 (13%)	NS
Diabetes mellitus	24 (16%)	16 (14%)	8 (26%)	NS
Cerebrovascular disease	30 (20%)	23 (20%)	7 (23%)	NS
Current or former smoker	81 (56)%	67 (58%)	14 (45%)	NS
Hypercholesterolemia	71 (49%)	54 (47%)	17 (55%)	NS
Aortic diameter by CT (mm)	51 ± 21	58 ± 16	21 ± 5	< 0.0001
Aortic diameter by USHH (mm)	49 ± 20	57 ± 15	21 ± 4	< 0.0001
Aortic volume by BVI (ml)	103 ± 60	119 ± 56	40 ± 13	< 0.0001

Data are expressed as mean ± SD or as number (percentage).

diameter measured by CT in the total study population and in patients with AAAs > 50 mm was significantly larger than the paired mean diameter measured by USHH (51 ± 21 vs 49 ± 20 mm, p <0.0001, and 65 ± 13 vs 63 ± 13 mm, p < 0.0001, respectively). There was no statistically significant difference in aortic diameters measured by CT and USHH in patients without AAAs and with AAAs of 30 to 50 mm (21 ± 5 vs 21 ± 4 mm, p > 0.05, and 41 ± 6 vs 40 ± 7 mm, p > 0.05, respectively). The LOAs between computed tomographic and USHH measurements were poor: -6.6 to +9.4 mm for the total population (Figure 2), –4.9 to +5.9 mm for non-aneurysmal aortas, –6.9 to 7.9 mm for AAAs of 30 to 50 mm, and -6.8 to +10.8 mm for AAAs > 50 mm. This implies that in 95% of cases, the difference in computed tomographic and USHH measurements was expected to be between these values, which clearly exceed the limit of clinical acceptability (±5 mm). However, the diameter measured by USHH closely correlated with the measurements by CT (r = 0.977, p < 0.0001, 95% confidence interval 0.968 to 0.983; Figure 3). In addition, the agreement between CT and USHH was 97% (*k* = 0.89). Sensitivity, specificity, and the positive and negative predictive values of

USHH in detecting AAA were 97%, 97%, 99%, and 88%, respectively. The coefficients of variation for the measurement of aortic diameter were 12% for 2 observers and 6% for the repeated measurements of 1 observer.

The median maximal aortic volume measured by the BVI was 87 ml (range 12 to 288) for the whole group, 39.5 ml (range 12 to 71) for nonaneurysmal aortas, 66.5 ml (range 25 to 157) for AAAs of 30 to 50 mm, and 132 ml (range 40 to 288) for AAAs > 50 mm. A good correlation was observed between computed tomographic and BVI measurements ($r = 0.857$, $p < 0.0001$, 95% confidence interval 0.807 to 0.895; Figure 3). The optimal cut-off value of the volume measured by the BVI to predict the presence of AAA was 56.5 ml, using receiver-operating characteristic curve analysis (area under the curve 0.96; Figure 4). Using this cut-off value, sensitivity, specificity, and the positive and negative predictive values of the BVI in detecting AAA were 90%, 90%, 97%, and 71%, respectively. The agreement between CT and the BVI was 90% ($k = 0.73$). The coefficients of variation for the measurement of aortic volume were 27% for 2 observers and 12% for the repeated measurements of 1 observer.

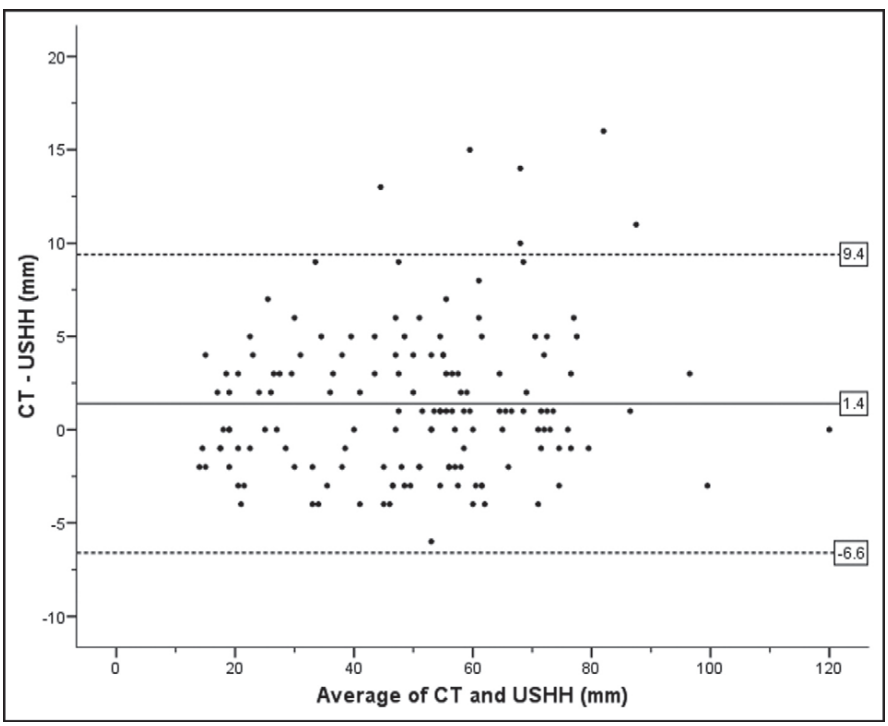

Figure 2 *Bland-Altman plot of the difference between USHH and CT. The solid line denotes the mean arithmetic difference, and the dashed lines denote 2 SDs (95% LOAs).*

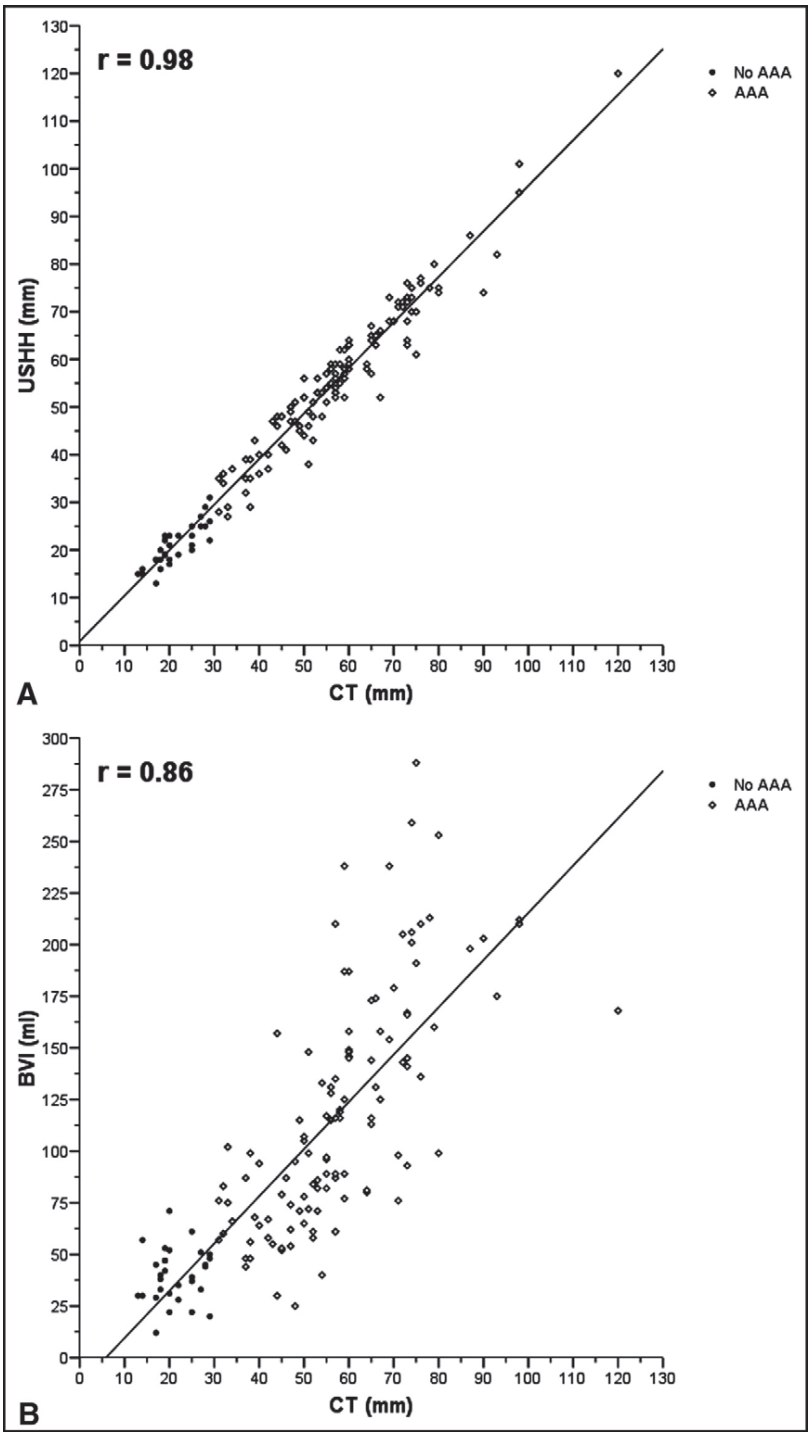

Figure 3 *(A) Correlation between USHH and CT. (B) Correlation between the BVI and CT.*

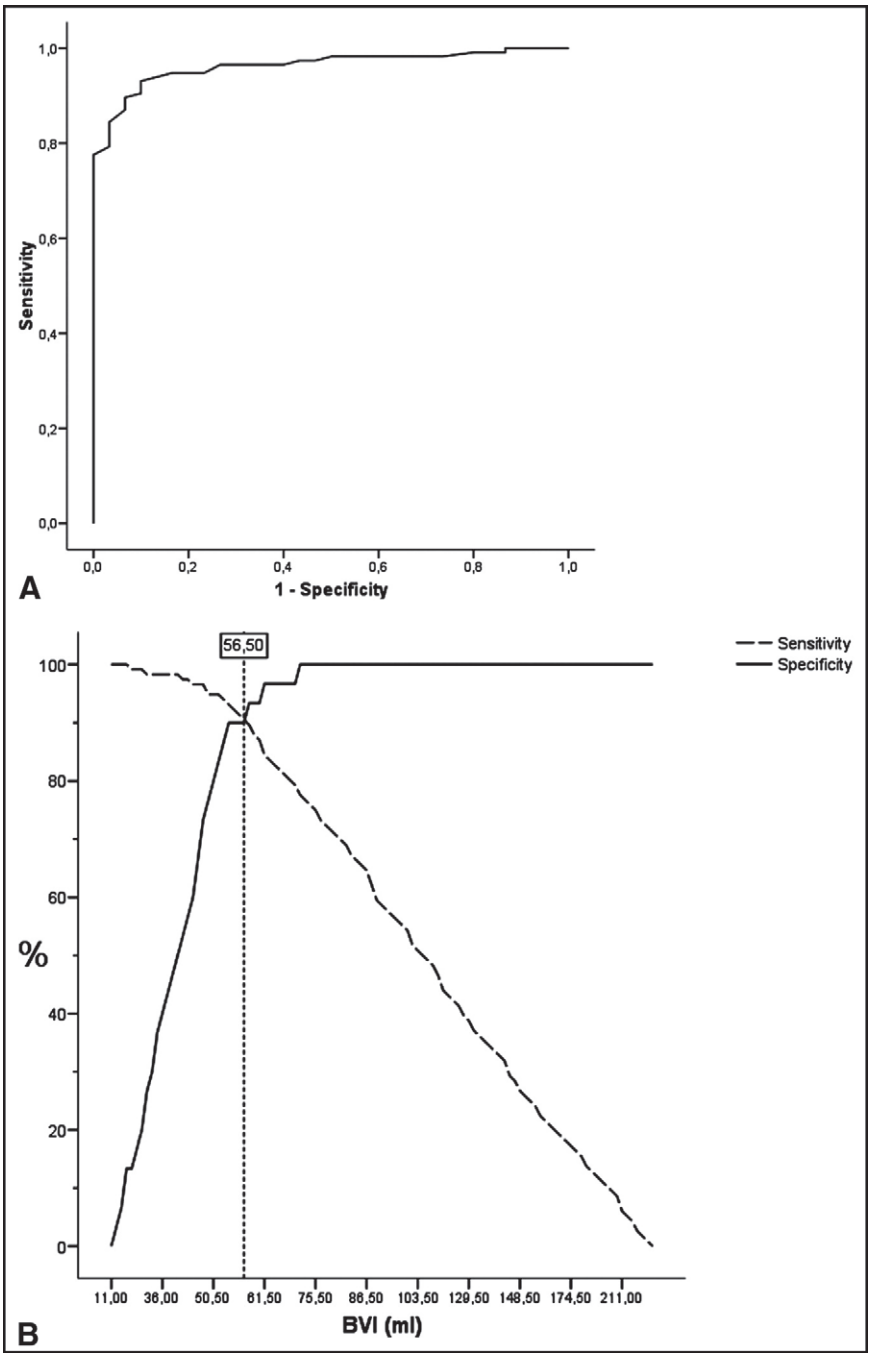

Figure 4 *Receiver-operating characteristic curve analysis demonstrating the optimal cut-off value of the BVI for the presence of AAA.*

DISCUSSION

This study shows that USHH and the BVI can effectively be used for the detection of AAAs in high-risk patients.

Advances in ultrasonography have led to the development of relatively inexpensive handheld devices with widespread clinical applicability. Ultrasound is practical for screening, whereas CT is the preferred method for preop-erative imaging in patients with AAAs. A number of studies have found contradictory results in comparing ultrasound technology with CT in patients with or without AAAs. Several studies reported larger aortic diameters during ultrasound compared with CT.[78] However, most studies found that aortic diameter tends to be smaller during ultrasound compared with CT.[349] The largest mean difference was 9.4 mm, as observed in a study by Sprouse et al.[5] The present study also found smaller aortic diameters with ultrasound compared with CT, with a mean difference of 1.4 mm. These findings may be explained by oblique slicing of AAAs during axial CT, with overestimation of the maximal aneurysmal diameter, especially in instances of significant vessel angulation. Despite the relative lack of agreement (-6.6 to +9.4 mm), the correlation between ultrasound and CT was excellent ($r = 0.98$). In addition, with the high sensitivity and specificity (97% for both) and low proportion of absolute difference in measured diameters > 5 mm (12%) in our study, ultrasound can be an excellent tool for the screening of AAA.

The low-cost handheld ultrasound scanner for 3-dimensional measurement, originally intended as an automatic BVI, is another device with potential widespread clinical applicability in AAA screening. Potential advantages of this device are its volumetric assessment with early detection of 3-dimenstional changes in aortic size. Wever et al[10] explained that the 3-dimensional change in AAA size is reflected by much less 2-dimensional change. This is especially important for the follow-up of patients after endovascular AAA repair, because volume measurements can encounter changes in aneurysm size due to endoleaks earlier than simple 2-dimensional measurements. However, volumetric measurements using CT are time consuming and require specific and expensive equipment for acquiring the data.[11–13] In addition, the BVI is simple to use, requires a short training period, is relatively cheap (about €8,000 for the BVI 6400), and can be used by a nurse or a technician. Several urologic studies found that the BVI is almost as accurate as standard ultrasonography in estimating postvoid residual urine. This study is the first to compare the BVI with CT in the setting of AAA screening.

This study found a good correlation (r = 0.86) and agreement (k = 0.73) between the 2 devices. The high specificity (90%) suggests an excellent screening potential in patients at risk for AAA.

Several factors influence BVI measurements. The BVI has a 120° angle of view for each of the 12 rotational planes and interpolates between planes, creating a 3-dimensional reconstruction of differently shaped cavities for the volume measurement. In the case a of tubelike cavity with open ends, such as the abdominal aorta, the BVI takes 1 sample of that cavity and calculates its volume. The size of that sample depends primarily on the depth at which the abdominal aorta lies and on the penetration depth of the ultrasound beam. This means that when the AAA is close to the anterior abdominal wall, the sample taken by the BVI for the volume measurement will be smaller than the sample of the same AAA that is positioned deeper in the abdomen. However, in the present study, we used sampling at several different points (6 symmetrical predefined points) to diminish the chance of missing aneurysmatically changed parts of the abdominal aorta.

At the time of writing, the BVI cannot be used as a diagnostic tool for AAA, because it is not officially registered for this indication. Our results imply that secondary examination by ultrasound or CT should be recommended in patients with measured volumes > 50 mm.

REFERENCES

1. Marks LS, Dorey FJ, Luz Marcarian M, Park C, deKernion JB. Three-dimensional ultrasound device for rapid determination of bladder volume. *Urology* 1997;50:341-348.
2. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;l:307-310.
3. Lederle FA, Wilson SE, Johnson GR, Reinke DB, Littooy FN, Acher CW, Messina LM, Ballard DJ, Ansel HJ; for the Abdominal Aortic Aneurysm Detection Management Veterans Administration Cooperative Study Group. Variability in measurement of abdominal aortic aneurysm. *J Vasc Surg* 1995;21:945-952.
4. Jaakkola P, Hippelainen P, Farin P, Rytkonen H, Kainulainen S, Partanen K. Intraobserver variability in measuring the dimension of the abdominal aorta: comparison of ultrasound and computed tomography. *Eur J Vasc Endovasc Surg* 1996;12:230-237.
5. Sprouse LRII, Meier GH III, LeSar CJ, DeMasi RJ, Sood J, Parent N, Marcinzyck MJ, Gayle RG. Comparison of abdominal aortic aneurysm diameter measurements obtained with ultrasound and computed tomography: is there a difference? *J Vasc Surg* 2003 ;38:466-472.

6. Fleiss JL, Levin B, Paik MC. The measurement of interrater agreement. In: Fleiss JL, Levin B, Paik MC, eds. Statistical Methods for Rates and Proportions. 3rd Ed. New York, New York: John Wiley, 2003:598-626.
7. Ellis M, Powell JT, Greenhalgh RM. Limitations of ultrasonography in surveillance of small abdominal aortic aneurysms. *Br J Surg* 1991 ;78: 614-616.
8. Wanhainen A, Bergqvist D, Bjorck M. Measuring the abdominal aorta with ultrasonography and computed tomography. *Eur J Vasc Endovasc Surg* 2002;24:428-434.
9. Singh K, Jacobsen BK, Solberg S, Kumar S, Arnesen E. The difference between ultrasound and computed tomography (CT) measurements of aortic diameter increases with aortic diameter: analysis of axial images of abdominal aortic and common iliac artery diameter in normal and aneurismal aortas. The Tromso Study, 1994-1995. *Eur J Vasc Endovasc Surg* 2004;28:158-167.
10. Wever JJ, Blankensteijn JD, Thmmali WP, Eikelboom BC. Maximal aneurysm diameter follow-up is inadequate after endovascular abdominal aortic aneurysm repair. *Eur J Vasc Endovasc Surg* 2000;20:177-182.
11. Wever JJ, Blankensteijn JD, van Rijn JC, Breeders IA, Eikelboom BC, Mali WP. Inter- and intra-observer variability of CT measurements obtained after endovascular repair of abdominal aortic aneurysms. *AJR Am J Roentgenol* 2000;175:1279-1282.
12. Rubin GD. Helical CT angiography of the thoracic aorta. *J Thorac Imaging* 1997;12:128-149.
13. Armon MP, Yusuf SW, Whitaker SC, Gregson RHS, Wenham PW, Hopkinson BR. Thrombus distribution and changes in aneurysm size following endovascular aortic aneurysm repair. *Eur J Vasc Endovasc Surg* 1998;16:472-476.

SUMMARY

This thesis gives insight in diagnostic burden of atherosclerosis as polyvascular disease (PVD), as well as in its prognostic burden since different manifestations of atherosclerosis are leading cause of morbidity and mortality in general population. Later is of paramount importance in surgical patients – each year about 100 million adults undergo some form of non-cardiac surgery, of whom 1 million will have some kind of postoperative atherosclerotic complication (predominantly cardiac); in 25% percents of those, cardiac complications will be the cause of death. At the highest risk for this kind of complications are the patients undergoing vascular surgery because they usually have symptomatic or asymptomatic atherosclerosis in multiple vascular territories. In order to prevent possible perioperative cardiovascular complications, it is of critical importance to identify patients with asymptomatic atherosclerotic disease and underlying risk factors, to estimate properly their perioperative risk using different scoring systems and non-invasive imaging techniques, and to treat them accordingly. This approach provides the reduction of short-term, as well as long-term adverse cardiovascular events.

Chapter 1 explains the prevalence of PVD, and its relationship with cardiovascular risk factors and hs-CRP. In patients with one symptomatic arterial territory, atherosclerotic disease in other arterial territories was common, with over two-thirds of these patients having more than one affected site. Importantly, when relying only on clinical history, 35% of patients would have been misclassified as having only one affected arterial territory. Systematical screening of patients with peripheral arterial disease using ultrasound modalities significantly increases the number of patients with PVD. Furthermore, hs-CRP showed a close relationship with the number of affected vascular territories and increased gradually with every additional vascular territory affected. When hs-CRP is added to clinical cardiovascular risk factors, it appears to be a strong predictor for the presence of PVD (OR 3.81, 95% CI 2.39-6.09).

Patients with PVD are often candidates for different surgical procedures. Early or late perioperative cardiovascular morbidity and mortality are among the major problems in those patients. The majority of postoperative cardiovascular complications are caused by sudden or prolonged myocardial ischemia due to a primary coronary event (such as plaque erosion and/or rupture, fissuring, or dissection) or due to either increased oxygen demand or decreased supply (such as coronary artery spasm,

coronary embolism, anemia, arrhythmias, hypertension, or hypotension). To reduce postoperative cardiovascular morbidity and mortality, preoperative screening is of paramount importance. This screening involves identification of potential risk factors, as well as different noninvasive imaging modalities. In **Chapters 2 and 3** is described the current status of preoperative risk stratification for patients undergoing non-cardiac surgery. Clinical cardiac risk markers, together with the type and urgency of planed surgery, can truly stratify patients in intermediate- and high-risk population. Intermediate-risk patients can probably be operated without any additional noninvasive screening, and should be treated with β-blockers (aiming HR 60-65/min) and statins. In addition to intensive medical therapy with β-blockers and statins, high-risk patients should be screened noninvasively for the extent of underlying CAD if that will change treatment management. The choice of the test should be based on the centers' experience and short-term availability. Although coronary revascularization did not show significant advantages compared to the medical therapy in high-risk patients, it has to be considered in patients with unstable CAD. In patients in whom coronary revascularization was done by PCI with stents, antiplatelet therapy should only be discontinued perioperatively if bleeding risks with increased mortality or sequels are comparable with the observed cardiovascular risks after its withdrawal.

Coronary artery disease, the major cause of postoperative morbidity and mortality, can be asymptomatic in quite a number of surgical patients. **Chapter 4** describes the prevalence and prognostic importance of asymptomatic coronary disease in patients undergoing major vascular surgery. Based on the findings of wall motion abnormalities on rest or stress echocardiography, asymptomatic coronary disease defined as unrecognized MI or silent myocardial ischemia was found in 23% and 28% of patients, respectively. Two main predictors of those serious preoperative finding were both diabetes and heart failure. Unrecognized MI and silent myocardial ischemia are significantly associated with poor long-term prognosis, with two-fold higher incidence of mortality and major cardiac events, which is comparable to the symptomatic coronary artery disease. This finding implies benefit from cardiovascular medication (beta-blockers and statins) in surgical patients with asymptomatic coronary artery disease.

Recent advances in medicine established endovascular procedures as an alternative to conventional surgical procedures, especially in cases of abdominal aortic aneurysms. Endovascular procedures are followed by less cardiac stress, and

subsequently lower incidence of postprocedural major cardiac events. In **Chapter 5** is shown that endovascular repair of abdominal aortic aneurysms in comparison with open surgery is associated with lower incidence of myocardial ischemia (OR 0.14, 95% CI 0.05 - 0.40, $p < 0.001$), troponin T release (OR 0.10, 95% CI 0.02 - 0.32, $p < 0.001$), and new-onset cardiac arrhythmias (14% vs. 29%, $p < 0.04$). Also, 30-day mortality (zero vs 8.7%, $p < 0.03$) and 30-day cardiac event rates (zero vs. 7.9%, $p < 0.04$) were significantly lower in patients who underwent endovascular AAA repair. In contrast, long-term mortality and cardiac event rates were not significantly lower in the endovascular AAA repair group.

In **Chapter 6** is demonstrated the value of glucose and HbA1c in defining perioperative and long-term risk in vascular surgery patients. The management of these patients remains a challenge. Patients with impaired glucose regulation do not meet the criteria for diabetes, but have impaired glucose metabolism, which places them at risk for developing diabetes or cardiovascular disease. We observed that survival in patients with impaired glucose metabolism was comparable with survival in patients with diabetes. Patients with impaired glucose regulation and diabetes were at 2.2- and 2.6-fold increased risk of ischemia, 3.8- and 3.9-fold for troponin T release, 4.3- and 4.8-fold for 30-day cardiac events and 1.9- and 3.1-fold for long-term cardiac events. Patients with HbA1c > 7.0% were at 2.8-fold, 2.1-fold, 5.3-fold and 5.6-fold increased risk for ischemia, troponin T release, 30-day and long-term cardiac events, respectively.

Positive correlation between elevated NT-proBNP with perioperative ischemia, shown in **Chapter 7**, supports its use as a marker of coronary artery disease and as prognostic marker in patients undergoing major vascular surgery. Increased preoperative NT-proBNP levels in patients scheduled for major vascular surgery are associated with an increased incidence of perioperative myocardial ischemia during 12-lead electrocardiographic monitoring (OR 1.59, 95% CI: 1.21 – 2.08, $P < 0.001$) and increased troponin T release (OR: 1.76, 95% CI: 1.33 – 2.34, $P < 0.001$), independent of clinical risk factors and preoperatively obtained dobutamine stress echocardiography results.

Patients with heart failure (HF) scheduled for vascular surgery have an increased risk of adverse postoperative outcome, and risk stratification usually depends on clinical risk factors. Dobutamine stress echocardiography is a useful tool for more precise risk stratification of this group of patients. In **Chapter 8** is shown the independent

prognostic value of wall motion patterns during DSE in patients with HF undergoing major vascular surgery for the prediction of cardiac events within 30 days after surgery and for all-cause mortality and hard cardiac events during a long-term mean follow-up of 5 years. Sustained wall motion improvement during DSE provides a protective effect in both the early perioperative period and for long-term cardiac events. Conversely, ischemia (worsening in wall motion) proved to be hazardous in both early and long-term follow-up periods.

It is believed that coronary revascularization prior to non-cardiac surgery might be prophylactic in high cardiac risk patients. As shown in **Chapter 9**, 101 vascular surgery patients with high cardiac risk (three or more clinical risk factors, and extensive ischemia on DSE) were randomly assigned to preoperative cardiac revascularization or no revascularization. Coronary angiography showed 2-vessel disease in 12 (24%), 3-vessel disease in 33 (67%), and left main in 4 (8%) patients, respectively. Revascularization did not improve 30-day outcome; the incidence of the composite end point was 43% versus 33% (odds ratio 1.4, 95% confidence interval 0.7 to 2.8; $p < 0.30$). Also, no benefit during 1-year follow-up was observed after coronary revascularization (49% vs. 44%, odds ratio 1.2, 95% confidence interval 0.7 to 2.3; $p < 0.48$).

Cardiovascular morbidity and mortality could be prevented by vascular screening and managing high-risk individuals. This screening programme can be cost effective and result in significant health improvements if appropriately targeted. Screening for abdominal aortic aneurysms (AAA) is cost-effective and timely repair improves outcome. In **Chapters 10 and 11** are evaluated two newly developed ultrasound devices in purpose of AAA screening. The first is a 2-dimensional, duplex, handheld ultrasound device (USHH), and the second is a newly developed, low-cost, handheld ultrasound volume scanner for 3-dimensional measurements, originally intended as an automatic bladder volume indicator (BVI). Validation of those two devices is done by comparing their measurement results with the results of two established techniques - standard ultrasound (US) and computerized tomography (CT). The aortic diameter by US and CT correlated closely with aortic volume by BVI ($r = 0.87$, and $r = 0.86$, respectively). Also, the aortic diameter by CT correlated closely with aortic diameter by USHH ($r = 0.98$). Both handheld devices showed high sensitivity, specificity, and the positive and negative predictive values for detecting AAA confirmed by US or CT.

SAMENVATTING

Dit proefschrift biedt inzicht in de diagnostische mogelijkheden om atherosclerotische aandoeningen op verschillende plaatsen in het lichaam op te sporen, immers atherosclerose is een gegeneraliseerde ziekte. Tevens wordt de prognostische waarde van deze aandoeningen besproken. In een volgende fase is dit van belang bij chirurgische patiënten – jaarlijks ondergaan 100 miljoen patiënten een chirurgische ingreep. Ongeveer 1 miljoen van deze patiënten hebben postoperatieve cardiovasculaire complicaties, waarvan een kwart met fatale uitkomst. Patiënten die een vaatchirurgische ondergaan hebben het hoogste risico omdat zij atherosclerotische afwijkingen hebben in meerdere vaatgebieden, symptomatisch dan wel asymptomatisch. Om cardiovasculaire complicaties te voorkomen is het van belang patiënten met asymptomatisch atherosclerose en onderliggende risicofactoren te identificeren. Het is dan mogelijk om op een juiste manier hun perioperatief risico voor hart- en vaatziekten in te schatten, gebruik makend van laboratorium bepalingen en niet invasieve screening methoden en daarna als zodanig te behandelen. Deze aanpak biedt de kans op een vermindering van cardiovasculaire complicaties, zowel binnen 30-dagen na de operatie als op lange termijn.

In **Hoofdstuk 1** wordt gegeneraliseerde atherosclerose besproken alsmede der relatie met risicofactoren voor hart- en vaatziekten en ontsteking parameters. Bij patiënten met één symptomatisch arterieel vaatgebied kwam atherosclerose ook in andere gebieden voor. Meer dan twee derde van deze patiënten heeft meer dan één aangetast vaatgebied. Het is belangrijk op te merken dat wanneer patiënten alleen aan de hand van klinische symptomen worden beoordeeld, 35% verkeerd zou worden geclassificeerd. Systematisch onderzoek van patiënten met perifeer arterieel vaatlijden met ultrageluid verbetert de diagnostiek van gegeneraliseerde atherosclerose. Tevens werd gevonden, dat een ontsteking parameter (hs-CRP) een relatie aantoont met het aantal aangetaste vaatgebieden. Deze waarde neemt toe met elk nieuw aangetast vaatgebied.

Patiënten met gegeneraliseerde atherosclerose moeten vaak operaties ondergaan. Het grootste deel van postoperatieve cardiovasculaire complicaties wordt veroorzaakt door myocard ischemie als gevolg van acute coronaire occlusie door erosie of scheuren van de coronaire plaque, gevolgd door thrombose vorming. Een andere oorzaak is zuurstof tekort tijdens de stress van de operatie ten gevolge van een verminderd aanbod door coronairlijden, embolie, bloedarmoede, aritmie, hypertensie, of

ernstige hypotensie. Om postoperatieve cardiovasculaire morbiditeit en mortaliteit te verminderen is pre-operatief screening van cruciaal belang.

In **Hoofdstukken 2 en 3** wordt de huidige status van pre-operatief risicostratificatie besproken bij patiënten die een chirurgische ingreep moeten ondergaan. Klinische risicomarkers voor hart- en vaatziekten, het type als mede ook de urgentie van de geplande ingreep kunnen patiënten stratificeren voor het perioperatieve risico. Bij patiënten met een laag risico is aanvullend onderzoek niet noodzakelijk. Onderzoek wordt alleen geadviseerd indien het noodzakelijk is om ischemische hartklachten vast te stellen en ook de behandeling zou veranderen. De keus van deze test moet gebaseerd zijn op de ervaring van een bepaald centrum en de mogelijkheid om op korte termijn het onderzoek te kunnen verrichten. Hoewel coronair revascularisatie geen voordeel heeft vergeleken met optimale medische therapie bij patiënten met een verhoogd risico, kan het overwogen worden bij patiënten met progressieve ischemische hartklachten. Indien coronaire revascularisatie was gedaan door een percutane interventie met stent dient rondom de operatie plaatjes aggregatie remmende therapie te worden gecontinueerd. Hiervan kan worden afgeweken als het risico op bloedingen te hoog is, waardoor het cardioprotectief effect wordt overtroffen.

Ischemische hartziekten zijn de voornaamste oorzaken van postoperatieve morbiditeit en mortaliteit, en kunnen volledig asymptomatisch zijn bij chirurgische patiënten. In **Hoofdstuk 4** wordt het belang besproken van asymptomatisch hartziekten bij patiënten die een grote vaatchirurgische ingreep moeten ondergaan. Aan de hand van wandbewegingsstoornissen tijdens echocardiografisch onderzoek, zowel in rust als bij inspanning, werd asymptomatisch coronaire hartziekte vastgesteld. Aanwijzingen voor een niet herkend MI of myocard ischemie werden gevonden bij respectievelijk 23% en 28% van de patiënten. Twee indicatoren voor deze bevindingen zijn diabetes melitus en hartfalen. Een asymptomatisch MI en myocard ischemie zijn geassocieerd met een slechte lange termijn prognose. Deze patiënten dienen behandeld te worden in het kader van secondaire preventie middels geneesmiddelen, bètablokkers en statines.

Een belangrijke vooruitgang in de geneeskunde is de introductie van de endovasculaire procedure als alternatief voor de conventionele, open, chirurgische ingrepen, met name bij de behandeling van het *Aneurysma Aortae Abdominalis*. Endovasculaire procedures geven minder cardiale stress, en cardiovasculaire complicaties. In **Hoofdstuk 5** wordt besproken dat in vergelijking met open chirurgie de endovasculaire behandeling van het *Aneurysma Aortae Abdominalis*

is geassocieerd met een verminderd optreden van myocard ischemie (OR 0.14, 95% BI 0.05 - 0.40, p < 0.001) en troponine T stijging (OR 0.10, 95% BI 0.02 - 0.32, p < 0.001), en hartritmestoornissen (14% vs. 29%, p < 0.04). De sterfte binnen 30-dagen was eveneens verminderd (0 vs 8.7%, p < 0.03).

In **Hoofdstuk 6** wordt de voorspellende waarde van glucose en HbA1c aangetoond bij het bepalen van perioperatieve en lange termijn risico's bij vaatchirurgiepatiënten. Behandeling van deze patiënten blijft een uitdaging. Patiënten met gestoorde glucose tolerantie voldoen niet aan de criteria voor diabetes, maar hebben het gevaar om diabetes of hart-en vaatziekten te ontwikkelen. Wij hebben vastgesteld dat de overleving bij patiënten met een gestoord glucosemetabolisme vergelijkbaar was met diabetes patiënten. Patiënten met een gestoord glucose metabolisme en diabetes hebben een 2.2- en 2.6-voudig verhoogd risico op ischemie, 3.8- en 3.9- voudig risico op troponine T stijging na de operatie, en een 4.3- en 4.8-voudig risico op cardiale complicaties binnen 30-dagen na de operatie. Op de lange termijn hebben zij een 1.9-en 3.1-verhoogd risico op cardiale aandoeningen. Patiënten met slecht gereguleerde diabetes mellitus, HbA1c> 7,0%, hebben een 2,8-voudig en een 5,3-voudig risico op ischemie, en verhoogde troponine T waarden binnen 30-dagen na de operatie. Tevens is de kans op en lange termijn cardiale complicaties 5,6-voudig verhoogd.

De relatie tussen verhoogde NT-proBNP met perioperatieve ischemie, is weergegeven in **Hoofdstuk 7**,. Deze bepaling ondersteunt het gebruik ervan als een marker van coronair vaatlijden en als prognostische marker bij patiënten die vasculaire chirurgie ondergaan. Verhoogde preoperatieve NT-proBNP waarden bij patiënten die vasculaire chirurgie ondergaan zijn geassocieerd met een verhoogd optreden van de perioperative myocard ischemie tijdens analyse door middel van een 12-afleidingen ECG (OR 1.59, 95% CI: 1.21 – 2.08, P < 0.001) en verhoogde troponine T waarden (OR: 1.76, 95% CI: 1.33 – 2.34, P < 0.001), onafhankelijk van de klinische risicofactoren en preoperatief verkregen resultaten van dobutamine stress echocardiografie.

Patiënten met hartfalen (HF) die gepland voor vasculaire chirurgie zijn hebben een verhoogd risico op postoperatieve cardiovasculaire complicaties en risicostratificatie hangt meestal af van de klinische risicofactoren. Dobutamine stress echocardiografie (DSE) heeft een aanvullende waarde voor risicostratificatie van deze patiënten.

In **Hoofdstuk 8** wordt het onafhankelijke prognostische waarde van wandbewegingsstoornissen tijdens DSE bij patiënten met HF die een vaatoperatie moeten ondergaan aangetoond voor de voorspelling van cardiale complicaties

binnen 30 dagen na de operatie en ook tijdens een follow-up van 5 jaar. Wandbewegingsstoornissen die een verbeterde contractie tonen tijdens lage dosis dobutamine infusie bieden een beschermend effect betreffende cardiale complicaties, zowel in het begin van de perioperative periode als op de lange termijn. Omgekeerd, ischemie (verslechtering van wandbewegingen) bleek geassocieerd te zijn met zowel vroege als in lange-termijn complicaties.

De hypothese was dat coronaire revascularisatie voorafgaand aan vaatchirurgie beschermend zou zijn bij patiënten die bij hoog cardiale risico groep behoren. Zoals het vermeld is in **Hoofdstuk 9**, zijn 101 patiënten die vasculaire chirurgie ondergaan met een hoog risico op hartaandoeningen (drie of meer klinische risicofactoren en een uitgebreide ischemie op DSE) gerandomiseerd voor preoperatieve cardiale revascularisatie of optimale medicamenteuze therapie. Angiografie toonde 2-taks coronairlijden bij 12 (24%), 3-takscoronairlijden bij 33 (67%), en een hoofdstam afwijking bij 4 (8%). Revascularisatie heeft de uitkomst binnen 30 dagen na de operatie niet verbeterd; de incidentie van het samengestelde studie eindpunt was 43% versus 33% (OR 1,4, 95% BI 0,7 tot 2,8, p <0,30). Ook werd geen voordeel gedurende 1 jaar follow-up waargenomen na coronaire revascularisatie (49% vs 44%, OR 1.2, 95% BI 0,7 tot 2,3, p <0,48).

Cardiovasculaire morbiditeit en mortaliteit kan voorkomen worden door vasculaire screening en behandeling van hoog-risicopatiënten. Dit screeningprogramma is kosteneffectief en kan leiden tot een aanzienlijke verbetering van de gezondheid. Screening van *Aneurysma Aortae Abdominalis* (AAA) is kostenbesparing en een tijdige ingreep verbetert overleving. In de **Hoofdstukken 10 en 11** worden twee nieuw ontwikkelde ultrageluid apparaten voor AAA screening geëvalueerd. De eerste is een 2-dimensionale, duplex, draagbare ultrageluid apparaat (USHH) en de tweede is een nieuw ontwikkelde, goedkopere, draagbare ultrageluid volume scanner voor 3-dimensionale metingen, oorspronkelijk bedoeld als automatisch 3-dimensioneel werkend ultrageluid apparaat, waarmee de inhoud van de blaas gemeten kan worden (BVI). Validatie van deze twee apparaten wordt gedaan door het vergelijken van de meetresultaten met de uitkomst van twee bestaande technieken - standaard echografie (US) en gecomputeriseerde tomografie (CT). Tussen de US en CT gemeten aortadiameter bestaat een nauwe relatie met het aortavolume gemeten door BVI (r = 0,87 en r = 0,86, respectievelijk). Ook de door CT gemeten aortadiameter correleert goed met de aortadiameter afgemeten door USHH (r = 0,98). Beide draagbare apparaten toonden hoge sensitiviteit, specificiteit en de positieve en negatieve voorspellende waarden voor het opsporen van AAA.

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Wonderful years are behind me – I've experienced living and working abroad, I've learned a lot about research, and I've established new friendships. Looking back, everything started in 2004 during the meeting of Echocardiographic Society of Serbia where I met Professor Don Poldermans under almost anecdotic circumstances. The day after his excellent lecture about usefulness of dobutamine stress echocardiography in preoperative risk stratification and importance of beta-blocker therapy in perioperative risk reduction, I was asked by Professor Aleksandar Neskovic, my former chief, to escort Professor Poldermans to the Belgrade Airport – since there was strike at Belgrade Airport, a flight to Amsterdam was delayed and I used that opportunity to ask him some questions about his lecture. Although his scientific work has been already known to me, I was very impressed by his expertise, knowledge, and scientific insight. At that moment I thought how good it would be to work with and learn from somebody like Professor Poldermans. Next year I went to the first "Cardiovascular Medicine – Update and Perspective" meeting in Rotterdam with only one goal – to meet Professor Poldermans again. This time we discussed possible research topics in his office, at the Erasmus MC. Few days after I came back to Belgrade, Professor Neskovic pleasantly surprised me with information that Professor Poldermans offered a scholarship for one Ph.D. candidate, and that he recommended me. I am very grateful to professor Neskovic that he believed in me, maybe more than I believed in myself. He is currently one of the most prominent European experts in the field of echocardiography, but also my teacher and my friend, and I know that I couldn't achieve anything so far without his support and encouragement. Also, I am very grateful to professor Poldermans for his patience, understanding, time and energy he invested in guiding and advising me through every process of research. You proved as the one of the most excellent professors one could wish for, and I am proud you were my mentor. A special thanks goes to the other member of Poldermans family, Virginie – thank you for sharing your wisdom with me. Your kindness, warmth, and heartiness are unique, and something I will remember forever.

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To fill like I'm at home ensured Rotterdam Serbian community – Tanja Nikolić, Aleksandar Vasić, Goran Rudež, Goran Balaban, Dragana Rakić, Sandra Janković, Rade and Nikola Klać, Saša Teodorović, Mladen Gavrilović, Ljiljana and Dragan Stevanović. Thank you all for the wonderful moments and provided support. But, I have to distinguish one person – my dear friend and colleague from Dedinje Cardioavsacular Institute, now senior operating room assistant at Thoraxcenter, Sonja Stevanović. Dear Sonja, in the most difficult moments for me you were there to help and to encourage, and I will never forget your kindness and generosity.

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CURRICULUM VITAE

The author of this thesis, Radosav Vidakovic, was born on August 7, 1971 in Prizren, Serbia. His family moved first to Pristina in 1973, and then to Belgrade in 1978, where he finished primary and secondary school. In 1990 he started studies of medicine at Belgrade University School of Medicine. He obtained medical degree in 1997, and upon that he started one-year internship. In 1998, he started residency in internal medicine at Belgrade University School of Medicine, which he finished in 2003 with the highest grades. During the period September 2003 – June 2009, he worked as the attending physician at Intensive Care Unit of Dedinje Cardiovascular Institute, Belgrade, Serbia. Since June 2009, he is a stuff-physician in the Cardiac CT lab of Dedinje Cardiovascular Institute. Since year 2004, he is a member of the STICH trial group of Dedinje Cardiovascular Institute.

At the beginning of 2006, he started Ph.D. studies at the Erasmus Medical Center, Rotterdam, the Netherlands, under supervision of Prof.dr. Don Poldermans.

LIST OF PUBLICATIONS

1. Vasiljević JD, Popović ZB, Otasević P, Popović ZV, **Vidaković R**, Mirić M, Nesković AN. Myocardial fibrosis assessment by semiquantitative, point-counting and computer-based methods in patients with heart muscle disease: a comparative study. Histopathology. 2001 Apr;38(4):338-43.
2. Miric M, Sagic D, Popovic Z, Zlatanovic M, Vlahovic A, **Vidakovic R**, Bojic M. [Percutaneous transluminal ablation of the myocardial septum by embolization of the first branch of the anterior descending coronary artery using a small amount of absolute alcohol]. Srp Arh Celok Lek. 2001 Jul-Aug;129(7-8):199-202. Serbian.
3. Otasević P, Popović ZB, Vasiljević JD, **Vidaković R**, Pratali L, Vlahović A, Nesković AN. Relation of myocardial histomorphometric features and left ventricular contractile reserve assessed by high-dose dobutamine stress echocardiography in patients with idiopathic dilated cardiomyopathy. Eur J Heart Fail. 2005 Jan;7(1):49-56.
4. Vasiljević JD, Otasević P, Popović ZB, Nesković AN, **Vidaković R**, Popović ZV, Radovancević B, Frazier OH, Gradinac S. Semiquantitative histomorphometric analysis of myocardium following partial left ventriculectomy: 1-year follow-up. Eur J Heart Fail. 2005 Aug;7(5):763-7.
5. Schouten O, van Laanen JH, Boersma E, **Vidakovic R**, Feringa HH, Dunkelgrün M, Bax JJ, Koning J, van Urk H, Poldermans D. Statins are associated with a reduced infrarenal abdominal aortic aneurysm growth. Eur J Vasc Endovasc Surg. 2006 Jul;32(1):21-6.
6. Feringa HH, van Waning VH, Bax JJ, Elhendy A, Boersma E, Schouten O, Galal W, **Vidakovic RV**, Tangelder MJ, Poldermans D. Cardioprotective medication is associated with improved survival in patients with peripheral arterial disease. J Am Coll Cardiol. 2006 Mar 21;47(6):1182-7.
7. Schouten O, Kok NF, Boersma E, Bax JJ, Feringa HH, **Vidakovic R**, Statius van Eps RG, van Sambeek MR, Poldermans D. Effects of statins on renal function after aortic cross clamping during major vascular surgery. Am J Cardiol. 2006 May 1;97(9):1383-5.
8. Dunkelgrun M, Schouten O, Feringa HH, Vidakovic R, Poldermans D. Beneficial effects of statins on perioperative cardiovascular outcome. Curr Opin Anaesthesiol. 2006 Aug;19(4):418-22.
9. Feringa HH, Schouten O, Dunkelgrun M, Bax JJ, Boersma E, Elhendy A, de Jonge R, Karagiannis SE, **Vidakovic R**, Poldermans D. Plasma N-terminal pro-B-type natriuretic peptide as long-term prognostic marker after major vascular surgery. Heart. 2007 Feb;93(2):226-31.
10. **Vidakovic R**, Schouten O, Feringa HH, Dunkelgrun M, Karagiannis SE, Merks E, Bosch J, Bom N, Neskovic AN, Bax JJ, Poldermans D. Abdominal aortic aneurysm screening using non-imaging hand-held ultrasound volume scanner--a pilot study. Eur J Vasc Endovasc Surg. 2006 Dec;32(6):615-9.
11. Feringa HH, Bax JJ, de Jonge R, Elhendy A, van Domburg RT, Dunkelgrun M, Schouten O, Karagiannis SE, **Vidakovic R**, Poldermans D. Impact of glomerular filtration rate on minor troponin T elevations for risk assessment in patients undergoing operation for abdominal aortic aneurysm or lower extremity arterial obstruction. Am J Cardiol. 2006 Dec 1;98(11):1515-8.
12. Karagiannis SE, Feringa HH, Bax JJ, Elhendy A, Dunkelgrun M, **Vidakovic R**, Hoeks SE, van Domburg R, Valhema R, Cokkinos DV, Poldermans D. Myocardial viability estimation during the recovery phase of stress echocardiography after acute beta-blocker administration. Eur J Heart Fail. 2007 Apr;9(4):403-8.

13. Schouten O, Dunkelgrun M, Feringa HH, Kok NF, **Vidakovic R**, Bax JJ, Poldermans D. Myocardial damage in high-risk patients undergoing elective endovascular or open infrarenal abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg. 2007 May;33(5):544-9.

14. Karagiannis SE, Elhendy A, Feringa HH, van Domburg R, Bax JJ, **Vidakovic R**, Cokkinos DV, Poldermans D. The long prognostic value of wall motion abnormalities during the recovery phase of dobutamine stress echocardiography after receiving acute beta-blockade. Coron Artery Dis. 2007 May;18(3):187-92.

15. Poldermans D, Schouten O, **Vidakovic R**, Bax JJ, Thomson IR, Hoeks SE, Feringa HH, Dunkelgrün M, de Jaegere P, Maat A, van Sambeek MR, Kertai MD, Boersma E; DECREASE Study Group. A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery: the DECREASE-V Pilot Study. J Am Coll Cardiol. 2007 May 1;49(17):1763-9.

16. Dunkelgrun M, Hoeks SE, Elhendy A, van Domburg RT, Bax JJ, Noordzij PG, Feringa HH, **Vidakovic R**, Karagiannis SE, Schouten O, Poldermans D. Significance of hypotensive response during dobutamine stress echocardiography. Int J Cardiol. 2008 Apr 25;125(3):358-63.

17. Feringa HH, Karagiannis SE, Chonchol M, **Vidakovic R**, Noordzij PG, Elhendy A, van Domburg RT, Welten G, Schouten O, Bax JJ, Berl T, Poldermans D. Lower progression rate of end-stage renal disease in patients with peripheral arterial disease using statins or Angiotensin-converting enzyme inhibitors. J Am Soc Nephrol. 2007 Jun;18(6):1872-9.

18. Feringa HH, Karagiannis SE, Schouten O, **Vidakovic R**, van Waning VH, Boersma E, Welten G, Bax JJ, Poldermans D. Prognostic significance of declining ankle-brachial index values in patients with suspected or known peripheral arterial disease. Eur J Vasc Endovasc Surg. 2007 Aug;34(2):206-13.

19. Feringa HH, Elhendy A, Karagiannis SE, Noordzij PG, Dunkelgrun M, Schouten O, **Vidakovic R**, van Domburg RT, Bax JJ, Poldermans D. Improving risk assessment with cardiac testing in peripheral arterial disease. Am J Med. 2007 Jun;120(6):531-8.

20. Karagiannis SE, Roelandt J, Qazi M, Krishnan S, Feringa HH, **Vidakovic R**, Karatasakis G, Cokkinos DV, Poldermans D. Automated coupled-contour and robust myocardium tracking in stress echocardiography. Eur J Echocardiogr. 2007 Dec;8(6):431-7.

21. Karagiannis SE, Feringa HH, **Vidakovic R**, van Domburg R, Schouten O, Bax JJ, Karatasakis G, Cokkinos DV, Poldermans D. Value of myocardial viability estimation using dobutamine stress echocardiography in assessing risk preoperatively before noncardiac vascular surgery in patients with left ventricular ejection fraction <35%. Am J Cardiol. 2007 Jun 1;99(11):1555-9.

22. Schouten O, Hoeks SE, Welten GM, Davignon J, Kastelein JJ, **Vidakovic R**, Feringa HH, Dunkelgrun M, van Domburg RT, Bax JJ, Poldermans D. Effect of statin withdrawal on frequency of cardiac events after vascular surgery. Am J Cardiol. 2007 Jul 15;100(2):316-20.

23. Feringa HH, Hendriks JM, Karagiannis S, Schouten O, **Vidakovic R**, van Sambeek MR, Klein J, Noordzij P, Bax JJ, Poldermans D. Carotid artery stenting versus endarterectomy in relation to perioperative myocardial ischemia, troponin T release and major cardiac events. Coron Artery Dis. 2007 Sep;18(6):483-7.

24. **Vidakovic R**, Feringa HH, Schouten O, Dunkelgrun M, Hoeks SE, van Domburg RT, Poldermans D. Coronary artery disease in patients with abdominal aortic aneurysm: a systematic review. Ital J Vasc Endovasc Surg. 2007 Sep; 14(3):247-55.

25. Feringa HH, Schouten O, Karagiannis SE, Brugts J, Elhendy A, Boersma E, **Vidakovic R**, van Sambeek MR, Noordzij PG, Bax JJ, Poldermans D. Intensity of statin therapy in relation to myocardial ischemia, troponin T release, and clinical cardiac outcome in patients undergoing major vascular surgery. J Am Coll Cardiol. 2007 Oct 23;50(17):1649-56.

26. Feringa HH, Karagiannis S, **Vidakovic R**, Noordzij PG, Brugts JJ, Schouten O, van Sambeek MR, Bax JJ, Poldermans D. Comparison of the incidences of cardiac arrhythmias, myocardial ischemia, and cardiac events in patients treated with endovascular versus open surgical repair of abdominal aortic aneurysms. Am J Cardiol. 2007 Nov 1;100(9):1479-84.

27. Feringa HH, Karagiannis SE, **Vidakovic R**, Elhendy A, ten Cate FJ, Noordzij PG, van Domburg RT, Bax JJ, Poldermans D. The prevalence and prognosis of unrecognized myocardial infarction and silent myocardial ischemia in patients undergoing major vascular surgery. Coron Artery Dis. 2007 Nov;18(7):571-6.

28. Feringa HH, Karagiannis SE, **Vidakovic R**, Elhendy A, Schouten O, Boersma E, Bax JJ, Poldermans D. Glycemic control, lipid-lowering treatment, and prognosis in diabetic patients with peripheral atherosclerotic disease. Ann Vasc Surg. 2007 Nov;21(6):780-9.

29. Feringa HH, **Vidakovic R**, Karagiannis SE, de Jonge R, Lindemans J, Goei D, Schouten O, Bax JJ, Poldermans D. Baseline natriuretic peptide levels in relation to myocardial ischemia, troponin T release and heart rate variability in patients undergoing major vascular surgery. Coron Artery Dis. 2007 Dec;18(8):645-51.

30. Feringa HH, Bax JJ, Hoeks S, van Waning VH, Elhendy A, Karagiannis S, **Vidakovic R**, Schouten O, Boersma E, Poldermans D. A prognostic risk index for long-term mortality in patients with peripheral arterial disease. Arch Intern Med. 2007 Dec 10;167(22):2482-9.

31. **Vidakovic R**, Feringa HH, Kuiper RJ, Karagiannis SE, Schouten O, Dunkelgrun M, Hoeks SE, Bom N, Bax JJ, Neskovic AN, Poldermans D. Comparison with computed tomography of two ultrasound devices for diagnosis of abdominal aortic aneurysm. Am J Cardiol. 2007 Dec 15;100(12):1786-91.

32. Karagiannis SE, Feringa HH, Elhendy A, van Domburg R, Chonchol M, **Vidakovic R**, Bax JJ, Karatasakis G, Athanasopoulos G, Cokkinos DV, Poldermans D. Prognostic significance of renal function in patients undergoing dobutamine stress echocardiography. Nephrol Dial Transplant. 2008 Feb;23(2):601-7.

33. Feringa HH, **Vidakovic R**, Karagiannis SE, Dunkelgrun M, Elhendy A, Boersma E, van Sambeek MR, Noordzij PG, Bax JJ, Poldermans D. Impaired glucose regulation, elevated glycated haemoglobin and cardiac ischaemic events in vascular surgery patients. Diabet Med. 2008 Mar;25(3):314-9.

34. Dunkelgrun M, Schreiner F, Schockman DB, Hoeks SE, Feringa HH, Goei D, Schouten O, Welten GM, **Vidakovic R**, Noordzij PG, Boersma E, Poldermans D. Usefulness of preoperative oral glucose tolerance testing for perioperative risk stratification in patients scheduled for elective vascular surgery. Am J Cardiol. 2008 Feb 15;101(4):526-9.

35. Dunkelgrun M, Hoeks SE, Schouten O, Feringa HH, Welten GM, **Vidakovic R**, van Gestel YR, van Domburg RT, Goei D, de Jonge R, Lindemans J, Poldermans D. Methionine loading does

not enhance the predictive value of homocysteine serum testing for all-cause mortality or major adverse cardiac events. Intern Med J. 2009 Jan;39(1):13-8.

36. Dunkelgrun M, Hoeks SE, Welten GM, **Vidakovic R**, Winkel TA, Schouten O, van Domburg RT, Bax JJ, Kuijper R, Chonchol M, Verhagen HJ, Poldermans D. Anemia as an independent predictor of perioperative and long-term cardiovascular outcome in patients scheduled for elective vascular surgery. Am J Cardiol. 2008 Apr 15;101(8):1196-200.
37. Welten GM, Schouten O, Hoeks SE, Chonchol M, **Vidakovic R**, van Domburg RT, Bax JJ, van Sambeek MR, Poldermans D. Long-term prognosis of patients with peripheral arterial disease: a comparison in patients with coronary artery disease. J Am Coll Cardiol. 2008 Apr 22;51(16):1588-96.
38. **Vidakovic R**, Schouten O, Kuiper R, Hoeks SE, Flu WJ, van Kuijk JP, Goei D, Verhagen HJ, Neskovic AN, Poldermans D. The prevalence of polyvascular disease in patients referred for peripheral arterial disease. Eur J Vasc Endovasc Surg. 2009 Oct;38(4):435-40.

PHD PORTFOLIO

Name PhD Student: Radosav Vidakovic Research School: COEUR PhD Period: 2006 – 2009 Promotor: Prof. dr. Don Poldermans Erasmus MC Department: Vascular Surgery		
	Year	**Workload (ECTS)**
In-depth COEUR courses		
– Cardiovascular Clinical Epidemiology	2006	1.5
– Cardiovascular Imaging and Diagnostics	2006	1.5
– Atherosclerosis Research	2006	1.5
– Heart-Failure Research	2006	1.5
– Molecular biology in atherosclerosis and cardiovascular research	2007	1.5
– Cardiovascular Medicine	2007	1.5
– Pathophysiology of Ischemic Heart Disease	2007	1.5
– Cardiovascular Pharmacology	2007	1.5
– Prophylaxis of sudden death	2007	1.5
– COEUR Research Seminars (Friday afternoon)	2006–2007	2.0
Other courses		
– NIHES – Erasmus Winter Program: Good Clinical Practice	2007	1
– Cardiology and Vascular Medicine, Rotterdam	2006	1
– Cardiology and Vascular Medicine, Rotterdam	2007	1
– Cardiac Cross-Sectional Imaging	2009	0.7
Conferences		
– European Society of Cardiology Meeting	2006	1
– American Heart Association Scientific Sessions	2006	1
– European Society of Cardiology Meeting	2007	1
– European Society of Cardiology Meeting	2008	1
– European Society of Cardiac Radiology	2009	1
Total ECTS		**24.2**