Risk Identification and Reduction Strategies in Surgical Patients

RISK IDENTIFICATION AND REDUCTION STRATEGIES IN SURGICAL PATIENTS

MARTIN DUNKELGRÜN

Martin Dunkelgrün

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Risicoschatting en reductie strategieën in chirurgische patiënten
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Martin Dunkelgrün
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PROMOTIECOMMISSIE

Promotores:	Prof.dr. D. Poldermans
	Prof.dr.ir. H. Boersma
Overige leden:	Prof.dr. J.N.M. IJzermans
	Prof.dr. H. van Urk
	Prof.dr. H.J.M. Verhagen

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Preface

RISK IDENTIFICAT
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Every year, approximately 4% of the Dutch population is scheduled for major noncardiac surgery, with an average preoperative mortality rate of 1.9%[1]. Patients undergoing major noncardiac surgery are at reisk for complications during the perioperative period, such as surgical site infection, pneumonia, myocardial infarction, and death. Cardiac events are estimated to be the most frequent cause of perioperative complications resulting in death. Recently, Boersma et al. conducted a 10-year surgical cohort study of over 100,000 noncardiac surgical patients in Rotterdam, the Netherlands[2]. They showed that at least 30% of mortality during the surgical period was caused by cardiac complications. Therefore, an estimated 3,600 patients die each year in the Netherlands alone due to cardiac complications after noncardiac surgery. Improving preoperative cardiac risk stratification and optimizing perioperative management is therefore of utmost importance.

OUTLINE OF THE THESIS

Perioperative myocardial infarction (PMI) is one of the most important predictors of short- and long term morbidity and mortality associated with noncardiac surgery[3-6]. Prevention of a PMI is therefore key to improving overall postoperative outcome. Unfortunately, the exact mechanism of PMI is not fully understood and remains a subject of continued debate[3,4,6]. Chapter one describes the current understanding of the pathophysiology of perioperative myocardial infarctions.

CARDIAC RISK IDENTIFICATION

Non-invasive cardiac stress testing can be applied to improve perioperative cardiac risk assessment in patients scheduled for elective non-cardiac surgery. While a hypotensive response to exercise testing has been associated with a poor prognosis, the prognostic significance of a hypotensive response during dobutamine stress echocardiography remains unclear. The second chapter of this thesis investigates the association between a severe hypotensive response during dobutamine stress echocardiography and long-term prognosis in 3381 patients who underwent non-invasive stress testing over a period of 13 years. Clinical risk markers can refine perioperative risk assessment and the expansion of inexpensive laboratory markers could significantly improve preoperative work up. Hyperhomocysteinemia is associated with atherosclerotic disease, but its use as a predictive marker is disputed. In chapter three, the beneficial effect of metionine loading on the predictive value for homocysteine testing is evaluated with regard to long term mortality and major adverse cardiac events 1122 patients with atherosclerotic disease. In chapter four, the usefulness of standardized preoperative oral glucose tolerance testing is prospectively investigated in 404 patients scheduled for elective vascular

surgery. The active detection of unknown diabetes mellitus and impaired glucose regulation could improve perioperative risk stratification and perioperative patient management. Chapter five investigates whether the long term result of the patients included in chapter four are different for patients with new onset diabetes, patients with impaired glucose regulation and patients with normal glucose regulation. Anemia, which is common in vascular patients, is a risk factor for adverse cardiac outcome, and has been related to underlying co-morbidities such as heart failure and renal dysfunction. Chapter six investigates whether preoperative anemia is an independent predictor of perioperative and long-term cardiovascular outcome in 1211 elective vascular surgery patients or whether it is merely an expression of co-morbidities. The role of uric acid as an independent marker of cardiovascular risk is unclear. Therefore, the aim of chapter seven was to assess the independent contribution of preoperative serum uric acid levels to the risk of perioperative and late mortality and major adverse cardiac events in 936 patients scheduled for open vascular surgery.

CARDIAC RISK REDUCTION

In diverse patient populations, is has been shown that different medical therapies can be used to reduce the risk of perioperative and long term cardiac risk, yet uncertainty remains as to which medical therapy should be implemented in which patients. The objective of chapter eight was to evaluate the use of Niaspan®, a prolonged-release nicotinic acid, in 612 patients in the Netherlands with elevated cholesterol with regard to tolerability, HDL-cholesterol elevation and cardiovascular risk reduction.

In chapter nine, the effect of the dosis of perioperative statins use is investigated in patients undergoing open vascular surgery, with regard to the efficacy and safety in the prevention of perioperative cardiovascular complications. In a case-control study of patients undergoing non-cardiovascular surgery at the Erasmus Medical Center, the relation between perioperative beta-blocker therapy, statin therapy and mortality is evaluated[7]. To prospectively validate this case-control study, the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo - IV (DECREASE-IV) trial was set up, which is described in chapter ten. In this multi-centre, open-label, randomized, controlled, clinical trial, the perioperative use of beta-blockers, statins, their combination or no medical therapy are evaluated in elective intermediate-risk surgical patients with regard to perioperative outcome. The primary endpoint of this study was the composite of cardiac death and non-fatal myocardial infarction at 30 days after non-cardiovascular surgery.

Finally, in chapter eleven, we selected from the DECREASE IV study those patients who underwent an esophagectomy for cancer. We investigated the effect of perioperative beta-blocker therapy in these patients with regard to cardiac risk reduction and the incidence of ischemia and leakage of the esophagogastric anastomosis.

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Chapter 1

Pathophysiology of Perioperative Myocardial Infarction

Dunkelgrun M
Poldermans D

INTRODUCTION

Perioperative myocardial infarction (PMI) is one of the most important predictors of short- and long-term morbidity and mortality associated with non-cardiac surgery[1-4]. Although the perioperative event rate has declined over the past decades as a result of achievements in anesthesiologic and surgical techniques, perioperative complications remain a significant problem. Importantly, a large study showed that long-term prognosis of vascular surgery patients was significantly worse than for patients with coronary artery disease[5]. Prevention of a PMI is therefore a prerequisite for the improvement in overall postoperative outcome. However, the exact nature of perioperative myocardial infarction remains unclear and an area of continued debate and controversy[1,2,4].

INCIDENCE

Estimations of cardiac outcome can be derived from the few large-scale clinical trials and registries that have been undertaken in patients undergoing noncardiac surgery. Lee et al. studied 4,315 patients undergoing elective major noncardiac procedures in a tertiary-care teaching hospital during 1989-1994[6]. Major cardiac complications, including cardiac death and myocardial infarction (MI), were observed in 2.1% of this patient cohort. In a cohort of 108,593 consecutive patients who underwent surgery during 1991-2000 in a university hospital in The Netherlands, perioperative mortality occurred in 1,877 (1.7%) cases, of whom 543 (0.5%) were attributed to cardiovascular causes[6]. The Dutch Echographic Cardiac Risk Evaluating Applying Stress Echo (DECREASE) -I, -II and -IV trials enrolled 3,893 surgical patients during 1996-2008, consisting of intermediate and high-risk patients, and 136 (3.5%) had perioperative cardiac death or MI[7-9].

The recently published PeriOperative ISchemic Evaluation trial (POISE) enrolled 8,351 patients noncardiac surgery in the period 2002-2007 and perioperative mortality occurred in 226 patients (2.7%), of whom 543 (1.7%) had cardiovascular death, whereas nonfatal MI was observed in another 367 (4.4%) subjects[10]. Overall, major noncardiac surgery is associated with an incidence of cardiac death between 0.5% and 1.5%, and an incidence of major cardiac complications in the range of 2.0% to 3.5%. The global ageing phenomenon will have a major impact on the incidence of perioperative cardiac complications and therefore on perioperative management in future years. It is estimated from primary care data that in the 75–84 year age group 19% of males and 12% of women have some degree of cardiovascular diaesase[11]. With the growing elderly population, increased incidence of cardiovascular disease, and the availability of advanced surgical techniques, preoperative cardiac risk assessment and perioperative cardiac management continues to be a major challenge.

PATHOPHYSIOLOGY OF ACUTE CORONARY SYNDROME

Acute coronary syndromes are associated with structurally as well as functionally complex plaques and coronary artery stenoses, coronary endothelial lesions, and plaque inflammation[12-17]. Systemic or multi-focal arterial inflammation may be independent risk factors for acute coronary events[12,17]. Plaque progression is frequently abrupt, mostly unpredictable[12], and often related to episodes of thrombosis (which, in turn, are triggered by plaque rupture, erosion, endothelial activation, or inflammation). In the absence of a hypercoagulable state, thrombi may remain mural rather than become occlusive, and may thus produce few if any symptoms unless they embolize[18]. If subsequent lysis is incomplete and is followed by re-endothelialization, the plaque will grow. The unpredictability of plaque progression is probably related to fluctuations in risk factors and triggers, for example physical activity, mental stress, environmental temperature, smoking, infection, hydration, and arterial pressure; to heterogeneity of plaque histology; and to differences in the physical forces to which plaques are exposed[17-21].

It is impossible to predict the time it will take a vulnerable plaque to become unstable, or the trigger that causes the plaque to rupture. Plaque vulnerability is probably caused by thrombogenic blood and/or local pro-inflammatory cytokines that trigger thrombosis, sometimes even in the absence of inflammatory cell infiltration and a lipid core. Rupture of the intimal surface of a plaque is the result of a combination of cellular processes that promote plaque instability, and of physical processes that influence the magnitude and distribution of stress on the plaque.

Plaque rupture is more common during various kinds of strenuous physical activity and emotional stress[22]. Activation of the sympathetic nervous system in these situations leads to increased plasma concentrations of catecholamines, blood viscosity, and of arterial pressure and heart rate, which are accompanied by detectable increases in platelet aggregation and decreases in fibrinolytic activity that both tend to favour thrombosis[23]. This combination of increased prothrombotic and reduced fibrinolytic activity could initiate propagation and total occlusion of the coronary artery by a mural thrombus overlying a small plaque erosion that might otherwise have been harmless. The perioperative period is characterized by comparable adrenergic stimulation, and increased prothrombotic and reduced fibrinolytic activity. In the event of plaque rupture, thrombus growth depends not only on the size and thrombogenicity of the fissured plaque, but also on the number and activation of exposed inflammatory cells[24]. Inflammatory activation of the endothelium can turn its physiological vasodilatory and antithrombotic properties into pathological vasoconstrictor and prothrombotic properties. In addition, the inflammatory response of the circulating blood may activate coagulation[25]. These many variables explain why coronary lesions that are angiographically fairly small may progress acutely to severe stenosis or total occlusion.

PATHOPHYSIOLOGY OF PERIOPERATIE MYOCARDIAL INFACTION

There is pathological and angiographic evidence that the aetiology of PMI resembles that in the non-surgical setting[26,27]. Surgery itself is a significant stress factor leading to an increased risk of plaque rupture. In PMI, acute plaque disruption and haemorrhage in the infarct-related coronary artery seems to be common[26-28], but the severity of underlying coronary artery stenosis does not necessarily predict the infarct territory[27]. In patients with significant coronary artery disease (CAD), PMI may also be caused by a sustained myocardial supply / demand imbalance due to tachycardia and increased myocardial contractility[29]. Episodes of perioperative ST-depression on an electrocardiogram, indicating subendocardial myocardial ischemia, has been described in up to 41% of vascular surgery patients mostly occurring within the first two days after operation[30]. The association of PMI with myocardial ischemia and non-transmural or circumferential subendocardial infarction supports this mechanism. However, myocardial oxygen supply / demand mismatch and plaque rupture are not mutually exclusive mechanisms, and PMIs may develop by different mechanisms at different locations in the same patient. Landesberg et al. demonstrated that 85% of postoperative cardiac complications were preceded by prolonged ST-segment depression[31]. Fleisher and colleagues found that 78% of patients with cardiac complications had at least one episode of prolonged myocardial ischemia either before or at the same time of the cardiac event[32]. In the majority of cases, it presents without Q waves. The hypothesis that ST-depression can lead to PMI is further supported by increased troponine T levels during or shortly after prolonged ST-depression ischemia[33]. The frequent combination of increases in heart rate preceding the ischaemic episodes, ST-segment depression rather than elevation during all ischaemic episodes; non-Q-wave rather than Q-wave MIs in almost all cases; the lack of angiographically visible thrombus or ruptured plaques in some patients who underwent coronary angiography following PMI; and complete reversal of ECG changes to baseline in all but one of the patients with ischaemia (including those with infarction)[34], are highly suggestive that prolonged stress-induced myocardial ischaemia is the likely primary cause of PMI. Repeated brief ischaemic episodes may well have a cumulative effect and ultimately cause myocardial necrosis[35].

Most ischaemic episodes tend to start at the end of surgery and during emergence from anaesthesia[34]. This period is characterized by increases in heart rate, arterial pressure, sympathetic tone, and procoagulant activity[36]. Increased sympathetic tone can result in increases in arterial pressure, heart rate, contractility, coronary vasomotor tone, and coronary vascular shear stress. This, in turn, may trigger coronary vasospasm, plaque disruption, and coronary thrombosis. Increases in arterial pressure, heart rate, and cardiac contractility lead to subendocardial ischaemia by increasing myocardial oxygen demands in the presence of limited or absent coronary vasodilator reserve as a result of underlying CAD. Surgery-induced simultaneous procoagulant and anti-fibrinolytic activity may trigger coronary artery thrombosis during

low-flow conditions in the presence of underlying stable CAD even in the absence of acute plaque disruption.

The ultimate fate of the thrombus and, thus, the extent of jeopardized myocardium will depend on the duration and degree of coronary occlusion. If the plaque disruption is major with extensive exposure of thrombogenic core material to the blood stream, acute total coronary occlusion with subsequent MI, or sudden death may develop. If the disruption is minor, the forming thrombus can be non-occlusive and the patient may stay asymptomatic or develop unstable angina or a non-Q-wave infarction. A concomitant increase in coagulability and coronary vasoconstriction (as is common in the perioperative setting) may, however, transform a non-occlusive thrombus to an occlusive thrombus. Ultimately, the balance between thrombosis and thrombolysis, and the flow conditions (affected by coronary vasomotor tone, perfusion pressure, and rheological properties) are the decisive factors in determining whether the clinical outcome will be myocardial ischaemia or an MI.

SUMMARY

The pathophysiology of PMI remains poorly understood[1,3,4]. Existing data are inconclusive and do not allow a definitive decision on whether long-duration subendocardial myocardial ischaemia or acute coronary occlusion as a result of plaque disruption or thrombosis is the primary mechanism of perioperative myocardial infarction in the individual patient. However, this is to be expected considering the enormous structural and functional diversity of coronary atherosclerosis, the unpredictability of plaque progression and vulnerability, and the outstanding methodological problems of reliably detecting and diagnosing perioperative myocardial ischaemia and infarction. Therefore, efforts to understand and treat both pathways leading up to possible perioperative myocardial infarctions is warranted.

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Risk Identification

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Chapter 2

Significance of Hypotensive Response during Dobutamine Stress Echocardiography

Dunkelgrun M
Hoeks SE
Elhendy A
van Domburg RT
Bax JJ
Noordzij PG
Feringa HH
Vidakovic R
Karagiannis SE
Schouten O
Poldermans D.

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Significance of hypotensive response during dobutamine stress echocardiography

Martin Dunkelgrun [a], Sanne E. Hoeks [b], Abdou Elhendy [c], Ron T. van Domburg [b], Jeroen J. Bax [d], Peter G. Noordzij [e], Harm H.H. Feringa [b], Radosav Vidakovic [b], Stefanos E. Karagiannis [b], Olaf Schouten [a], Don Poldermans [e,*]

[a] *Vascular Surgery, Erasmus Medical Center, Rotterdam, The Netherlands*
[b] *Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands*
[c] *Internal Medicine, Marshfield Clinic, Marshfield, WI, United States*
[d] *Cardiology, Leiden University Medical Center, Leiden, The Netherlands*
[e] *Anesthesiology, Erasmus Medical Center, Rotterdam, The Netherlands*

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Abstract

Background: In patients undergoing exercise testing a hypotensive response is associated with a poor prognosis. There is limited information regarding the prognostic significance of hypotension during dobutamine stress test. This study investigates the association between a severe hypotensive response during DSE and long-term prognosis.
Methods: Patients (3381) underwent dobutamine stress echocardiography (DSE). Blood pressure was measured automatically at rest and at the end of every dose-step. Wall motion was scored using a 16-segement, 5-point score. Ischemia was defined by the presence of new wall motion abnormalities. Hypotensive response during DSE was defined as mild (MHR) when systolic blood pressure (SBP) dropped <20 mmHg between rest and peak stress, and severe (SHR) when SBP dropped <20 mmHg. During follow-up all cause mortality and MACE (cardiac death or non-fatal myocardial infarction) were noted.
Results: MHR and SHR occurred in 936 (28%) and 521 (15%) patients, respectively. Independent predictors of SHR were older age, new or worsening wall motion abnormalities and history of hypertension. During follow-up of 4.5 (±3.3) years, 920 patients died, of which 555 due to cardiac causes, and 713 patients experienced a MACE. After adjustment for baseline characteristics and DSE results SHR during DSE was independently associated with increased long-term cardiac death (HR: 1.3, 95% CI: 1.03–1.6) and MACE (HR: 1.34, 95% CI: 1.1–1.6), while MHR was not associated with a worse outcome.
Conclusions: Severe hypotensive response during DSE independently predicts cardiac death and MACE in patients with known or suspected coronary artery disease.

Keywords: Dobutamine stress echocardiography; Hypotensive response; Beta-blocker, Prognosis; Mortality

1. Introduction

Exercise stress test is a widely used technique for evaluation of coronary artery disease. In patients unable to perform exercise testing, dobutamine stress echocardiography (DSE) is a useful alternative because of its ability to reproduce physiologic responses to exercise stress, ease of use, patient acceptance and safety [1–4]. A hypotensive response to exercise stress has been shown to correlate with severe coronary artery disease as well as poor cardiac prognosis [5–7]. Hypotensive response occurring during dobutamine stress testing appears to be more common, with an occurrence of 14–48% [8,9]. Moreover, a hypotensive response during dobutamine

* Corresponding author. Department of Vascular Surgery, Room H 973, Erasmus MC, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. Tel.: +31 104639222; fax: +31 104634957.
E-mail address: d.poldermans@erasmusmc.nl (D. Poldermans).

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stress echocardiography has, to our knowledge, not yet been invariably associated with advanced coronary artery disease or an adverse outcome [10]. Severe anatomic and functional cardiac impairment may be associated with the development of severe hypotensive response occurring during dobutamine stress echocardiography. Therefore, its presence may be related to wall motion abnormalities observed during dobutamine stress. The current study sought to examine the relation of hypotensive response induced during DSE and long-term cardiac outcome.

2. Materials and methods

2.1. Patient population

The study population was composed of a series of 3875 consecutive patients with limited exercise capacity and known or suspected CAD, who were referred for DSE between January 1990 and January 2003 to the Thoraxcenter, Rotterdam, the Netherlands. Follow-up was successful in 3705 patients (99%). A total of 455 patients (12%) underwent early coronary revascularization within the first 60 days after DSE and were excluded from analysis because the test results directly altered patient management. The final population consisted of 3310 patients. The protocol was approved by the hospital ethics committee and all patients gave informed consent before the test. Clinical characteristics and indications for testing were noted before DSE. Known CAD was defined as documentation of previous myocardial infarction or myocardial revascularization, or angiographic documentation of significant coronary artery stenosis. Suspected CAD was defined as the presence of symptoms related to CAD or the evidence of an abnormal baseline electrocardiogram associated with the presence of cardiac risk factors for CAD. Diabetes mellitus was defined as fasting glucose level of ≥126 mg/dl (7.0 mmol/L) or the use of insulin or oral hypoglycemic agents. Hyperlipidemia was defined as total cholesterol ≥200 mg/dl (≥5.5 mmol/L) or the use of lipid-lowering medication. Patients were considered to have hypertension if they had systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or if they used antihypertensive medication.

2.2. Dobutamine stress echocardiography

Dobutamine was infused at a dose of 5 to 10 μg/kg/min (5-min stages) and increased by 10 μg/kg/min every 3 min to a maximum of 40 μg/kg/min. Atropine, starting at 0.25 mg and continued up to 2 mg, was given to patients who did not achieve 85% of age- and gender-predicted maximal heart rate after maximum dose of dobutamine. The electrocardiograph was monitored throughout the test every minute. Blood pressure was measured by sphygmomanometer (Accutorr A1; Datascope Corp., Paramus, New York, USA) at baseline and at the end of every stage. Antihypertensive medication was not withheld prior to the DSE, nor was any other medication. Mild hypotensive response (MHR) during DSE was defined a decrease in SBP from <20 mmHg between rest and peak stress. Severe hypotensive response (SHR) was defined as a ≥20 mmHg decrease in SBP from baseline. Test end points were achievement of target heart rate (85% of maximal age- and gender-predicted heart rate), maximal dose of dobutamine and atropine, extensive new wall motion abnormalities, >2 mV downsloping ST-segment depression measured 80 ms after the J point compared with baseline, hypertension (blood pressure >240/120 mmHg), a symptomatic decrease in systolic blood pressure of >40 mmHg compared with at rest, significant arrhythmias or any severe adverse effect considered to be the result of dobutamine or atropine.

2.3. Echocardiographic imaging and interpretation

Two-dimensional echocardiographic images were acquired at rest, during dobutamine stress and during recovery using standard views. Regional wall motion and systolic wall thickening were scored on a five-point scale using a standard 16-segment left ventricular model by two independent readers. In case of disagreement, a third reader settled the dispute. Ischemia was defined as new or worsened wall motion abnormalities during stress indicated by an increase of wall motion score ≥1 grade in ≥1 segment. A biphasic response in an akinetic or hypokinetic segment was considered as an ischemic response. Ischemia was not considered present when akinetic segments at rest became dyskinetic during stress. For each patient, a wall motion score index was calculated by dividing the sum of segment scores by the total number of interpreted segments.

Table 1
Baseline characteristics of the study population

Variables	Normal (n=1853)	MHR (n=936)	SHR (n=521)	p value
Age, years (SD)	58.8 (13.0)	63.7 (11.5)	66.1 (10.3)	<0.001
Male (%)	1268 (69.4)	587 (63.8)	352 (68.0)	0.013
Diabetes (%)	182 (9.8)	125 (13.4)	97 (12.9)	0.010
Smoking (%)	538 (29.0)	272 (29.1)	162 (31.1)	0.641
Hypercholesterolemia (%)	398 (21.5)	228 (24.4)	141 (27.1)	0.017
History of heart failure (%)	237 (12.8)	148 (15.8)	67 (12.9)	0.076
Hypertension (%)	467 (25.2)	327 (34.9)	203 (39.0)	<0.001
Previous MI (%)	707 (38.2)	336 (35.9)	203 (39.0)	0.405
Previous revascularization (%)	334 (18.0)	216 (23.1)	121 (23.2)	0.001
Beta-blockers (%)	612 (33.0)	304 (32.5)	177 (34.0)	0.844
ACE inhibitors (%)	387 (20.9)	282 (30.1)	174 (33.4)	<0.001
Statins (%)	124 (6.7)	47 (5.0)	31 (6.0)	0.217
Calcium channel blockers (%)	410 (22.1)	245 (26.2)	148 (28.3)	0.003
Diuretics (%)	200 (10.8)	173 (18.5)	102 (19.6)	<0.001
Nitrates (%)	123 (6.6)	47 (5.0)	31 (6.0)	0.239
Digitalis (%)	78 (4.2)	63 (6.7)	47 (9.0)	<0.001

MHR=mild hypotensive response; SHR=severe hypotensive response; SD=standard deviation; MI=myocardial infarction; ACE=angiotensin-converting enzyme.

Table 2
Dobutamine stress echocardiography data

Variables	Normal (n=1853)	MHR (n=936)	SHR (n=521)	p value
Fixed defects, patients (%)	1110 (59.9)	591 (63.1)	337 (64.7)	0.071
Segments with RWMA (SD)	1.45 (0.60)	1.54 (0.64)	1.49 (0.59)	0.001
New or worsening wall motion abnormalities, patients (%)	846 (45.7)	469 (50.1)	286 (54.9)	<0.001
Segments with PWMA (SD)	2.90 (4.5)	3.64 (5.0)	3.8 (4.9)	0.001
Resting heart rate (SD)	71.9 (13.8)	73.8 (16.6)	73.5 (13.5)	<0.001
Peak heart rate (SD)	130.5 (15.5)	129.6 (13.4)	128.5 (13.5)	0.013
Resting systolic blood pressure (SD)	128.7 (23.3)	134.8 (23.9)	146.2 (24.2)	<0.001
Peak systolic blood pressure (SD)	144.8 (27.0)	125.2 (24.0)	110.8 (24.2)	<0.001
Resting diastolic blood pressure (SD)	74.9 (13.4)	74.9 (13.4)	78.4 (13.4)	<0.001
Peak diastolic blood pressure (SD)	76.2 (15.4)	67.9 (14.4)	62.1 (14.6)	<0.001

RWMA=rest wall motion abnormalities; PWMA=peak wall motion abnormalities; other abbreviations as in Table 1.

2.4. Follow-up

Follow-up data collection was performed by contacting the patient's general practitioner and by review of hospital records. The date of the last review or consultation was used to calculate follow-up time. Follow-up events noted were overall mortality, cardiac death and non-fatal myocardial infarction. The composite of non-fatal myocardial infarction and cardiac death was defined as a major adverse cardiac event (MACE).

2.5. Statistical analysis

Continuous data were expressed as mean values±standard deviation and compared using the ANOVA test. Categorical data were presented as percent frequencies and differences between proportions were compared using the chi-square test. Logistic regression analysis was used to determine the predictors for hypotensive response during dobutamine stress echocardiography. Multivariate Cox proportional hazard regression models (SPSS-12.0 statistical software, SPSS inc., Chicago, Illinois) were used to identify independent predictors of follow-up events. Adjustments were made for the variables; age, gender, diabetes, smoking, hypercholesterolemia, heart failure, hypertension, previous revascularization, rest wall motions score, peak wall motion score and hypotensive response. The probability of survival was calculated using the Kaplan–Meier method, and survival curves were compared using the log-rank test. A p value <0.05 was considered statistically significant. A subanalysis to determine the effect of beta-blockers on cardiovascular outcome was performed in patients with SHR during dobutamine stress echocardiography, adjusting for clinical characteristics, DSE results and use of cardiovascular medication.

3. Results

3.1. Patient characteristics

Of 3310 patients, 2207 (67.6%) were male; mean age was 61±10 years. Clinical characteristics are presented in Table 1. Arrhythmias during testing were non-sustained ventricular tachycardia in 124 patients (4%), atrial fibrillation in 43 patients (1%) and ventricular fibrillation in four patients (0.1%). Defibrillation was successful and no electrocardiographic or cardiac enzymatic changes suggestive of myocardial infarction were observed in these four patients. The test was terminated for achievement of the target heart rate in 3009 patients (89%), maximal dobutamine/atropine dose in 101 patients (3%), ST-segment changes in 99 patients (3%), arrhythmias in 30 patients (1%), angina in 40 patients (1%), abnormal blood pressure in 38 patients (1%) and other symptoms in 64 patients (2%).

Table 3
Multivariate predictors of cardiac death and major adverse cardiac event

	Cardiac death			MACE		
Variables	HR	95% CI	p value	HR	95% CI	p value
Age	1.047	1.038–1.056	<0.001	1.033	1.025–1.041	<0.001
Male gender	1.465	1.187–1.809	<0.001	1.536	1.275–1.852	<0.001
Diabetes	1.496	1.172–1.911	0.001	1.528	1.230–1.897	<0.001
Smoking	1.584	1.326–1.892	<0.001	1.383	1.180–1.620	<0.001
Heart failure	1.813	1.448–2.207	<0.001	1.599	1.297–1.971	<0.001
Hypertension	–	–	–	1.218	1.028–1.442	0.023
Previous revascularization	0.707	0.554–0.901	0.005	0.774	0.626–0.958	0.018
Segments with RWMA	1.820	1.485–2.229	<0.001	1.665	1.384–2.003	<0.001
Segments with PWMA	–	–	–	1.028	1.003–1.054	0.026
Tensive response						
Normal	Reference					
MHR	1.046	0.852–1.283	0.668	1.124	0.938–1.346	0.206
SHR	1.289	1.027–1.619	0.029	1.342	1.093–1.647	0.005

HR=hazard ratio; 95% CI=95% confidence interval; MACE=major adverse cardiac event; other abbreviations as in Tables 1 and 2.

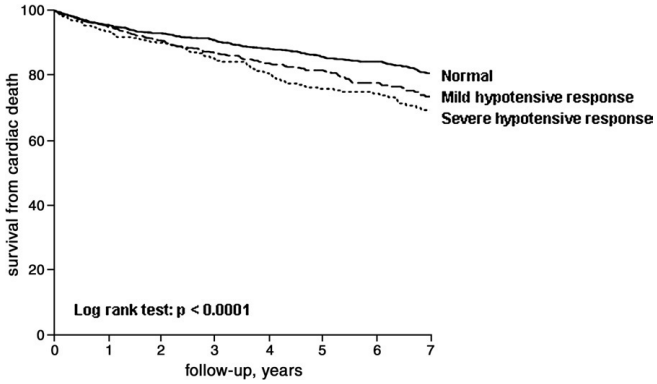

Fig. 1. Survival from cardiac death according to hypotensive response during DSE.

3.2. Dobutamine stress echocardiography

DSE was normal in 1170 patients (35%). Ischemia on DSE was detected in 1610 patients (49%); of these patients 1441 patients (44%) had resting wall motion abnormalities as well. Dobutamine stress echocardiography results are presented in Table 2.

MHR occurred in 963 (28%) patients and SHR occurred in 521 (15%) patients. Independent predictors of SHR were older age (OR: 1.04, 95% CI: 1.033–1.052), history of hypertension (OR: 1.44, 95% CI: 1.170–1.760) and new or worsening wall motion abnormalities (OR: 1.33, 95% CI: 1.043–1.684).

3.3. Cardiac events

During a mean follow-up of 4.5±3.3 years, 920 deaths (28%) occurred, of which 555 (17%) were attributed to cardiac causes. In addition, 158 (5%) patients experienced a non-fatal myocardial infarction, resulting in 713 (22%) patients who had a MACE.

3.4. Predictors of outcomes

Variables associated with a significantly increased risk of cardiac death and major adverse cardiac events in multivariate analysis are listed in Table 3. After adjustment for baseline characteristics and dobutamine stress echocardiography, SHR during DSE was associated with an increased risk of cardiac death (HR: 1.29, 95% CI: 1.03–1.62) and MACE (HR: 1.34, 95% CI: 1.09–1.65), compared to patients without hypotensive response. Notably, MHR was not associated with a worse outcome. The Kaplan–Meier curves for cardiac death according to blood pressure response during dobutamine stress echocardiography are illustrated in Fig. 1. The log rank test gave a significant difference among the tensive groups (p value <0.0001).

3.5. Subanalysis for severe hypertension during DSE

Among the patients with an SHR during DSE, 117 (22%) used beta-blockers. These patients were chronic users of beta-blocker and were not withheld their medication prior to testing. After adjustment for baseline characteristics, DSE results and other cardiovascular medication, the use of beta-blockers significantly reduced the risk of cardiac death in patients experiencing SHR during dobutamine stress echocardiography (HR: 0.60, 95% CI: 0.365–0.981). The Kaplan–Meier curves for cardiac death free survival in patients with SHR during dobutamine stress echocardiography showed an increased survival for beta-blocker users, compared to those who did not use beta-blockers (Fig. 2). However, the use of beta-blockers was not significantly associated with an improved survival for all cause mortality or major adverse cardiac events in these patients. During

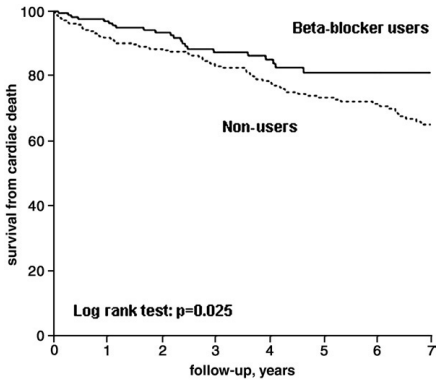

Fig. 2. Survival from cardiac death in severe hypotensive response group.

follow-up, beta-blocker therapy was started in 23 patients and discontinued in 8 patients at the discretion of the referring physician. Similar results were obtained after excluding these patients.

4. Discussion

4.1. Main findings

This study showed that there is a relation between hypotensive response occurring during DSE and long-term prognosis, independent from traditional risk markers such as myocardial function and stress induced myocardial ischemia. The incidence of SHR during DSE in this study was 16%. The combined incidence of mild and severe hypotensive response during DSE was 44%. Previous studies reported an incidence ranging from 14 to 38%. This wide range is mainly due to the different definitions of hypotensive response used. Multiple studies used the drop in blood pressure from peak blood pressure throughout the DSE protocol [8,10], while other studies used the drop from base blood pressure [9,11] or a combination of end points [12,13]. Also, the cut-off point for hypotensive response in the various studies ranged from 0 to $\geq$50 mmHg. In this study hypotensive response during DSE was measured from base blood pressure to peak stress blood pressure, which therefore takes into account, the chronotropic reserve/functional capacity the heart has and possible hypertensive state at rest. The cut-off point was divided into mild and severe hypotensive response at a drop of $\geq$20 mmHg since this is the most commonly used cut-off point. In addition, this distinction was made because of the hypothesis that a moderate degree of hypotensive response may be inherent to DSE due to peripheral vasodilatation, unlike exercise testing. This would not be associated with adverse outcome, while SHR may reflect poor ventricular function and could be associated with a worse prognosis. In exercise stress testing, the occurrence of hypotensive response is less frequent, ranging from 2.7 to 6% [14,15]. The occurrence of hypotensive response during exercise stress testing has been proven to be a strong marker for significant CAD, impaired left ventricular function and poor prognosis. The mechanism proposed for hypotensive response during exercise testing is the reduction of ejection fraction caused by large areas of ischemic myocardium [14,15]. This is the first large-scale study designed to assess the independent association of dobutamine induced hypotensive response with the long-term outcome.

4.2. Characteristics of patients at risk for Severe hypotensive response

In our study the occurrence of SHR during DSE was associated with the presence of wall motion abnormalities at peak stress. This correlates with the presence of global left ventricular dysfunction, which could explain the drop in systolic blood pressure. The occurrence of SHR in patients without the presence of induced myocardial dysfunction could perhaps be caused by the presence of single vessel disease in these patients. In such cases myocardial ischemia might not be detected by DSE but would affect the functional capacity, as hypothesized by Rallidis et al. [13] in their study. In addition, older age and the history of hypertension were associated with the occurrence of SHR during DSE. These are well-established risk factors for coronary artery disease and are associated with an increased occurrence of cardiac events.

4.3. Potential mechanisms of hypotensive response

Dobutamine is a sympathicomimetic drug, which stimulates α1, β1 and β2 adrenoreceptors. In peripheral vasculature, α1-mediated vasoconstriction is offset by β2-mediated vasodilatation. Unlike exercise testing, hypotensive response during DSE was disregarded as a specific indicator of functional abnormalities because of the diversity of mechanisms which may contribute to hypotensive response during dobutamine stress such as poor left ventricular function [16,17], dynamic intraventricular obstruction [18], a vasodepressor reflex due to vagal stimulation [19] and ischemia [10]. It is presumable that one or a combination of these different mechanisms plays a role in the development hypotensive response during DSE. The current study showed that SHR was associated with inducible ischemia, while MHR was not, supporting the poorer prognosis in these patients. The development of SHR, in patients without inducible ischemia, could have been caused by impaired left ventricular filling and contractile reserve.

Most studies on the topic of hypotension during DSE so far did not report a significant association between hypotensive response and a higher rate of cardiac complications. However, these studies were conducted with much smaller groups of patients and must be regarded as such. Furthermore, most of these studies did not evaluate mild versus severe hypotensive response.

On the other hand, Day et al. [12] conducted a study in 300 patients, in which they reported a significant relation between dobutamine induced hypotensive response and perioperative cardiac events, even after adjustment for rest wall motion score and inducible ischemia. They attributed their findings to a limitation of cardiac reserve.

4.4. Clinical implications

Beta-blockers are established therapeutic agents for patients with hypertension and coronary artery disease. In addition, the use of beta-blockers has been proven to be effective as long-term secondary prevention after myocardial infarction and reduces the risk of long-term death [20]. In this study, patients with SHR also benefited from beta-blocker use, showing a significant reduction of the risk of cardiac death, compared to patients not using beta-blockers.

4.5. Limitations

The limitations of this study include those inherent to a retrospective analysis. The study population consisted of patients referred to a tertiary care center, with high prevalence of established coronary artery disease and therefore the results of this study may not fully represent a general population undergoing DSE. In addition, patients with chronic non-cardiac diseases such as end-stage renal disease or chronic obstructive pulmonary disease were not excluded from the study. These patients may be at a higher risk for cardiac death despite a negative stress test for ischemia. Finally, since simultaneous angiography was not routinely performed in this study, coronary angiographic abnormalities, possibly responsible for hypotensive response occurring during DSE, were not investigated.

4.6. Conclusion

Severe hypotensive response occurring during dobutamine stress echocardiography is associated with the presence of left ventricular dysfunction and increased incidence of cardiac death and MACE. The adverse outcome in these patients was observed even after adjustment for clinical data and abnormalities on the DSE. These patients should be closely observed even in the absence of inducible ischemia.

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Chapter 3

Methionine Loading Does Not Enhance the Predictive Value of Homocysteine Serum Testing for All Cause Mortality or Major Adverse Cardiac Events

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.

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Methionine Loading Does Not Enhance the Predictive Value of Homocysteine Serum Testing for All Cause Mortality or Major Adverse Cardiac Events

Martin Dunkelgrun[a], Sanne E Hoeks[b], Olaf Schouten[a], Harm HH Feringa[c], Gijs MJM Welten[a], Radosav Vidakovic[c], Yvette RBM van Gestel[b], Ron T van Domburg[c], Dustin Goei[a], Robert de Jonge[d], Jan Lindemans[d], Don Poldermans[b]

ABSTRACT

Hyperhomocysteinemia is independently associated with atherosclerotic disease. Methionine loading could improve the predictive value of hyperhomocysteinemia by detecting mild disturbances in enzyme activity. The goal of this study was to determine the beneficial effect of methionine loading on the predictive value of homocysteine testing for long term mortality and major adverse cardiac events. In an observational study, 1122 patients with suspected or known vascular disease, underwent homocysteine testing, which was measured fasting and again six hours after methionine loading. Hyperhomocysteinemia was defined as a fasting level ≥15 µmol/l and post-methionine loading level ≥55 µmol/l or an increase of ≥30 µmol/l above fasting levels. Primary endpoints were death and major adverse cardiac event. Multivariate Cox regression analysis was used, adjusting for all cardiac risk factors. During follow-up (mean; 8.9 ± 3.4 years), 98 patients died (8.7%), 86 had a major adverse cardiac event (7.7%), 579 patients had normal tests, 134 patients had only fasting hyperhomocysteinemia, 226 only post-methionine hyperhomocyseteinemia, and 183 patients had both. In multivariate analysis, overall survival and major adverse cardiac event free survival were significantly worse for those with fasting hyperhomocysteinemia, with hazard ratios of 1.86 (95% confidence interval; 1.20-2.87) and 2.24 (95% confidence interval; 1.41-3.53), respectively. The presence of post-methionine hyperhomocysteinemia did not significantly alter risk of death or major adverse cardiac events

[a] Surgery, Erasmus Medical Center, Rotterdam, the Netherlands; [b] Anesthesiology, Erasmus Medical Center, Rotterdam, the Netherlands; [c] Cardiology, Erasmus Medical Center, Rotterdam, the Netherlands; [d] Clinical Chemistry, Erasmus Medical Center, Rotterdam, the Netherlands

in patients with normal or raised fasting homocysteine levels, respectively. In conclusion, methionine loading does not improve the predictive value of homocysteine testing with regard to long term mortality or major adverse cardiac events.

Key words: homocysteine, methionine, atherosclerosis, mortality, cardiac event

INTRODUCTION

Elevated levels of homocysteine are associated with atherosclerotic disease[1-4]. The exact mechanism by which homocysteine causes vascular disease remains unclear. However, there is considerable evidence that homocysteine is toxic to vascular endothelial cells[5,6]. Several retrospective, case-controlled and prospective studies have implied a pathological role of homocysteine in atherosclerotic disease, with prospective studies reporting a weaker association between homocysteine and atherosclerotic disease compared to retrospective and case control studies[7,8].

Methionine loading can be used to stress the homocysteine metabolism pathways and thereby detect mild disturbances in enzyme activity not registered by fasting homocysteine levels alone[9]. It remains unclear whether fasting homocysteine measurement alone, can fully uncover all patients at risk. These undiscovered patients could be monitored more closely and possibly treated if proper risk assessment were to be made.

This study investigated the beneficial effect of methionine loading on the predictive value of serum homocysteine testing for long term mortality and major adverse cardiac events (MACE).

METHODS

The study population was composed of a series of 1328 consecutive patients who were referred for fasting and post-methionine loading serum homocysteine testing for atherosclerotic risk evaluation in the Erasmus Medical Centre between March 1995 and August 2006. All patients gave informed consent and clinical characteristics and indication for testing were noted before homocysteine testing. All patients referred for testing for cardiovascular risk evaluation due to diagnosed or suspected atherosclerosis were included. Patients were also tested for folic acid, vitamin B_6, and vitamin B_{12} deficiencies and were excluded if any deficiency was present. Furthermore, of this series, 88 patients were tested due to the development of hypertension and proteinuria in pregnancy due to preeclampsia, and were excluded from the study as these patients were not at increased risk for atherosclerosis. Additionally, this series contained the serum of 118 patients under treatment in other hospitals, which was analyzed in our hospital laboratory due to limited laboratory capacity of the referring hospitals. These patients were also excluded from the study. The hospital medical ethics committee gave approval for this study. The final population consisted of 1122 patients.

Blood samples were taken in the morning from patients following an overnight fast and once again 6 hours after receiving an oral load (0.1 g/Kg body weight) of L-methionine.

Fasting hyperhomocysteinemia was defined as serum homocysteine levels ≥ 15 μmol/l. Post-methionine loading hyperhomocysteinemia was defined as serum homocysteine levels ≥ 55 μmol/l or an increase of ≥ 30 μmol/l above fasting levels, as currently recommended by the Netherlands Heart Foundation[10].

Diabetes mellitus was defined as the use of glucose lowering agents and/or a fasting serum glucose concentration ≥ 7.0 mmol/l (126 mg/dL), renal failure as a serum creatine concentration ≥ 176 μmol/l (2.0 mg/dL) and hypertension as blood pressure ≥ 140/90 mmHg or medical treatment for hypertension. Ischemic heart disease was defined as a history of angina and/or myocardial infarction, and congestive heart failure was defined as a history of congestive heart failure, pulmonary edema, paroxysmal nocturnal dyspnea, physical examination showing bilateral rales or S3 gallop, or chest radiograph showing pulmonary vascular redistribution. Stroke was defined as a history of either a cerebral vascular accident or a transient ischemic attack, and smoking was noted in patients who currently smoked or had a history of smoking.

Follow-up data collection was performed by review of hospital records, contacting the patients' general practitioners and obtaining the patients' vital status from the Office of Civil Registry. Follow-up events noted were overall mortality, cardiac death and non fatal myocardial infarction. For patients who died at our hospital during follow-up, hospital records and autopsy results were reviewed. For patients who died outside our hospital, death certificates were reviewed and general practitioners were approached to ascertain the cause of death. A cardiac cause of death was defined as death caused by cardiac arrhythmias, congestive heart failure, or acute myocardial infarction. Acute myocardial infarction was defined by postmortem evidence or the presence of at least two of the following factors ≤4 weeks before death:

1. elevated cardiac enzyme levels, defined as creatine kinase (CK) level >190 U/L and CK-MB >14 U/L, or CK-MB fraction >10% of total CK, or cardiac troponin T >0.1 ng/mL;
2. development of typical electrocardiographic changes, defined as new Q waves >1 mm or > 30 milliseconds; and
3. typical symptoms of angina pectoris.

Sudden unexpected death in a previously stable patient was also considered cardiac death if pathology did not reveal a conclusive cause of death. The composite of non fatal myocardial infarction and cardiac death was defined as a major adverse cardiac event. Follow-up was successful in all 1122 patients (100%).

Continuous data was expressed as mean values ± standard deviation and compared using the ANOVA test. Categorical data was presented as percent frequencies and differences between proportions were compared using the chi-square test. Logistic regression analysis was used to determine the predictors for fasting hyperhomocysteinemia. Multivariate Cox proportional hazard regression models (SPSS-14.0 statistical software, SPSS inc., Chicago, Illinois) were used to identify independent predictors of Follow-up events. Adjustments were made for the variables; age, gender, ischemic heart disease, heart failure, history of stroke, diabetes mellitus, renal failure, hypertension, smoking and hyperhomocysteinemia. The probability of survival was

calculated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. A p-value <0.05 was considered statistically significant.

RESULTS

Of the 1120 patients, 512 (45.6%) were male; mean age was 43 ± 12 years. A total of 805 patients (72%) had a normal fasting serum homocysteine level, while 317 patients (28%) had elevated fasting serum homocysteine. Of the 805 patients with normal fasting serum homocysteine, 226 (28%) had elevated homocysteine after methionine loading, while 579 (72%) retained normal homocysteine levels. Of the 317 patients with an abnormal fasting homocysteine, 183 (58%) increased to abnormal homocysteine values after methionine loading, while 134 patients (42%) did not. Clinical characteristics are presented in table 1. Independent predictors of elevated fasting homocysteine were older age, per year increase (odds ratio: 1.01, 95% confidence interval: 1.00-1.02), smoking (odds ratio: 2.05, 95% confidence interval: 1.05-4.01) and renal failure (odds ratio: 8.22, 95% confidence interval: 2.55-26.49). Independent predictors of elevated homocysteine after methionine loading were older age, per year increase (odds ratio: 1.02, 95% confidence interval: 1.01-1.03), history of stroke (odds ratio: 1.42, 95% confidence interval: 1.05-1.91), smoking (odds ratio: 1.28, 95% confidence interval: 1.00-1.64) and renal failure (odds ratio: 2.70, 95% confidence interval: 1.01-7.51).

During a mean Follow-up period of 8.9 years (±3.4years) a total of 98 patients died (8.7%) and 86 patients had a MACE (7.7%). The Kaplan-Meier curves for overall survival according to fasting and post-methionine loading hyperhomocysteinemia are illustrated in Figure 1, illustrating the increased risk of death for patients with fasting hyperhomocysteinemia, but lack of effect of post-methionine homocysteine levels (Log rank test p-values of 0.65 and 0.44). After adjusting for baseline characteristics, fasting hyperhomocysteinemia was associated with increased risk of death (hazard ratio: 1.86, 95% confidence interval: 1.20-2.87). Variables associated with a significantly increased risk of death in multivariate analysis are listed in Table 2. In patients with normal fasting serum

Table 1 - Baseline characteristics, cardiac risk factors

(%)	normal test	only FHH	only PMH	both FHH and PMH	Total population	p-value
Male	43.2	62.4	36.6	51.9	45.6	<0.001
Age (mean)	41.6	44.6	44.5	44.0	42.8	0.003
IHD	18.6	25.7	19.9	22.2	20.1	0.325
Heart failure	1.4	2.0	1.9	1.9	1.6	0.937
Stroke	19.0	24.8	25.5	27.3	22.5	0.089
Diabetes	9.5	9.9	8.7	8.3	9.2	0.948
Hypertension	18.3	20.8	19.9	18.1	18.7	0.906
Renal failure	0.5	4.0	0.6	3.7	1.4	0.001
Smoking	42.7	46.5	45.1	53.2	45.5	0.063

FHH = fasting hyperhomocystenemia, IHD = ischemic heart disease, PMH = post-methionine loading hyperhomocysteinemia

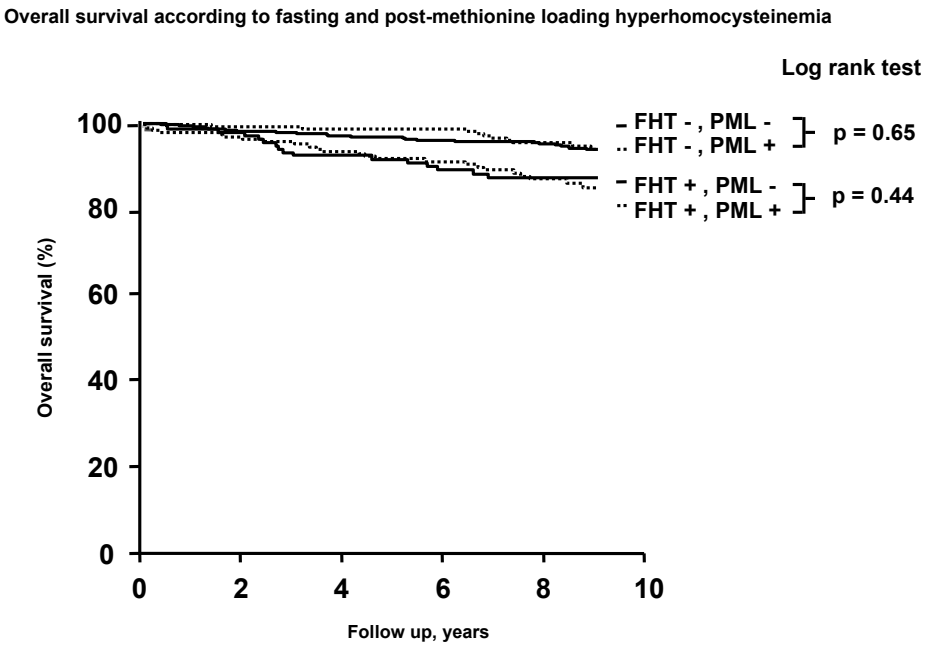

Figure 1 – Overall survival for fasting and post-methionine loading hyperhomocysteinemia

homocysteine, the presence of hyperhomocysteinemia after methionine loading was not associated with a worse outcome, compared to those who retained normal serum homocysteine levels after loading (hazard ratio: 0.72, 95% confidence interval: 0.31-1.43). Furthermore, in patients with fasting hyperhomocysteinemia, the presence of post-methionine loading hyperhomocysteinemia was also not associated with a worse outcome, compared to those without raised serum homocysteine levels after loading (hazard ratio: 0.97, 95% confidence interval: 0.52-1.81).

The Kaplan-Meier curves for MACE free survival according to fasting and post-methionine loading hyperhomocysteinemia are illustrated in Figure 2, illustrating the increased risk of MACE for patients with fasting hyperhomocysteinemia, but lack of effect of post-methionine homocysteine levels (Log rank test p-values of 0.63 and 0.43). The presence of fasting hyperhomocysteinemia was

Table 2 – independent predictors of all cause mortality

Mortality	p-value	HR	95% CI
FHH	0.005	1.86	1.20-2.87
Age, per year	<0.001	1.07	1.06-1.09
Heart failure	<0.001	6.83	3.03-15.37
Stroke	0.009	1.81	1.16-2.82
Renal failure	0.001	4.08	1.80-9.26

CI = confidence interval, FHH = fasting hyperhomocysteinemia, HR = hazard ratio

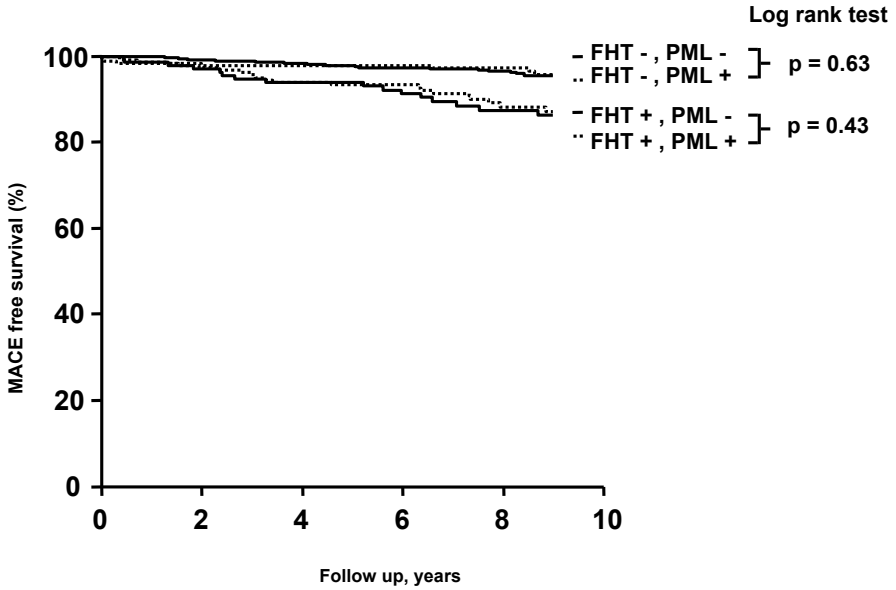

Figure 2 – MACE free survival for fasting and post-methionine loading hyperhomocysteinemia

more strongly associated with an increased risk of experiencing a MACE after adjusting for baseline characteristics, compared to all cause mortality (hazard ratio: 2.24, 95% confidence interval: 1.41-3.53). Variables associated with a significantly increased risk of experiencing a MACE in multivariate analysis are listed in Table 3. However, in patients with normal fasting serum homocysteine, the presence of post-methionine loading hyperhomocysteinemia was again not associated with a worse outcome, compared to those who retained normal serum homocysteine levels after loading (hazard ratio: 1.34, 95% confidence interval: 0.67-2.69). Additionally, among the patients who

Table 3 - independent predictors of major adverse cardiac events

MACE	p-value	HR	95% CI
FHH	0.001	2.24	1.41-3.53
Age, per year	<0.001	1.05	1.03-1.07
Male sex	0.002	2.15	1.32-3.51
IHD	0.001	2.27	1.43-3.60
Heart failure	0.001	4.96	1.92-12.80
Diabetes	0.001	2.57	1.50-4.40
Renal failure	0.043	3.07	1.04-9.10
Smoking	0.017	1.75	1.10-2.77

CI = confidence interval, FHH = fasting hyperhomocysteinemia, HR = hazard ratio, IHD = ischemic heart disease, MACE = major adverse cardiac event

already had fasting hyperhomocysteinemia, the development of post-methionine loading hyperhomocysteinemia did not result in a worse outcome (hazard ratio: 0.89, 95% confidence interval: 0.47-1.69), compared to those who did not develop post-methionine hyperhomocysteinemia.

DISCUSSION

This study compared fasting homocysteine with post-methionine loading homocysteine levels in relation to long term outcome. The presence of fasting hyperhomocysteinemia resulted in a 1.86 fold increase in mortality and a 2.24 fold increase in MACE. Compared to fasting homocysteine levels, methionine loading added 226 more patients with hyperhomocysteinemia, constituting 20% (226/1122) of all patients and 42% (226/543) of patients at risk. However, compared to the patients who did not develop post-methionine loading hyperhomocysteinemia, these patients did not differ in their risk for death or MACE. Also, among the patients who had fasting hyperhomocysteinemia, the addition of methionine loading homocysteine levels did not result in an altered prognosis in these patients either.

Previous studies investigating the effect of methionine loading on homocysteine levels have also reported an increase in patients at risk detected after methionine loading. Notably, Graham et al.[11] reported a large case-control study, in which 750 cases were compared to 800 controls. In total, 13% of all cases had hyperhomocysteinemia only after methionine loading (27% of cases with hyperhomocysteinemia), which is comparable to the findings in this study (14% of all patients and 34% of patients with hyperhomocysteinemia). In this case-control study, patients with fasting hyperhomocysteinemia had a relative risk of 1.9 for vascular disease and all patients with post-methionine hyperhomocysteinemia had a relative risk of 1.8. The relative risk for patients with only post-methionine hyperhomocysteinemia was 1.5 with a 95% confidence interval of 1.0 to 2.2, providing only a borderline significance. Therefore, it remains unclear whether extra patients at risk were discovered, which is the primary reason for methionine loading prior to homocysteine testing. Additionally, Graham et al. showed that the addition of post-methionine loading hyperhomocysteinemia in patients who already had fasting hyperhomocysteinemia, increased the relative risk from 1.9 to 2.5 (95% confidence interval; 1.7-3.5). However, in this study, blood samples were taken only after the cases were diagnosed with a vascular event. It has been shown that homocysteine typically rises and falls after an acute vascular event, suggesting that hyperhomocysteinemia may not be causative of vascular disease, but rather a consequence of it[12]. This finding makes the interpretation homocysteine levels determined after a vascular event, at the very least unreliable.

The precise mechanism by which hyperhomocysteinemia induces atherosclerotic events is unclear. However, laboratory studies have identified several potential mechanisms by which elevated serum homocysteine levels can impair vascular function. These are impairment of endothelial function, increased lipid uptake and retention, oxidation of low-

density lipids, activation of the inflammatory pathway, increased monocyte adhesion to the vessel wall, stimulatory effects on smooth muscle proliferation, and thrombotic tendency mediated by activation of coagulation factors and platelet dysfunction[13].

However, stronger associations between homocysteine and atherosclerotic disease were reported in studies that used less robust methods (case-control and retrospective studies) and weaker associations were found in prospective cohort studies, which strengthens the theory that the relationship between homocysteine and ischemic heart disease is indirect and possibly confounded by other factors that influence both serum homocysteine levels and cardiac risk[7,8]. Moreover, multiple randomized controlled trials evaluating homocysteine lowering therapy, were unable to reduce the incidence of atherosclerotic vascular disease, despite a significant drop in serum homocysteine levels, further weakening the theory that hyperhomocysteinemia is the cause, rather than the effect of atherosclerotic disease[14-16].

The limitations of this study include those inherent to a retrospective analysis. The study population consisted of patients referred to a tertiary care center and may not fully represent a general population subjected to homocysteine testing. Also, the patient population was relatively young (mean age 43 ± 12), compared to average populations who undergo testing for atherosclerosis[7,8]. Also, this study contained a small percentage of men (45.6%), compared to the 85% in the meta-analysis by Wald et al.[7]. This could be the basis for the relatively low event rate witnessed in this study.

Fasting hyperhomocysteinemia is associated with an increased incidence of all cause mortality and MACE. The adverse outcome in these patients was observed even after adjustment for clinical characteristics influencing cardiac outcome. Even though methionine loading can more sensitively identify patients who truly have hyperhomocysteinemia, the addition of methionine loading does not alter the prognosis of patients with respect of overall mortality and MACE. Therefore, there is no justification for routine homocysteine testing using methionine loading in the general population referred for atherosclerotic risk evaluation.

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Chapter 4

Usefulness of Preoperative Oral Glucose Tolerance Testing for Perioperative Risk Stratification in Patients Scheduled for Elective Vascular Surgery

Dunkelgrun M
Schreiner F
Schockman DB
Hoeks SE
Feringa HH
Goei D
Schouten O
Welten GM
Vidakovic R
Noordzij PG
Boersma E
Poldermans D
Am J Cardiol. 2008;101:526-9.

Usefulness of Preoperative Oral Glucose Tolerance Testing for Perioperative Risk Stratification in Patients Scheduled for Elective Vascular Surgery

Martin Dunkelgrun, MD[a], Frodo Schreiner, MD[b], David B. Schockman, MD[b], Sanne E. Hoeks, MD[d], Harm H.H. Feringa, MD[c], Dustin Goei, MD[a], Olaf Schouten, MD[a], Gijs M.J.M. Welten, MD[a], Radosav Vidakovic, MD[c], Peter G. Noordzij, MD[b], Eric Boersma, MD[d], and Don Poldermans, MD[b,*]

Patients scheduled for major vascular surgery are screened for cardiac risk factors using standardized risk indexes, including diabetes mellitus (DM). Screening in patients without a history of DM includes fasting glucose measurement. However, an oral glucose tolerance test (OGTT) could significantly improve the detection of DM and impaired glucose tolerance (IGT) and the prediction of perioperative cardiac events. In a prospective study, 404 consecutive patients without signs or histories of IGT or DM were included and subjected to OGTT. The primary study end point was the composite of perioperative myocardial ischemia, assessed by 72-hour Holter monitoring using ST-segment analysis and troponin release. The primary end point was noted in 21% of the patients. IGT was diagnosed in 104 patients (25.7%), and new-onset DM was detected in 43 patients (10.6%). The OGTT detected 75% of the patients with IGT and 72% of the patients with DM. Preoperative glucose levels significantly predicted the risk for perioperative cardiac ischemia; odds ratios for DM and IGT were, respectively, 3.2 (95% confidence interval 1.3 to 8.1) and 1.4 (95% confidence interval 0.7 to 3.0). In conclusion, the prevalence of undiagnosed IGT and DM is high in vascular patients and is associated with perioperative myocardial ischemia. Therefore, an OGTT should be considered for all patients who undergo elective vascular surgery. **(Am J Cardiol 2008;101:526–529)**

This study assessed the usefulness of an oral glucose tolerance test (OGTT) in patients who underwent vascular surgery to detect formerly unknown diabetes mellitus (DM) and impaired glucose tolerance (IGT) compared with screening with fasting plasma glucose (FPG) alone and assessed in what manor newly found DM and IGT affect the risk for perioperative cardiac morbidity and mortality.

Methods and Results

The study population was composed of a series of 404 consecutive patients scheduled for elective noncardiac vascular surgery who were referred for further testing from November 2004 to May 2007 and had no signs or histories of IGT or DM. In a prospective study, all patients were subjected to OGTTs. All patients gave informed consent, and clinical characteristics and medication use were noted before glucose testing. Also, the cardiac risk score was calculated according to the adapted cardiac risk index by Boersma et al.[1] Blood samples were taken in the morning after overnight fasting and once again 2 hours after the ingestion of a 75-g oral glucose load. Impaired fasting glucose was defined as plasma glucose of 100 to 125 mg/dl and IGT as plasma glucose of 140 to 199 mg/dl. DM was defined as FPG ≥126 mg/dl and/or plasma glucose ≥200 mg/dl after the OGTT, as defined by the American Diabetes Association.[2]

Patients were excluded from the study if they had DM, which was defined as a known history of DM with or without the use of insulin or glucose-lowering agents. Renal failure was defined as a serum creatine concentration ≥2.0 mg/dl and hypertension as blood pressure ≥140/90 mm Hg or medical treatment for hypertension. Ischemic heart disease was defined as a history of angina and/or myocardial infarction, and congestive heart failure was defined as a history of congestive heart failure, pulmonary edema, paroxysmal nocturnal dyspnea, physical examination showing bilateral rales or S3 gallop, or chest x-ray showing pulmonary vascular redistribution. Stroke was defined as a history of either a cerebral vascular accident or a transient ischemic attack, and smoking was noted in patients who currently smoked or had histories of smoking.

Patients were continuously monitored with a 10-electrode, 12-lead digital electrocardiographic recorder (DR180+ Digital Holter Recorder; NorthEast Monitoring, Inc., Maynard, Massachusetts), starting 1 day before surgery and up to 2 days after by means of Holter electrocardiography. Recordings were performed in the continuous 12-lead mode, with a recording length of 10 seconds every minute. The frequency response was 0.05 to 150 Hz. Electrocardiographic data were initially processed by a technician and

[a]Departments of Vascular Surgery, [b]Anesthesiology, [c]Cardiology, and [d]Clinical Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands. Manuscript received July 20, 2007; revised manuscript received and accepted September 17, 2007.

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*Corresponding author: Tel: 31-104634613; fax: 31-104634957.
E-mail address: d.poldermans@erasmusmc.nl (D. Poldermans).

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Table 1
Baseline characteristics according to glucose regulation groups

Variable	Total (n = 404)	Normal (n = 257)	IGT (n = 104)	DM (n = 43)	p Value
Age (yrs), mean ± SD	68.4±11.7	68.2±11.7	68.5±12.3	69.1±10.8	0.89
Men	74.3%	72.0%	76.9%	81.4%	0.32
Ischemic heart disease	38.1%	36.6%	40.6%	41.5%	0.71
Heart failure	3.2%	3.3%	1.0%	7.7%	0.13
Previous coronary revascularization	16.1%	14.1%	22.0%	12.8%	0.17
Hypertension	49.7%	46.3%	51.0%	66.7%	0.05
Stroke	28.3%	26.7%	33.0%	26.2%	0.48
Renal failure	11.1%	10.3%	12.9%	11.9%	0.78
Chronic obstructive pulmonary disease	27.0%	30.0%	21.0%	23.1%	0.20
Body mass index (kg/m^2), mean ± SD	25.5±4.0	25.1±3.8	25.8±4.0	27.1±4.9	0.01
Hypercholesterolemia	54.7%	50.3%	59.2%	68.8%	0.10
β-blocker use	82.6%	81.9%	83.8%	83.7%	0.90
Aspirin use	62.3%	63.6%	56.6%	67.4%	0.36
Angiotensin-converting enzyme inhibitor use	31.6%	30.0%	36.4%	30.2%	0.51
Calcium antagonist use	20.0%	20.6%	18.2%	20.9%	0.87
Angiotensin antagonist use	11.4%	10.5%	10.1%	19.0%	0.25
Diuretic use	25.8%	22.5%	31.3%	32.6%	0.14
Clopidogrel use	14.9%	17.3%	13.0%	7.1%	0.20

analyzed by 2 experienced investigators who were blinded to patients' clinical data. After excluding all abnormal QRS complexes, the ambulatory electrocardiographic 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 defined as the average ST segment during a stable period (duration 20 minutes) 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. Myocardial infarction was diagnosed when ≥2 of the following were present: elevated cardiac enzyme levels (creatine kinase [CK] level >190 U/L and CK-MB >14 U/L, or CK fraction >10% of total CK, or troponin T >0.1 ng/ml), the development of typical electrocardiographic changes (new Q waves >1 nm or >30 ms), and typical symptoms of angina pectoris. Cardiovascular death was defined as death caused by cardiac arrhythmias, congestive heart failure, or acute myocardial infarction. Sudden unexpected death in a previously stable patient was also considered cardiac death if pathology did not reveal a conclusive cause of death.

The primary end point was cardiac ischemia, defined as the composite of perioperative myocardial ischemia assessed by Holter monitoring and/or troponin release ≥0.01 ng/ml. Further end points were 30-day myocardial infarction and cardiovascular mortality and the detection of fasting and post-glucose-loading DM and IGT. Follow-up was successful in all 404 patients (100%). Continuous data were compared using analysis of variance, including a p-for-trend analysis, and are expressed as mean ± SD. Categorical data are presented as percentage frequencies, and differences between proportions were compared using the chi-square test. Multivariate logistic regression models (using SPSS version 14.0; SPSS, Inc., Chicago, Illinois) were used to identify independent predictors of postoperative events. Adjustments were made for age, gender, body mass index, ischemic heart disease, heart failure, history of stroke, renal failure, hypertension, smoking, and hypercholesterolemia. A p value <0.05 was considered statistically significant.

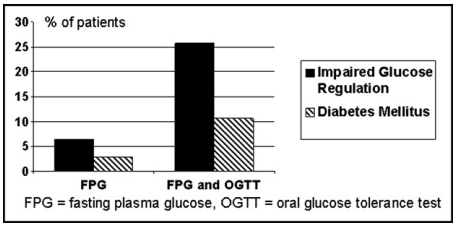

Figure 1. FPG and OGTT results.

A total of 404 patients were included in the study. Baseline characteristics of the tested patients are listed in Table 1. The mean age of the patients tested was 68 ± 11.7 years, and 74% of the patients were men. IGT was detected in 104 patients (25.7%), and DM was diagnosed in 43 patients (10.6%). The presence of hypertension and body mass index were the only statistically significant predictors of IGT and DM. However, there was a slight trend between the presence of hypercholesterolemia and the incidence of IGT or DM (Table 1).

Of the 104 patients with IGT, 26 patients (25%) presented with impaired fasting glucose, whereas in 78 patients, impaired fasting glucose was detected only after the OGTT. Of the 43 patients who were diagnosed with DM, only 12 patients (28%) presented with diabetic fasting glucose levels, whereas in 31 patients, diabetic fasting glucose levels were detected after glucose loading. This means that 75% of patients with IGT and 72% of patients with DM would have been missed if only fasting glucose levels had been examined (Figure 1). Among the 43 patients with newly found DM, the addition of this cardiac risk factor resulted in 24 patients' increasing from 1 to 2 clinical risk

Table 2
Distribution of 30-day cardiac ischemia, myocardial infarction, and cardiovascular mortality according to glucose regulation groups

Variable	Total	Normal	IGT	DM	p Value
Cardiac ischemia	21.0%	18.3%	21.2%	37.2%	0.02
Myocardial infarction	4.5%	3.9%	4.8%	6.9%	0.29
Cardiovascular mortality	2.0%	1.6%	2.0%	4.7%	0.40

factors, 12 patients' increasing from 2 to 3 risk factors, and 7 patients' increasing from 3 to 4 risk factors.

Cardiac ischemia was observed in 84 patients (21%), myocardial infarction in 18 patients (4.5%), and cardiovascular mortality in 8 patients (2.0%), as listed in Table 2. There was a significant increase in the incidence of cardiac ischemia with worsening glucose regulation and nonsignificant trends in myocardial infarction and cardiovascular mortality (Table 2). Of the patients with postoperative ischemia, half of those with DM and 2/3 of those with IGT were identified only after oral glucose loading. Univariate risk factors for postoperative events are listed in Table 3. After adjusting for age, gender, and baseline characteristics, the presence of IGT was not independently associated with an increased risk for myocardial ischemia (Table 4). However, in multivariate analysis, the presence of DM was independently associated with an increased risk for cardiac ischemia (Table 4). Other independent predictors of cardiac ischemia were age, ischemic heart disease, heart failure, and renal failure.

Discussion

This study showed that of the 404 patients with no histories of IGT of DM who were tested, 104 (25.7%) had IGT and 43 (10.6%) had DM. DM is an acknowledged clinical risk factor for perioperative cardiac complications. Further preoperative testing in patients scheduled for elective surgery is recommended by the American Heart Association and American College of Cardiology guidelines in patients with ≥2 clinical risk factors.[3] The addition of newly found DM resulted in 24 patients' (6%) becoming eligible for further preoperative cardiac risk testing. The detection is also of clinical importance, because postoperative plasma glucose levels should be monitored more closely in patients with DM. Furthermore, the detection of DM helps better assess the long-term risk for cardiac events.

If only fasting glucose levels had been examined, 75% of patients with IGT and 72% of patients with DM would have been missed. The presence of IGT or DM did not influence the 30-day cardiovascular mortality after vascular surgery. However, the presence of DM was associated with an increased risk for postoperative myocardial ischemia.

To our knowledge, no other studies have been published evaluating an OGTT before elective vascular surgery. However, a few published studies have evaluated the value of preoperative OGTTs before cardiac interventions. Lankisch et al[4] evaluated 141 patients scheduled for elective coronary angiography who had no histories of IGT or DM and found a very high prevalence of IGT (40.4%) and DM (22.7%). If only fasting glucose levels had been used, 71.9% of patients with DM would have been missed, which is comparable with the findings in this study. Also, patients with IGT and newly diagnosed DM showed significantly increased incidence of hypertension, as seen in this study. Unfortunately, this study did not examine the postoperative results with respect to the preoperative blood glucose levels.

Greberski et al examined 117 patients scheduled for elective coronary artery bypass graft and found that 39% had DM and 29% had IGT. Had OGTTs not been performed, the investigators would have missed 73% of the patients with DM and 94% of the patients with IGT.[5] In this study, no significant differences between the analyzed groups were found with regard to either CK activity or troponin release. However, cardiac ischemia was not measured through continuous monitoring, and the total number of patients analyzed was small.

The advantage of using an OGTT over FPG testing for screening is the detection of patients with IGT. This group

Table 3
Univariate associations of glucose regulation groups and cardiac ischemia, myocardial ischemia, and cardiovascular mortality

Variable	Ischemia		Myocardial Infarction		Cardiovascular Death	
	OR	95% CI	OR	95% CI	OR	95% CI
Normal	Reference		Reference		Reference	
IGT	1.2	0.7–2.1	1.0	0.6–3.1	1.0	0.4–3.7
DM	2.6	1.3–5.3	2.5	0.9–6.8	2.4	0.5–12.7
Age	1.02	1.00–1.05	1.04	1.00–1.09	1.06	1.00–1.15
Men	1.3	0.7–2.3	1.2	0.4–3.6	1.0	0.2–4.9
Ischemic heart disease	2.2	1.2–3.9	1.9	0.7–5.0	1.4	0.3–7.2
Heart failure	4.2	1.3–13.3	4.3	1.0–23.9	4.7	0.5–42.6
Previous coronary revascularization	2.2	1.2–4.0	2.0	0.9–4.0	1.7	0.3–8.9
Hypertension	1.5	0.3–2.5	1.4	0.5–13.1	7.6	0.9–62
Stroke	1.3	0.8–2.3	1.5	0.7–4.1	1.6	0.4–6.8
Renal failure	2.3	1.2–4.6	2.5	0.8–6.6	2.5	0.5–12.9
Chronic obstructive pulmonary disease	1.5	0.9–2.5	1.0	0.7–3.0	0.9	0.2–4.7
Body mass index	1.0	0.9–1.1	1.0	0.9–1.2	1.0	0.8–1.2
Hypercholesterolemia	1.1	0.6–1.9	1.9	06–4.4	3.2	0.5–24

CI = confidence interval; OR = odds ratio.

Table 4
Multivariate associations of glucose regulation groups and cardiac ischemia, myocardial ischemia, and cardiovascular mortality

Variable	Cardiac Ischemia		Myocardial Infarction		Cardiovascular Mortality	
	OR	95% CI	OR	95% CI	OR	95% CI
Normal	Reference		Reference		Reference	
IGT	1.39	0.7–3.0	1.29	0.4–4.3	1.20	0.2–9.3
DM	3.23	1.3–8.1	2.76	0.5–6.8	2.51	0.3–19.1

Adjusted for age, gender, body mass index, ischemic heart disease, heart failure, previous coronary revascularization, stroke, renal failure, hypertension, hypercholesterolemia, and chronic obstructive pulmonary disease.
Abbreviations as in Table 3.

is associated with cardiovascular disease risk factors and cardiac events, whereas impaired fasting glucose is much less associated with cardiac events and mortality.[6–9] Patients with IGT have a high risk for developing type 2 DM.[10,11] Identifying this group of patients has therapeutic value, because lifestyle and pharmacologic interventions reduce the rate of progression to diabetes in these patients.

The American Heart Association and American College of Cardiology guidelines recommend that patients with peripheral artery disease be treated with statins to reduce low-density lipoprotein cholesterol to <100 mg/dl, unless they have DM, in which case cholesterol should be lowered to <70 mg/dl.[3] Likewise, antihypertensive regulation in patients with diabetes is recommended, with a goal of 130/80 mm Hg; patients with peripheral artery disease who do not have DM have a goal of 140/90 mm Hg.[12] Also, the guidelines recommend that all patients with DM be treated with angiotensin-converting enzyme inhibitors. However, in patients with peripheral artery disease, there is insufficient evidence that this medication is to be preferred over β blockers.[3] Overall, the treatment for cardiovascular risk reduction in patients with peripheral artery disease with DM is more vigorous than in those without DM.

The main limitation of this study was that fasting glucose levels were measured only once, not twice, for diagnostic purposes, as recommended by the World Health Organization. This could have an impact on the prevalence of detected glucose regulation disorders. Perioperative cardiovascular mortality was not significantly influenced by OGTT outcomes, but this could very well be due to a power problem, because a nonsignificant increase in cardiovascular mortality was seen in patients with IGT and DM. The presence of DM did influence the risk for myocardial ischemia.

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Chapter 5

Preoperative Oral Glucose Tolerance testing in Vascular Surgery; Long-term Cardiovascular outcome

van Kuijk JP
Dunkelgrun M
Schreiner F
Flu WJ
Galal W
van Domburg RT
Hoeks SE
van Gestel YR
Poldermans D
Submitted.

Preoperative Oral Glucose Tolerance testing in Vascular Surgery; Long-term Cardiovascular outcome

Jan-Peter van Kuijk, MD[a], Martin Dunkelgrun, MD[b], Frodo Schreiner MD[a], Willem-Jan Flu MD[a], Wael Galal, MD[a], Ron T van Domburg[c], Sanne E. Hoeks, MSC[c], Yvette R.B.M. van Gestel[c], and Don Poldermans, MD PhD[a]

ABSTRACT

Background: Diabetes Mellitus (DM) is an important risk factor in vascular surgery patients, influencing postoperative and long-term outcome. Screening for diabetes includes fasting glucose measurement in patients without DM. Oral glucose tolerance testing (OGTT) could significantly improve the detection of impaired glucose tolerance (IGT) and DM.

Aim: To asses the usefulness of OGTT in vascular surgery patients to predict long-term cardiovascular outcome.

Methods: 404 patients without signs or histories of IGT and DM were prospectively included and subjected to OGTT. All cardiac risk factors were noted. Primary outcome was the occurrence of a composite of cardiovascular death, angina pectoris, myocardial infarction, coronary intervention and CVA/TIA during the postoperative follow-up.

Results: IGT and DM were detected by fasting glucose levels in 26 (25%) and 12 (28%) patients, and by OGTT in 78 (75%) and 31 (72%) patients, respectively. During a median follow-up of 3.0 [interquartile range 2.4 - 3.8] years, 128 patients experienced a cardiovascular event. Patients with IGT showed a significant increase in cardiovascular events in both univariate (HR 2.45, 95% C.I. 1.65-3.63, p<0.001) and multivariate analysis (HR 2.77, 95% C.I. 1.83-4.20, p<0.001). Patients with DM showed a nonsignificant increase in cardiovascular events.

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

Key Words: Vascular Surgery, Diabetes Mellitus, Glucose Loading Tests, Cardiovascular outcome

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Departments of Anesthesiology[a], Vascular Surgery[b], and Clinical Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands.

INTRODUCTION

Patients with diabetes are at increased risk for developing peri-operative complications. Dysregulation of glucose hemostasis, especially during (surgical) stress, is an important characteristic of the pre-diabetes phase. Impaired fasting glucose (IFG) has been shown to be associated with adverse cardiovascular outcome.[1, 2] Therefore, the American Diabetes Association recommends pre-operative assessment of fasting glucose levels.[3]

However, during the last decade, other studies showed an increased value of oral glucose tolerance testing (OGTT) for the prediction of postoperative cardiovascular events.[4-7] The DECODE (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europa) study demonstrated substantial discrepancies between the predictive values of IFG compared to OGTT.[8] The risk of death from all-cause, cardiovascular and coronary artery disease was significantly increased in subjects with impaired glucose tolerance (IGT) and newly diagnosed DM. Furthermore; the predictive value of IFG depended strongly on the OGTT. Currently, the use of pre-operative OGTT is only recommended in patients undergoing cardiac surgery with ≥ 2 clinical risk factors.[9] The ACC/AHA guidelines for preoperative management in patients with peripheral arterial disease (PAD) undergoing noncardiac surgery, do not recommend a pre-operative glucose-loading test.

To our knowledge, no prior studies investigated the predictive value of IGT on long-term cardiovascular outcome in vascular surgery patients. Since we know that IGT leads to impaired outcome in cardiac surgery patients, we hypothesize that this association could be present in vascular surgery patients as well.

METHODS

Study design and population

The study population consisted of 404 consecutive patients scheduled for elective vascular surgery in the Erasmus medical centre during the time period from November 2004 till May 2007. Patients were included prospectively. After the patients gave informed consent, clinical characteristics, medication use and previous medical history were noted.

Study protocol

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

Patient data

Previous medical history was obtained from the outpatient clinic visits and the patients' medical record. The exclusion criterion was the presence of DM, defined as a known history

of DM, with or without the use of insulin or oral glucose-lowering agents. The cardiac risk score was calculated according the adapted Lee cardiac index.[10] Ischemic heart disease was defined as a history of angina and/or myocardial infarction. Renal failure was defined as a serum creatinine concentration of ≥2.0 mg/dl and hypertension was defined as blood pressure ≥140/90mmHg or the use of blood pressure lowering agents. Congestive heart failure was defined according the American Heart Association (AHA) and the American College of Cardiology (ACC) guidelines.[11] Stroke was defined as a history of either a cerebral vascular accident (CVA), either ischemic or hemorrhagic, or a transient ischemic attack (TIA). Smoking status was defined as current smoking or a history of smoking.

Echocardiography

Preoperatively, a two-dimensional transthoracic echocardiogram was performed at the outpatient clinic or at the ward. Echocardiography was performed using a handheld Acuson Cypress Ultrasound System (copyright by Acuson corporation) with a 7V3c transducer. M-mode, two-dimensional imaging and Doppler were performed according to the guidelines of the American Society of Echocardiography[12] Standard parasternal and apical views were obtained during rest with the patient in the left lateral decubitus position. Left-ventricular ejection fraction [LVEF] was assessed using the semiquantitative two-dimensional visual estimate method from multiple echocardiographic views. Systolic ventricular function was categorised (severely) impaired (LVEF < 40%) or normal (LVEF > 40%).

Follow-up

During hospital stay, type of surgery was recorded and classified into the following categories: Carotid surgery, abdominal and thoracic aortic surgery (dilatating or occlusive), and lower extremity (dilatating or occlusive). One year after inclusion of the last patient, mortality rates were verified according the Civil Registry. The survivors were sent a questionnaire for the registration of major adverse cardiovascular events during the post-operative period. Furthermore, current medication use was assessed with the questionnaire as well.

Endpoints

The primary endpoint was the occurrence of cardiovascular events during long-term follow-up, with a minimum of at least one year. Cardiovascular events were defined as the composite of cardiovascular death, angina pectoris, myocardial infarction, Percutaneous Coronary Intervention / Coronary Artery bypass grafting (PCI/CBAG) and CVA/TIA. Noncardiovascular events included infectious disease and non-surgery related bleedings. Secondary endpoints included cardiovascular and noncardiovascular mortality rates. Cardiovascular death was defined as any death with a cardiovascular complication as the primary or secondary cause (according to the definition of the World health Organization), including deaths following myocardial infarction, cardiac arrhythmia rescucitation, heart failure, or stroke. Noncardiovascular death was defined as any death with a principal noncardiovascular cause, including surgery-related bleeding complications, cancer, trauma, and infection. Sudden death in a previously

stable patient, and death in patients with an extended history of cardiovascular disease, was considered as cardiovascular.

Statistics

Continuous data were compared using analysis of variance, including a p-for-trend analysis, and are expressed as mean ± SD. Categorical data are presented as percentage frequencies, and differences between proportions were compared using chi-square test. Multivariate logistic regression models (using SPSS version 15.0; SPSS, Inc., Chicago, Illinois) were used to identify independent predictors for postoperative events. Adjustments were made for age, gender, history of myocardial infarction, angina pectoris, PCI/CABG, congestive heart failure, CVA/TIA,

Table 1. Baseline characteristics of the study population

BASELINE CHARACTERISTICS	Total [n=404]	Normal [n=257]	IGT [n=104]	DM [n=43]	P Value
DEMOGRAPHICS					
Age (yrs), mean ± SD	66 ± 13	65 ± 14	66 ± 12	67 ± 11	0.68
Male (%)	74	72	76	81	
MEDICAL HISTORY					
Myocardial infarction (%)	25	22.8	30.0	28.6	0.33
Angina Pectoris (%)	26	26	24	29	0.84
PCI / CABG (%)	16	14	22	13	0.15
Ischemic Heart Disease (%)	26	26	28	22	0.78
Chronic Heart Failure (%)	3	3	1	8	0.13
CVA /TIA (%)	28	27	32	26	0.59
CARDIOVASCULAR RISK FACTORS					
Smoking					0.17
No	19	4	5	28	
Current	33	37	27	26	
History	56	52	69	57	
Hypertension	56	53	58	70	0.12
Hypercholesterolemia	55	50	60	69	0.09
Renal failure	11	10	13	12	0.75
COPD	27	30	22	23	0.30
PRE-OPERATIVE MEDICATION USE					
Statin	71	67	79	77	0.19
Beta-blocking agents	83	82	85	84	0.76
Diuretics	26	22	33	33	0.07
ACE-inhibitors	32	31	35	30	0.75
Calcium antagonists	20	21	18	21	0.90
Angiotensin II antagonists	11	10	10	19	0.25
Nitrates	10	10	12	9	0.78
Aspirin	62	63	57	67	0.42
Clopidogrel	15	17	13	7	0.21

IGT: Impaired Glucose Tolerance, DM: Diabetes Mellitus, PCI/CABG: Percuteneous Coronary Intervention / Coronary Artery Bypass Grafting, CVA/TIA: Cerebro Vascular Accident / Transient Ischemic Attack, COPD: Chronic Obstructive Pulmonary Disease, ACE-inhibitors: Angiontensin Converting Enzyme-inhibitors.

renal insufficiency, hypertension and type of surgery. A p value<0.05 was considered statistically significant.

RESULTS

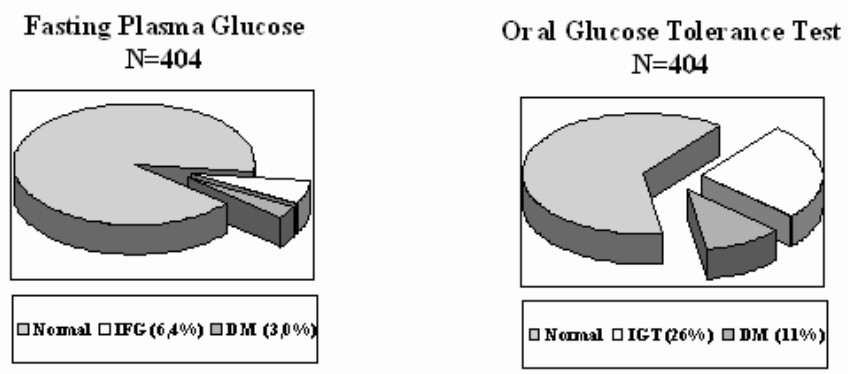
Description of the study population

Elective vascular surgery was performed in 404 patients, who underwent a preoperative FPG and OGTT measurement. Baseline characteristics of the patient population are listed in Table 1. Mean age of the study population was 66 ± 13 years, and 74% of the patients were male. Normal glucose levels were observed in 257 (63%) patients after both tests. Impaired glucose tolerance was detected in 104 (26%) patients, of which 26 (25%) patients presented with impaired fasting glucose (IFG). In the remaining 78 (75%) patients, IGT was only detected after the OGTT. Forty-three (11%) patients were diagnosed as having DM, of which 12 (28%) patients presented with diabetic fasting glucose levels. In the remaining 31 (72%) patients, diabetic fasting glucose levels were only detected after glucose loading. [Figure 1] At baseline, no significant differences were detected in medication use and previous history, especially regarding the presence of cerebro-cardiovascular disease.

Cardiovascular events and mortality

Peri-operative myocardial ischemia, assessed by ECG changes and troponin T release, was detected in 21% of the patients. Patients with DM had a significant increased risk for developing cardiac ischemia during short-term follow-up (p=0.02). During a median follow-up period of 3.0 [interquartile range 2.4 - 3.8] years, 131 patients experienced a cardiovascular event. [Table 2] Patients with IGT showed a significant increase in cardiovascular events during long-term follow-up in both univariate (HR 2.41, 95% C.I. 1.65-3.53, p<0.001) and multivariate analysis (HR 2.68, 95% C.I. 1.80-3.98, p<0.001). [Figure 2] In patients with DM, a borderline significant increase in cardiovascular events was seen in univariate analysis (HR 1.68, 95% C.I. 0.96-2.95). In multivariate analysis the increase in cardiovascular events showed a clear trend, but was not significant as well (HR 1.59, 95%

Figure 1. Additional value of OGTT compared to FPG for the detection of Diabetes Mellitus.



IFG: Impaired Fasting Glucose, DM: Diabetes Mellitus, IGT: Impaired Glucose Tolerance

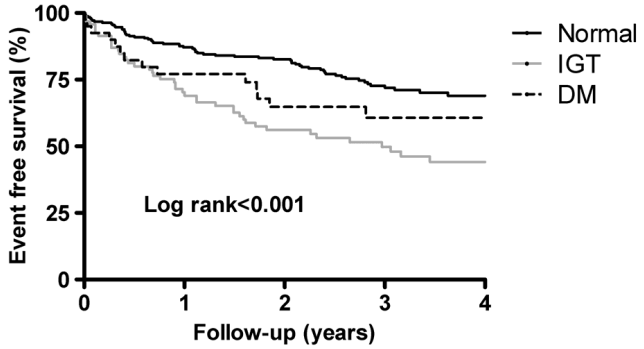
Table 2. Cardiovascular events and mortality rates in patients with normal glucose tolerance, impaired glucose tolerance or diabetes mellitus.

	EVENTS	UNIVARIABLE		**MULTIVARIABLE**	
	N (%)	**HR**	**[95% CI]**	**HR**	**[95% CI]**
CARDIOVASCULAR EVENTS					
Normal (n=257)	67 (25)	1		1	
IGT (n=104)	49 (46)	2.41	1.65 – 3.53	2.68	1.80 – 3.98
DM (n=43)	15 (35)	1.68	0.96 – 2.95	1.59	0.89 – 2.82
All CAUSE MORTALITY					
Normal (n=257)	49 (18)	1		1	
IGT (n=104)	27 (26)	1.35	0.83 – 2.20	1.54	0.93 – 2.55
DM (n=43)	11 (26)	1.43	0.72 – 2.83	1.49	0.73 – 3.01

IGT: Impaired Glucose Tolerance, DM: Diabetes Mellitus

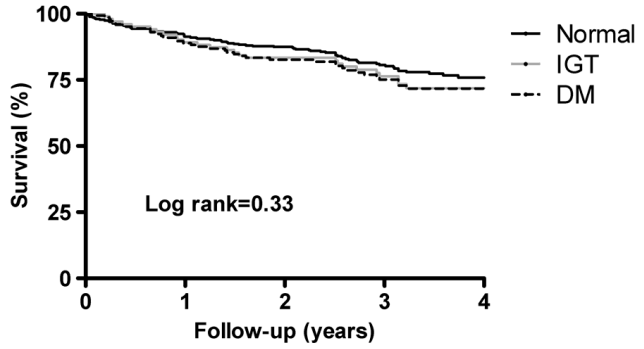
C.I. 0.89 – 2,82). During follow-up, 87 (22%) patients died. Cerebro-cardiovascular death occurred in 40 (46%) patients. All cause mortality showed a clear but non-significant trend in patients with IGT and DM. [Figure 3]

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



Normal: normal test result, IGT: Impaired Glucose Tolerance, DM: Diabetes Mellitus

Figure 3. Survival during long-term follow-up after glucose loading test.



Normal: normal test result, IGT: Impaired Glucose Tolerance, DM: Diabetes Mellitus

Lee Risk index

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

Echocardiography

Pre-operative echocardiographic evaluation was performed in 279 (69%) patients. Impaired ejection fraction (EF) was detected in 23% of patients with IGT and 25% of patients with DM, respectively. In patients with normal glucose tests, 21% had an impaired ejection fraction. However, this difference was not statistically significant. [Table 3]

Laboratory measurements

Pre-operatively measured glycosylated hemoglobine (HbA1C) was significantly higher in patients with IGT and DM (p<0.0001). Renal function, estimated by serum kreatinine and Modification of Diet in Renal Disease (MDRD) in patients with IGT and DM was significantly worse than in patients with a normal test (p=0.007). During the perioperative period, the highest glucose level was measured in all three groups and showed significant higher levels in the IGT and DM groups (p=0.008).

DISCUSSION

Long-term Cardiovascular outcome

To our knowledge, this study is the first to describe long-term cardiovascular outcome in vascular surgery patients who underwent a pre-operative glucose-loading test. The present data show a significant increase in cardiovascular events during the follow-up in patients with IGT or DM. Vascular surgical patients diagnosed with IGT and DM by OGTT seem to have a grave prognosis. Until now, only in cardiac surgery, impaired glucose tolerance was shown as an important cardiovascular risk factor with a strong influence on cardiovascular outcome.[1, 4-7, 13] We showed that especially patients with IGT had a grave prognosis, even worse than patients with DM. A reasonable explanation for this difference in outcome could be under-treatment of vascular surgery patients with IGT.[14] We

Table 3. Pre-operative left ventricular ejection fraction assessed by echocardiography

	Systolic Left Ventricular Function	
	EF > 40%	**EF <40%**
Normal (n=187)	148 (79%)	39 (21%)
IGT (n=64)	49 (77%)	15 (23%)
DM (n=28)	21 (75%)	7 (25%)

EF: Ejection Fraction, IGT: Impaired Glucose Tolerance, DM: Diabetes Mellitus

found a clear trend for less use of statins, beta-blocking agents, and aspirin in patients with IGT compared to DM. However, no significant differences in current medication use between the patients groups were detected, likely due to a study power problem. Nowadays, vascular surgery patients with IGT are not recognized as being at increased risk of diminished cardiovascular outcome. Therefore, they receive less pharmacological preventive treatment. On the contrary, patients with PAD and concomitant DM receive standard treatment according the ACC/AHA guidelines, including ACE-inhibition, aspirin and statins.[15] The reduction of cardiovascular events in diabetic patients by pharmacological treatment is an important topic, as the elderly population is growing. However, in this population, the general practitioner should pay attention to proper foot care and urgent attention to skin lesions and ulcerations as well.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study group showed an increased mortality and no reduction in cardiovascular events in intensive regulated DM type 2.[16] However, in this study, treatment was only directed at strict regulation of glycosylated hemoglobin levels. Other important studies, like the ongoing Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial, are focusing on a broader scale of pharmacological interventions.[17]

Mortality

During the follow-up period, 87 (22%) patients died. There was a clear, non-significant, trend for higher mortality rates in patients with IGT and DM. Cardiovascular and non-cardiovascular death were nearly equally distributed among the patient groups. Although in this study no significant increase in mortality was shown, this is very likely to be a power problem. The DECODE study showed an increased risk of death in patients with OGTT compared to patients with only fasting plasma glucose measured.[4] These findings were confirmed in several other trials, all showing a superiority of 2-hour glucose loading to fasting glucose in assessing the risk of future cardiac events. [1, 6]

IFG vs IGT

Impaired glucose tolerance was found in 104 (26%) patients, and DM in 43 (11%). In this study we used the cutoff values for IFG according the 2003 guidelines of the American Diabetes Association (ADA). The ADA lowered, in 2003, the cutoff value of plasma glucose for IFG from 6.1 mmol/l to 5.6 mmol/l. [18, 19] There has been debate about the influence of this lower cutoff for the prediction of cardiovascular events. Nowadays, the new cutoff is used in most studies comparing IFG and 2-hr glucose loading.[2]

In this study, use of OGTT showed a clear additional effect on diagnosing IGT and DM. Seventy-five percent of the patients with IGT and 72% of patients with DM would have been missed, if only the fasting glucose levels were measured. The OGTT provides additional prognostic information and enables detection of individuals with IGT.[8]

Lee Risk Index

The ACC/AHA identified DM as an atherosclerotic risk factor for perioperative cardiac complications in patients with PAD scheduled for vascular surgery.[9, 11] Pre-operative risk

stratification according to the Lee cardiac index has a proven association with perioperative outcome.[10] The detection of IGT and DM has a significant clinical relevance, both in pre-operative cardiovascular risk stratification and treatment. In the present study, DM was detected in 43 patients. Addition of this clinical risk factor to the pre-operative cardiac risk score increased the risk score to ≥2 in 19 patients. Use of the OGTT provides the physician to make more accurate risk stratification and the possibility to perform additional pre-operative (non-) invasive testing and subsequent treatment. These patients with newly found DM need additional treatment, compared to PAD patients without DM. Target blood pressure should be lowered to 130/80 mmHG in stead of 140/90mmHg, using ACE-inhibitors and Beta-blocking agents. The presence of DM deserves attention during the perioperative and postoperative phase as well. Plasma glucose levels need to be closely monitored.[11] In a recent study by Hoeks et al. the pre-operative Lee Risk Index was shown to be an important prognostic factor for late mortality and impaired health status in patients with PAD.[20] The present study confirmed these results by showing a significant increase in cardiovascular events during long-term follow-up if ≥2 clinical risk factors are present at baseline.

Currently, the use of pre-operative OGTT is only recommended in patients undergoing cardiac surgery with ≥2 clinical risk factors. [9] The ACC/AHA guidelines for pre-operative management in patients with peripheral arterial disease (PAD) undergoing noncardiac surgery, do not recommend a pre-operative glucose-loading test. This study showed that patients with IGT and DM have a worse prognosis following vascular surgery both during short –and long-term follow-up. Therefore, pre-operative glucose loading testing and subsequent expanded medical treatment should be recommended.

Study Limitations

The main limitation of this study was the single measurement of fasting glucose levels. The World Health Organization recommends a repeated measurement for diagnostic purposes. This could have influenced the prevalence of the detected glucose regulation disorders. Cardiovascular events were not significantly increased in patients with DM, however a clear trend was shown. As patients with IGT showed a significant increase in cardiovascular events in multivariate analysis, the lack of significance in the DM group is very likely due to a study power problem. This same trend was shown regarding mortality rates.

CONCLUSION

Patients scheduled for vascular surgery with IGT or DM detected by pre-operative glucose loading test, have a significantly increased risk of developing cardiovascular events during long-term follow-up. Therefore, It is recommended that non-diabetic vascular surgery patients should be tested for glucose regulation disorders prior to surgery and receive adequate pharmacological treatment.

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Chapter 6

Anemia as an independent predictor of perioperative and long term cardiovascular outcome in patients scheduled for elective vascular surgery

Dunkelgrun M
Hoeks SE
Welten GM
Goei D
Vidakovic R
Winkel TA
Schouten O
van Domburg TR
van Gestel YR
Bax JJ
Verhagen HJ
Poldermans D
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Anemia as an Independent Predictor of Perioperative and Long-Term Cardiovascular Outcome in Patients Scheduled for Elective Vascular Surgery

Martin Dunkelgrun, MD[a], Sanne E. Hoeks, MsC[b], Gijs M.J.M. Welten, MD[a], Radosav Vidakovic, MD[c], Tamara A. Winkel, MD[a], Olaf Schouten, MD[a], Ron T. van Domburg, PhD[b], Jeroen J. Bax, MD[e], Ruud Kuijper, MD[d], Michael Chonchol, MD[f], Hence J.M. Verhagen, MD[a], and Don Poldermans, MD[d,*]

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

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

Methods

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

[a]Departments of Vascular Surgery, [b]Clinical Epidemiology, [c]Cardiology, and [d]Anesthesiology, Erasmus Medical Centre, Rotterdam, and [e]Department of Cardiology, Leiden University Medical Centre, Leiden, The Netherlands; and [f]Division of Renal Diseases and Hypertension, University of Colorado Health Sciences Center, Denver, Colorado. Manuscript received October 1, 2007; revised manuscript received and accepted November 21, 2007.

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*Corresponding author: Tel: 3110-463-4613; fax: 3110-463-4957.
E-mail address: d.poldermans@erasmusmc.nl (D. Poldermans).

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

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

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

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

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

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

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

Results

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

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

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

Table 1
Baseline characteristics according to presence or absence of anemia

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

ACE = angiotensin-converting enzyme.

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

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

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

Discussion

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

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

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

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

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

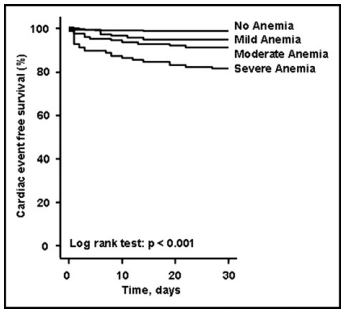

Figure 1. Thirty-day MACE-free survival for severity of preoperative anemia.

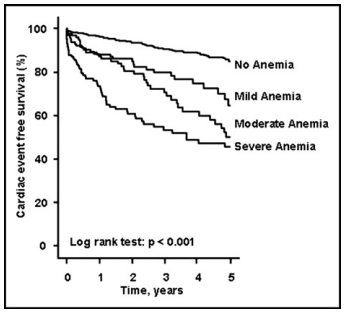

Figure 2. Five-year MACE-free survival for severity of preoperative anemia.

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

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

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

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

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

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

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

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Chapter 7

Association between serum uric acid and perioperative and late cardiovascular outcome in patients undergoing elective open vascular surgery.

Dunkelgrun M
Hoeks SE
Welten GM
Goei D
Vidakovic R
Winkel TA
Schouten O
van Doburg RT
van Gestel YR
Bax JJ
Verhagen HJ
Poldermans D
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Association Between Serum Uric Acid and Perioperative and Late Cardiovascular Outcome in Patients With Suspected or Definite Coronary Artery Disease Undergoing Elective Vascular Surgery

Martin Dunkelgrun, MD[a], Gijs M.J.M. Welten, MD[a], Dustin Goei, MD[a], Tamara A. Winkel, MD[a], Olaf Schouten, MD[a], Ron T. van Domburg, PhD[b], Yvette R.B.M. van Gestel, MSc[b], Willem-Jan Flu, MD[c], Sanne E. Hoeks, MSc[b], Jeroen J. Bax, MD[e], and Don Poldermans, MD[d,*]

The role of uric acid as an independent marker of cardiovascular risk is unclear. Therefore, our aim was to assess the independent contribution of preoperative serum uric acid levels to the risk of 30-day and late mortality and major adverse cardiac event (MACE) in patients scheduled for open vascular surgery. In total, 936 patients (76% male, age 68 ± 11 years) were enrolled. Hyperuricemia was defined as serum uric acid >0.42 mmol/l for men and >0.36 mmol/l for women, as defined by large epidemiological studies. Outcome measures were 30-day and late mortality and MACE (cardiac death or myocardial infarction). Multivariable logistic and Cox regression analysis were used, adjusting for age, gender, and all cardiac risk factors. Data are presented as odds ratios or hazard ratios, with 95% confidence intervals. Hyperuricemia was present in 299 patients (32%). The presence of hyperuricemia was associated with heart failure, chronic kidney disease, and the use of diuretics. Perioperatively, 46 patients (5%) died and 61 patients (7%) experienced a MACE. Mean follow-up was 3.7 years (range: 0 to 17 years). During follow-up, 282 patients (30%) died and 170 patients (18%) experienced a MACE. After adjustment for all clinical risk factors, the presence of hyperuricemia was not significantly associated with an increased risk of 30-day mortality or MACE, odds ratios of 1.5 (0.8 to 2.8) and 1.7 (0.9 to 3.0), respectively. However, the presence of hyperuricemia was associated with an increased risk of late mortality and MACE, with hazard ratios of 1.4 (1.1 to 1.7) and 1.7 (1.3 to 2.3), respectively. In conclusion, the presence of preoperative hyperuricemia in vascular patients is a significant predictor of late mortality and MACE. **(Am J Cardiol 2008;102:797–801)**

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

Methods

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

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

[a]Departments of Vascular Surgery, [b]Clinical Epidemiology, [c]Cardiology, and [d]Anesthesiology, Erasmus Medical Centre, Rotterdam, the Netherlands; and [e]Department of Cardiology, Leiden University Medical Centre, Leiden, the Netherlands. Manuscript received Feb 5, 2007; revised manuscript received and accepted May 14, 2007.

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*Corresponding author: Tel: +31107034613; fax: +31107034957.
E-mail address: d.poldermans@erasmusmc.nl (D. Poldermans).

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Table 1
Baseline characteristics according to uric acid levels

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

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

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

of either a cerebral vascular accident or a transient ischemic attack; chronic obstructive pulmonary disease was defined as a forced expiratory volume in 1 second (FEV1) <70% of age- and gender-predicted value or medication use; hypercholesterolemia was defined as a plasma low-density lipoprotein (LDL) cholesterol >200 mg/dl or medication use; and smoking was noted in patients who currently smoked or had a history of smoking. Patients underwent a resting 2-dimensional echocardiographic examination. Left ventricular end-diastolic and end-systolic volumes were obtained from the apical 4- and 2-chamber views by using the Simpson's rule formula, from which the ejection fraction was calculated. The presence of heart failure was defined as a left ventricular ejection fraction of <35%. Preoperative serum creatinine levels were used to estimate the glomerular filtration rate according to the equation from the Modification of Diet in Renal Disease study.[9] Chronic kidney disease was defined as glomerular filtration rate <60. Finally, preoperative blood samples were used to determine hyperuricemia, which was defined as serum uric acid exceeding 0.42 mmol/L in men and 0.36 mmol/L in women, as defined by large epidemiological studies.[2–3]

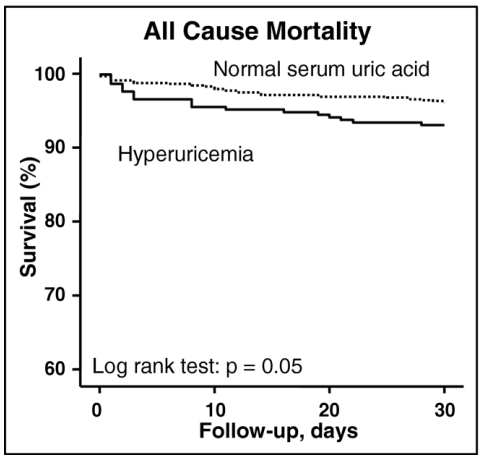

Figure 1. Thirty-day all-cause, mortality-free survival for serum uric acid levels.

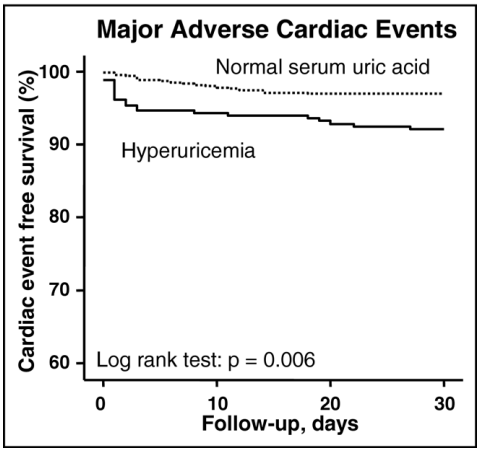

Figure 2. Thirty-day MACE-free survival for serum uric acid levels.

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

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

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

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

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

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

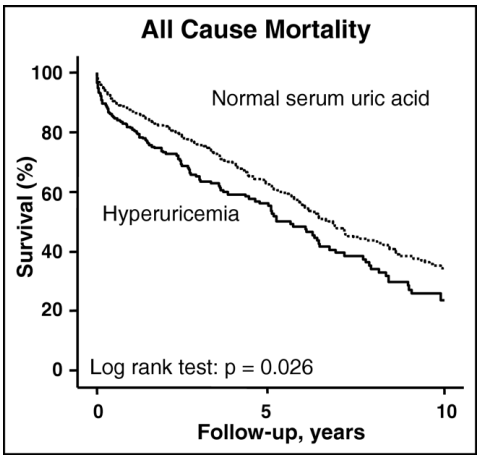

Figure 3. Long-term all-cause, mortality-free survival for serum uric acid levels.

Results

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

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

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

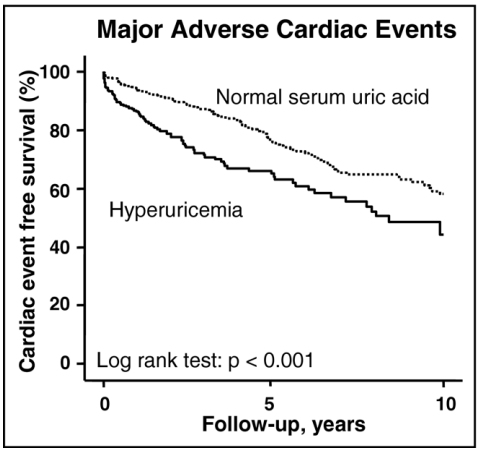

Figure 4. Long-term MACE-free survival for serum uric acid levels.

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

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

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

MACE = major adverse cardiac event.

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

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

Discussion

Preoperative cardiac risk evaluation is assessed by using clinical risk factors. Commonly used is the revised cardiac risk index, described by Lee et al,[10] which includes congestive heart failure and renal disease as risk factors. These co-morbidities are also known to influence the uric acid concentrations,[11–13] which may therefore be an objective prognostic marker for perioperative events. However, this study shows that hyperuricemia is an independent predictor of long-term mortality and MACE in patients after open vascular surgery.

To our knowledge, no other studies have been published evaluating hyperuricemia before elective vascular surgery. However, the relationship of serum uric acid and risk of fatal coronary heart disease has been researched in multiple cohort studies during the past decades.[2–5,14,15] Although hyperuricemia was associated with an increased risk of fatal coronary heart disease in these investigations, the univariate associations appeared to be largely explained by the relation of serum uric acid with other CHD risk factors and mostly disappeared after additional adjustment for confounding factors. However, Fang et al[16] reported in a follow-up study from the First National Health and Nutrition Examination Survey (NHANES 1), in which 5,926 subjects (mean age 48.1 years) were followed for a mean of 16.4 years, that in addition to cardiovascular mortality, hyperuricemia was also independently associated with an increased risk of ischemic heart disease mortality.

Recently, Strasak et al[17] studied the predictive role of serum uric acid for the risk of all major forms of cardiovascular death in a prospective population-based cohort study of 286,613 elderly women who were followed for a median of 15.2 years. The mean age was 62.3 (±8.8) years, comparable to the population in our study. The end points of this study were death from congestive heart failure, stroke, and coronary heart disease as well as from total cardiovascular disease. The highest quartile of serum uric acid levels (≥0.32 mmol/L) was associated with mortality from total cardiovascular disease, with adjusted hazard ratios for the highest versus lowest quartile of 1.35 (1.20 to 1.52). Serum uric acid levels were further significantly related to all other end points, including coronary heart disease with an adjusted hazard ratio of 1.37 (1.15 to 1.63).

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

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

In regard to underlying pathophysiological mechanisms explaining the association of serum uric acid levels and increased risk of cardiovascular events, atherosclerotic plaques have been shown to contain uric acid, and hyperuricemia may promote thrombus formation via purine metabolism[18,19] in addition to increasing the production of oxygen-free radicals and facilitating lipid peroxidation.[20] Furthermore, recent in vitro and in vivo studies suggest that serum uric acid contributes to endothelial dysfunction by inducing antiproliferative effects and impairing nitric oxide production.[21] Although it is not possible to conclude that hyperuricemia is a causal risk factor because of the observational nature of this study, these results indicate a clinical importance of monitoring hyperuricemia in patients scheduled for vascular surgery because these patients are at increased risk for coronary heart disease.

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

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Risk Reduction

Prolonged-release nicotinic acid in patients with atherosclerotic disease in the Netherlands.
Eur Surg Res. 2008; 41:313-318.

Are Statins Cardio-Protective in Patients Undergoing Major Vascular Surgery?
Cardiology Review. 2008; 25:46-50.

Bisoprolol and fluvastatin for the reduction of perioperative cardiac mortality and morbidity in intermediate-risk patients undergoing non-cardiovascular surgery; a randomized controlled trial (DECREASE-IV trial).
Submitted.

Safety and efficacy of beta-blocker therapy in patients undergoing esophagectomy for cancer.
Submitted.

RISK IDENTIFICAT
AND REDUCT
STRATEGIES
SURGICAL PATIE

Chapter 8

Prolonged-release nicotinic acid in patients with atherosclerotic disease in the Netherlands

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Dunkelgrun M
Schouten O
Hostalek U

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Prolonged-Release Nicotinic Acid in Patients with Atherosclerotic Disease in The Netherlands

D. Poldermans[a] M. Dunkelgrun[a] O. Schouten[a] U. Hostalek[b]

[a]Erasmus Medical Centre Rotterdam, Rotterdam, The Netherlands; [b]Merck KGaA, Darmstadt, Germany

Key Words
Atherosclerotic disease · High-density lipoprotein cholesterol · Dyslipidaemia · Nicotinic acid, tolerability · Niacin

Abstract
Objectives: High-density lipoprotein (HDL) cholesterol elevation is associated with an improved outcome in patients with atherosclerotic disease. Niaspan®, a prolonged-release nicotinic acid, was evaluated during the Niaspan-Induced HDL Elevation for Optimizing Risk Control (NEMO) study in The Netherlands. ***Methods:*** NEMO was a 6-month, prospective, observational, multicentre, open-label study. Niaspan was prescribed in statin-treated patients with known or suspected atherosclerotic disease. The main outcome measures were treatment-related adverse drug reactions (ADRs) and effects on lipids and cardiovascular-risk score based on the algorithm derived from the Prospective Cardiovascular Münster study. ***Results:*** 612 patients were included in The Netherlands. Flushing was the most common ADR (29% of patients during the first month of treatment). The main reasons for treatment discontinuation were flushing (10.5%), patient request (8.0%) and being lost to follow-up (6.0%). About half of all patients (52%) continued treatment after the study. Tolerability was rated 'good' or 'very good' in 54% of these patients. HDL cholesterol increased by 23% from baseline, and triglycerides were reduced by 16%, with little change in low-density lipoprotein or total cholesterol. Cardiovascular risk score was reduced by 3.3 points. ***Conclusions:*** The use of the prolonged-release nicotinic acid Niaspan in patients with or at risk for atherosclerotic disease showed good tolerability, a marked increase in HDL cholesterol and a reduced cardiovascular risk score.

Introduction

Atherosclerosis is a generalized disease affecting multiple organs and is associated with a poor cardiovascular outcome [1, 2]. Current European guidelines for the management of elevated cardiovascular risk focus strongly on the control of low-density lipoprotein (LDL) cholesterol with HMG-CoA reductase inhibitors (statins) [3, 4]. Numerous trials in tens of thousands of patients have demonstrated, beyond any doubt, that these drugs reduce the risk of adverse cardiovascular outcomes in a wide range of patients, whether or not LDL cholesterol was markedly elevated before treatment [5]. However, the magnitude of benefit from statins appears to be limited: half or more of the initial cardiovascular risk remains unaddressed by statins, even where LDL cholesterol levels are reduced to 2.0 mmol/l, or below [6–8]. Additional approaches to control excess cardiovascular risk, which are suitable for use in combination with statins, are required.

In the 1970s, the Framingham Study identified low levels of high-density lipoprotein (HDL) cholesterol as an

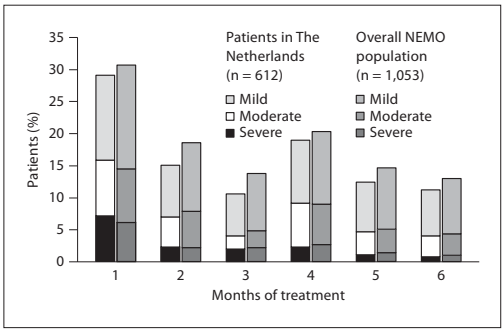

Fig. 1. Frequency and severity of flushing in patients receiving treatment with prolonged-release nicotinic acid in The Netherlands and in the overall NEMO population. Percentages relate to the overall safety population. The severity of flushing was rated by investigators.

independent risk factor for cardiovascular disease (CVD) [9]. This finding was subsequently confirmed by numerous observational analyses [10–15]. One of these, an epidemiological analysis of the UK Prospective Diabetes Study, ranked HDL cholesterol as the second most important variable determining overall cardiovascular risk in type 2 diabetes patients [15]. Additionally, low HDL-cholesterol has also been shown to be an independent risk factor for the progression of atherosclerotic disease, thus increasing cardiovascular risk [16].

Nicotinic acid (niacin) increases HDL cholesterol by about 30% in patients with peripheral artery disease [17]. Interventions to correct low HDL cholesterol in combination with this agent have resulted in significant improvements in cardiovascular outcomes [18]. A prolonged-release formulation of nicotinic acid (Niaspan®) has been developed with the intention of providing once-daily administration and reducing the incidence of flushing, the main tolerability issue with nicotinic acid [19, 20]. Prolonged-release nicotinic acid is as effective as the standard formulation of nicotinic acid in increasing HDL cholesterol levels [21], and has been shown to induce regression of atherosclerosis of the carotid artery when added to a statin [22, 23].

The Niaspan-Induced HDL Elevation for Optimizing Risk Control (NEMO) study recently evaluated the safety and tolerability of prolonged-release nicotinic acid in patients already receiving a statin in the usual care setting in 4 European countries [24]. We present a subgroup analysis of the NEMO study, in which we compare the therapeutic profile of prolonged-release nicotinic acid in patients with known or suspected atherosclerotic disease, who received treatment at centres in The Netherlands, and in the overall study population (fig. 1).

Patients and Methods

The methodology of the NEMO study, a prospective, multicentre, open-label, observational, uncontrolled trial, has been presented in detail elsewhere [24]. This was not an interventional study, and patients received all treatments according to the usual care provided by their physicians. It was recommended that the dose of prolonged-release nicotinic acid should be titrated according to its manufacturer's recommendations [25]. These include the recommendation that the dose should not be increased by more than 500 mg in a 4-week period where patients are already receiving a daily dose of at least 1,000 mg. The maximum recommended daily dose of prolonged-release nicotinic acid is 2,000 mg.

The main objective of the study was to evaluate the tolerability and safety of prolonged-release nicotinic acid under usual-care conditions, in a 6-month observation period. Of particular interest were treatment-related adverse drug reactions (ADRs), which were defined as ADRs where a causal relationship with prolonged-release nicotinic acid could not be ruled out (possible, probable, not assessable or missing relationship to treatment). Standard definitions were used to define ADRs and serious ADRs. As a secondary objective, data on lipid parameters were collected and presented as a global cardiovascular-risk score based on the algorithm derived from the Prospective Cardiovascular Münster (PROCAM) study [26]. The estimation of coronary risk in this algorithm is calculated by using 8 variables: age, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, smoking status, family history of myocardial infarction, and presence or absence of diabetes mellitus. The PROCAM score can range from 0 to 87, correlating with an estimated 10-year risk of a coronary event ranging from <0.1 to 30%, respectively.

All history of diagnosed atherosclerotic disease was documented, including peripheral arterial disease, history of stroke and transient ischemic attack, and coronary heart disease (defined as a history of previous myocardial infarction), percutaneous transluminal coronary angioplasty/stent, or coronary artery bypass graft. Risk factors for CVD, such as hypertension and diabetes mellitus, were also documented.

Eligible patients were aged ≥18 years, had started treatment with prolonged-release nicotinic acid within the previous 2 months in addition to existing treatment with a statin and had HDL cholesterol <1.3 mmol/l and/or triglycerides >1.7 mmol/l at baseline. All patients were at elevated atherosclerotic cardiovascular risk due to 1 or more of the following: (a) proven or suspected atherosclerotic disease resulting in a 10-year PROCAM risk of myocardial infarction >20%, (b) coronary heart disease with at least 1 previous myocardial infarction or stroke, (c) coronary artery disease proven by prior coronary artery bypass graft or percutaneous transluminal coronary angioplasty (including insertion of a stent) applied to a coronary stenosis of at least 70%, as documented by angiography, or (d) type 2 diabetes mellitus.

As this was not an interventional study, ethical approval or informed consent by patients was not required. Local authorities

were informed of the study, which was performed in accordance with relevant legislation. All considerations regarding the protection of human subjects throughout the course of the study outlined in international agreements such as the Declaration of Helsinki were upheld as far as applicable. The processing and handling of patient observational data was compliant with EU Directive 5/46/EC on the processing of personal data and on the free movement of such data (24 October 1995). Data were analysed using descriptive statistics and no significance testing was performed. All percentages are based on the total number of patients who received treatment.

Results

Patients

Of the 1,053 patients in the overall NEMO population, 612 received treatment in The Netherlands. Principal reasons for premature treatment discontinuation during the study (The Netherlands/overall population) were: flushing (10.5/11.1% of the total populations for each analysis), ADRs unrelated to flushing (7.2/8.5%), patient declined further treatment (8.0/10.5%) and patient was lost to follow-up (6.0/6.2%). Data on the persistency rate (the proportion of patients taking prolonged-release nicotinic acid beyond the end of the study) were available from 496 patients (81% of the study population): 52% of patients who received study treatment continued to take Niaspan beyond the study period and 29% did not.

There were no marked differences in demographic or disease characteristics between The Netherlands and the overall population at baseline (table 1). Both populations displayed an atherogenic dyslipidaemic phenotype, on average, with hypertriglyceridaemia and low HDL cholesterol, without evidence of marked hypercholesterolaemia. In total, 83% of the Dutch patients had at least 1 diagnosed CVD: 15.8% had peripheral arterial disease, 8.2% had a history of cerebrovascular disease (stroke 8.0%) and 51% were suffering from coronary heart disease, of which 30.6% had a prior myocardial infarction, 23% had received a percutaneous transluminal coronary angioplasty/stent, and 14% had received a coronary bypass graft. The remaining 17% of the population were at risk for atherosclerotic disease based upon clinical risk factors. In total, more than 50% of the patients had been diagnosed as having hypertension.

The most common statins received by patients were atorvastatin (39% in The Netherlands and 38% in the overall population), rosuvastatin (23 and 16%, respectively) and simvastatin (16 and 21%, respectively). Fluvastatin and pravastatin were each taken by <10% of patients.

Table 1. Demographic parameters and status of cardiometabolic risk at baseline

	Patients in The Netherlands (n = 612)	All patients (n = 1,053)
Males, %	81.7	79.3
Mean age, years	57 ± 11	58.4 ± 10.9
Mean weight, kg	89 ± 16	88.0 ± 16.0
Ethnicity, %		
White/Caucasian	93.5	94.5
Asian	3.6	2.6
Black	1.1	0.8
Other/not recorded	1.8	2.2
Total cholesterol, mmol/l	4.6 ± 1.2	4.7 ± 1.4
Triglycerides, mmol/l	3.6 ± 2.9	3.2 ± 2.5
LDL cholesterol, mmol/l	2.4 ± 1.0	2.6 ± 1.1
HDL cholesterol, mmol/l	0.9 ± 0.3	0.9 ± 0.3
Fasting plasma glucose, mmol/l	7.1 ± 2.6	6.8 ± 2.4
HbA_{1C}, %	6.7 ± 1.4	6.6 ± 1.4
Systolic blood pressure, mm Hg	137 ± 19	136 ± 19
Diastolic blood pressure, mm Hg	80 ± 9	80 ± 10
Hypertension, %	50.3	56.7
Coronary heart disease, %	50.8	53.0
Prior myocardial infarction, %	30.6	30.3
PTCA or stent, %	23.8	23.8
CABG, %	14.2	14.2
Cerebrovascular disease, %	8.2	10.3
Peripheral vascular disease, %	15.8	12.9
Diabetes, %	44.0	42.1
Metabolic syndrome, %	56.2	53.1
Family history for CVD, %	49.5	42.1
Smoking, %		
Current smoker	23.2	21.7
Ex-smoker	41.7	38.8
Mean PROCAM score	45.4 ± 10.3	45.6 ± 10.1

HbA_{1C} = Glycosylated haemoglobin A_{1C}; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass graft.

Tolerability and Safety

Flushing was the most common treatment-related ADR, with 29% of patients in The Netherlands flushing in the first month (fig. 1). Most flushes were mild or moderate in severity, as rated by the investigators, and this ADR occurred with similar frequency in patients in The Netherlands and in the overall population (fig. 1). The overall incidence of flushing tended to decrease over time (fig. 2). The median number of flushes each month also declined during the study, from 10 in the first month to 4 in the final month. However, this decrease may have part-

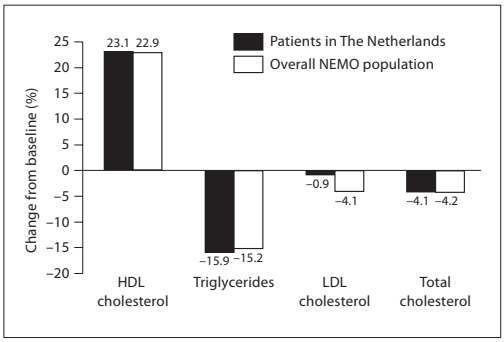

Fig. 2. Effects on lipid parameters.

Table 2. Treatment-related ADRs unrelated to flushing (% of patients)

ADR	Patients in The Netherlands (n = 612)	All patients (n = 1,053)
Skin and subcutaneous disorders (any)	3.8	4.1
Pruritus	2.9	2.7
Erythema	0.3	0.6
Gastro-intestinal disorders (any)	2.3	3.8
Upper abdominal pain	–	1.1
Nausea	0.8	1.0
Diarrhoea	0.2	0.6
Abdominal pain	0.2	0.5
Nervous system disorders (any)	2.9	3.8
Headache	0.8	0.9
Burning sensation	0.5	0.7
Dizziness	0.3	0.6
Insomnia	0.2	0.6
Musculoskeletal/connective tissue disorders (any)	1.5	1.2
Myalgia	1.1	0.8
General disorders/administration site conditions	0.7	0.9
Cardiac disorders (any)	0.3	0.7
Palpitations	0.3	0.7
Psychiatric disorders (any)	0.5	0.6
Sleep disorders	0.2	0.3

ADRs that occurred in at least 0.5% of patients in any Medical Dictionary for Research Activities system organ class in the overall population are shown, with specific clinical ADRs within each body system that occurred in more than 0.5% of patients for either population (this approach lists ADRs that occurred in more than 3 patients in the population in The Netherlands). Treatment-related ADRs were those for which investigators did not rule out a causal relationship with prolonged-release nicotinic acid.

ly been caused by early discontinuation of the patients most prone to flushing. Between 34.1 and 37.8% of patients took a non-steroidal anti-inflammatory agent as prophylaxis for flushing in a given month. In total, 233 patients (36.4%) were on aspirin therapy when starting the study, with 12 patients (2.0%) stopping and 25 patients (4.1%) starting during the study period. In total, 52 (23%) of the patients on aspirin therapy developed flushing in the first month, compared to 126 (32%) of the patients who were not on previous aspirin therapy ($p = 0.02$). However, during the rest of the study period, there were no significant differences in the incidence of flushing between patients taking and not taking aspirin therapy.

Other ADRs occurred with similar frequency in The Netherlands and internationally (table 2). The most common ADRs other than flushing occurred in the gastrointestinal and nervous systems, but the frequency of individual clinical ADRs was low in both cases. Only 1 patient (0.2%) reported a serious treatment-related ADR (gouty arthritis), which was considered possibly related to treatment by the investigator.

Physicians rated the overall tolerability of Niaspan for 435 patients (71%). In these patients, they rated tolerability as 'poor' for 25%, 'acceptable' for 22%, 'good' for 41% and 'very good' for 13%. Corresponding figures for the overall study population were 27, 19, 36 and 18%, respectively.

Lipid Profiles and Cardiovascular-Risk Score

The main effects of prolonged-release nicotinic acid on the lipid profile were a marked elevation of HDL cholesterol and a marked decrease in triglycerides (fig. 2). In general, effects on lipid parameters in The Netherlands were similar to those observed in the overall population of the study. The PROCAM score (a score for the risk of experiencing a cardiovascular event in the following 10 years; mean ± SEM) was 45.4 ± 0.5 at baseline and 41.8 ± 0.6 at the study end, resulting in a mean decrease and improvement of 3.3 ± 0.4 points. These values were similar to those in the overall study population at baseline and at the study end (45.6 ± 0.4 and 41.3 ± 0.4, respectively).

Discussion

Atherosclerotic disease is a major risk factor for cardiovascular outcome and has been recognized as a growing worldwide health burden, with prevalence rates reaching up to 29% in the USA [27, 28]. Among other classic risk factors, low HDL cholesterol had been shown to

independently increase the progression of systemic atherosclerosis, thus continually adding to the cardiovascular risk of the patient [16]. In a double-blind trial, Rubins et al. [29] showed that raising HDL cholesterol in 2,531 men with coronary heart disease significantly reduced the risk of major cardiovascular events. Postulated mechanisms of improved outcome included the theory that HDL exerts an antithrombotic effect by transporting cholesterol out of the arterial wall and by transporting anti-oxidants to LDL, thus making it less susceptible to oxidation within the endothelium. Furthermore, niacin has been shown to effectively raise the levels of HDL cholesterol in atherosclerotic patients treated for peripheral artery disease [30].

The NEMO study was designed to evaluate the effects of prolonged-release nicotinic acid in a statin-treated population of patients with known or suspected atherosclerotic disease, who were at elevated cardiovascular risk due to established dyslipidaemia, cardiovascular disease, a cardiovascular heart disease equivalent (type 2 diabetes mellitus) or a markedly elevated global cardiovascular-risk score. The study therefore set out to recruit patients typical of those presenting in routine clinical practice, who require intervention to manage their cardiovascular risk. The observational nature of the study, in which patients received the study treatment as part of the usual care provided by their physician, adds to the relevance of this trial to actual clinical practice.

The publication of the overall results of the study did not include an evaluation of the study drug in patients treated within the individual countries that participated [24]. Such information is useful, as the nature of the cardiovascular risk is known to vary between countries in Europe [31, 32]. Our data suggest that the patient population in The Netherlands was typical of the overall population of the NEMO study, with similar demographic and disease characteristics, a similar incidence of ADRs or serious ADRs (related or not to flushing), and similar effects on HDL cholesterol and triglycerides. The modest decrease in LDL cholesterol observed in the overall NEMO population is typical of the results of other clinical trials with prolonged-release nicotinic acid [19], although such an effect was not observed in The Netherlands. The reason for this difference is not clear.

The need to intervene to correct low HDL cholesterol may be particularly strong in The Netherlands. A survey of lipid profiles in 8,545 patients under treatment for dyslipidaemia in 11 European countries, published in 2005, demonstrated a prevalence of low HDL cholesterol (<1.03 mmol/l for men and <1.29 mmol/l for women) of 49%, compared with 37% for the European population as a whole [31]. The results of this analysis provide specific information to guide the therapeutic application of prolonged-release nicotinic acid in high-risk, statin-treated dyslipidaemic patients with atherosclerotic disease in The Netherlands.

International experts in Europe [33] and the USA [34] support the concept of correcting low HDL cholesterol as a therapeutic strategy for improving cardiovascular outcomes. Initial clinical experience with the first of a new class of cholesteryl ester transfer protein inhibitors has been disappointing, however, with adverse effects on atherosclerosis despite marked increases in HDL cholesterol [35, 36]. It is important to note that this was likely not due to HDL cholesterol raising per se, and may have been due to increased blood pressure observed with this agent or a consequence of the mechanism by which this agent modulates cholesterol efflux from macrophages [37, 38].

In conclusion, the use of the prolonged-release nicotinic acid Niaspan in patients with or at risk for atherosclerotic disease showed a good tolerability and a marked increase in HDL cholesterol and reduction in cardiovascular risk score. Although its overall tolerability is moderate, Niaspan is currently the only medicine available that increases HDL cholesterol levels with once-daily administration. Correction of low HDL cholesterol with nicotinic acid or other treatments has been shown in numerous studies to inhibit the progression of atherosclerosis and to improve cardiovascular outcomes [18, 39], and it remains a valid therapeutic target for the management of cardiovascular risk.

Acknowledgements

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Chapter 9

Are Statins Cardio-Protective in Patients Undergoing Major Vascular Surgery?

Dunkelgrun M
Feringa HH
Goei D
Bax JJ
Poldermans D

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Are Statins Cardio-Protective in Patients Undergoing Major Vascular Surgery?

Martin Dunkelgrun MD[1], Harm H.H. Feringa MD[2], Dustin Goei MD[1], Tamara A. Winkel MD[1], Radosav Vidakovic MD[2], Gijs M.J. Welten MD[1], Sanne E. Hoeks MSc[3], Yvette R. van Gestel MSc[3], Olaf Schouten MD[1], Eric Boersma PhD[3], and Don Poldermans MD[4]

SYNOPSIS

The cardioprotective effects of statins remain unclear in patients scheduled for major vascular surgery. In a prospective study, statin dose and cholesterol levels were recorded in 359 patients before major vascular surgery. After multivariate analysis, lower LDL-cholesterol was associated with lower myocardial ischemia, troponin T release, and 30-day and late cardiac events. Also, higher doses of Statins were associated with better cardiac outcome, even after adjusting for LDL-cholesterol.

Cardiac complications remain the leading cause of perioperative morbidity and mortality following non-cardiac vascular surgery. Recently, statins have emerged as promising cardioprotective drugs in the primary prevention of cardiac events and mortality in patients undergoing major vascular surgery ([3], [4] and [5]). The main effect of statins is the reduction of cholesterol levels, but may also have effects beyond their lipid-lowering properties (7), and may have a positive effect on the cardiac autonomous nervous system (8). Since decreased heart rate variability may trigger ischemic events, an improvement of heart rate variability by statins may be the mechanism of cardioprotection (9). This study was conducted to clarify whether higher statin doses and lower cholesterol levels are associated with reduced myocardial ischemia. Furthermore, we assessed whether higher statin doses and lower cholesterol levels were associated with improved clinical cardiac outcome, whether statins are cardioprotective independent of cholesterol levels; and if statins are associated with perioperative heart rate variability.

[1]Department of Vascular Surgery, Erasmus Medical Center, Rotterdam, the Netherlands
[2]Department of Cardiology, Erasmus Medical Center, Rotterdam, the Netherlands
[3]Department of Clinical Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands [4]Department of Anesthesiology, Erasmus Medical Center, Rotterdam, the Netherlands

PATIENTS AND METHODS

The study population consisted of 359 patients undergoing elective non-cardiac vascular surgery, during the period of 2002 to 2006. At study enrollment, all baseline cardiac risk factors were noted. In all patients, beta-blockers were considered before surgery to obtain perioperative heart rates of 60 to 65 beats/min. Before surgery, all patients underwent dobutamine stress echocardiography for the assessment of coronary artery disease. Patients with positive dobutamine stress echocardiography results were referred for further cardiac management. Type, dose, and duration of statins were noted at enrollment in all statin users. The dose of statin therapy was converted to the percentage of maximum recommended therapeutic. The duration of statin therapy was calculated from time of prescription to time of surgery. Long-term statin therapy was defined as statin treatment ≥3 months before surgery. All patients who presented with hypercholesterolemia at enrollment received statins. Patients continued statin treatment after hospital discharge. Patients were continuously monitored with a 10-electrode, 12-lead digital electrocardiogram recorder starting 1 day before surgery up to 2 days after. Episodes of ischemia were defined as reversible ST-segment changes, lasting at least 1 min and shifting from baseline to more than 0.1 mV (1 mm). Troponin T levels were measured on postoperative days 1, 3, and 7, before discharge, and whenever clinically indicated by electrocardiogram changes. The recommended lower limit of 0.03 ng/ml was used to define positive troponin T levels. Study end points were 30-day and long-term major cardiac events (cardiac death and nonfatal myocardial infarction). Cardiac death was defined as death caused by acute myocardial infarction, cardiac arrhythmias, congestive heart failure, or sudden death. Nonfatal myocardial infarction was diagnosed when at least the following 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. Heart rate variability was computed for each subject. Consecutive 5-min recordings of 2-h periods were obtained. The average heart rate variability 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). The standard deviation of the average NN intervals (SDANN) and the mean of the 5-min standard deviations (SDNN index) also were calculated for the first 24-h recording. Binary logistic regression analysis was used to evaluate the association of statin dose and cholesterol levels on perioperative myocardial ischemia, troponin T release, and 30-day clinical cardiac outcome. Cox proportional hazard analysis was used to assess the association of statin dose and cholesterol levels with late cardiac events. A propensity score for statin therapy was calculated to correct for selection bias, which was constructed using multiple logistic regression analysis. In multivariate analysis, adjustments were made for age, gender, baseline characteristics, and propensity scores. Analysis of variance techniques were used to compare heart rate variability between groups of patients with

different statin doses. Tests for heterogeneity were used to reveal a differential effect of statins between patients with or without perioperative myocardial ischemia and/or troponin T release.

RESULTS

The mean age of the study population was 67 ± 10 years, and 79% were male. A total of 187 (52%) patients received statin therapy. The following statins were used: simvastatin in 54 patients, pravastatin in 42 patients, fluvastatin in 35 patients, atorvastatin in 49 patients, and rosuvastatin in 7 patients. Long-term statin therapy was recorded in 150 patients (42%). Statins were newly prescribed in 37 patients (10%). The mean dose of statins was 41 ± 32% of MRTD. Patients with statins more frequently had a history of cerebrovascular events, hypertension, and hypercholesterolemia as compared with patients without statins (Table 1). Propensity analysis showed that patients were more likely to have statins if they had a history of cerebrovascular events ($p < 0.001$) and hypercholesterolemia ($p < 0.001$). No further differences were observed between the 2 groups. A total of 187 ischemic episodes in 103 patients (29%) were detected during continuous electrocardiography. Univariate (Figure 1 and Figure 2, Table 2) and multivariate analysis (Table 2) showed that higher statin doses and lower LDL cholesterol levels were both significantly associated with a lower incidence of myocardial ischemia.

Table 1. Baseline Characteristics of the Study Population According to Statin Therapy (n = 359)

Characteristic	Statins (n = 187)	No Statins (n = 172)	p Value
Age (yrs)	66 ± 10	67 ± 10	0.8
Male	141 (75.4)	143 (83.1)	0.07
Angina pectoris	35 (18.7)	27 (15.7)	0.5
History of myocardial infarction	68 (36.4)	68 (39.5)	0.5
Previous coronary revascularization	33 (17.6)	21 (12.2)	0.2
History of congestive heart failure	9 (4.8)	5 (2.9)	0.4
History of cerebrovascular event	64 (34.2)	33 (19.2)	0.001
Renal failure	11 (5.9)	6 (3.5)	0.3
Diabetes	30 (16.0)	25 (14.5)	0.7
Hypertension	87 (46.5)	59 (34.4)	0.02
Hypercholesterolemia	107 (57.2)	22 (12.8)	<0.001
Current or past smoking	113 (60.4)	105 (61.0)	1.0
Aspirin	102 (54.5)	93 (54.1)	1.0
Angiotensin-converting enzyme inhibitors	52 (27.8)	40 (23.3)	0.4
Beta-blockers	139 (74.3)	124 (72.7)	0.8
Calcium channel blockers	45 (24.1)	49 (28.5)	0.3
Stress-induced myocardial ischemia	36 (19.3)	42 (24.4)	0.2
Low-density lipoprotein cholesterol (mg/dl)	106 ± 38	136 ± 43	<0.001
High-density lipoprotein cholesterol (mg/dl)	50 ± 16	45 ± 17	0.02
Triglycerides (mg/dl)	152 ± 71	190 ± 101	<0.001
Total cholesterol (mg/dl)	175 ± 42	212 ± 51	<0.001

Values are expressed as mean (± SD) or n (%).

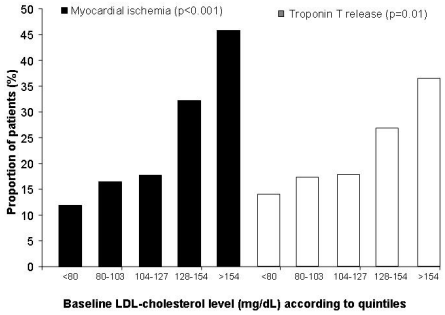

Figure 1. Incidence of Myocardial Ischemia and Troponin T Release

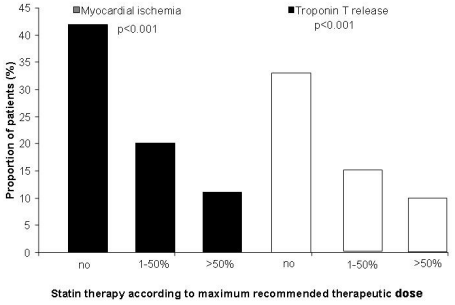

Figure 2. Incidence of Myocardial Ischemia and Troponin T Release

Table 2. Statin Therapy in Relation to Perioperative Ischemia and Troponin T Release in Patients Undergoing Major Vascular Surgery

	Perioperative Myocardial Ischemia (n = 103) OR (95% CI)		Perioperative Troponin T Release (n = 83) OR (95% CI)	
Characteristic	**Univariate**	**Multivariate***	**Univariate**	**Multivariate***
Statins				
Statin therapy (n = 187)	0.29 (0.17–0.47)	0.33 (0.18–0.60)	0.33 (0.19–0.55)	0.24 (0.12–0.47)
Statin treatment <3 months† (n = 37)	0.22 (0.08–0.58)	0.52 (0.13–2.03)	0.25 (0.08–0.72)	0.75 (0.19–2.96)
Statin treatment ≥3 months† (n = 150)	0.31 (0.18–0.51)	0.30 (0.17–0.53)	0.35 (0.18–0.62)	0.32 (0.17–0.59)
Statin dose per 10% increase of MRTD	0.82 (0.75–0.89)	0.85 (0.76–0.93)	0.85 (0.77–0.94)	0.84 (0.76–0.93)
Statin dose per 10% increase of MRTD (with adjustment for baseline LDL cholesterol)	0.87 (0.80–0.95)	0.88 (0.80–0.96)	0.90 (0.81–0.98)	0.87 (0.79–0.95)
Level of baseline cholesterol*				
LDL cholesterol (per 10-mg/dl decrease)	0.89 (0.83–0.96)	0.87 (0.80–0.95)	0.93 (0.87–1.00)	0.89 (0.82–0.96)
HDL cholesterol (per 10-mg/dl decrease)	1.07 (0.91–1.25)	1.06 (0.88–1.28)	1.14 (0.95–1.37)	1.19 (0.96–1.47)
Triglycerides (per 10-mg/dl decrease)	0.96 (0.93–0.99)	0.96 (0.93–0.98)	0.96 (0.93–0.98)	0.95 (0.93–0.98)
Total cholesterol (per 10-mg/dl decrease)	0.87 (0.83–0.93)	0.86 (0.81–0.91)	0.93 (0.87–0.98)	0.91 (0.85–0.96)

CI = confidence interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MRTD = maximum recommended therapeutic dose; OR = odds ratio.

* Adjusted for age, gender, coronary artery disease (according to medical history or stress test results), history of congestive heart failure, cerebrovascular disease, diabetes, renal failure, hypertension, type of surgery and cardiovascular medication (beta-blockers, aspirin, angiotensin-converting enzyme inhibitors, and calcium-channel blockers), and propensity scores.

† In comparison with patients with no statin treatment.

Higher statin doses remained significantly associated with a lower incidence of perioperative myocardial ischemia, after adjusting for baseline cholesterol levels (Table 2).

The lowest incidence of myocardial ischemia and troponin T release in the perioperative period was observed in patients with statin doses of more than 50% of the maximum recommended therapeutic dose. The incidence of myocardial ischemia and troponin T release in the perioperative period was lowest in patients with baseline LDL-cholesterol levels below 80 mg/dl. Troponin T release was detected in 83 patients (23%). Univariate (Fig. 1, Table 2) and multivariate analysis (Table 2) showed that higher statin doses and lower LDL cholesterol levels were both significantly associated with a lower incidence of troponin T release. Higher statin doses remained significantly associated with a

Table 3. Statin Therapy in Relation to Perioperative and Late Cardiac Outcome in Patients Undergoing Major Vascular Surgery

	Perioperative Cardiac Death or Nonfatal Q-Wave Myocardial Infarction (n = 15) OR (95% CI)		**Late Cardiac Death or Nonfatal Q-Wave Myocardial Infarction (n = 64) HR (95% CI)**	
Characteristic	**Univariate**	**Multivariate***	**Univariate**	**Multivariate***
Statins				
Statin therapy (n = 187)	0.31 (0.10–0.96)	0.32 (0.10–0.96)	0.42 (0.23–0.77)	0.41 (0.21–0.75)
Statin treatment <3 months† (n = 37)	‡	‡	0.75 (0.02–3.22)	0.81 (0.05–4.15)
Statin treatment ≥3 months† (n = 150)	0.24 (0.05–0.98)	0.25 (0.06–0.97)	0.50 (0.28–0.90)	0.52 (0.29–0.93)
Statin dose per 10% increase of MRTD	0.60 (0.39–0.95)	0.62 (0.40–0.96)	0.75 (0.64–0.89)	0.76 (0.65–0.89)
Statin dose per 10% increase of MRTD (with adjustment for baseline LDL cholesterol)	0.60 (0.37–0.95)	0.66 (0.42–0.98)	0.78 (0.65–0.96)	0.80 (0.67–0.94)
Level of baseline cholesterol*				
LDL cholesterol (per 10-mg/dl decrease)	0.86 (0.76–0.98)	0.89 (0.78–1.00)	0.93 (0.86–0.99)	0.91 (0.84–0.96)
HDL cholesterol (per 10-mg/dl decrease)	1.05 (0.69–1.55)	1.10 (0.72–1.70)	0.92 (0.78–1.09)	1.05 (0.87–1.24)
Triglycerides (per 10-mg/dl decrease)	1.01 (0.93–1.08)	1.01 (0.93–1.08)	0.99 (0.97–1.02)	1.01 (0.97–1.03)
Total cholesterol (per 10-mg/dl decrease)	0.98 (0.87–1.12)	0.95 (0.85–1.07)	0.94 (0.90–1.01)	0.94 (0.88–1.00)

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

* Adjusted for age, gender, coronary artery disease (according to medical history or stress test results), history of congestive heart failure, cerebrovascular disease, diabetes, renal failure, hypertension, type of surgery and cardiovascular medication (beta-blockers, aspirin, angiotensin-converting enzyme inhibitors, and calcium-channel blockers), and propensity scores.

† In comparison with patients with no statin treatment.

‡ No perioperative major cardiac events occurred in patients with statin treatment <3 months.

lower incidence of troponin T release, irrespective of baseline cholesterol levels (Table 2).

Perioperative cardiac death and nonfatal Q-wave myocardial infarction occurred in 3% and 1% of patients, respectively. Late cardiac death and nonfatal Q-wave myocardial infarction occurred in 13% and 5% of patients, respectively. During follow-up, statins were discontinued in 2 patients (1%) because of side effects (myopathy in 1 patient and nausea and/or diarrhea in another). In multivariate analysis, higher statin doses and lower LDL cholesterol levels were both significantly associated with a lower incidence of 30-day and late cardiac events (Table 3). Higher statin doses remained significantly associated with lower 30-day and late cardiac events, after adjusting for absolute baseline cholesterol levels.

Heart rate variability was highest before and lowest during surgery (SDNN 47 ± 28 ms, 34 ± 23 ms, and 39 ± 29 ms before, during, and after surgery, respectively [p = 0.007]). We found that lower heart rate variability before surgery (SDNN per 10 ms decrease) significantly predicted myocardial ischemia during or after surgery (OR 1.59, 95% CI 1.19 to 2.13) and troponin T release after surgery (OR 1.54, 95% CI 1.17 to 2.01). Lower heart rate variability during surgery (SDNN per 10-ms decrease) also significantly predicted myocardial ischemia after surgery (OR 1.71,

Table 4. Association Between Heart Rate Variability and Statin Therapy

Characteristic	Statins >50% of MRTD (n = 53)	Statins 1% to 50% of MRTD (n = 134)	No Statins (n = 172)	p Value
Before surgery				
SDNN (ms)	52 ± 29	48 ± 28	37 ± 19	<0.001
rMSSD (ms)	40 ± 35	36 ± 31	28 ± 22	0.01
Heart rate (beats/min)	68 ± 11	67 ± 12	68 ± 12	0.7
During surgery				
SDNN (ms)	39 ± 27	32 ± 21	29 ± 19	0.002
rMSSD (ms)	32 ± 31	26 ± 19	25 ± 23	0.06
Heart rate (beats/min)	73 ± 13	71 ± 14	72 ± 13	0.4
After surgery				
SDNN (ms)	48 ± 45	39 ± 24	36 ± 31	0.04
rMSSD (ms)	34 ± 32	33 ± 30	29 ± 28	0.1
Heart rate (beats/min)	76 ± 13	77 ± 14	77 ± 14	0.8
First 24-h recording				
SDNN (ms)	139 ± 44	131 ± 45	119 ± 42	<0.001
SDANN (ms)	116 ± 39	114 ± 39	88 ± 30	<0.001
SDNN index (ms)	47 ± 28	40 ± 18	38 ± 17	0.002
rMSSD (ms)	53 ± 47	49 ± 29	50 ± 37	0.3
Heart rate (beats/min)	72 ± 12	72 ± 13	72 ± 13	0.9

MRTD = maximum recommended therapeutic dose; rMSSD = square root of the mean squared differences of successive normal-to-normal intervals; SDANN = standard deviation of the average normal-to-normal intervals; SDNN = standard deviation of the normal-to-normal intervals.

95% CI 1.14 to 2.57) and troponin T release after surgery (OR 1.55, 95% CI 1.13 to 2.11). Higher statin doses correlated significantly with higher SDNN before, during, and after surgery (Table 4).

DISCUSSION

This study found that higher statin doses and lower LDL cholesterol levels were both significantly associated with a lower incidence of perioperative myocardial ischemia, perioperative troponin T release, and 30-day and late cardiac events in patients undergoing major vascular surgery. Higher statin doses remained significantly associated with improved cardiac outcome, irrespective of baseline cholesterol levels. Higher statin doses also correlated significantly with higher perioperative heart rate variability. These results suggest that statins are cardioprotective on a clinical and subclinical level and that they should be considered in all patients undergoing major vascular surgery.

The association between statin treatment and temporary or prolonged myocardial ischemia is not well known. Myocardial ischemia in the perioperative setting may arise either 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 beta-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. Experimental animal studies have shown that administration of statins before induction of myocardial ischemia improved myocardial viability, reduced the extent of inflammatory cell accumulation in the ischemic myocardium, and preserved coronary blood flow, which was attributed to a reduction in adhesion molecule expression of the endothelial monolayer and to an increase in the bioavailability of nitric oxide (12). The results of the current study support the view that myocardial ischemia is limited not only by cholesterol-lowering properties of statin therapy, but also by potential mechanisms such as endothelial function improvement and increase in nitric oxide with preservation of coronary blood flow (13).

Large trials have consistently shown that statins reduce cardiovascular morbidity and mortality in high-risk patients ([14], [15], [16] and [17]). Marked reductions in perioperative cardiovascular events have also been shown in patients undergoing major vascular surgery ([3], [4] and [5]). The reduction of acute thrombotic events may be explained by atherosclerotic plaque attenuation and stabilization. Intensive statin therapy can result in significant regression of atherosclerosis, as shown in the ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial (18). In human carotid plaques, statins have been shown to decrease lipids, lipid oxidation, inflammation, matrix metalloproteinase-2, and cell death and to increase tissue inhibitor of metalloproteinase 1 and collagen (7). According to the current results, every 10-mg/dl reduction in baseline LDL cholesterol was significantly associated with a 13% lower risk of perioperative cardiac

events. Moreover, a sustained beneficial effect of high-dose statins and low LDL cholesterol levels was observed for late cardiac events.

Reduced heart rate variability during surgery is most probably the result of anesthetic agents and can be a sign of increased sympathetic or reduced vagal activity. Reduced heart rate variability has been associated with sudden arrhythmic cardiovascular and noncardiovascular mortality in many studies. A recent study showed that a temporal decrease in heart rate variability, i.e., vagal withdrawal, can act as a precipitating factor for myocardial ischemia (9). High-frequency components of heart rate variability showed a consistent decrease before an ischemic event and before the electrocardiographic appearance suggestive of coronary spasm (9). We also observed that lower heart rate variability in the period preceding myocardial ischemia and troponin T release significantly predicted its occurrence in the period after this measurement. The beneficial effect of statins on autonomic function has been suggested in previously published studies ([8], [19] and [20]). Our results showed that higher statin doses were significantly associated with higher SDNN. Heart rate, a determinant of heart rate variability, was similar between patients with different statin doses. These observations led us to the hypothesis that in situations of decreased heart rate variability and increased myocardial oxygen demand, statins may exert an anti-ischemic effect by modulating the autonomic nervous system.

An important observation in this study was that statins were only prescribed in 52% of patients. This reflects the need for evidence supporting the benefit of statin treatment in patients undergoing major vascular surgery and the need for awareness among physicians. Statins have not yet been recommended as perioperative medical treatment by the American College of Cardiology/ American Heart Association (21). Coronary atherosclerosis is highly prevalent among patients undergoing major vascular surgery, with angiographic coronary abnormalities observed in up to 92% of patients (22). Surgery places the patient at additional increased risk of perioperative events (23). Therefore, the recommendations to achieve LDL cholesterol levels <100 mg/dl in people with (risk equivalents of) coronary artery disease according to the guidelines of the National Cholesterol Education Program Adult Treatment Panel III and the European guidelines on cardiovascular disease prevention in clinical practice should be extrapolated to patients undergoing major vascular surgery ([24] and [25]). The current study further provides evidence that additional risk reduction can be achieved by achieving LDL cholesterol levels <80 mg/dl.

Several limitations should be addressed. In this observational study, statins were not assigned randomly; however, the 2 groups were comparable in demographics and cardioprotective drugs. In addition, multivariate analysis and propensity scores were used to adjust for possible confounding factors. Second, the results apply to patients undergoing major noncardiac vascular surgery, and our findings may not be generalized to patients undergoing general or low-risk surgery. Third, a lower cutoff level of 0.03 ng/ml was used to define positive troponin T levels. Lower troponin T levels were not used because they do not meet the imprecision criteria (coefficient

of variation) of <10%. Finally, carotid artery surgery has been associated with heart rate change secondary to baroreceptor reflexes. The inclusion of these patients may potentially have confounded the heart rate variability results.

CONCLUSIONS

Higher statin doses and lower LDL cholesterol levels were both significantly associated with a lower incidence of perioperative myocardial ischemia during continuous 12-lead electrocardiographic monitoring, perioperative troponin T release, and 30-day and late cardiac events. Analysis of the 72-h 12-lead electrocardiographic recordings further showed that perioperative heart rate variability was significantly higher in patients with higher statin doses. These results suggest that statins are cardioprotective on a clinical and subclinical level.

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Chapter 10

Bisoprolol and fluvastatin for the reduction of perioperative cardiac mortality and morbidity in intermediate-risk patients undergoing non-cardiovascular surgery; a randomized controlled trial (DECREASE-IV trial).

Dunkelgrun M
Boersma E
Schouten O
Koopman-Van Gemert AW
van Poorten F
Bax JJ
Thomson IR
Poldermans D

Submitted.

Bisoprolol and fluvastatin for the reduction of perioperative cardiac mortality and myocardial infarction in intermediate-risk patients undergoing non-cardiovascular surgery; a randomized controlled trial (DECREASE-IV).

Martin Dunkelgrun MD[a], Eric Boersma PhD[b], Ankie WMM Koopman-van Gemert MD[c], Frans van Poorten MD[d], Cor Kalkman MD[e], Olaf Schouten MD[a], Wahjudi Siphanto MD[f], Dustin Goei MSc[a], Tamara A Winkel MD[a], Jeroen J Bax MD[f], Ian R Thomson MD[g], Don Poldermans MD[h]

ABSTRACT

Aims: Beta-blockers and statins reduce perioperative cardiac events in high-risk patients undergoing vascular surgery by restoring the myocardial oxygen supply/demand balance and/or stabilizing coronary plaques. This study evaluated the effectiveness and safety of these agents in intermediate-risk patients.

Methods and Results: Prior to surgery, 1066 patients were assigned to bisoprolol, fluvastatin, combination treatment or control therapy. Intermediate-risk patients were defined by an estimated risk of perioperative cardiac death and myocardial infarction (MI) of 1-6%, using clinical data and type of surgery. Starting dose of bisoprolol was 2.5mg daily, titrated to a perioperative heart rate of 50-70 beats per minute. Fluvastatin was prescribed in a fixed dose of 80mg. The primary endpoint was the composite of 30-day cardiac death and MI. Patients randomized

[a] *Department of Vascular Surgery, Erasmus Medical Centre, Rotterdam, the Netherlands;* [b] *Department of Clinical Epidemiology, Erasmus Medical Centre, Rotterdam, the Netherlands;* [c] *Department of Anesthesiology, Albert Schweitzer Ziekenhuis, Dordrecht, Netherlands;* [d] *Department of Anesthesiology, Reinier de Graaf Gasthuis, Delft, Netherlands;* [e] *Department of Anesthesiology, Universitair Medisch Centrum, Utrecht, Netherlands;* [f] *Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands;* [g] *Department of Anaesthesia, University of Manitoba, Winnipeg, Manitoba, Canada;* [h] *Department of Anesthesiology, Erasmus Medical Centre, Rotterdam, the Netherlands*

to bisoprolol (N=533) had a lower incidence of the endpoint than those randomized to bisoprolol-control (2.1% vs. 6.0% events; HR 0.34; 95% CI: 0.17-0.67; p=0.002). Patients randomized to fluvastatin experienced a lower incidence of the endpoint than those randomized to fluvastatin-control therapy (3.2% vs. 4.9% events; HR 0.65; 95% CI 0.35-1.10), but statistical significance was not reached (p=0.17).

Conclusion: Bisoprolol was associated with a significant reduction of 30-day cardiac complications, while fluvastatin showed a trend for improved outcome.

Word count: 200

Key Words: beta-blocker, statin, prevention, non-cardiac surgery, cardiac death, myocardial infarction

INTRODUCTION

Roughly 3.8% of the Netherlands' population undergo non-cardiac surgery annually[1]. Cardiac events are a major cause of perioperative morbidity and mortality, resulting in a mortality rate of 1%[2]. A myocardial infarction (MI) accounts for 10 - 40% of postoperative fatalities[3]. Both beta-blockers and statins reduce perioperative cardiac events in high-risk patients[4-7]. The pathophysiology of a fatal MI is complex. It can be related to myocardial oxygen demand/supply mismatch, due to perioperative surgical stress, tachycardia, hypertension, and pain[8]. Alternatively, coronary plaque instability and subsequent rupture may lead to infarction[9]. Drugs that influence plaque stability and myocardial oxygen balance may influence the incidence and severity of perioperative MI. Beta-blockers improve myocardial oxygenation by decreasing heart rate and myocardial contractility[10]. Additionally, by reducing mechanical and shear stresses, beta-blockers may also promote coronary plaque stability. Additionally, beta-blockers might have anti-inflammatory effects[11]. Statins aim at coronary plaque stabilization by decreasing lipids, lipid oxidation, inflammation, matrix metalloproteinase and cell death, and increasing tissue inhibitor of metalloproteinase and collagen[12]. Both therapies have been associated with improved outcome in high-risk surgery. However, the vast majority of patients scheduled for surgery are at low- and intermediate-risk; perioperative incidence of cardiac death and MI of <1 and 1-6 percent, respectively. In this population, the effect of perioperative beta-blockers and statins remains undefined. Our primary goal was to assess the effectiveness and safety of beta-blockers, statins and their combination, on the incidence of perioperative cardiac death and myocardial infarction in intermediate-risk surgical patients undergoing non-cardiovascular surgery.

METHODS

Study design

The DECREASE-IV study was a prospective, open-label, multicenter, randomized, controlled trial and was done in accordance with the Declaration of Helsinki. The protocol was approved by all hospital ethics committees. All patients gave written informed consent.

Study population

The design of DECREASE-IV has been published[13]. Briefly, patients aged ≥ 40 years, who were scheduled for elective non-cardiovascular surgery and had an estimated risk for a perioperative cardiovascular event between ≤ 5 % were eligible. The risk-estimation was based on clinical characteristics and an electrocardiogram (ECG) [2]. Exclusion criteria for enrolment were: the use of or a contraindication for beta-blocker or statin use; emergency surgery; inability to provide written informed consent; and previous participation in this trial. The exclusion of patients on beta-blocker or statin therapy was based on ethical considerations, being unable to withhold the use of these medications in the presence of an existing indication.

Treatment

A 2x2 factorial study design was used[14]. After signing informed consent, patients were randomized on a 1:1 ratio to receive beta-blocker therapy (bisoprolol, Merck KGaA, Darmstadt, Germany) or beta-blocker control. Patients were also randomized on a 1:1 ratio to receive statin therapy (fluvastatin XL, Novartis, Basel, Switzerland) or statin control. Hence, there were 4 treatment groups: bisoprolol alone, fluvastatin alone, both, or neither (double control). Randomization was applied by using a computer algorithm, and was stratified according to hospital. Study medication was started immediately after randomization and continued until 30 days after surgery.

The starting dose of bisoprolol was 2.5 mg orally per day, if resting heart rate was >50 bpm. During hospitalization, resting heart rate was evaluated on a daily basis and drug dose was modified with steps of 1.25 or 2.5 mg per day, up to a maximum dose of 10 mg, aiming at a heart rate of 50 - 70 bpm. The use of an open-label design was therefore necessary in order to titrate the bisoprolol dose to the therapeutic heart rate. Patients unable to take bisoprolol orally received intravenous metoprolol until the patient was able to switch back to oral medication. Bisoprolol administration was temporarily withheld if any of the following developed: resting heart rate <50 bpm; systolic blood pressure <100 mmHg; heart failure; bronchospasm; PR interval >0.30 s; second or third degree AV block. Fluvastatin was prescribed in a fixed daily dose of 80 mg. The "slow-release" statin fluvastatin 80 XL was chosen, to overcome problems in those patients who could not take statins early after surgery orally. If patients used nasogastric feeding, standard fluvastatin therapy was administered. Perioperatively, patient treatment was left to the attending physician's discretion as needed, with no restrictions imposed.

Endpoints

The primary efficacy endpoint was a composite of cardiac death and non-fatal MI until 30-days after surgery[13]. MI was defined on the basis of cardiac troponins and ECG-measurements, which were systematically collected on days 1, 3 and 7 postoperatively and whenever clinically indicated. Secondary efficacy endpoints included all-cause mortality, cardiac arrythmias, acute heart failure, and coronary revascularization. Safety endpoints included stroke, clinically significant bradycardia and hypotension (bisoprolol), clinically significant liver dysfunction or myopathy (fluvastatin). All

endpoints that occurred since randomisation until 30 days after surgery were counted.

Sample size calculation

The incidence of the primary efficacy endpoint in patients randomized to double control was estimated at 6.0%. We anticipated a 30% relative risk reduction (odds ratio 0.7) associated with bisoprolol as well as fluvastatin therapy. The combination of bisoprolol and fluvastatin was anticipated to result in a 50% relative risk reduction (odds ratio 0.7*0.7=0.49), compared to double control therapy. A total of 6000 patients are needed (1500 per group) to detect the anticipated risk reduction with a power of 81% and a two-sided α of 5%.

In the participating hospitals a total of 10,000 patients undergo elective non-cardiovascular surgery annually. We had anticipated that 2,000 of them would be eligible and provide informed consent, so that patient enrolment would be completed within 3 years. Actual enrolment started in July 2004 and ended in February 2008. The study was terminated early because of slow patient recruitment. During the study period, roughly 45,000 patients were screened, of whom 6,460 met the inclusion criteria. However, 78% of these otherwise eligible patients were receiving beta-blocker or statin therapy, instead of the anticipated 20%. Of the remaining patients, 355 did not provide informed consent or had previously participated in the study, leaving 1066 patients to be included.

Data analysis

The time to the first occurrence of the primary efficacy endpoint was determined according to the Kaplan-Meier method, and differences between allocated groups were evaluated by log-rank statistics. The Cox proportional hazards (PH) model was applied to obtain treatment effects on the primary efficacy endpoint, which are presented as hazard ratio's (HR) and 95% confidence intervals (CI). Cox PH models including interaction terms were applied to evaluate the effects of bisoprolol and fluvastatin treatment in each other's presence or absence. Analyses of other endpoints were based on contingency tables and chi-square tests. All 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

Patients

A total of 264 patients were randomized to bisoprolol therapy, 265 to fluvastatin therapy, 269 to combination therapy and 268 patients to double control therapy. Patient characteristics are presented in tables 1 and 2. The key characteristics were as follows: median age 64 years; 60% male; 11% diabetes mellitus; 6% angina pectoris; 5% prior MI; 4% prior stroke. Most common types of surgery were general (39%), urological (19%), orthopedic (16%), and ear-nose-throat (12%). General anesthesia was used in 94%, and 91% of patients were in ASA class 1 or 2. The treatment groups did not differ with respect to baseline or operative characteristics (Tables 1-2).

Outcome

The median time between starting medication and surgery was 34 (21-53) days, with

Table 1 – Baseline characteristics, medication use and preoperative 12-lead ECG findings per treatment group

Variable	Total (N=1066)	bisoprolol only (N=264)	fluvastatin only (N=265)	combination therapy (N=269)	Double control (N=268)
Baseline characteristics					
Male gender (%)	369 (60.0)	160 (60.8)	163 (61.5)	163 (60.8)	153 (57.1)
Age, years (*IQR)	65.4 (57,74)	66.8 (58,74)	65.4 (59,73)	63.8 (56,74)	65.6 (57,74)
Diabetes Mellitus (%)	115 (10.8)	29 (11.0)	32 (12.1)	30 (11.2)	24 (9.0)
Angina Pectoris (%)	55 (5.6)	11 (4.2)	15 (5.7)	14 (5.2)	15 (5.6)
Myocardial infarction (%)	54 (5.1)	16 (6.1)	16 (6.0)	13 (4.8)	9 (3.4)
Chronic heart failure (%)	8 (0.8)	3 (1.1)	3 (1.1)	2 (0.7)	0
Stroke (%)	46 (4.3)	11 (4.2)	10 (3.8)	13 (4.8)	12 (4.5)
Renal failure (%)	11 (1.0)	2 (0.8)	3 (1.1)	2 (0.7)	4 (1.5)
Medication use					
Diuretics (%)	102 (9.6)	24 (9.1)	20 (7.6)	29 (10.8)	29 (10.8)
Aspirin (%)	102 (9.6)	26 (9.6)	27 (10.2)	25 (9.3)	24 (9.0)
Calcium antagonists (%)	34 (3.2)	8 (3.0)	7 (2.6)	11 (4.1)	8 (3.0)
ACE inhibitors (%)	96 (9.0)	23 (8.7)	26 (9.8)	23 (8.6)	24 (9.0)
Angiotensin II inhibitors (%)	58 (5.4)	11 (4.2)	16 (6.0)	15 (5.6)	16 (6.0)
Anticoagulants (%)	48 (4.5)	11 (4.2)	16 (6.0)	12 (4.5)	9 (3.4)
Antiarrythmics (%)	9 (0.8)	1 (0.4)	2 (0.8)	4 (1.5)	2 (0.8)
Nitrates (%)	11 (1.0)	1 (0.4)	4 (1.5)	2 (0.7)	4 (1.5)
Digoxin (%)	15 (1.4)	3 (1.1)	6 (2.3)	1 (0.4)	5 (1.9)
Oral antidiabetics (%)	78 (7.3)	21 (8.0)	19 (7.2)	20 (7.4)	18 (6.7)
Insuline (%)	48 (4.5)	7 (2.7)	18 (6.8)	11 (4.1)	12 (4.5)
Glucocorticoids (%)	88 (8.3)	18 (6.8)	19 (7.2)	31 (11.5)	20 (7.5)
Preoperative 12-lead ECG findings					
Abnormal ECG (%)	487 (45.7)	122 (46.2)	122 (46.0)	124 (46.1)	119 (44.4)
Atrial fibrillation (%)	15 (1.4)	4 (1.5)	5 (1.9)	3 (1.1)	3 (1.1)
Right bunble branch block (%)	90 (8.4)	18 (6.8)	21 (7.9)	20 (7.4)	31 (11.6)
Left bundle branch block (%)	74 (6.9)	18 (6.8)	19 (7.2)	22 (8.2)	15 (5.6)
Q-waves (%)	103 (9.7)	22 (8.3)	32 (12.1)	27 (10.0)	22 (8.2)
Left ventricle hypertrophy (%)	83 (7.8)	24 (9.1)	21 (7.9)	22 (8.2)	16 (6.0)
Right ventricle hypertrophy (%)	1 (0.1)	1 (0.4)	0	0	0
Preventricular contractions (%)	78 (7.3)	20 (7.6)	24 (9.1)	23 (8.6)	11 (4.1)

*IQR = interquartile range

no differences between treatment groups (Table 3). Two patients died from non-cardiac complications while awaiting surgery. Twenty four patients died within 30 days after surgery. Five patients suffered cardiac death and 38 patients had nonfatal MI within 30 days. Thus, 43 (4.0%) patients reached the primary efficacy endpoint of cardiac death or nonfatal MI (Table 3). Time-to-event curves for the primary end point, by treatment group, are presented in Figure 1. The incidence of the primary outcome differed significantly between allocated groups, being lowest in the patients randomized to bisoprolol alone (1.9%) and highest in the patients randomized to double control (7.8%).

Table 2. Surgery details per treatment group

Variable	Total (N=1066)	bisoprolol only (N=264)	fluvastatin only (N=265)	combination therapy (N=269)	Double control (N=268)
Anesthesia					
General (%)	1001 (93.9)	249 (94.3)	246 (92.8)	253 (94.1)	253 (94.4)
Spinal (%)	29 (2.7)	8 (3.0)	7 (2.6)	7 (2.6)	7 (2.6)
Local (%)	36 (3.4)	7 (2.7)	12 (4.8)	9 (3.3)	8 (3.0)
Specialism					
General surgery (%)	514 (38.9)	97 (36.9)	96 (36.2)	106 (39.4)	116 (43.3)
Urology (%)	205 (19.3)	58 (22.1)	53 (20.0)	46 (17.1)	48 (17.9)
Orthopedics (%)	174 (16.3)	50 (19.0)	43 (16.2)	48 (17.8)	33 (12.3)
Ear-nose-throat (%)	133 (12.4)	30 (11.4)	30 (11.3)	35 (13.0)	38 (14.2)
Gynecology (%)	53 (5.0)	8 (3.0)	13 (4.9)	17 (6.2)	15 (5.6)
Plastic surgery (%)	55 (5.1)	12 (4.6)	22 (8.3)	9 (3.4)	12 (4.5)
Dental surgery (%)	10 (0.9)	1 (0.4)	4 (1.5)	2 (0.7)	3 (1.1)
Ophthalmology (%)	10 (0.9)	4 (1.5)	3 (1.1)	1 (0.4)	2 (0.8)
Other (%)	10 (0.9)	3 (1.1)	1 (0.4)	5 (1.9)	1 (0.4)
*ASA score					
1 (%)	392 (36.8)	95 (36.0)	96 (36.2)	105 (39.0)	96 (35.8)
2 (%)	573 (53.8)	144 (54.6)	140 (52.8)	140 (52.0)	149 (55.6)
3 (%)	101 (9.5)	25 (9.5)	29 (11.0)	24 (8.9)	23 (8.6)

*ASA = American Society of Anesthesiologists

Comparison of the 533 patients allocated to bisoprolol therapy with the 533 patients allocated to bisoprolol-control therapy

Baseline heart rate was similar in patients randomized to bisoprolol and the patients randomized to bisoprolol-control, but pre-operative heart rate was significantly lower in patients randomized to bisoprolol (Table 2), indicating adequate drug compliance. On the day of surgery, the bisoprolol dose was 2.5 mg in 99% of patients and 5.0 mg in 1%.

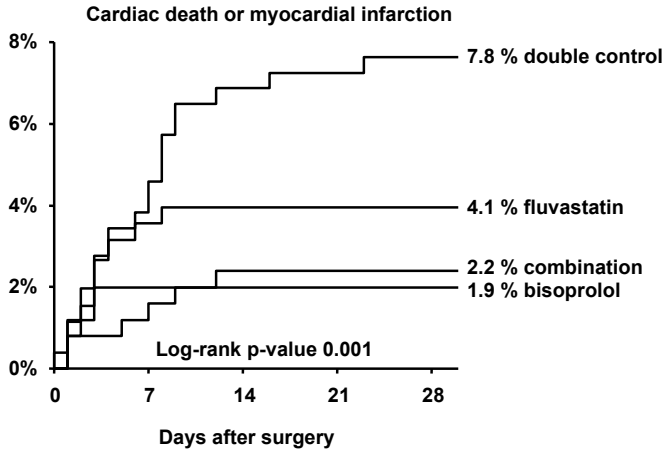

Figure 1 : Incidence of primary study end point by treatment group

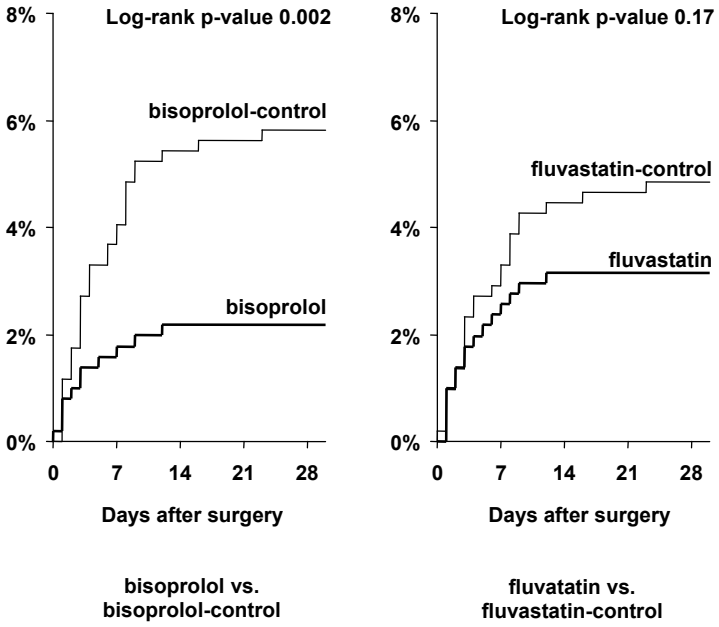

Figure 2 : Incidence of primary study end point for each individual treatment vs. control

A total of 11 (event rate according to the Kaplan-Meier method 2.1%) patients allocated to bisoprolol therapy reached the primary efficacy endpoint, compared to 32 (6.0%) allocated to bisoprolol-control (Figure 2). Hence, bisoprolol therapy was associated with a 67% relative reduction in the incidence of cardiac death or MI (HR 0.34; 95% CI: 0.17-0.67; p = 0.002). There was no evidence of heterogeneity in the beneficial effect of bisoprolol between patients randomized to fluvastatin versus fluvastatin-control (p-value associated with the interaction term 0.26).

Ischemic stroke occurred in 7 (0.7%) patients, of which 4 (0.8%) were randomized to bisoprolol and 3 (0.6%) to bisoprolol-control (p = 0.68). In total, 3 (0.6%) patients randomized to bisoprolol reached one other beta-blocker-related safety endpoint (heart failure clinically significant bradycardia or hypotension), compared to 2(0.4%) patients randomized to bisoprolol-control (p = 0.65).

Comparison of the 534 patients allocated to fluvastatin therapy with the 532 patients allocated to fluvastatin-control therapy

A total of 17 (event rate according to the Kaplan-Meier method 3.2%) patients allocated to fluvastatin therapy reached the primary endpoint, compared to 26 (4.9%) allocated to therapy without fluvastatin (Figure 2). Hence, a reduction in the incidence of the primary endpoint was observed in favor of fluvastatin therapy, but statistical significance was not reached (HR: 0.65; 95% CI: 0.35-1.20; p = 0.17).

A stroke occurred in 3(0.6%) patients who were randomized to fluvastatin therapy and in 4 (0.7%) patients randomized to fluvastatin-control (p = 0.71). In total, 8(1.5%) patients

randomized to fluvastatin therapy had clinically significant liver dysfunction compared to 11(2.1%) on fluvastatin-control therapy (p = 0.48). No patient experienced myopathy.

DISCUSSION

The DECREASE-IV study convincingly demonstrates that treatment with bisoprolol, titrated to a perioperative heart rate of 50-70 beats per minute and initiated at a median of 34 days prior to surgery, resulted in a significant reduction of perioperative cardiovascular complications, particularly MI. Only 26 patients need to receive bisoprolol prophylaxis to prevent one perioperative cardiac event. This study was not able to demonstrate a significant reduction in cardiovascular complications by fluvastatin therapy. However, we appreciate that – due to its early termination – DECREASE-IV lacked statistical power to reveal clinically relevant differences in this respect. Slow enrolment occurred due to the fact that 78% of the patients who met the inclusion criteria were on beta-blocker and/or statin therapy, as opposed to the estimated 10% of patients receiving beta-blocker and 10% receiving statin therapy.

Beta-blocker therapy for perioperative cardiac risk reduction

Although widely prescribed, there is still considerable debate about the protective effect of beta-blockers, with several studies showing a benefit of perioperative beta-blocker treatment [2-5], while others found no cardioprotective effect[15-17]. The POISE study showed, similar to DECREASE-IV, that beta-blocker therapy reduced the risk of MI but increased the incidence of stroke and overall mortality, a finding that was not confirmed in DECREASE-IV[18,19]. There are two major design differences between DECREASE-IV and POISE that may explain the differential findings: dose titration and timing of therapy.

It is well-known that initiation time and dose titration influence the effectiveness of perioperative beta-blocker therapy. The effects of acute beta-blockade include a reduction of myocardial oxygen demand. However, a beneficial effect of beta-blockade on coronary plaque stability, related to sustained mechanical and anti-inflammatory effects, might require weeks to develop. Prolonged beta-blockade has been shown to decrease the level of inflammatory cytokines both in the myocardium and the systemic circulation[11,20,21], as well as decreasing the progression of coronary atherosclerosis[22]. Additionally, it seems crucial to continue beta-blockers postoperatively. It has been shown that withdrawal of beta-blocker therapy early after surgery was associated with a 2.7-fold increased risk of 1-year mortality compared to patients not using beta-blockers[23].

In addition to initiation time, dose adjustment for heart rate control is important in beta-blocker therapy[24]. Accordingly, the new ACC/AHA guidelines on perioperative care strongly recommend achieving and maintaining a heart rate of 60-65 beats per minute[25]. The POISE trial initiated metoprolol treatment just before surgery and the maximum recommended therapeutic dose (MRTD) was achieved within the first day of treatment[18]. In contrast, the DECREASE studies employed a relatively low bisoprolol dose

(12.5% of MRTD) that was carefully titrated during approximately 30 days[5,13,26]. Notably, the POISE trial observed a 1% incidence of stroke in the group randomized to metoprolol compared to 0.5% in the control group. In comparison the incidence of stroke was 0.4% in the DECREASE studies, with no difference between groups.

The outcome of these studies suggest that two different treatment protocols applying beta-blockers are effective in reducing perioperative cardiac complications; one prescribing a high dose immediately prior to surgery, the other a dose titration approach over a prolonged period. However, the cardioprotective effect of the high dose regimen comes at the cost of an increased incidence of side effects, such as stroke.

Statin therapy for perioperative cardiac risk reduction

Statins are widely prescribed in patients with or at risk of coronary artery disease (CAD) because of their lipid lowering capacity. Beyond this property, statins may stabilize coronary artery plaque and thereby prevent plaque rupture and subsequent MI in the perioperative period[27].

Multiple large clinical trials and observational studies have demonstrated a beneficial effect of perioperative statin use[6,7,28-30]. The first prospective, randomized controlled, clinical trial evaluating the effects of statin therapy on perioperative cardiovascular complications was performed by Durazzo et al.[7] After six months follow-up, the incidence of cardiovascular events was more than 3-fold higher with placebo than with atorvastatin (26% vs. 8%, p=0.031).

A major concern of statin therapy is the potential for side effects including myopathy and rhabdomyolysis. In a retrospective study, Schouten et al. studied the potential risk of myopathy from perioperative statin therapy[31]. After correcting for cardiac risk factors and clinical risk factors for myopathy, length of surgery remained the only factor independently associated with creatine kinase elevations. Rhabdomyolysis was not observed[31]. Considering that the risk of perioperative cardiovascular complications is far greater than the risk of statin-induced myopathy and rhabdomyolysis, the potential benefits of perioperative statin use seem to outweigh the hazards. However, despite a numerical reduction in cardiac events in patients on fluvastatin therapy, statistical significance was not achieved in this study. Larger randomized controlled trials investigating perioperative statin therapy are indicated.

Limitations

A potential limitation of this study was is its open-label design and lack of blinding, with a consequent risk of treatment bias. However, since beta-blocker therapy cannot be titrated to heart rate in a double-blind setting, an open-label design was employed. In addition, the recognizable hemodynamic effects of bisoprolol potentially decrease the effectiveness of a double-blind design. The statin arms of this study were also not blinded as this would severely complicate the 2 by 2 study design. Finally, the study was terminated before the target sample size was achieved, with a resultant decrease in statistical power. This may explain the failure to achieve statistical significance regarding the efficacy

of fluvastatin therapy. Therefore, further large, randomized controlled trials of statin therapy are indicated. Finally, our results are applicable only to intermediate-risk patients undergoing non-cardiovascular surgery and are not applicable to the large population of low-risk patients.

CONCLUSION

Although, the identification of patients at risk has improved recently, no widely applicable perioperative cardiovascular risk reduction strategies for intermediate-risk patients have been developed. The current trial demonstrates that bisoprolol treatment, begun one month preoperatively, and titrated to heart rate, significantly reduces the incidence of perioperative cardiac death and MI, without increasing morbidity or non-cardiac mortality. This represents a significant advance in the management of this sizable patient population.

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APPENDIX

The members of the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography) IV Study Group and the participating centers were as follows:
Steering Committee: D Poldermans, E Boersma, FJ ten Cate, J Klein, MRHM van Sambeek*; Statistical analysis: E* Boersma; *Data-base management:* M Dunkelgrun; *Adverse-Events Committee:* P Klootwijk, and D Poldermans; *Safety Committee:* ML Simoons, and H van Urk.
Participating centers:
-Rotterdam, the Netherlands: Erasmus University Medical Center (M Dunkelgrun, E Boersma, O Schouten, D Goei, S Hoeks, TA Winkel, RT van Domburg, YRBM van Gestel, GMJM Welten, W Siphanto, L Visser, D Poldermans);
-Dordrecht, the Netherlands: Albert Schweitzer Ziekenhuis (AWMM Koopman-van Gemeren);
-Delft, the Netherlands: Reinier de Graaf Gasthuis (F van Poorten);
-Utrecht, the Netherlands: University Medical Center Utrecht (C Kalkman);
-Winipeg, AB, Canada: University of Alberta (IR Thomson).

Table 3. Treatment information, primary and secondary study end points per treatment group

Variable	Total (N=1066)	bisoprolol only (N=264)	fluvastatin only (N=265)	combination therapy (N=269)	Double control (N=268)	p-value
Treatment information						
*Time to surgery, days (IQR)	34 (21,53)	34.5 (22,52)	36 (22,56)	35 (20,52)	34 (20,53)	0.88
Heart rate at screening, bpm (IQR)	77 (70,85)	76.5 (71,84)	77 (68,85)	77 (72,85)	77 (67,87)	0.60
Heart rate preoperative, bpm (IQR)	68 (62,76)	64 (60,68)	78 (68,84)	65 (62,68)	76 (68,84)	<0.001
Heart rate difference, bpm (IQR)	-8 (-14,0)	-12 (-21,-7)	0 (-7,6)	-12 (-19,-8)	0 (-8,6)	<0.001
Primary end points						
†Cardiac death or MI (%)†	43 (4.0)	5 (1.9)	11 (4.1)	6 (2.2)	21 (7.8)	0.001
Myocardial infarction (%)	38 (3.6)	5 (1.9)	9 (3.4)	6 (2.2)	18 (6.7)	0.01
30-day total mortality (%)	26 (2.4)	3 (1.1)	7 (2.6)	7 (2.6)	9 (3.4)	0.41
Cardiac (%)	5 (0.5)	0	2 (0.8)	0	3 (1.1)	0.15
Sepsis (%)	11 (1.0)	3 (1.1)	2 (0.8)	4 (1.5)	2 (0.7)	0.80
Other (%)	10 (0.9)	0	3 (1.1)	3 (1.1)	4 (1.5)	0.31
Secondary end points						
Hospital stay, days (IQR)	8 (5,15)	8.5 (5,14)	8 (5,15)	8 (5,14)	9 (5,15)	0.71
‡ICU admittance (%)	213 (20.0)	53 (20.1)	52 (19.6)	50 (18.6)	58 (21.6)	0.85
‡ICU stay, days (IQR)	2 (1,6)	2 (2,5)	3 (1,11)	2 (1,4)	2 (1,4)	0.68
Arrhythmia (%)	9 (0.8)	2 (0.8)	3 (1.1)	1 (0.4)	3 (1.1)	0.74
Heart failure (%)	3 (0.3)	1 (0.4)	1 (0.4)	0	1 (0.4)	0.79
Revascularization (%)	1 (0.1)	0	1 (0.4)	0	0	0.39

* IQR = interquartile range, † MI = myocardial infacrtion, ‡ ICU = intensive care unit

Chapter 11

Safety and efficacy of beta-blocker therapy in patients undergoing esophagectomy for cancer

Schouten O
Dunkelgrun M
Winkel TA
Boersma E
Tilanus HW
Poldermans D

Submitted.

Safety and efficacy of beta-blocker therapy in patients undergoing esophagectomy for cancer

Olaf Schouten MD[1], Martin Dunkelgrun MD[2], Tamara A. Winkel MD[1], Eric Boersma PhD[3], Hugo W. Tilanus MD[1], Don Poldermans MD[1]

ABSTRACT

Background: Perioperative beta-blocker therapy is associated with a reduction in cardiac events. However, concerns exist regarding beta-blocker use in patients undergoing esophagectomy because of a possible increased risk of ischemia and leakage of the esophagogastric anastomosis. Therefore we selected patients from the randomized DECREASE IV undergoing esophagectomy and evaluated the efficacy and safety of beta-blocker therapy.

Method: A total of 101 patients scheduled for esophagectomy were randomized to beta-blocker therapy (n=52) or no beta-blocker therapy (n=49). Postoperatively data on troponin release and ECG were collected on day 1, 3, 7, before discharge, and on day 30. Results of radiology, gastroscopy, and clinical signs of ischemia or leakage of the esophagogastric anastomosis were noted.

Results: Beta-blocker use was associated with a reduction in the combination of myocardial damage, myocardial infarction and cardiac death (16% vs 4%, p=0.04). The rate of radiologic anastomotic leakage was similar in both groups (16% vs 16%, p=0.96), as well as the rate of ischemia at gastroscopy (26% vs 17%, p=0.32) and the number of reoperations (16% vs 14%, p=0.69).

Conclusion: Perioperative beta-blocker use in patients undergoing esophagectomy is associated with a reduction in cardiac events and is not associated with an increased risk for ischemic complications.

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[1]Department of Surgery, Erasmus MC, Rotterdam, the Netherlands; [2]Department of Anesthesiology, Erasmus MC, Rotterdam, the Netherlands; [3]Department of Cardiology, Erasmus MC, Rotterdam, the Netherlands

INTRODUCTION

Patients undergoing major non-cardiac surgery are at significant risk of cardiovascular morbidity and mortality. Although the perioperative event rate has declined over the past 30 years, 30-day cardiovascular mortality in major non-cardiac surgery remains as high as 3% to 6%[1]. Myocardial infarction (MI) is the most frequent fatal complication in this respect, accounting for up to 50% of postoperative fatalities[2,3].

Due to the role of sympathetic activation in adverse perioperative cardiac outcomes, beta-adrenergic receptor blocking drugs have been proposed as a means for providing cardioprotection. Potential cardioprotective mechanisms of beta-blockers include a reduced heart rate and contractility and subsequently lower myocardial oxygen demand; a shift in energy metabolism from free fatty acids to the more energy efficient glucose; anti-arrhythmic effects; anti-renin/angiotensin properties; and anti-inflammatory effects possibly promoting plaque stability[4,5]. Several studies have suggested that perioperative beta-blocker use is indeed associated with a reduction of perioperative cardiac complications in patients at high cardiac risk[6,7].

According to the recent ACC/AHA guidelines patients undergoing esophagectomy for cancer are at increased risk for perioperative events[8]. Therefore this group of patients might benefit from perioperative beta-blocker therapy. However, there are serious concerns on the safety of perioperative beta-blocker use in this patient population. The blood flow to the new esophagogastric anastomosis after esophagectomy is of critical importance and might be compromised by the use of beta-blockers. Consequently this might lead to an increased incidence of anastomotic leakage and reoperation, resulting in major morbidity.

The randomized Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography IV study (DECREASE IV) was set up to test whether patients at intermediate cardiac risk benefit from perioperative beta-blocker and/or statin therapy. We used data of patients undergoing esophagectomy in this study to evaluate the possible cardioprotective effect of beta-blocker use and assess the safety of beta-blockers after esophagectomy.

METHODS

Patient population

The study design of the DECREASE IV study has been published previously[9]. A total of 1,066 patients were randomized for the DECREASE IV trial and received either perioperative beta-blocker therapy, statin therapy, both or neither[10]. For the current study we selected those patients who underwent esophagectomy for cancer, either by means of extended transthoracic resection or by limited transhiatal resection, and compared patients who were allocated to perioperative beta-blocker therapy (with or without statins) or no beta-blocker therapy (with or without statins).

Briefly, patients who were (1) aged 40 years or older, (2) scheduled for elective noncardiac surgery and (3) have an estimated risk for cardiovascualar death of more than 1%, were eligible for enrollment in in the DECREASE-IV trial. Importantly, according to the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery[8] esophagectomy should be considered an intermediate risk surgical procedure with a cardiac risk of >1%.

Exclusion criteria for the trial were: (1) current use of beta-blockers, (2) contraindication for beta-blocker use, (3) the use of statins prior to randomisation, (4) a contraindication for statin use, (5) unstable coronary artery disease, (6) extensive stress induced myocardial ischemia suggestive for left main disease or equivalent, (7) emergency surgery, (8) previous participation in the same trial study, (9) unability or unwillingness to provide written informed consent.

Beta-blocker treatment regimen

The starting dose of bisoprolol, a so-called cardioselective beta-blocker, was 2.5 mg orally per day, if resting heart rate was >50 bpm. During hospitalization, resting heart rate was evaluated on a daily basis and drug dose was modified with steps of 1.25 or 2.5 mg per day, up to a maximum dose of 10 mg, aiming at a heart rate of 50 - 70 bpm. The use of an open-label design was therefore necessary in order to titrate the bisoprolol dose to the therapeutic heart rate. Patients unable to take bisoprolol orally received intravenous metoprolol until the patient was able to switch back to oral medication. Bisoprolol administration was temporarily withheld if any of the following developed: resting heart rate <50 bpm; systolic blood pressure <100 mmHg; heart failure; bronchospasm; PR interval >0.30 s; second or third degree AV block.

Efficacy endpoint

The efficacy endpoint for the current study was a composite of myocardial damage, assessed by cardiac troponin T (cTnT) release, cardiac death and non-fatal myocardial infarction (MI) until 30-days after surgery. Cardiac troponin T was sampled systematically on days 1, 3 and 7 postoperatively and whenever clinically indicated. Additionaly ECGs were collected on the same days. Nonfatal MI required any of the following: (1) characteristic ischemic symptoms lasting > 20 minutes; (2) ECG changes including acute ST elevation followed by appearance of Q waves or loss of R waves, or new left bundle branch block, or new persistent T wave inversion for at least 24 hours, or new ST segment depression which persists for at least 24 hours; (3) a positive troponin T measurement with characteristic rise and fall[11]. All deaths were classified as either cardiovascular or non-cardiovascular. Cardiovascular death is defined as any death with a cardiovascular complication as the primary or secondary cause, and includes deaths following myocardial infarction, cardiac arrhythmia, resuscitation, heart failure, or stroke. Non-cardiovascular death is defined as any death with a primary non-cardiovascular cause, including surgery-related bleeding complications, cancer, trauma and infection. Sudden death in a previously stable patient is considered as cardiovascular[12].

Safety endpoint

The safety endpoints for the current analysis consisted of radiologic anastomotic leakage, clinical anastomotic leakage or infection of the cervical wound requiring opening of the wound, signs of ischemia during gastroscopy, and reoperation. It should be noted that these endpoints were not pre-specified in the original DECREASE IV study design. Data on these safety endpoints were identified independently by two investigators by meticulous screening of medical charts, radiology reports and reports of gastroscopy. If consensus could not be reached, the opinion of a third, independent investigator was final.

STATISTICAL ANALYSIS

Continuous data are presented as median values and corresponding 25th and 75th percentiles, whereas dichotomous data are presented as percentages. Differences in clinical characteristics between patients with or without beta-blocker therapy evaluated by Wilcoxon's nonparametric tests, Chi-square tests or Fisher's exact tests, as appropriate. Differences in the incidence of the endpoints were evaluated by a Chi-square test or Fisher's exact tests. The limit of statistical significance was set at P = 0.05 (two sided). All analysis was performed using the statistical software SPSS for Windows 15.0.1 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Baseline characteristics

A total of 101 patients underwent esophagectomy, 72 by transhiatal resection and 29 by transthoracic resection. Baseline clinical characteristics are shown in table 1. Due to randomization there were no statistically significant differences in baseline characteristics and medication use. Preoperative ECG abnormalities were found in 39 (39%) patients; q-waves in 10 (10)%, right bundle branch block in 8 (8%), left bundle branch block in 5 (5%), left ventricular hypertrophy in 4 (4%), and preventricular contractions in 6 (6%). Heart rate was similar at baseline in both groups, ie 77 ± 12.4 beats/min in patients allocated to beta-blocker therapy and 80 ± 12.7 beats/min in patients allocated to the control group. Importantly at the day of hospital admission, median 34 days after the start of beta-blocker therapy, patients on beta-blocker therapy had a significantly lower mean heart rate (62 ± 7.4 beats/min vs 79 ± 12.6 beats/min, p<0.001).

Perioperative cardiac outcome

A total of 10 (9.9%) patients reached the combined efficacy endpoint of myocardial damage, myocardial infarction and cardiac death. Patients on beta-blocker therapy had a significant reduced risk for perioperative events; 3.8% vs 16.3% (OR 0.21, 95% CI 0.04-0.98, p=0.036, figure 1). The majority of cardiac events was asymptomatic. If no routine sampling of cTnT would have been performed 8 out of 10 events would have been missed. Of the 10 patients who reached the combined efficacy endpoint 5 met the criteria for

Table 1. Baseline characteristics and medication use per treatment group.

	Beta-blocker (N=52)	Control (N=49)	P-value
Baseline characteristics			
Male gender (%)	46 (85)	37 (76)	0.23
Age, years (IQR)	64.5 (56,72)	61.8 (57,71)	0.64
Diabetes Mellitus (%)	3 (6)	5 (10)	0.48
Angina Pectoris (%)	1 (2)	3 (6)	0.35
Myocardial infarction (%)	2 (4)	3 (6)	0.67
Chronic heart failure (%)	1 (2)	0	1
Stroke (%)	1 (2)	0	1
Renal failure (%)	0	0	1
Medication use			
Statins (%)	24 (46)	21 (42)	0.67
Diuretics (%)	4 (8)	2 (4)	0.68
Aspirin (%)	4 (8)	1 (2)	0.36
Calcium antagonists (%)	2 (4)	0	0.50
ACE inhibitors (%)	5 (10)	4 (4)	0.44
Angiotensin II inhibitors (%)	3 (6)	2 (4)	1
Anticoagulants (%)	1 (2)	1 (2)	1
Oral antidiabetics (%)	1 (2)	1 (2)	1
Insuline (%)	1 (2)	4 (8)	0.20
Glucocorticoids (%)	4 (8)	4 (8)	1

*IQR denotes interquartile range; ACE denotes angiotensin converting enzyme

myocardial infarction. All of these patients were allocated to the control group.

Safety outcome

The safety outcomes are shown in table 2. Of the 101 patients 87 (86%) underwent X-ray with contrast. There was no difference in the incidence of radiological anastomotic leakage; 7/44 (15.9%) patients on beta-blockers vs 7/43 (16.3%) patients not on beta-blockers (p=0.96). Clinical leakage or infection of the cervical wound requiring opening of the wound was scored in 19 patients, 9/52 (17.3%) vs 10/49 (20.4%) for users and non-users respectively (p=0.69). Gastroscopy was performed in 91 (91%) patients. Ischemia was found in 8/48 (16.7%) using beta-blockers and in 11/43 (25.6%) of patients not using beta-blockers (p=0.32). In total 15 (16.8%) patients underwent reoperation, 7/52 (13.5%) beta-blocker users and 8/49 (16.3%) non-users (p=0.69). Overall 41 (40.6%) patients had either a radiological and/or clinical anastomotic leakage and/or ischemia during gastroscopy or a reoperation. There was no difference in the incidence of the combined

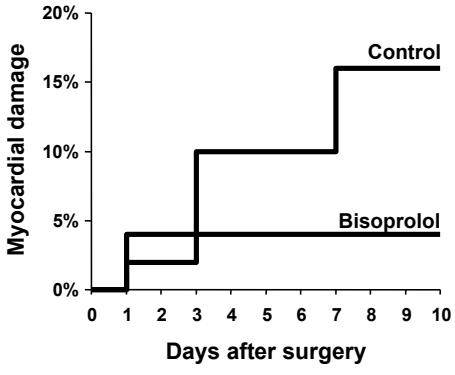

Figure 1

Table 2. Safety outcome

	Beta-blocker	Control	P-value
Radiological anastomotic leakage	7/44	7/43	0.96
Clinical leakage or infection of the cervical wound	17.3%	20.4%	0.69
Ischemia at gastroscopy	8/48	11/43	0.32
Reoperation, any	13.5%	16.3%	0.69
Reoperation, because of ischemia	5.8%	6.1%	1.0
Combined	38.5%	42.9%	0.65

Combined is the comination of radiological anastomotic leakage, clinical leakage or infection of the cervical wound , ischemia at gastroscopy, and reoperation.

safety endpoint between both groups; 38.5% vs 42.9% for users and non-users respectively (p=0.65).

DISCUSSION

The current study shows that perioperative beta-blocker therapy in patients undergoing esophagectomy for cancer is associated with a reduction in cardiac events. Importantly the blood flow to the gastroesophageal anastomosis seems not to be affected by the use of selective beta-blockers as the rate of anastomotic leakage and ischemia is similar in users and non-users.

Patients undergoing major non-cardiac surgery are at increased risk for perioperative cardiac events even if the number of clinical risk factors is limited. As described in the ACC/AHA guidelines esophagectomy should be considered an intermediate risk surgical procedure in terms of cardiac risk[8]. The pathophysiology of perioperative cardiac events is complex and not fully understood. However, similar to the non-operative setting two mechanisms seems to be involved in most cases: (1) coronary plaque rupture leading to thrombus formation and subsequnt vessel occlusion, and (2) increased myocardial oxygen demand (e.g., tachycardia and increased contractility) leading to myocardial oxygen supply/demand mismatch that when sustained might lead to myocardial infarction. In patients undergoing noncardiovascular surgical procedures in particular the latter mechanism seems to play an important role. Due to the role of myocardial oxygen/supply mismatch in adverse perioperative cardiac outcomes, beta-adrenergic receptor blocking drugs have been proposed as a means for providing cardioprotection. In particular beta-blockers reduce heart rate and contractility and subsequently lower myocardial oxygen demand, cause a shift in energy metabolism from free fatty acids to the more energy efficient glucose, have anti-arrhythmic effects and some other potentially cardioprotective characteristics.

Large series of patients undergoing esophagectomy have shown cardiac complication rates, such as myocardial infarction, of approximately 1%[13-15]. It must be noted however that in these studies there was no systematic screening for adverse cardiac events such as the frequent sampling of cardiac troponins which was performed in the current study. This might explain why the

event rate in the current study was higher than what has been reported in literature so far. It should be noted that 80% of perioperative cardiac events in the current study would have been missed if routine sampling of cTnT had not been performed. In postoperative patients, symptoms of cardiac complications might very well be atypical or absent even when ECG and/or biomarkers are abnormal. It is important to realize that myocardial infarction might occur with atypical symptoms, or even without symptoms, being detected only by ECG, biomarker elevations, or cardiac imaging. Classical symptoms of myocardial ischemia include various combinations of chest, upper extremity, jaw, or epigastric discomfort with exertion or at rest. Often, the discomfort is diffuse, not localized, not positional, not affected by movement of the region, and it may be accompanied by dyspnea, diaphoresis, nausea, or syncope. Considering these classical symptoms it is hardly surprising that such a large number of episodes of myocardial ischemia and infarction are missed in the perioperative period because symptoms are masked by residual anaesthetic effects, administration of analgesic agents, competing somatic stimuli such as incisional pain, and other factors.

Though beta-blockers have shown to be effective in reducing the risk of cardiac events, they have also been linked to serious adverse events in the perioperative period. The recently published POISE trial showed that starting high doses of metoprolol hours before surgery resulted in an increased risk for postoperative stroke[16]. Most of these strokes seem to have been attributable to perioperative episodes of hypotension which might have been caused by beta-blocker use. On the other hand, in the DECREASE trials, starting bisoprolol at a relatively low dose of 2.5 mg approximately 30 days prior to surgery, there was no association between beta-blocker use and perioperative stroke[17]. Similar to the brain the new gastroesophageal anastomosis after esophagectomy is vulnerable for hypotensive episodes. These episodes my may lead to a insufficient blood flow to the anastomosis resulting in ischemia and subsequently leakage of the anastomosis. This fear might prevent the prescribtion of perioperative beta-blocker therapy in these patients. However, as shown in the current study, a regimen of perioperative beta-blocker use starting low dose cardioselective beta-blockers approximately 30 days prior to surgery did not result in an increased risk for anastomotic leakage or ischemia nor in an increased risk for reoperation.

In conclusion, though the number of studied patients is relatively small, patients undergoing esophagectomy seem to benefit from perioperative beta-blocker therapy as it is associated with improved cardiac outcome while the gastroesophageal anastomosis is not compromised.

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RISK IDENTIFICAT
AND REDUCT
STRATEGIES
SURGICAL PATIE

Summary and Conclusion

In this thesis, factors influencing cardiac risk identification in patients scheduled for elective non cardiac surgery and medical interventions aimed at cardiac risk reduction are described.

Chapter one describes the pathophysiology of perioperative myocardial infarction (PMI). Perioperative myocardial infarction is one of the most important predictors of short- and long-term morbidity and mortality associated with non-cardiac surgery. Although the perioperative event rate has declined over the past decades as a result of achievements in anesthesiologic and surgical techniques, perioperative complications remain a significant problem. The pathophysiology of perioperative cardiac events is complex and not fully understood. However, similar to the non-operative setting two mechanisms seems to be involved in most cases: (1) coronary plaque rupture leading to thrombus formation and subsequnt vessel occlusion, and (2) increased myocardial oxygen demand (e.g., tachycardia and increased contractility) leading to myocardial oxygen supply/demand mismatch that when sustained might lead to myocardial infarction. In patients undergoing non cardiac surgical procedures in particular the latter mechanism seems to play an important role.

CADIAC RISK IDENTIFICATION

Chapter two describes a retrospective cohort study 3381 patients who underwent dobutamine stress echocardiography (DSE). A hypotensive response during DSE was defined as mild (MHR) when systolic blood pressure (SBP) dropped < 20 mmHg between rest and peak stress, and severe (SHR) when SBP dropped < 20 mmHg. End points were all cause mortality and major adverse cardiac events (MACE). MHR and SHR occurred in 936 (28%) and 521 (15%) patients, respectively. During follow-up of 4.5 (± 3.3) years, 920 patients died, of which 555 due to cardiac causes, and 713 patients experienced a MACE. After adjustment for baseline characteristics and DSE results SHR during DSE was independently associated with increased long term cardiac death (HR: 1.3, 95% CI: 1.03-1.6) and MACE (HR: 1.34, 95% CI: 1.1-1.6), while MHR was not associated with a worse outcome.

In chapter three, the effect of methionine loading on the predictive value of homocysteine serum testing is evaluated in a large observational cohort study in 1122 patients with suspected or known vascular disease. Elevated levels of homocysteine are associated with atherosclerotic disease. Methionine loading can be used to stress the homocysteine metabolism pathways and thereby detect mild disturbances in enzyme activity not registered by fasting homocysteine

levels alone. This study investigated the beneficial effect of methionine loading on the predictive value of serum homocysteine testing for long term mortality and major adverse cardiac events. During a mean follow-up of 8.9 years, 98 patients died (8.7%), 86 had a major adverse cardiac event (7.7%). In multivariate analysis, overall survival and major adverse cardiac event free survival were significantly worse for those with fasting hyperhomocysteinemia, with hazard ratios of 1.86 (95% confidence interval; 1.20-2.87) and 2.24 (95% confidence interval; 1.41-3.53), respectively. The presence of post-methionine hyperhomocysteinemia did not significantly alter risk of death or major adverse cardiac events in patients with normal or raised fasting homocysteine levels, respectively. In conclusion, methionine loading does not improve the predictive value of homocysteine testing with regard to long-term mortality or major adverse cardiac events.

Preoperative screening in patients without a history of DM includes fasting glucose measurement. However, an oral glucose tolerance test (OGTT) could significantly improve the detection of DM and impaired glucose tolerance (IGT) and the prediction of perioperative cardiac events. Chapter four describes a prospective study, in which 404 consecutive patients without signs or history of IGT or DM were included and subjected to OGTT. Primary study endpoint was the incidence of perioperative myocardial ischemia. The primary endpoint was noted in 21% of the patients. IGT was diagnosed in 104 patients (25.7%) and new onset DM was detected in 43 patients (10.6%). The OGTT detected 75% of the patients with IGT and 72% of the patients with DM. Preoperative glucose levels significantly predicted the risk for perioperative cardiac ischemia, odds ratios for DM and IGT were respectively 3.2, 95% CI: 1.3-8.1, and 1.4, 95% CI: 0.7-3.0. In conclusion, prevalence of undiagnosed IGT and DM are high in vascular patients and is associated with perioperative myocardial ischemia. Therefore an OGTT should be considered for all patients undergoing elective vascular surgery.

Chapter five describes the long-term results of the patients evaluated in chapter four. During a median follow-up of 3.0 years, 128 patients experienced a cardiovascular event. Patients with IGT showed a significant increase in cardiovascular events in both univariate (HR 2.45, 95% C.I. 1.65-3.63, $p<0.001$) and multivariate analysis (HR 2.77, 95% C.I. 1.83-4.20, $p<0.001$). Patients with DM showed a non-significant increase in cardiovascular events, indicating an under-treatment of vascular surgery patients with IGT. In conclusion, vascular surgery patients with IGT or DM detected by pre-operative OGTT, have a significant increased risk of developing cardiovascular events during long-term follow-up. It is recommended that non-diabetic vascular surgery patients should be tested for glucose regulation disorders prior to surgery.

Anemia is common in patients scheduled for vascular surgery and is a risk factor for adverse cardiac outcome. Since it is unknown whether anemia is a primary risk factor for poor cardiac outcome, or whether it is secondary to other underlying comorbidities, anemia has not been

included as a factor for cardiac risk assessment in the preoperative setting. In chapter six, the independent contribution of anemia to the risk of perioperative and long term cardiac outcome was assessed in 1211 patients (77% male, age 68 ± 11 years). Anemia was divided into tertiles to compare mild (haemoglobin levels in men 12.2-13 g/dl, women 11.2-12g/dl), moderate (haemoglobin levels in men 11-12.1 g/dl, women 10.2-11.1 g/dl) and severe (haemoglobin levels in men 7.2-11 g/dl, women 7.5-10.1 g/dl) with non-anemic patients. Outcome measures were 30-day and 5-year MACE. The presence of anemia was associated with renal dysfunction, diabetes and heart failure. After adjustment for all clinical risk factors, patients with anemia had an independent increased risk for 30-day and 5-year MACE. Therefore, anemia might be used for preoperative cardiac risk assessment in vascular patients.

Hyperuricemia has been associated with an increased incidence of cardiovascular events. In chapter seven, the independent contribution of preoperative serum uric acid levels to the risk of 30-day and late mortality and MACE was examined in 936 patients (76% male, age 68 ± 11 years) vascular surgery patients. Hyperuricemia was defined as serum uric acid >0.42 mmol/l for men and >0.36 mmol/l for women. Hyperuricemia was present in 299(32%) patients. The presence of hyperuricemia was associated with heart failure, chronic kidney disease and the use of diuretics. Perioperatively, 46(5%) patients died and 61(7%) patients experienced a MACE. Mean follow-up was 3.7 years (range: 0-17 years). During follow-up, 282 (30%) patients died and 170(18%) patients experienced a MACE. After adjustment for all clinical risk factors, the presence of hyperuricemia was not significantly associated with an increased risk of 30-day mortality or MACE, but was a significant predictor of late mortality and MACE, Therefore, hyperuricemia should be added as a risk factor for long term cardiac risk assessment in vascular patients.

CARDIAC RISK REDUCTION

Niaspan®, a prolonged-release nicotinic acid, was evaluated during the Niaspan®-induced HDL-Elevation for Optimizing Risk Control (NEMO) study in the Netherlands and is described in chaspter eight.

NEMO was a 6-month, prospective, observational, multicentre, open-label study. Niaspan® was prescribed in statin-treated patients with known or suspected atherosclerotic disease. The main outcome was treatment-related adverse drug reactions (ADRs) and effects on lipids and cardiovascular risk score based on the algorithm derived from the Prospective Cardiovascular Münster [PROCAM] study.

In total, 612 patients were included in the Netherlands. Flushing was the most common ADR (29% of patients during the first month of treatment). Main reasons for treatment discontinuation were flushing, patient request, and lost to follow-up. About half of all patients (52%) continued treatment after the study. Tolerability was rated "good" or "very good" in 54% of these

patients. HDL-cholesterol increased with 23% from baseline and triglycerides were reduced by 16%, with little change in LDL- or total cholesterol. Cardiovascular risk score was reduced by 3.3 score points. In conclusion, the use of the prolonged-release nicotinic acid Niaspan® in patients with or at risk for atherosclerotic disease showed good tolerability and a marked increase in HDL-cholesterol and reduced cardiovascular risk score.

Chapter nine examines whether higher statin doses and lower low-density lipoprotein (LDL)-cholesterol are associated with improved cardiac outcome in vascular surgery patients. In a prospective study of 359 vascular surgery patients, statin dose and cholesterol levels were recorded preoperatively. Myocardial ischemia and heart rate variability were assessed by 72-hour 12-lead electrocardiography starting 1 day before to 2 days after surgery. Troponin T was measured on postoperative day 1, 3, 7 and before discharge. Cardiac events included cardiac death or non-fatal myocardial infarction at 30 days and follow-up (mean: 2.3 years). Perioperative MI, troponin T release, 30-day and late cardiac events occurred in 29%, 23%, 4% and 18%, respectively. In multivariate analysis, lower LDL-cholesterol (per 10 mg/dL) correlated with lower myocardial ischemia (OR: 0.87, 95% CI: 0.80-0.95), troponin T release (OR: 0.89, 95% CI: 0.82-0.96), 30-day (OR: 0.89, 95% CI: 0.78-1.00) and late cardiac events (HR: 0.91, 95% CI: 0.84-0.96). Higher statin doses (per 10% of maximum recommended dose) correlated with lower myocardial ischemia (OR: 0.85, 95% CI: 0.76-0.93), troponin T release (OR: 0.84, 95% CI: 0.76-0.93), 30-day (OR: 0.62, 95% CI: 0.40-0.96) and late cardiac events (HR: 0.76, 95% CI: 0.65-0.89), even after adjusting for LDL-cholesterol.

Beta-blockers and statins reduce perioperative cardiac events in high-risk patients undergoing vascular surgery by restoring the myocardial oxygen supply/demand balance and/or stabilizing coronary plaques. In chapter ten, the DECREASE IV study is described. This study evaluated the effectiveness and safety of these agents in intermediate-risk patients. Prior to surgery, 1066 patients were assigned to bisoprolol, fluvastatin, combination treatment or control therapy. Intermediate-risk patients were defined by an estimated risk of perioperative cardiac death and myocardial infarction (MI) of 1-6%, using clinical data and type of surgery. Starting dose of bisoprolol was 2.5mg daily, titrated to a perioperative heart rate of 50-70 beats per minute. Fluvastatin was prescribed in a fixed dose of 80mg. The primary endpoint was the composite of 30-day cardiac death and MI. Patients randomized to bisoprolol (N=533) had a lower incidence of the endpoint than those randomized to bisoprolol-control (2.1% vs. 6.0% events; HR 0.34; 95% CI: 0.17-0.67; p=0.002). Patients randomized to fluvastatin experienced a lower incidence of the endpoint than those randomized to fluvastatin-control therapy (3.2% vs. 4.9% events; HR 0.65; 95% CI 0.35-1.10), but statistical significance was not reached (p=0.17). Bisoprolol was associated with a significant reduction of 30-day cardiac complications, while fluvastatin showed a trend for improved outcome.

While perioperative beta-blocker therapy may reduce cardiac events, concerns exist regarding beta-blocker use in patients undergoing esophagectomy because of a possible increased risk of ischemia and leakage of the esophagogastric anastomosis. In chapter eleven, we selected patients from the randomized DECREASE IV trial, undergoing esophagectomy and evaluated the efficacy and safety of beta-blocker therapy. A total of 101 patients scheduled for esophagectomy were randomized to beta-blocker therapy (n=52) or no beta-blocker therapy (n=49). Results of radiology, gastroscopy, and clinical signs of ischemia or leakage of the esophagogastric anastomosis were noted as well as cardiac complications. Beta-blocker use was associated with a reduction in the combination of myocardial damage, myocardial infarction and cardiac death (16% vs 4%, p=0.04). The rate of radiologic anastomotic leakage was similar in both groups (16% vs 16%, p=0.96), as well as the rate of ischemia at gastroscopy (26% vs 17%, p=0.32) and the number of reoperations (16% vs 14%, p=0.69). In conclusion, perioperative beta-blocker use in patients undergoing esophagectomy is associated with a reduction in cardiac events and is not associated with an increased risk for ischemic complications.

CONCLUSION

Patients undergoing major surgery are at significant risk for perioperative and long term cardiac complications. Preoperative cardiac risk stratification and optimization of perioperative management is of utmost importance. Selected patients could benefit from statin and beta-blocker therapy, as these appear to be independently associated with a reduction in cardiac complications, both perioperatively and for the long term. Athough perioperative medical therapy has been proven to improve cardiac outcome, it is still under discussion which patients should be treated and with which exact medicine. We hope that our research has contributed to the understanding of cardiac risk stratification and perioperative medical management.

Samenvatting en conclusie

In dit proefschrift worden factoren beschreven die de kans op cardiale complicaties beïnvloeden bij patiënten die electieve niet-cardiale chirurgie ondergaan. Verder worden medicamenteuze interventies ten behoeve van het verlagen van de kans op cardiale complicaties onderzocht.

Hoofdstuk één beschrijft de pathofysiologie van het perioperatieve myocardinfarct (PMI). Perioperatieve myocardinfarcten zijn één van de belangrijkste voorspellers voor korte en lange termijn morbiditeit en mortaliteit na niet cardiale chirurgie. Ondanks dat de incidentie van PMI's in de afgelopen tientallen jaren is gedaald door technische ontwikkelingen in de chirurgie en de anesthesiologie, blijven perioperatieve cardiale complicaties een significant probleem. De precieze pathofysiologie van het PMI is zeer complex en nog niet volledig begrepen. Er zijn waarschijnlijk, zoals bij myocardinfarcten in een niet-operatieve setting, twee mechanismen die bijdragen aan het tot stand komen van een PMI: (1) coronaire plaque ruptuur, die leidt tot thrombusformatie met daaropvolgend vaatocclusie en (2) verhoogde cardiale zuurstofbehoefte (bijvoorbeeld op basis van tachycardie en/of verhoogde contractiliteit), resulterend in een myocard zuurstof aanbod/behoefte mismatch. Dit kan bij persisteren leiden tot een myocard infarct. In patiënten die een niet cardiale operatie ondergaan lijkt vooral het tweede mechanisme een belangrijke rol te spelen.

CARDIALE RISICOSCHATTING

In hoofdstuk twee wordt een retrospectieve cohortstudie van 3381 patiënten beschreven die een dobutamine stress echocardiografie (DSE) hebben ondergaan. Een hypotensieve reactie tijdens de DSE test werd gedefinieerd als mild, indien de systolische bloeddruk < 20 mmHg daalde tussen rust en piekstress tijdens de DSE. Een ernstige hypotensieve reactie werd geconstateerd indien de systolische bloeddruk > 20 mmHg daalde tijdens de DSE. De eindpunten van de studie waren mortaliteit, cardiale dood en een ernstige cardiale complicatie. Milde en ernstige hypotensie werd gezien in respectievelijk 936 (28%) en 521 (15%) patiënten. Gedurende een follow-up van 4.5 (± 3.3) jaar, overleden 920 patiënten (555 aan een cardiale oorzaak) en kregen 713 patiënten een ernstige cardiale complicatie. Multivariabele analyse liet zien dat een ernstige hypotensieve reactie tijdens de DSE geassocieerd is met een verhoogde kans op cardiale dood (HR: 1.3, 95% betrouwbaarheidsinterval [BI]: 1.03–1.6) en ernstige cardiale complicaties (HR: 1.3, 95% BI: 1.1–1.6), terwijl een milde hypotensieve reactie geen significante invloed had op de eindpunten.

In hoofdstuk drie wordt het effect van het opladen met methionine bij het testen van serum homocysteïne geëvalueerd in een grote observationele cohort studie van 1122 patiënten met een verdenking op, of bewezen vaatlijden. Verhoogde waarden van homocysteïne zijn geassocieerd met een verhoogd risico op atherosclerose en cardiale complicaties. Het opladen met methionine kan het homocysteïne metabolisme activeren en zo milde afwijkingen in enzymactiviteit opsporen. In deze studie werd de toegevoegde waarde van het opladen met methionine voor het voorspellen van late mortaliteit en ernstige cardiale complicatie onderzocht. Gedurende een gemiddelde follow-up van 8.9 jaar, overleden 98 patiënten (8.7%) en kregen 86 patiënten een ernstige cardiale complicatie (7.7%). Uit multivariabele analyse bleek dat de incidentie van mortaliteit en ernstige cardiale complicatie significant verhoogd was voor patiënten met hyperhomocysteïnemie, met hazard ratio's van 1.86 (95% BI; 1.20-2.87) en 2.24 (95% BI; 1.41-3.53). De aanwezigheid van post-methionine hyperhomocysteïnemie had geen significante invloed op de incidentie van mortaliteit en ernstige cardiale complicatie, ongeacht de nuchtere homocysteïne serumwaarden. Concluderend geeft het opladen met methionine geen significante verbetering van de sensitiviteit van homocysteïne testen met betrekking tot mortaliteit en ernstige cardiale complicatie.

Nuchtere glucose meting is een onderdeel van preoperatief screenen van patiënten die niet bekend zijn met diabetes mellitus (DM). Een orale glucose tolerantie test (OGTT) zou DM en verstoorde glucose regulatie (VGR) mogelijk beter kunnen opsporen en perioperatieve cardiale complicaties kunnen voorspellen. Hoofdstuk vier beschrijft een prospectieve studie waarin 404 opeenvolgende patiënten zonder bekende DM of VGR een preoperatieve OGTT hebben ondergaan. Het eindpunt van de studie was de incidentie van perioperatieve ischemie. Het eindpunt werd in 21% van de patiënten gediagnostiseerd. VGR werd in 104 patiënten (25.7%) geconstateerd en DM de novo in 43 patiënten (10.6%). 75% van de patiënten met VGR werden gediagnosticeerd met behulp van de OGTT en 72% van de patiënten met DM. Preoperatieve glucose waarden waren een significante voorspeller voor perioperatieve ischemie, met odds ratio's voor DM en VGR van respectievelijk 3.2 (95% BI: 1.3-8.1) en 1.4 (95% BI: 0.7-3.0). De prevalentie van onbekende VGR en DM is hoog in vaatpatiënten en is geassocieerd met verhoogde kans op perioperatieve myocardischemie. Preoperatief testen door middel van een OGTT is daarom aan te raden voor patiënten die een electieve vasculaire ingreep ondergaan.

In hoofdstuk vijf worden de late resultaten van de patiënten die in hoofdstuk vier zijn geïncludeerd beschreven. Gedurende een gemiddelde follow-up van 3.0 jaar, kregen 128 patiënten een cardiale complicatie. Patiënten met VGR hadden een significant hogere kans op cardiale complicaties in univariate (HR 2.45, 95% BI: 1.65-3.63) en multivariabele analyse (HR 2.77, 95% BI: 1.83-4.20). Patiënten met DM hadden geen significant verhoogd risico op het krijgen van cardiale complicaties vergeleken met patiënten met normale bloedsuiker regulatie. Dit impliceert een gebrek aan behandeling van vaatpatiënten met VGR. Vaatpatiënten bij wie preoperatief

VGR of DM wordt vastgesteld, hebben een hoge incidentie van late cardiale complicaties. Het is aan te raden alle niet-diabetische vaatpatiënten middels een OGTT preoperatief te onderzoeken op afwijkingen in de glucoseregulatie.

Anemie komt vaak voor bij vaatpatiënten en is een risicofactor voor een slechtere cardiale uitkomst. Aangezien het onbekend is of anemie een primaire risicofactor is voor een slechte cardiale prognose of secundair is aan het onderliggende lijden, wordt anemie niet gebruikt als een risicofactor voor cardiale risicostratificatie in preoperatieve screening. In hoofdstuk zes wordt de onafhankelijke bijdrage van anemie op het risico voor vroege en late cardiale complicaties onderzocht in 1211 patiënten. Anemie werd verdeeld in tertielen om milde (serum hemoglobine 12.2-13 g/dl voor mannen, 11.2-12g/dl voor vrouwen), matige (mannen 11-12.1 g/dl, vrouwen 10.2-11.1g/dl) en ernstige anemie (mannen 7.2-11 g/dl, vrouwen 7.5-10.1g/dl) te kunnen vergelijken. Eindpunten waren vroege (binnen 30 dagen) en late (binnen 5 jaar) ernstige cardiale complicaties. Een hogere incidentie van nierfalen, DM en hartfalen werd gevonden in patiënten met anemie. In multivariabele analyse hadden patiënten met anemie een onafhankelijk verhoogd risico voor vroege en late ernstige cardiale complicatie. Gezien deze bevindingen, zou preoperatieve anemie gebruikt kunnen worden voor de inschatting van de kans op cardiale complicaties bij vaatchirurgische patiënten.

Verhoogd urinezuur is geassocieerd met een verhoogde kans op cardiale complicaties. In hoofdstuk zeven wordt de onafhankelijke bijdrage van de waarde van preoperatief serum urinezuur onderzocht op de kans op vroege en late ernstige cardiale complicatie in 936 vaatchirurgische patiënten. Verhoogd urinezuur werd gedefinieerd als serum urinezuur >0.42 mmol/l voor mannen en >0.36 mmol/l voor vrouwen. Verhoogd urinezuur werd geconstateerd in 299 (32%) patiënten. Verhoogd urinezuur was geassocieerd met hartfalen, nierfunctiestoornissen en het gebruik van diuretica. In totaal stierven 46 (5%) patiënten en kregen 61 (7%) patiënten een ernstige cardiale complicatie binnen 30 dagen na de operatie. De gemiddelde follow-up was 3.7 jaar (range: 0-17 jaar). Gedurende follow-up stierven 282 (30%) patiënten en kregen 170 (18%) patiënten een ernstige cardiale complicatie. In multivariabele analyse was verhoogd urinezuur niet onafhankelijk geassocieerd met perioperatieve uitkomst, maar wel met late sterfte en ernstige cardiale complicatie. Verhoogd urinezuur zou daarom toegevoegd moeten worden als risicofactor voor cardiaal risicostratificatie op lange termijn.

CARDIALE RISICOREDUCTIE

Hoofdstuk acht beschrijft de Niaspan®-induced HDL-Elevation for Optimizing Risk Control (NEMO) studie, waarin Niaspan®, een langzame-afgifte nicotinezuur, in Nederland werd onderzocht. NEMO was een half jaar durende, prospectieve, observationele, multicentre, open

label studie. Niaspan® werd aan vaatpatiënten voorgeschreven die met een statine behandeld werden. De eindpunten waren de incidentie van behandelingsgerelateerde bijwerkingen en het effect op lipide- en cardiovasculaire risicoscore, welke berekend werd door middel van het algoritme uit de Prospective Cardiovascular Münster [PROCAM] studie. In totaal, zijn 612 patiënten in Nederland geïncludeerd in de studie. Blozen was de meest voorkomende bijwerking (29% van de patiënten leed aan blozen in de eerste maand van behandeling). De meest voorkomende oorzaken voor vroegtijdig beëindigen van de studie waren blozen, het actief onttrekken van de studie door de patiënt en het niet verschijnen voor follow-up. Ongeveer de helft van de patiënten (52%) is na de studie met de medicatie doorgegaan. De tolerantie voor Niaspan® werd in 54% van de gevallen als goed of zeer goed aangegeven. HDL-cholesterol steeg met 23% van baseline en triglyceriden zakten met 16%, zonder significante verandering in LDL- of totale cholesterolwaarden. De cardiovasculaire risicoscore zakte met 3.3 punten. Concluderend, liet het gebruik van Niaspan® in vaatpatiënten een goede tolerantie, een verhoging van HDL-cholesterol en een vermindering van cardiovasculaire risicoscore zien.

In hoofdstuk negen wordt onderzocht of hoge doses statinetherapie en laag LDL-cholesterol gehalte onafhankelijk geassocieerd zijn met een verminderde incidentie van cardiale complicaties in vaatchirurgische patiënten. In een prospectieve studie van 359 patiënten, werden perioperatieve statine dosis en cholesterolwaarden geregistreerd. Perioperatieve myocardischemie en hartvariabiliteit werden door middel van continu Holter-echocardiografie van één dag voor tot twee dagen na de operatie gemeten. Troponine T werd op dag 1, 3 en 7 postoperatief gemeten. Eindpunten waren perioperatieve en lange termijn (gemiddelde follow-up: 2.3 jaar). In multivariabele analyse was een lager LDL-cholesterol (per 10 mg/dl) geassocieerd met een lagere incidentie van myocardischemie (OR: 0.87, 95% BI: 0.80-0.95), troponine T stijging (OR: 0.89, 95% BI: 0.82-0.96), perioperatieve ernstige cardiale complicatie (OR: 0.89, 95% BI: 0.78-1.00) en late ernstige cardiale complicatie (HR: 0.91, 95% BI: 0.84-0.96). Een hogere dosis statinetherapie (per 10% van de maximale dosis) was onafhankelijk geassocieerd met een lagere incidentie van myocardischemie (OR: 0.85, 95% BI: 0.76-0.93), troponine T stijging (OR: 0.84, 95% BI: 0.76-0.93), perioperatieve ernstige cardiale complicatie (OR: 0.62, 95% BI: 0.40-0.96) en late ernstige cardiale complicatie (HR: 0.76, 95% BI: 0.65-0.89).

Bètablokkers en statines verminderen de incidentie van perioperatieve cardiale complicaties in hoog risicopatiënten die vaatchirurgie ondergaan. In hoofdstuk tien wordt de DECREASE IV studie beschreven. In deze studie wordt de effectiviteit van deze medicijnen onderzocht in patiënten met een matig verhoogd cardiaal risico en die een niet cardiovasculaire operatie ondergaan. In totaal, zijn 1066 patiënten gerandomiseerd in vier groepen: bisoprolol, fluvastatine, combinatietherapie of geen medicatie. Matig verhoogd risico werd gedefinieerd als een risico van 1-6% kans op perioperatieve cardiale dood of myocard infarct. De begindosis van bisoprolol was 2.5mg per dag, wat getitreerd werd naar een perioperatieve hartslag van 50-70

slagen per minuut. Fluvastatine werd in een dosis van 80mg per dag voorgeschreven. Het primaire eindpunt van de studie was de combinatie van perioperatieve cardiale dood en myocard infarct. Patiënten die bisoprolol kregen (N=533) hadden een significant lagere incidentie van het eindpunt vergeleken met patiënten zonder bisoprolol (2.1% vs. 6.0% events; HR 0.34, 95% BI: 0.17-0.67). Patiënten die fluvastatine kregen lieten een trend tot een lagere incidentie van het eindpunt zien vergeleken met patiënten zonder fluvastatine (3.2% vs. 4.9% events; HR 0.65, 95% BI: 0.35-1.10). Concluderend, leverde het perioperatieve gebruik van bisoprolol een significant lagere incidentie van cardiale complicaties in patiënten met een matig verhoogd cardiaal risico.

Ondanks dat periopertief bètablokkergebruik de incidentie van cardiale complicaties kan verminderen, bestaat een terughoudendheid hiervoor bij patiënten die een oesofagusresectie ondergaan, omdat bètablokkers mogelijk meer ischemie en lekkage van de oesofagusanastomose zouden kunnen veroorzaken. In hoofdstuk elf hebben we de patiënten uit de DECREASE IV trial geselecteerd, die een oesofagusresectie hebben ondergaan en hebben het effect en de veiligheid van bètablokkergebruik onderzocht. In totaal hebben 101 patiënten een oesofagusresectie ondergaan (52 patiënten gerandomiseerd voor bètablokker therapie, 49 patiënten zonder). Uitslagen van radiologie, gastroscopie en klinische tekenen van ischemie of lekkage werden naast cardiale complicaties geregistreerd.

Het perioperatief gebruik van bètablokkers was geassocieerd met een vermindering van cardiale complicaties (16% vs 4%, p=0.04). Er was geen verschil in incidentie tussen beide groepen voor gediagnosticeerde anastomoselekkage (16% vs 16%, p=0.96), naadischemie (26% vs 17%, p=0.32) of reoperaties (16% vs 14%, p=0.69). Concluderend, is het perioperatief gebruik van bètablokkers in patiënten die een oesofagusresectie ondergaan geassocieerd met minder cardiale complicaties, zonder een toename van ischemische complicaties.

CONCLUSIE

Patiënten die grote operaties ondergaan hebben een verhoogd risico op perioperatieve en late cardiale complicaties. Preoperatieve cardiale risicostratificatie en een optimaal perioperatief beleid zijn daarom van uiterste belang. Een grote selectie patiënten zou baat bij statine- en bètablokkertherapie kunnen hebben, aangezien deze onafhankelijk geassocieerd zijn met een lagere incidentie van cardiale complicaties. Hoewel het aangetoond is dat medicamenteuze therapie de cardiale uitkomst kan verbeteren, blijft het een discussie welke patiënten behandeld dienen te worden en met welke medicijnen. Wij hopen dat wij door middel van dit onderzoek hebben bijgedragen aan het inzicht in cardiale risicostratificatie en perioperatieve medicamenteuze therapie.

Publications and Presentations

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PRESENTED ABSTRACTS

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Curriculum Vitae

Martin Dunkegrün werd op 23 maart 1979 geboren te Leidschendam. In 1997 slaagde hij voor het eindexamen VWO-gymnasium aan het 1e Vrijzinnig Christelijk Lyceum te 's-Gravenhage. Na een jaar pre-med te hebben gestudeerd aan de University of Pennsylvania te Philadelphia, PA, ging hij in 1998 Geneeskunde studeren aan de Universiteit Leiden. Tijdens zijn studie werkte hij als donatie coördinator en explantatie teamleider voor Bio Implant Services. Zijn keuze co-schap chirurgie volgde hij in het Reinier de Graaf Gasthuis te Delft (Dr. L. Stassen). Verder heeft hij extra co-schappen gevolgd in de chirurgie in het Massachusetts General Hospital te Boston, MA (Prof.dr. C. Fergussen) en plastische chirurgie aan het Carmel Hospital te Haifa, Israel (Prof.dr. Y. Har-Shai). Eind 2005 behaalde hij zijn artsexamen cum laude en startte zijn promotieonderzoek naar cardiale risicoschatting en risicoreductie strategieën in het Erasmus MC te Rotterdam (Prof. dr. D. Poldermans). Een door de Nederlandse Harstichting gesubsidieerde, gerandomiseerde studie, waarin perioperative behandeling met bisoprolol en fluvastatine werd onderzocht in patiënten die een niet cardiovasculaire operatie ondergingen, vormde de basis van zijn onderzoek en heeft geresulteerd in dit proefschrift. Op 1 mei 2008 begon hij als ANIOS chirurgie in het IJsselland Ziekenhuis te Capelle aan den IJssel (Dr. I. Dawson). Sinds 1 januari 2009 is hij in opleiding tot chirurg in het Eramus MC te Rotterdam (Prof.dr. J.N.M. IJzermans).

Martin Dunkelgrün was born on March 23rd 1979 in Leidschendam, the Netherlands. He attended secondary school at the 1e Vrijzinnig Christelijk Lyceum in The Hague, where he matriculated in 1997. After studying pre-med at the University of Pennsylvania in Philadelphia, PA for one year, he started medical school at Leiden University, the Netherlands in 1998. During his studies, he worked for Bio Implant Services in the field of Tissue Donation. He followed elective clinical clerckships in general surgery at the Reinier de Graaf Gasthuis in Delft, the Netherlands (Dr. L. Stassen), in general surgery at Massachusetts General Hospital in Boston, MA (Prof.dr. C. Fergussen) and Plastic Surgery at Carmel Hospital in Haifa, Israel (Prof.dr. Y. Har-Shai). In the autumn of 2005 he obtained his medical degree (cum laude) and started his research in cardiac risk identification and reduction strategies at the Erasmus MC in Rotterdam, the Netherlands (Prof.dr. D. Poldermans). A randomized, controled trial investigating the impact of perioperative use of bisoprolol and fluvastatin in non-cardiovascular surgery patients (supported by the Netherlands Heart Foundation) was the cornerstone of his research that resulted in this thesis. On May 1st 2008 he became a surgical resident at the IJsselland Hospital in Capelle aan den IJssel, the Netherlands (Dr. I. Dawson) and on January 1st 2009 he started his specialization in general surgery at the Eramus MC in Rotterdam (Prof.dr. J.N.M. IJzermans).

Erasmus MC
Universitair Medisch Centrum Rotterdam

PhD Portfolio Summary

SUMMARY OF PHD TRAINING AND TEACHING ACTIVITIES

Name PhD student:	M. Dunkelgrün	PhD period:	2005-2009
Erasmus MC Department:	Vascular Surgery	Promotor:	Prof.dr. D. Poldermans,
Research School:	COEUR		Prof.dr.ir H. Boersma

1. PhD training

	Year	Workload (Hours/ECTS)
General academic skills		
-	-	-
Research skills		
- Statistics	2008	4.5 ECTS
- Methodology	2008	1.5 ECTS
In-depth courses (e.g. Research school, Medical Training)	2009	-
- ANIOS chirurgie		
Presentations		
International conferences	2006	1.0 ECTS
National conferences	2006	0.6 ECTS
International conferences	2007	1.0 ECTS
National conferences	2007	0.6 ECTS
National conferences	2008	0.6 ECTS
Conferences		
International conferences	2006	3.0 ECTS
National conferences	2006	1.2 ECTS
International conferences	2007	3.0 ECTS
National conferences	2007	1.2 ECTS
National conferences	2008	1.2 ECTS
Seminars and workshops		
COEUR vascular medicine	2006	1.5 ECTS
Clinical cardiovascular epidemiology	2007	1.5 ECTS