Colophon

ISBN:	978 90 70062 521
Copyright:	Tamara A. Winkel
Publisher:	Jongbloed, The Hague
Print:	Microweb Edu b.v.
Cover:	Stephanie Bloemarts - Brederode

Financial support for this thesis was generously provided by:
Biotronik Nederland BV,
Eli Lilly Nederland BV,
BV Jongbloed Juridische Boekhandel,
Medtronic Bakken Research Center BV,
Merck Sharp & Dohme BV,
Servier Nederland Farma BV.

How to Reveal Arrhythmias in Vascular Surgery Patients

Hartritmestoornissen bij vaatchirurgische patiënten

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof. dr. H.G. Schmidt

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 29 september 2010 om 15.30 uur

door

Tamara Adele Winkel
geboren te Curaçao

PROMOTIECOMMISSIE:

Promotor:	Prof. dr. D. Poldermans
Overige leden:	Prof. dr. H.J.M. Verhagen
	Prof. dr. R.J. Stolker
	Prof. dr. ir. H. Boersma

aan mijn moeder

Ku henter mi alma, ku henter mi bida, lo mi sigui stimabo.

Padu Lampe

Contents

Part II: Perioperative serum biomarker

Part III: Perioperative and Long-term Risk Reduction

Preface

In Europe, with an overall population of approximately 490 million, crude estimates of 7 million major surgical procedures are conducted annually. Cardiac events, such as myocardial infarction (MI) and cardiac death, are a major cause of perioperative morbidity and mortality in these patients. After major surgery the incidence of cardiac death varies between 0.5% and 1.5%, with non-fatal cardiac complications ranging between 2.0% and 3.5%. When applied to the European population these figures translate into 150,000 to 250,000 life-threatening cardiac complications due to non-cardiac surgical procedures annually. The risk of perioperative cardiac complications depends on the condition of the patient prior to surgery, the prevalence of co-morbidities, and the magnitude and duration of the surgical procedure. Despite the decline in complication rates over the past decades, perioperative adverse cardiac events still remain a significant problem, therefore persisting as an area of clinical interest and concern.

Cardiac arrhythmias are of special interest, due to their unique place within the pathophysiology of perioperative cardiac adverse events. Firstly, arrhythmias can be of diagnostic value, if detected early in the perioperative period. There is often an instigating factor for an arrhythmia to occur in a postoperative patient. These are usually transient incidents, such as hypoxemia, cardiac ischemia, catecholamine excess, or electrolyte abnormalities, which warrant immediate treatment to prevent further complications. This includes correction of these imbalances and medical therapy directed at the arrhythmia itself.
Secondly, arrhythmias can be considered as an adverse cardiac event on its own, enhancing thromboembolic processes, resulting in stroke and death in some cases. Following both cardiac and non-cardiac surgical procedures, arrhythmias are common and represent a major source of postoperative morbidity. Arrhythmias are therefore both of diagnostic and prognostic value to treating physicians. However, the majority of arrhythmias is asymptomatic and often transient, causing them to be frequently missed.

Part One of this thesis focuses on the detection, prediction and prognostic value of perioperative arrhythmias. For detection, the use of an electrocardiogram (ECG) monitor continues to be the gold standard for the diagnosis of cardiac arrhythmias and (acute) myocardial ischemia. Current guidelines by the European Society of Cardiology recommend a baseline 12-lead ECG be made in all patients with one or more cardiac risk factors, prior to surgery. Perioperative arrhythmias are most likely to occur in patients with structural heart disease. The diagnosis of arrhythmias, such as supraventricular or ventricular tachyarrhythmia's, is made by routine ECG recordings and ambulatory Holter monitoring. Recently, extended monitoring methods have been introduced, including transtelephonic ECG transmissions, 72-hour and 7-day Holter ECG monitoring, and 30-day event recording. The reported incidence of cardiac arrhythmias following non-cardiac surgery depends on the timing and duration of the cardiac monitoring used to detect them. Depending on the specific monitoring method, the sensitivity lies between 31.3% and 71.0%, whereas the negative predictive value (NPV) ranges between 21.5% and 64.6%, with better estimates being obtained using continuous monitoring. The standard surface 12-lead ECG and 72-hour continuous ECG (Holter) are all capable of continuous ECG recording; however, none of them is practical for long-term continuous monitoring. An implantable loop recorder is capable of monitoring the heart rhythm for a longer period of time. Using this method, the true prevalence of perioperative arrhythmias was investigated.

For prediction of arrhythmias, traditional cardiac risk factors and several other factors were evaluated for their association with cardiac arrhythmias. The physiologic impact of arrhythmias depends on arrhythmia duration, ventricular response rate, and underlying cardiac function, assessed with preoperative echocardiography and measurement of N-terminal pro-B-type natriuretic peptide (NT-proBNP).

For the prognostic value of arrhythmias, especially the influence of arrhythmias on outcome after vascular surgery, several studies are described in the first part of this thesis. By using Holter recordings the heart rate variability can be calculated,

providing a sensitive, noninvasive measurement of the autonomic input and overall health of the cardiac muscle. The heart rate variability was subsequently correlated to postoperative outcome.

Part Two of this thesis expands focus from cardiac arrhythmias to perioperative damage to the myocardium by any cause. A direct and objective marker of perioperative myocardial damage is cardiac troponin T (cTnT). This biomarker is highly sensitive and specific for the detection of myocardial cell death and subsequently perioperative MI. The predictive value of asymptomatic cardiac damage, defined as cTnT release without clinical symptoms or ECG changes, is assessed in patients undergoing endovascular repair of an abdominal aortic aneurysm. The second part of this thesis also investigates the extent of myocardial damage assessed with an integrated area under the curve analysis. The area under the curve could also be of prognostic value for the long-term outcome after vascular surgery.

Part Three of this thesis discusses treatment possibilities, once the perioperative cardiac risk is assessed. Several possible perioperative risk reduction strategies – including beta-blocker and statin therapy – and their effect on perioperative and long-term outcome are evaluated.
Beta-blockers are widely used for the treatment of hypertension, angina pectoris, congestive heart failure, are recommended in patients with ischemic heart disease, stress-inducible myocardial ischemia on preoperative testing, those scheduled for high-risk surgery (e.g. aortic, peripheral and major vascular surgery), and should be considered in patients scheduled for intermediate-risk surgery (e.g. endovascular aneurysm repair, carotid, peripheral arterial angioplasty, abdominal, head and neck, major orthopedic procedures etc). In the third part of this thesis potential cardioprotective mechanisms of beta-blockers are described extensively. Perioperative MIs have similar coronary artery pathology to non-operative MIs with regard to coronary plaque hemorrhage, rupture, and thrombus formation and probably occur by a similar mechanism. Unstable plaques have a large lipid core and a thin, weakened fibrous cap infiltrated by macrophages

and other inflammatory cells that are vulnerable to disruption. Inflammatory processes in general, and monocyte-derived macrophages in particular, play a critical role in the progression and destabilization of coronary plaque. Several trials involving the non-surgical and surgical population have shown a beneficial role of statin therapy on cardiac outcome. The third part of this thesis also elaborates on the cardioprotective mechanism of statins, their so-called pleiotropic effects beyond the lipid-lowering mechanism.

PART I

Perioperative cardiac arrhythmias

1

The feasibility of using a single lead bipolar electrode for detection of cardiac ischemia during vascular surgery.

submitted

Tamara A. Winkel
David Hampton
Mirko de Melis
Anneke Pietersma
Hence J.M. Verhagen
Don Poldermans

Abstract

Patients undergoing non-cardiac vascular surgery frequently suffer cardiovascular events, like transient arrhythmias and myocardial ischemia, during the perioperative period as documented using 12-lead Holter electrocardiography (Holter-ECG). Implanted loop recorders (ILRs; bipolar-ECG) could be used to continuously monitor for arrhythmias during a longer period of time. This investigation assesses the feasibility of using the same device to monitor for ischemic events.

A total of 115 vascular surgery patients were monitored with Holter-ECG during a 72 hour perioperative period, and 20 patients (17%) with episodes of ischemia were noted by physician overread. Holter-ECG recordings, together with a matching non-ischemic sample set, were extrapolated to predict bipolar-ECG morphology at standard ILR shoulder implant position. The correspondence between detected ischemic episodes was assessed and 11/20 patients showed ST deviations characteristic of transient ischemia in bipolar-ECG estimated recordings. Further extrapolations to alternative ILR implant positions and orientations suggest that transient ST deviations can also be detected at chest positions V2 and V3, although with lower accuracy.

In conclusion, an ILR monitor used for monitoring patients for postoperative arrhythmia may also have use for detecting perioperative transient ischemic events. However, current data could not yield an acceptable sensitivity for the use of a single bipolar-ECG in ischemia detection, suggesting that wider bipolar lead spacing may be needed in order to improve correspondence with conventional surface recordings.

Introduction

Patients undergoing non-cardiac vascular surgery are at significant risk of cardiovascular morbidity and mortality due to underlying coronary artery disease which predisposes them to ischemic events[1-2].

Meticulous preoperative screening of vascular surgery patients with cardiac stress testing may identify patients at particular risk, who can then be asked to act on characteristic symptoms. Almost all ischemic events are thought to be silent and patients may doubt the significance of chest pain or wait before notifying physicians. This results in delays in treatment, leading to larger infarct size, decreased left ventricle function (LVF)[3], and worse outcomes[4].

Earlier detection with better accuracy can be achieved using continuous 12-lead ECG monitoring (Holter-ECG) during the postoperative period, supplemented by serial cardiac troponin measurements (cTn I or T). However, conventional Holter-ECG can only be used for a period of days rather than for weeks, the more typical interval when high-risk patients suffer events[4]. Furthermore, ECG wires and electrodes can interfere in the surgical area and Holter monitors are cumbersome for the patient, leading to compliance issues after discharge.

Bipolar implantable loop recorders (ILRs; bipolar-ECG) may be a simple solution. These devices, placed on or beneath the skin, are already used for syncope and arrhythmia detection[5], and are well tolerated by patients over longer periods of time. Current commercial devices may only require bandwidth modification to record ECG features characteristic of ischemia.

The aim of the present study was to assess the feasibility of using ILRs for ischemia detection, using bipolar-ECG recordings estimated from 12-lead Holter-ECG recordings acquired from patients undergoing vascular surgery. These estimates could further be used to determine whether ST changes in the bipolar-ECG were likely to be time-synchronous with changes seen in the Holter-ECG and to characterize the effect of implant position on detection accuracy.

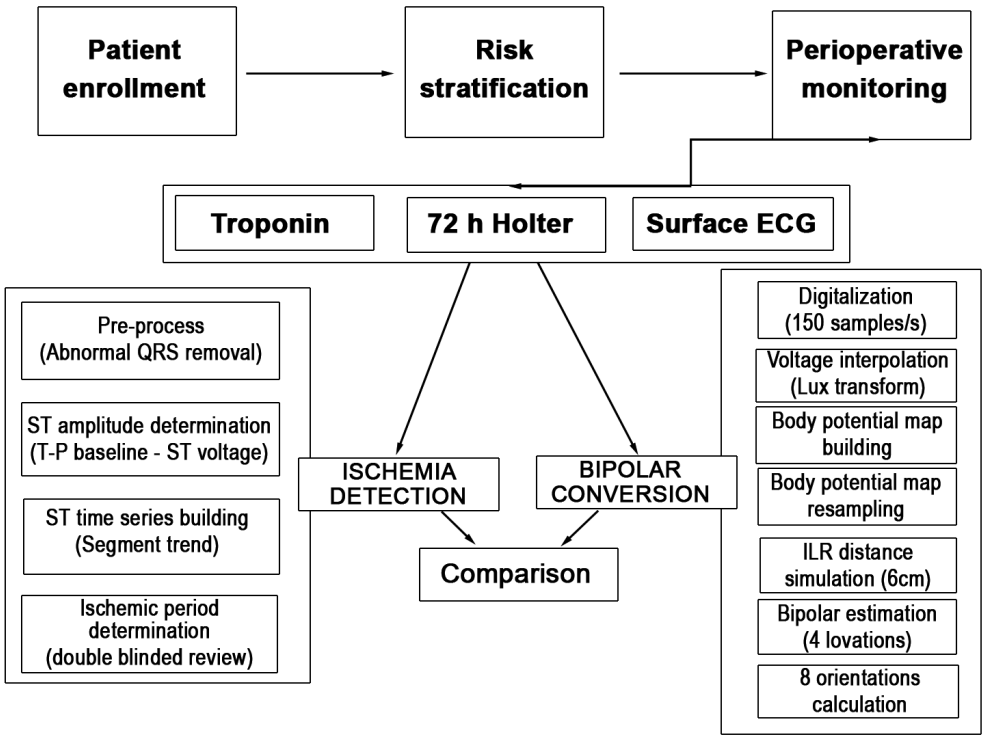
Methods

Study population

The study population consisted of a convenience sample of 115 patients undergoing elective vascular surgery at the Erasmus Medical Center in Rotterdam, the Netherlands. Patients with a history of cardiac arrhythmias, an implantable cardioverter defibrillator or cardiac pacemaker were excluded. The hospital's ethical committee approved the study. No extramural funding was used to support this work.

Patients were enrolled up to 3 months prior to surgery at the outpatient clinic. We determined the cardiac risk score for each patient in our dataset, and one point was assigned to each of the following characteristics: advanced age (>70 years), angina pectoris (AP), history of MI, congestive heart failure (CHF), stroke (transient ischemic attack [TIA] and/or cerebral vascular accident [CVA]), diabetes mellitus (fasting glucose level ≥7.0 mmol/L or use of insulin or oral glucose lowering medication), and renal dysfunction (serum creatinine level > 170 μmol/L). Based on the number of these risk factors, patients were stratified into low-risk (no cardiac risk factors), intermediate-risk (1 or 2 risk factors), and high-risk (≥ 3 risk factors) categories[6]. Furthermore, all patients were screened for hypertension (blood pressure ≥140/90 mmHg or blood pressure lowering medication), hypercholesterolemia (plasma cholesterol level ≥5.5 mmol/L or use of cholesterol-lowering medication), smoking status, and chronic obstructive pulmonary disease (defined as a FEV1 < 70% of age and gender predictive value or medication use[7]). In all patients beta-blockers were prescribed prior to surgery to obtain perioperative heart rates of 60-70 beats per minute[8] (**Figure 1**). Preoperative medication use was continued during the perioperative period, and adjusted to the European Society of Cardiology guidelines[9].

Figure 1: A scheme of the complete study phases from the patient enrollment to the final comparison between Holter-ECG and single-lead bipolar recordings.



Perioperative chemical markers outcome

After surgery, cTnT levels were routinely measured on postoperative days 1, 3, 7, 30, and/or at discharge and whenever clinically indicated by chest pain complaints or ECG changes consistent with myocardial ischemia or infarction. cTnT level was measured using a whole blood rapid test (TropT version 2, Roche Diagnostics GmbH, Mannheim, Germany) (**Figure 1**).

Myocardial ischemia during Holter- ECG

Patients were continuously monitored with a 10-electrode, 12-lead digital ECG recorder (DR180+ Digital Recorder, NorthEast Monitoring Inc., MA, USA), starting 1 day before surgery and continuing for up to 2 days after. Recordings were done in the continuous 12-lead mode with a recording cycle of 10 seconds every minute, acquiring approximately 500 segments for each patient. The frequency response

was 0.05-150Hz. The data was transferred to an ECG data management system for subsequent off-line analysis and review. In addition to Holter-ECG recordings, a standard 12-lead ECG was recorded on days 3, 7, and 30 after surgery, and/or at discharge (**Figure 1**).

Holter-ECG data were initially processed by a technician using automatic analysis software to exclude abnormal QRS complexes and then to define the remaining normal complexes in order to automatically measure the ST-amplitude[10]. The baseline ST-segment level was defined as the average ST-segment value during a 20-minute stable period. The resulting series of Holter ST-segment measures were displayed as a continuous ST-segment trend, which was visually analyzed by two experienced investigators, each blinded to the patient's clinical data and symptoms. Ischemic periods were located using standard criteria of 0.1mV (1mm) deviation from baseline values lasting more than 60 seconds and then were classified as ST-elevation or depression[11] (**Figure 1**).

Conversion of Holter-ECG recordings to ILR bipolar-ECG

Single-lead bipolar-ECG recordings were estimated by interpolating 12-lead sample data to full body surface potential maps, then re-sampling to estimate the corresponding bipolar samples that could be seen by an ILR.

Each patient's digitized Holter-ECG consists of a series of voltage measurements, collected 150 times each second. Twelve data points, one for each lead, are available at each sampling instant and are used to estimate the body surface potential map of the torso using a linear transformation defined by Lux[12].

Each body surface potential map can then be used to estimate a corresponding bipolar ECG value by calculating the voltage difference between any two arbitrary points. The distance between the bipolar samples was fixed at a physical distance of 6 cm, corresponding to the inter-electrode spacing used by commercial ILR devices. The series of difference calculations made at each sampling instant

reconstruct the bipolar-ECG as would be recorded by an ILR implanted between the two points.

Using this method, bipolar-ECG estimations were calculated for four torso locations, the traditional left shoulder position currently used for ILR implants, and three alternative positions, centered on standard lead positions V2, V3 and V4, that might be expected to show the largest ST deviations during ischemia.[13]. At each location, bipolar differences were calculated for eight orientations at 45-degree increments around a 360-degree circle giving estimated bipolar recordings at total of 32 implant positions.

Each of the 32 estimated bipolar-ECG recordings was automatically analyzed using a commercial ECG Interpretive Program (Glasgow ECG Analysis Program, Glasgow, UK), adapted for processing the single-lead ECG data. The program automatically determined the ST deviation at the J point relative to a baseline-adjusted reference. The resulting matrix of ST measurements for each interpretable beat, performed across the 32 exploratory positions, and indexed to known ischemic and non-ischemic periods derived from the Holter-ECG overread, formed the data set for answering the study questions (**Figure 1**).

Results

Study population

The baseline characteristics of the 115 included patients are listed in **table 1.** The mean age at baseline was 68 ± 10 years and 75% were male. Fifty four percent of the patients underwent abdominal aortic surgery, 22% lower extremity bypass surgery, and 24% underwent carotid artery surgery. According to the cardiac risk score 14% of patients had low cardiac risk, 62% intermediate and 24% high cardiac risk.

Perioperative chemical markers outcome

A total of 26 (23%) patients were identified as experiencing acute ischemic events by serial cTnT changes, of which 2/26 patients had chest pain complaints. The average amount of cTnT release was 0.13 mg/mL (0.05-0.28 mg/mL). In 17/26 patients cTnT was positive in the first 3 days postoperatively and also had ischemia detection on Holter-ECG monitoring.

Myocardial ischemia during Holter-ECG

Continuous Holter-ECG monitoring started 13.6 ± 7.4 hours prior to surgery. Holter-ECG showed myocardial ischemia in 20/115 patients; transient ST-elevation was detected in 4 (3.5%) and ST-depression in 16 (13.9%). During 8,017 patient-hours of Holter-ECG monitoring (70.3 ± 18.1 h/patient), these patients had a total of 63 ischemic episodes. The median duration of the total ischemic episodes in each patient was 49 min (IQR: 2 to 1208 min). Of the 20 patients with ST-segment changes 19 (95%) were asymptomatic.

Bipolar extraction and comparison with Holter-ECG

Only half of the 20 patients showing ST-segment changes on Holter-ECG could be used for bipolar estimation and analysis: the other patient's Holter recordings had artifacts that made the ECG uninterpretable by the automated analysis algorithm. These artifacts were mainly related to Holter-ECG telemetry errors and noise that impacted on the extraction process.

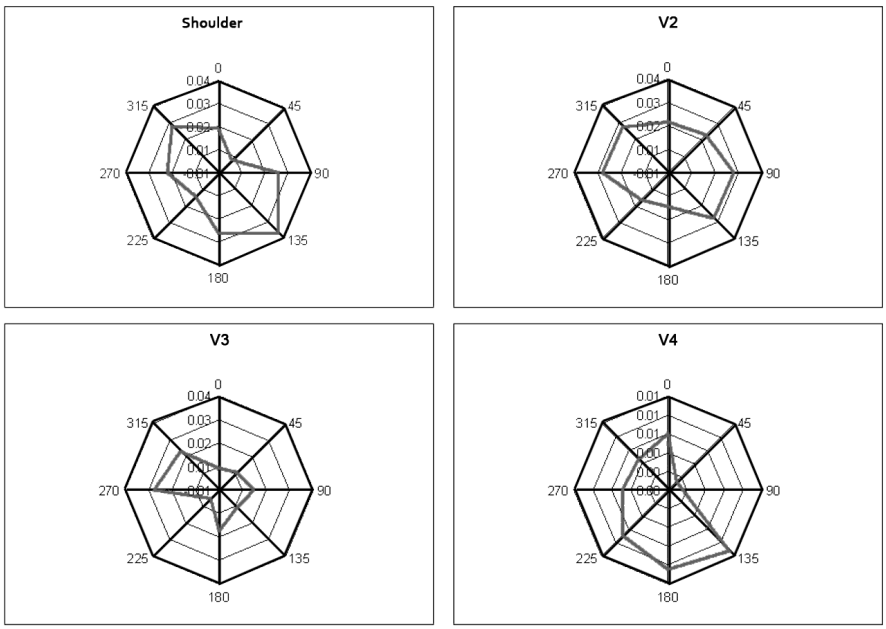
Table 1: Baseline characteristics.

	n=115
Clinical characteristics	
Age, years	68 ± 10
Males	86 (75%)
History of myocardial infarction	36 (31%)
History of angina pectoris	24 (21%)
History of congestive heart failure	6 (5%)
Diabetes mellitus	23 (20%)
Renal dysfunction	9 (8%)
History of TIA and/or CVA	44 (38%)
Hypertension	61 (53%)
COPD	42 (37%)
Smoking	82 (71%)
Medication	
Beta-blockers	103 (90%)
Statins	94 (82%)
Antiplatelet therapy	75 (65%)
Oral anticoagulants	25 (22%)
ACE-inhibitors	30 (26%)
Angiotensin II antagonist	17 (15%)
Calcium Channel Blocking agents	26 (23%)
Site of surgery	
Abdominal aorta	62 (54%)
Lower extremity artery	25 (22%)
Carotid artery	28 (24%)
Open surgery	86 (75%)
Endovascular surgery	29 (25%)

Ischemic episodes location in Bipolar leads

Six patients had extensive ischemic events, with large ST deviations involving several adjacent leads in Holter-ECG recordings. Three of these patients also had corresponding ST deviations in standard ILR implant positions in the shoulder. The magnitude of the deviation varied with the orientation of the bipolar recording pair. The variation in amplitude with orientation is summarized in the polar plot (shoulder; **figure 2)**, showing that the first preferred position with largest ST deviations is at an angle of 135 degrees from the vertical.

Figure 2: Trends of the ischemic-baseline deltas over all the possible 32 bipolar orientations and positions; on the Y-axes variations amplitudes are reported and on the rotating mean X-axes all the positions: shoulder, V2, V3, and V4 in all the possible 8 orientations.



The time course of ST changes followed the same trajectory observed in the Holter-ECG: no time lags in the onset of ECG changes were noted, and the slope of change was similar in Holter-ECG and Bipolar recordings. However, as shown in **figure 3**, the maximum amplitude among the bipolar leads is half the amplitude or less compared to the maximum value in the Holter-ECG for each patient.

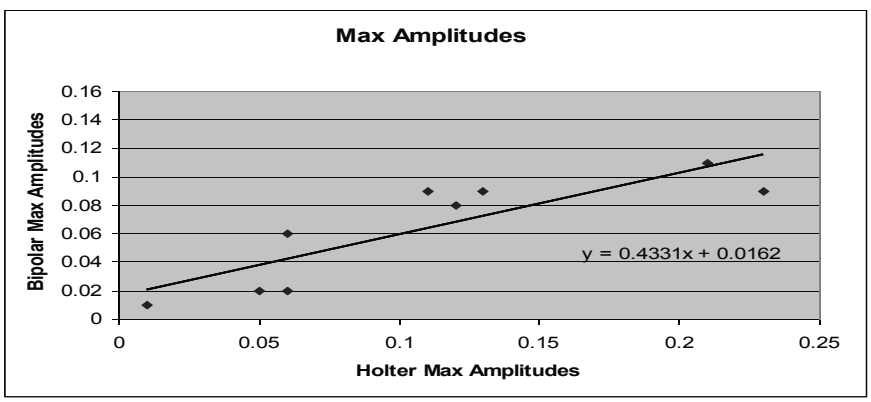


Figure 3: Comparison between highest amplitudes in variations between ischemic and baseline periods between Holter-ECG and Bipolar lead detections; patient 4 (0.04 vs 0.14) and patient 8 (0.26 versus 0.02) were taken out as outliers.

ST deviations were not observed as often in estimated bipolar-ECG from precordial positions V2, V3 or V4. Estimations at V2 had the highest sensitivity among the three, but not as good as the shoulder position. The best implant orientation at V2 and V3 was 270 degrees angle, while V4 doesn't show relevant changes that are related to 135 or 180 degrees angle. In one notable case involving inferolateral ischemia patient #3 in **table 2**, the high gradients across precordial leads (0.23±0.018 mV) would be expected to produce correspondingly large deviations in bipolar derived leads, and this was, in fact, observed (0.09±0.029 mV).

Table 2: Identification of myocardial infarction.

	Holter max amp (12-lead)	**Shoulder max amp (bipolar)**	**V2 max amp (bipolar)**	**V3 max amp (bipolar)**	**V4 max amp (bipolar)**
Patient # 1	0.04±0.01 (V3)	0.02±0.002	0.02±0.001	0.02±0.008	0.014±0.04 (V4-0)
Patient # 2	0.06±0.002 (V5)	0.02±0.008 (Shoulder-315)	0.01±0.004	0.005±0.001	0.01±0.001
Patient # 3	0.23±0.018 (V6)	/	0.06±0.019	0.04±0.013	0.09±0.029 (V4-135)
Patient # 4	0.11±0.005 (V5)	0.03±0.001 (Shoulder-90)	0.02±0.001	0.02±0.003	0.02±0.001
Patient # 5	0.01±0.004 (V6)	0.01±/	0.01±0.02	0.01±0.003 (V3-270)	/
Patient # 6	0.21± 0.03 (V1)	0.11±0.015 (Shoulder-135)	0.04±0.001	0.03±0.001	0.03±0.002
Patient # 7	0.05± 0.02 (V5)	0.01±0.001	0.02±0.001 (V2-270)	0.01±0.001	0.01±0.001
Patient # 8	0.26±0.06 (III)	/	0.02±0.007 (V2-270)	0.02±0.015	0.01±/
Patient # 9	0.12±0.05 (V3)	0.05±0.02	0.08± 0.004 (V2-270)	0.06±0.005	0.02±0.003
Patient # 10	0.12± 0.016 (V4)	0.09±0.009 (Shoulder-135)	0.06±0.016	0.08±0.026	0.01±0.001
Patient # 11	0.06± 0.007 (V6)	0.06± 0.004 (Shoulder-135)	0.05±0.003	0.04±0.004	/

Discussion

Principal Findings

Transient ST deviations are identified in 12-lead Holter-ECG using standard diagnostic criteria. Corresponding changes were seen in a minority of patients using bipolar leads, with amplitude changes only half as large. These changes were best seen in traditional shoulder implant locations with 135 degree orientation. Alternative precordial implant positions, which might have been expected to perform better, were, in fact, less sensitive. The best precordial position was the V2 lead with a 270 degrees angle.

In the context of the current literature

Early detection of acute ischemic events is the basis for early treatment to salvage myocardium[1], allowing more timely identification of patients which in turn could facilitate effective intervention. In previous studies, myocardial ischemia during major vascular surgery has been observed in as many as 41% of patients and has been demonstrated to be a strong predictor of subsequent clinical cardiovascular events[14]. The present study detected perioperative myocardial ischemia on Holter-ECG in 17% of patients. Raby et al. also found a similar incidence of 18% myocardial ischemia in a study of 176 patients undergoing peripheral vascular surgery[15], in which a sensitivity of 75% and a specificity of 83% for the prediction of a combined endpoint ((non)fatal MI, unstable angina, and ischemic pulmonary oedema) was reported. When considering all preoperative risk factors, preoperative ischemia was the most significant correlate of postoperative events[15]. Myocardial ischemia in the perioperative setting may arise from increased myocardial oxygen demand or reduced supply[16]. It is estimated that the incidence of perioperative MI is up to 5 to 10% in unselected patient populations[6]. Perioperative myocardial ischemia occurs frequently in high-risk patients undergoing non-cardiac surgery[17]. An estimated 75% of patients who have objective evidence of MI are not diagnosed as such because symptoms are masked by residual anaesthetic effects, administration of analgesic agents, competing somatic stimuli such as incisional pain, and other factors[18]. Currently,

the gold standard for detecting an acute MI is according to the universal definition of MI[19]. Up to 25% of surgical patients could have detectable elevations in cTnT levels[20-22]. In a study by Landesberg et al. 14.8% of 447 vascular surgery patients had perioperative ST-segment changes. Furthermore, 23.9% of patients experienced cTnT or cTnI release[23]. While cTnT often becomes positive only hours after the onset of cardiac complications, when myocardial necrosis already is present and irreversible, continuous 12-lead ECG might instantly detect these complications[10] and appropriate therapy can be initiated in order to prevent irreversible myocardial damage.

In a study by Horácek et al. results suggested that sampling outside the 12-lead ECG was optimal for detecting ischemia of the 3 coronary arteries with bipolar leads[24]. Yet the V3 location was most sensitive for LAD-related and RCA-related ischemia[24]. This finding is consistent with earlier experimental data collected from direct recordings in ambulatory animals experiencing transient ischemic events by Wesselink et al.[24]. However, in the current study the shoulder location was found to be best for ischemia detection followed by V2. Currently ILRs are most often implanted at the V2 location.

Strengths and Limitations

In the majority of cases, no corresponding ST-segment changes were observed, since in many cases, excess noise and telemetry errors prevented measurement of the ST-segment value. Bipolar ECG recordings may give information about transient ischemic episodes that are equivalent to precordial ECG, but further technical refinement is needed, since it uses shorter spacing and the extraction algorithm can partially smooth the amplitudes. Wider inter-electrode distance is the most likely enhancement. The latter mentioned technical questions remain to be addressed by future work. The standard 12-lead ECG and the Holter-ECG are all capable of continuous ECG monitoring. The clinical implications of the continuous ECG monitoring are that therapeutic consequences can be adjusted to measurement of ischemia and arrhythmia and that medical management can be initiated earlier. However, standard 12-lead ECG nor Holter-ECG is practical for long-term continuous monitoring[13]. A subcutaneous ILR could solve this problem.

The potential benefits of a subcutaneous device are: the capacity of prolonged monitoring (instead of intermittent recording), has a better quality of recording, will not interfere with the surgical area, and could be more comfortable for the patient.

Conclusions

This study assessed the feasibility of using a single bipolar-ECG monitor to assist in ischemia detection as a supplement to arrhythmia detection following vascular surgery. The potential to identify ischemia could shift the entire paradigm of care from interruption of MI to the prevention of myocardial necrosis. A successful implantable system would thus offer clear advantages in monitoring patients during and after vascular surgery procedures. Unfortunately, current data could not yield an acceptable sensitivity for the use of a single bipolar-ECG in ischemia detection.

References:

1. Kastrati A, Mehilli J, Dirschinger J, Schricke U, Neverve J, Pache J, Martinoff S, Neumann FJ, Nekolla S, Blasini R, Seyfarth M, Schwaiger M, Schomig A. Myocardial salvage after coronary stenting plus abciximab versus fibrinolysis plus abciximab in patients with acute myocardial infarction: a randomised trial. *Lancet* 2002;359:920-5.
2. Hertzer NR, Beven EG, Young JR, O'Hara PJ, Ruschhaupt WF, 3rd, Graor RA, Dewolfe VG, Maljovec LC. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. *Ann Surg* 1984;199:223-33.
3. Garcia-Alvarez A, Sitges M, Delgado V, Ortiz J, Vidal B, Poyatos S, de Caralt TM, Heras M, Bosch X, Azqueta M, Pare C, Brugada J. Relation of plasma brain natriuretic peptide levels on admission for ST-elevation myocardial infarction to left ventricular end-diastolic volume six months later measured by both echocardiography and cardiac magnetic resonance. *Am J Cardiol* 2009;104:878-82.
4. Solomon SD, Zelenkofske S, McMurray JJ, Finn PV, Velazquez E, Ertl G, Harsanyi A, Rouleau JL, Maggioni A, Kober L, White H, Van de Werf F, Pieper K, Califf RM, Pfeffer MA. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *N Engl J Med* 2005;352:2581-8.
5. Leitch J, Klein G, Yee R, Lee B, Kallok M, Combs W, Erickson M, Bennett T. Feasibility of an implantable arrhythmia monitor. *Pacing Clin Electrophysiol* 1992;15:2232-5.
6. Boersma E, Poldermans D, Bax JJ, Steyerberg EW, Thomson IR, Banga JD, van De Ven LL, van Urk H, Roelandt JR. Predictors of cardiac events after major vascular surgery: Role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. *Jama* 2001;285:1865-73.
7. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van Weel C, Zielinski J. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;176:532-55.
8. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, Freeman WK, Froehlich JB, Kasper EK, Kersten JR, Riegel B, Robb JF, Smith SC, Jr., Jacobs AK, Adams CD, Anderson JL, Antman EM, Buller CE, Creager MA, Ettinger SM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Ornato JP, Page RL, Tarkington LG, Yancy CW. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *Circulation* 2007;116:e418-99.
9. Poldermans D, Bax JJ, Boersma E, De Hert S, Eeckhout E, Fowkes G, Gorenek B, Hennerici MG, Iung B, Kelm M, Kjeldsen KP, Kristensen SD, Lopez-Sendon J, Pelosi P, Philippe F, Pierard L, Ponikowski P, Schmid JP, Sellevold OF, Sicari R, Van den Berghe G, Vermassen F, Hoeks SE, Vanhorebeek I, Vahanian A, Auricchio A, Bax JJ, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, McGregor K, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas P, Widimsky P, De Caterina R, Agewall S, Al Attar N, Andreotti F, Anker SD, Baron-Esquivias G, Berkenboom G, Chapoutot L, Cifkova R, Faggiano P, Gibbs S, Hansen HS, Iserin L, Israel CW, Kornowski R, Eizagaechevarria NM, Pepi M, Piepoli M, Priebe HJ, Scherer M, Stepinska J, Taggart D, Tubaro M. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: The Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur Heart J* 2009.
10. Bottiger BW, Motsch J, Teschendorf P, Rehmert GC, Gust R, Zorn M, Schweizer M, Layug EL, Snyder-Ramos SA, Mangano DT, Martin E. Postoperative 12-lead ECG predicts peri-operative myocardial ischaemia associated with myocardial cell damage. *Anaesthesia* 2004;59:1083-90.
11. Bjerregaard P, El-Shafei A, Kotar SL, Labovitz AJ. ST segment analysis by Holter Monitoring: methodological considerations. *Ann Noninvasive Electrocardiol* 2003;8:200-7.

12. Lux RL, Smith CR, Wyatt RF, Abildskov JA. Limited lead selection for estimation of body surface potential maps in electrocardiography. *IEEE Trans Biomed Eng* 1978;25:270-6.
13. Song Z, Jenkins J, Burke M, Arzbaecher R. The feasibility of ST-segment monitoring with a subcutaneous device. *J Electrocardiol* 2004;37 Suppl:174-9.
14. Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, Tateo IM. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. *N Engl J Med* 1990;323:1781-8.
15. Raby KE, Goldman L, Creager MA, Cook EF, Weisberg MC, Whittemore AD, Selwyn AP. Correlation between preoperative ischemia and major cardiac events after peripheral vascular surgery. *N Engl J Med* 1989;321:1296-300.
16. Landesberg G, Beattie WS, Mosseri M, Jaffe AS, Alpert JS. Perioperative myocardial infarction. *Circulation* 2009;119:2936-44.
17. Fleisher LA, Nelson AH, Rosenbaum SH. Postoperative myocardial ischemia: etiology of cardiac morbidity or manifestation of underlying disease? *J Clin Anesth* 1995;7:97-102.
18. Devereaux PJ, Goldman L, Yusuf S, Gilbert K, Leslie K, Guyatt GH. Surveillance and prevention of major perioperative ischemic cardiac events in patients undergoing noncardiac surgery: a review. *Cmaj* 2005;173:779-88.
19. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *Eur Heart J* 2007;28:2525-38.
20. Abraham N, Lemech L, Sandroussi C, Sullivan D, May J. A prospective study of subclinical myocardial damage in endovascular versus open repair of infrarenal abdominal aortic aneurysms. *J Vasc Surg* 2005;41:377-80; discussion 380-1.
21. Le Manach Y, Perel A, Coriat P, Godet G, Bertrand M, Riou B. Early and delayed myocardial infarction after abdominal aortic surgery. *Anesthesiology* 2005;102:885-91.
22. Schouten O, Dunkelgrun M, Feringa HH, Kok NF, Vidakovic R, Bax JJ, Poldermans D. Myocardial damage in high-risk patients undergoing elective endovascular or open infrarenal abdominal aortic aneurysm repair. *Eur J Vasc Endovasc Surg* 2007;33:544-9.
23. Landesberg G, Shatz V, Akopnik I, Wolf YG, Mayer M, Berlatzky Y, Weissman C, Mosseri M. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. *J Am Coll Cardiol* 2003;42:1547-54.
24. Horacek BM, Warren JW, Penney CJ, MacLeod RS, Title LM, Gardner MJ, Feldman CL. Optimal electrocardiographic leads for detecting acute myocardial ischemia. *J Electrocardiol* 2001;34 Suppl:97-111.

2

Cardiac arrhythmias in vascular surgery patients; is 72-hour continuous Holter monitoring long enough?

submitted

Tamara A. Winkel
Michiel T. Voûte
Mirko de Melis
Roger Kessels
Willem-Jan Flu
Jan P.C.M. Oomen
Jeroen J. Bax
Hence J.M. Verhagen
Don Poldermans

Abstract

Background and aim: Vascular surgery is accompanied by cardiac arrhythmias. However, arrhythmias are often short-lived and asymptomatic, making detection difficult and causing the true incidence to be understated. In this ongoing study we compared the incidence of arrhythmias using two different monitoring devices.

Methods: Patients with sinus rhythm were monitored with a 72-hour Holter electrocardiography (Holter-ECG) (n=352). Some of the patients also received a subcutaneously implanted loop recorder (ILR; Reveal® XT) (n=28). The Reveal® was implanted one month prior to surgery, and left in place until one month after surgery. New-onset arrhythmias were noted. Study endpoint was cardiovascular events including cardiac death, non-fatal myocardial infarction, unstable angina, and stroke at 30-days postoperatively.

Results: Arrhythmias were recorded in 49 (13.9%) and 10 (36%) patients with Holter-ECG and Reveal® respectively. In multivariate analysis, after correction for preoperative cardiac risk score and type and site of surgery, patients with new-onset perioperative cardiac arrhythmias were associated with significantly worse 30-day cardiovascular outcome (odds ratio 3.0, 95% confidence interval 1.3-6.8). Using the Reveal® device 4 additional patients were identified having perioperative arrhythmias who experienced perioperative cardiovascular events. The incidence of cardiovascular events with Holter-ECG and Reveal® monitoring was 42/352 (12%) and 9/28 (32%) respectively.

Conclusion: Vascular surgery patients may develop new-onset paroxysmal arrhythmias outside the recording window of the 72-hour Holter-ECG and these are generally asymptomatic. Continuous implanted cardiac monitors can detect these paroxysmal episodes of arrhythmias, which in turn could have important therapeutic consequences. Furthermore the Reveal® device is implanted subcutaneously and therefore does not interfere with the surgical area.

Introduction

Cardiovascular complications are a major cause for morbidity and mortality in patients undergoing non-cardiac vascular surgery. In addition to ischemic complications, it is estimated that up to 20% of patients develop cardiac arrhythmias postoperatively, of which atrial fibrillation (AF) is the most common form. Potential consequences of cardiac arrhythmias include sudden cardiac death, congestive heart failure, and stroke.[1-3]

Cardiac arrhythmias most often initiate within the first few postoperative days. The reported incidence of cardiac arrhythmias following non-cardiac surgery depends on the timing and duration of cardiac monitoring used to detect them.[1] The reported incidence of perioperative arrhythmias particularly depends on the type of cardiac monitoring, with better estimates being obtained using long-term continuous monitoring. In a study by Mathew et al. it was noted that continuous electrocardiography (ECG) monitoring diagnoses 76.8% of perioperative arrhythmias, whereas intermittent 12-lead ECG or physical examination detect only 17.5% and 12.8%, respectively.[4] The majority of perioperative arrhythmias is asymptomatic, transient, and unpredictable, causing them to be frequently missed, and, hence, undertreated.[5-7] Thus, their true prevalence may be underestimated, and continuous cardiac monitoring may significantly increase the number of detected arrhythmias.[1, 3, 8] The standard surface 12-lead ECG and 72-hour continuous-ECG (Holter) are all capable of continuous ECG monitoring, however, none of them is practical for long-term continuous monitoring.

Therefore, we conducted the current study to estimate the true prevalence of new-onset cardiac arrhythmias in vascular surgery patients, comparing the Holter device with an implantable loop recorder (ILR).

Methods

Study population

The study population consisted of 352 patients undergoing elective abdominal aortic aneurysm repair or peripheral artery bypass surgery at the Erasmus Medical Center in Rotterdam, the Netherlands, during the period December 2004 to March 2010. Patients with a history of cardiac arrhythmias, cardiac pacemaker or implantable cardioverter defibrillator, and procedures that precluded continuous ECG monitoring were excluded. The hospital's ethical committee approved the study. No extramural funding was used to support this work. In an ongoing study at the same center, 28 of the 352 vascular surgery patients were implanted with an subcutaneous ILR (Reveal® XT, Model 9529, Medtronic Inc., Minneapolis, MN, USA), approximately 25 days prior surgery.

Preoperative cardiovascular screening

We determined the cardiac risk score for each patient in our dataset, and one point was assigned to each of the following characteristics: advanced age (>70 years), a history of angina pectoris (A, myocardial infarction (MI), congestive heart failure (CHF), stroke (transient ischemic attack [TIA] and/or cerebral vascular accident [CVA]), diabetes mellitus (fasting glucose level ≥7.0 mmol/L or use of insulin or oral glucose lowering medication), and renal dysfunction (serum creatinine level > 170 µmol/L). Based on the number of these risk factors, patients were stratified into low-risk (no cardiac risk factors), intermediate-risk (1 or 2 risk factors), and high-risk (≥ 3 risk factors) categories.[9] All patients were screened for hypertension (blood pressure ≥140/90 mmHg or blood pressure lowering medication), hypercholesterolemia (plasma cholesterol level ≥5.5 mmol/L or use of cholesterol-lowering medication), smoking status, and chronic obstructive pulmonary disease (defined as a FEV1 < 70% of age and gender predictive value or medication use[10]). The left ventricular ejection fraction was assessed with a transthoracic echocardiogram.[11-12] Venous blood samples for C-Reactive Protein (CRP), cardiac troponin T (cTnT), and N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP) were routinely performed at the outpatient clinic. In all patients beta-blockers were

prescribed prior to surgery to obtain perioperative heart rates of 60-70 beats per minute[13]. After the visit to the outpatient-clinic patients were prescribed with beta-blockers, statins, antiplatelet and/or anticoagulant medication.

Continuous ECG monitoring; Holter-ECG

Patients were continuously monitored with a 10-electrode, 12-lead digital ECG recorder (DR180+ Digital Recorder, NorthEast Monitoring Inc. Massachusetts) for 72 hours perioperatively, starting one day before their surgical procedure and continuing until two days after. Recordings were performed in the continuous 12-lead mode with a recording cycle of 10 seconds every minute. Signal bandwidth was 0.05Hz to 150Hz. Electrocardiographic data were initially processed by a technician to exclude artefacts, afterwards analyzed off-line by two physicians unaware of the clinical information for each patient, and then verified for the presence of new-onset cardiac arrhythmias (atrial fibrillation [AF], supraventricular tachycardia [SVT], sustained ventricular tachycardia [VT], and/or ventricular fibrillation [VF][14-15]). Standard postoperative 12-lead ECG recordings were made on days 3, 7 and 30, and/or at discharge, and whenever clinically indicated by chest pain or dyspnea complaints.

AF was defined by characteristic absolute irregularity of RR intervals and concurrent loss of identifiable P waves in the ECG recordings[14]. VT was characterized by three or more consecutive QRS complexes with a wide QRS complex at a rate of greater than 100 bpm and duration greater than 30 seconds. SVT was identified as a narrow QRS complex (< 0.12 sec) and a rate greater than 180 bpm. VF was defined as chaotic ventricular electrical discharge with marked variability in QRS cycle length, morphology, and amplitude[15].

Continuous ECG monitoring; ILR

Approximately 25 days preoperatively the Reveal® XT device was implanted subcutaneously, under local anaesthetics, by creating a subcutaneous pocket in a left parasternal position at the level of the 4th or 5th intercostal space. The device was left in situ for an average of 66 ± 90 days. The memory of the Reveal® device

was read one day prior to surgery, three to five days postoperatively, and finally at the moment the device was explanted.

The Reveal® XT is equipped with a new AF detection algorithm which is designed to detect the presence of AF episodes and to quantify the AF burden. Physiologic sinus rhythm and AF each have a unique RR interval pattern. The dedicated AF detection algorithm uses irregularity and incoherence of RR intervals to identify and classify patterns in the ventricular two minute period of time and the difference in duration between consecutive delta RR intervals is calculated. Subsequently the variability of these delta RR intervals is calculated, similar to constructing a Lorenz plot. When the RR intervals within the 2 minute interval show a certain pattern of uncorrelated irregularity, the heart rhythm in this interval is classified as AF. If RR intervals are regular with some sinus node modulations, the interval is defined as normal sinus rhythm[16].

In addition, the leadless implantable cardiac monitor (ICM) also features detection algorithms for bradyarrhythmias and ventricular tachyarrhythmia's[16]. The ICM can store up to 49.5 minutes of recorded ECG, which is allocated to 27 minutes of automatically activated events and 22.5 minutes of patient activated events. In addition, the ICM has an episode log that can catalogue 30 automatically detected AF episodes and up to 10 patient-activated episodes. When the memory is full, an additional episode will overwrite the oldest stored episode.

Perioperative cardiovascular events and outcome

Study endpoint was cardiovascular events, including cardiac death, non-fatal MI, unstable angina, and stroke, at 30-days postoperatively. Also, serum cardiac troponin T (cTnT) serum levels were routinely measured on postoperative days 1, 3, 7, 30 and/or before discharge, and whenever clinically indicated by chest pain complaints or ECG changes consistent with myocardial ischemia or infarction. The cTnT level was measured using a whole blood rapid test by an electrochemiluminescence immuneassay (TropT version 2, Roche Diagnostics GmbH, Mannheim, Germany). The lower limit of cTnT detection was 0.01 ng/mL and the upper limit of detection was 25 ng/mL, with the limit of quantification set at

0.03 ng/mL. If cTnT release occurred, measurements were repeated every day until the level returned to a normal value.

The first follow-up visit at the outpatient clinic was scheduled one month after discharge. Besides presence at the out-patient follow-up visits, survival status was determined by contacting the municipal civil service registry and looking into the patient's electronic medical file. Myocardial infarction was defined according to the universal definition of MI[17]. Cardiovascular death was defined as any death with a cardiovascular cause, including deaths following a cardiac procedure, cardiac arrest, MI, pulmonary embolus, stroke, or sudden death not ascribed to other causes.

Data analysis

Categorical data are described as numbers and percentages and continuous data are expressed as means ± standard deviation (SD). Continuous data with a skewed distribution are expressed as medians with interquartile ranges (IQR) and were compared using the Mann-Whitney *U* test. Binary logistic regression analysis was used to evaluate the association of perioperative new-onset cardiac arrhythmias on 30-day clinical cardiac outcome. In multivariate analyses, adjustments were made for gender, cardiac risk index, type of surgery, perioperative myocardial ischemia, and perioperative serum cTnT release. The odds ratio (OR) is given with 95% confidence intervals (CI). For all tests, a p-value of less than 0.05 (two-sided) was considered significant. All analysis was performed using SPSS 15.0 statistical software (SPSS Inc., Chicago, Illinois).

Results

Study population

The baseline clinical characteristics and medication use of the 352 included patients undergoing elective abdominal aortic aneurysm (AAA) repair (open [n=131] and endovascular [n=119] repair) and lower extremity bypass surgery (n=102) are listed in **table 1**. The mean age at baseline was 68.7 ± 9.2 years and 79% were male. The baseline clinical characteristics, preoperative cardiac risk index and cardioprotective medication of the 28 Reveal® patients undergoing AAA repair (open [n=12] and endovascular [n=9] repair) and lower extremity reconstruction (n=7) are also listed in **table 1**. There is a higher prevalence of high cardiac risk patients in the Reveal® population compared to the patients monitored with a Holter-ECG device (42% versus 22% respectively).

Continuous ECG monitoring and arrhythmia detection

In **table 2** the incidence of perioperative new-onset cardiac arrhythmias is shown for both continuous ECG modes (Reveal® 10/28 and Holter-ECG 49/352). The Reveal® device was implanted approximately 25 days prior to surgery and showed that in only 2/28 patients there were preoperative new-onset arrhythmia detection. Strikingly, there is a higher incidence of new-onset perioperative AF detection on the Reveal® device compared to the Holter-ECG recordings (25% and 14%). Perioperative cardiac arrhythmias on Holter-ECG presented on average 11 hours (1.5-12 hr) postoperatively, while on the Reveal® device arrhythmias were averagely detected 3 days (1-7 days) postoperatively. Similar types of cardiac arrhythmias, presenting at the same time and moment of the day as registered on the Reveal®, were only seen in 3/10 patients with arrhythmias on Holter-ECG. The majority of patients developing perioperative arrhythmias were asymptomatic (97%). Patients with new-onset AF received oral anticoagulant therapy next to antiplatelet medication. Those patients undergoing peripheral artery bypass surgery were also started on oral anticoagulants.

Table 1. Baseline clinical characteristics

	Holter-ECG n=352	Reveal® XT n=28
Age, years	68.7 ± 9.2	68.0 ± 8.6
Males – no. (%)	277 (79)	23 (82)
History of MI – no. (%)	108 (31)	15 (54)
History of AP – no. (%)	68 (19)	10 (36)
History of CHF – no. (%)	27 (8)	6 (21)
Diabetes mellitus – no. (%)	69 (20)	5 (18)
Renal dysfunction – no. (%)	34 (10)	7 (25)
History of stroke – no. (%)	51 (15)	3 (11)
Hypertension – no. (%)	176 (50)	18 (64)
COPD – no. (%)	149 (42)	11 (39)
Smoking – no. (%)	288 (82)	26 (93)
BMI – kg/m^2	22.5 ± 9.1	22.8 ± 8.7
Cardiac Risk Index		
Low-risk (0 risk factors) – no. (%)	86 (25)	5 (18)
Intermediate-risk (1 to 2 risk factors) – no. (%)	187 (53)	11 (39)
High-risk (≥ 3 risk factors) – no. (%)	79 (22)	12 (42)
Medication use		
Beta-blockers – no. (%)	336 (96)	27 (96)
Statins – no. (%)	291 (83)	25 (89)
Antiplatelet therapy – no. (%)	252 (72)	24 (86)
Oral anticoagulants – no. (%)	50 (14)	5 (18)

Perioperative cardiovascular events

The incidence of cardiovascular events with Holter-ECG and Reveal® monitoring was 42/352 (12%) and 9/28 (32%) respectively (**table 2**). Using the Reveal® device 4 additional patients were identified having perioperative arrhythmias who suffered perioperative cardiovascular events. The detection of perioperative arrhythmias was associated with an increased risk in the incidence of death from cardiovascular causes. In multivariate analyses, perioperative new-onset cardiac arrhythmias were found to independently associated with 30-day cardiovascular events (OR 2.96, 95% CI 1.28–6.83, p=0.01).

Table 2. Perioperative cardiovascular events

	Holter-ECG n=352	Reveal® XT n=28
Postoperative arrhythmias	49 (14)	10 (36)
AF – no. (%)	14 (4)	7 (25)
SVT – no. (%)	10 (3)	4 (14)
VT – no. (%)	29 (8)	1 (4)
VF – no. (%)	1 (0.3)	0
Myocardial Ischemia – no. (%)	73 (21)	N.A.
Serum cTnT release – no. (%)	72 (21)	7 (25)
Perioperative cardiovascular events – no. (%)	42 (12)	9 (32)
Death – no. (%)	16 (5)	2 (7)

Discussion

This study shows that extending the period of continuous heart rhythm monitoring using an ILR improves the detection of perioperative arrhythmias, which were found to be associated with an increased incidence of 30-day cardiovascular events.

In the context of literature

AF is the most common cardiac arrhythmia in clinical practice and is gaining attention from the medical community due to the aging general population.[18-19] as its epidemiological weight is increasing [19]. Most patients with AF are over 65 years of age and present with many co-morbidities, in particular, hypertension, CHF, coronary artery disease, and diabetes.[20] Previously published by this research group[7, 21], there is a high incidence of AF in the vascular surgery patients (4.7%). In this study we demonstrate that by expanding duration of recording in these patients, by using an implantable monitor, more cardiac arrhythmias are detected, subsequently making them at a 6-fold and 4-fold increased risk of perioperative and late cardiovascular events respectively. These findings are in accordance with other studies, where the conclusion was drawn that better estimates of perioperative arrhythmias were obtained using continuous monitoring.[4] In a study by Botto et al., 568 patients with a pacemaker and a history of AF were continuously monitored for 1-year and concluded that the sensitivity in detecting AF episodes lasting > 5 min. was 44.4%, 50.4%, and 65.1% for 24-hr Holter, 1-week Holter, and 1-month Holter monitoring, respectively[22-23]. Hindricks et al. stated that the use of traditional methods to diagnose AF, such as standard surface ECG, 24-hour Holter recordings and more, are limited by the short documentation period covered and the high incidence of asymptomatic episodes. The sensitivity for AF detection when using external ECG monitors lies between 31.3% and 71.0%[24]. However, conventional Holter-ECG can only be used for a period of days rather than for weeks, the more typical interval when high-risk patients suffer events[25]. In the current study, there is a significant increase in prevalence of perioperative arrhythmias when comparing the two different continuous ECG monitoring devices.

Also, the additional patients identified with arrhythmia episodes are most frequently registered beyond the 72-hr Holter-ECG recordings window, which would be missed otherwise. Furthermore, ECG wires and electrodes can interfere in the surgical area and Holter-ECG monitors are cumbersome for the patient, leading to compliance issues after discharge. Bipolar ILRs (Reveal® XT) are already used for syncope and arrhythmia detection[26-27], and are well tolerated by patients over longer periods of time. Another major advantage of the ILR is that recordings can be analyzed on-line during the surgery, in contrast to the off-line analyses of the Holter-ECG recordings used in this study. Additionally an ICM reliably detects the presence or absence of AF, with a high sensitivity and negative predictive value, while showing a good specificity and PPV[24]. Much of the morbidity and mortality associated with cardiac arrhythmias is attributed to the thrombo-embolic complications, resulting in increased risk of cardiovascular death[5, 18]. Several studies, as is also shown in the current study, have concluded that the development of cardiac arrhythmias is an independent predictor of adverse outcome. The detection of cardiac arrhythmias has several therapeutic consequences, antithrombotic therapies for patients with AF with current guidelines recommending warfarin for patients who have AF and are at risk of stroke.[18] More recently, Connolly et al. assessed the value of dabigatran, administered at a dose of 150 mg in patients with AF, and found that this was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage as compared with warfarin.[28] These results could likely increase the intake of these new thrombin inhibitors since these are less cumbersome than vitamin-K antagonists. A previous study by Vyas et al. concluded that statin use in patients with an implantable cardioverter defibrillator (ICD) were associated with fewer VT/VF episodes and a 28% reduction in risk of a first VT/VF episode.[29] According to the perioperative care guidelines patients should at least receive beta-blockers, statins, and most commonly an antiplatelet agent.[30]

Limitations

The study population with patients with implanted Reveal® devices has identified a larger group of vascular surgery patients at potential risk of cardiovascular events. By recording vascular surgery patients for a longer duration of time clinicians might be helped in their treatment options and duration of medical or interventional therapy. Larger studies with ILRs will be necessary to give more specific estimates on the true prevalence of cardiac arrhythmias, and possibly the type and duration of treatment of this high-risk group of patients.

Conclusion

Vascular surgery patients may develop new-onset paroxysmal arrhythmias outside the recording window of the 72-hour Holter-ECG Implanted loop recorders providing continuous long-term monitoring can detect these paroxysmal episodes which were associated with an increased incidence of cardiovascular events at 30 days. Detecting arrhythmias that occur during the perioperative period may thus have important therapeutic consequences.

References

1. Brathwaite D, Weissman C. The new onset of atrial arrhythmias following major noncardiothoracic surgery is associated with increased mortality. *Chest*. 1998;114:462-8.
2. Polanczyk CA, Goldman L, Marcantonio ER, Orav EJ, Lee TH. Supraventricular arrhythmia in patients having noncardiac surgery: clinical correlates and effect on length of stay. *Ann Intern Med*. 1998;129:279-85.
3. Walsh SR, Tang T, Wijewardena C, Yarham SI, Boyle JR, Gaunt ME. Postoperative arrhythmias in general surgical patients. *Ann R Coll Surg Engl*. 2007;89:91-5.
4. Mathew J, Hunsberger S, Fleg J, Mc Sherry F, Williford W, Yusuf S. Incidence, predictive factors, and prognostic significance of supraventricular tachyarrhythmias in congestive heart failure. *Chest*. 2000;118:914-22.
5. Goto S, Bhatt DL, Rother J, Alberts M, Hill MD, Ikeda Y, et al. Prevalence, clinical profile, and cardiovascular outcomes of atrial fibrillation patients with atherothrombosis. *Am Heart J*. 2008;156:855-63, 63 e2.
6. Hoeks SE, Scholte Op Reimer WJ, Schouten O, Lenzen MJ, van Urk H, Poldermans D. Statin use in the elderly: results from a peripheral vascular survey in The Netherlands. *J Vasc Surg*. 2008;48:891-5; discussion 5-6.
7. Winkel TA, Hoeks SE, Schouten O, Zeymer U, Limbourg T, Baumgartner I, et al. Prognosis of Atrial Fibrillation in Patients with Symptomatic Peripheral Arterial Disease: Data from the REduction of Atherothrombosis for Continued Health (REACH) Registry. *Eur J Vasc Endovasc Surg*.
8. Bender JS. Supraventricular tachyarrhythmias in the surgical intensive care unit: an under-recognized event. *Am Surg*. 1996;62:73-5.
9. Boersma E, Poldermans D, Bax JJ, Steyerberg EW, Thomson IR, Banga JD, et al. Predictors of cardiac events after major vascular surgery: Role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. *Jama*. 2001;285:1865-73.
10. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2007;176:532-55.
11. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification. *Eur J Echocardiogr*. 2006;7:79-108.
12. Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2002;15:167-84.
13. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *Circulation*. 2007;116:e418-99.
14. Estes NA, 3rd, Halperin JL, Calkins H, Ezekowitz MD, Gitman P, Go AS, et al. ACC/AHA/Physician Consortium 2008 Clinical Performance Measures for Adults with Nonvalvular Atrial Fibrillation or Atrial Flutter: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and the Physician Consortium for Performance Improvement (Writing Committee to Develop Clinical Performance Measures for Atrial Fibrillation) Developed in Collaboration with the Heart Rhythm Society. *J Am Coll Cardiol*. 2008;51:865-84.

15. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). *J Am Coll Cardiol*. 2006;48:e247-346.
16. Sarkar S, Ritscher D, Mehra R. A detector for a chronic implantable atrial tachyarrhythmia monitor. *IEEE Trans Biomed Eng*. 2008;55:1219-24.
17. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *Eur Heart J*. 2007;28:2525-38.
18. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol*. 2006;48:854-906.
19. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *Jama*. 2001;285:2370-5.
20. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *Jama*. 1994;271:840-4.
21. Winkel TA, Schouten O, Hoeks SE, Verhagen HJ, Bax JJ, Poldermans D. Prognosis of transient new-onset atrial fibrillation during vascular surgery. *Eur J Vasc Endovasc Surg*. 2009;38:683-8.
22. Botto GL, Padeletti L, Santini M, Capucci A, Gulizia M, Zolezzi F, et al. Presence and duration of atrial fibrillation detected by continuous monitoring: crucial implications for the risk of thromboembolic events. *J Cardiovasc Electrophysiol*. 2009;20:241-8.
23. Ziegler PD, Koehler JL, Mehra R. Comparison of continuous versus intermittent monitoring of atrial arrhythmias. *Heart Rhythm*. 2006;3:1445-52.
24. Hindricks G, Pokushalov E, Urban L, Taborsky M, Kuck KH, Lebedev D, et al. Performance of a new leadless implantable cardiac monitor in detecting and quantifying atrial fibrillation: Results of the XPECT trial. *Circ Arrhythm Electrophysiol*. 2010;3:141-7.
25. Solomon SD, Zelenkofske S, McMurray JJ, Finn PV, Velazquez E, Ertl G, et al. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *N Engl J Med*. 2005;352:2581-8.
26. Leitch J, Klein G, Yee R, Lee B, Kallok M, Combs W, et al. Feasibility of an implantable arrhythmia monitor. *Pacing Clin Electrophysiol*. 1992;15:2232-5.
27. Task Force m, Brignole M, Vardas P, Hoffman E, Huikuri H, Moya A, et al. Indications for the use of diagnostic implantable and external ECG loop recorders. *Europace*. 2009;11:671-87.
28. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139-51.
29. Vyas AK, Guo H, Moss AJ, Olshansky B, McNitt SA, Hall WJ, et al. Reduction in ventricular tachyarrhythmias with statins in the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II. *J Am Coll Cardiol*. 2006;47:769-73.
30. Poldermans D, Bax JJ, Boersma E, De Hert S, Eeckhout E, Fowkes G, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: the Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur Heart J*. 2009;30:2769-812.

3

Risk factors and outcome of new-onset cardiac arrhythmias in vascular surgery patients.

American Heart Journal 2010;159(6):1108-1115

Tamara A. Winkel
Olaf Schouten
Sanne E. Hoeks
Willem-Jan Flu
Dave Hampton
Paulus Kirchhof
Jan-Peter van Kuijk
Jan Lindemans
Hence J.M. Verhagen
Jeroen J. Bax
Don Poldermans

Abstract

Aim: The pathophysiology of new-onset cardiac arrhythmias is complex and may bring about severe cardiovascular complications. The relevance of perioperative arrhythmias during vascular surgery has not been investigated. The aim of this study was to assess risk factors and prognosis of new-onset arrhythmias during vascular surgery.

Methods and results: A total of 513 vascular surgery patients, without a history of arrhythmias, were included. Cardiac risk factors, inflammatory status and left ventricular function (LVF: NT-proBNP and echocardiography) were assessed. Continuous electrocardiography (continuous-ECG) recordings for 72 hours were used to identify ischemia and new-onset arrhythmias; atrial fibrillation (AF), sustained ventricular tachycardia (VT), supraventricular tachycardia (SVT) and ventricular fibrillation (VF). Logistic regression analysis was applied to identify preoperative risk factors for arrhythmias. Cox regression analysis assessed the impact of arrhythmias on cardiovascular event-free survival during 1.7 years. New-onset arrhythmias occurred in 55/513 (11%) patients: AF, VT, SVT and VF occurred in 4%, 7%, 1% and 0.2% respectively. Continuous-ECG showed myocardial ischemia and arrhythmias in 17/513 (3%) patients. Arrhythmia was preceded by ischemia in 10/55 cases. Increased age and reduced LVF were risk factors for the development of arrhythmias. Multivariate analysis showed that perioperative arrhythmias were associated with long-term cardiovascular events, irrespective of the presence of perioperative ischemia (HR 2.2, 95% CI 1.3–3.8, p=0.004).

Conclusion: New-onset perioperative arrhythmias are common after vascular surgery. The elderly and patients with reduced left ventricular function show arrhythmias. Perioperative continuous-ECG monitoring helps to identify this high-risk group at increased risk of cardiovascular events and death.

Introduction

Postoperative cardiac arrhythmias occur in up to 20% of patients undergoing non-cardiac surgery and have been associated with an increased length of hospital stay and higher cardiac morbidity and mortality[1-3]. While it has long been recognized that cardiac surgical procedures are associated with subsequent development of supraventricular arrhythmias[2], it is less widely appreciated that the risk of cardiovascular events is elevated even in non-cardiac vascular surgery patients[4].

Observed perioperative cardiac arrhythmias are presumed to be a key factor underlying this finding[1]. For patients undergoing non-cardiac surgery, these arrhythmias are most often atrial in origin[5] and initiate within the first few postoperative days[1]. The pathophysiology of cardiac arrhythmias is complex and several causal factors may be involved, including myocardial ischemia, electrolyte disorders, cardiac valve abnormalities and sudden withdrawal of medication[6-8]. Recent studies suggest that alterations in autonomic regulation, neuro-hormonal activation and systemic inflammatory state may also play an important role[6].

The reported incidence of cardiac arrhythmias following non-cardiac surgery depends on the timing and duration of cardiac monitoring used to detect them[3]. Events may be asymptomatic, and are often transient and unpredictable. Thus, their true prevalence may be underestimated, and continuous cardiac monitoring may significantly increase the number of detected arrhythmias[1, 3, 9].

Therefore, we conducted the current study (1) to estimate the true prevalence of cardiac arrhythmias in this population, (2) to identify preoperative risk factors leading patients to develop new-onset cardiac arrhythmias and (3) to assess the impact of perioperative new-onset cardiac arrhythmias on postoperative outcome in patients undergoing non-cardiac vascular surgery.

Methods

Study population

The study population consisted of 547 patients undergoing vascular surgery at the Erasmus Medical Center in Rotterdam, the Netherlands, during the period December 2004 to April 2009. Patients with a history of cardiac arrhythmias (n=28), cardiac pacemaker or implantable cardioverter defibrillator (n=6), and procedures that precluded continuous-ECG monitoring were excluded. The hospital's ethical committee approved the study. No extramural funding was used to support this work.

Preoperative cardiovascular screening

The following potential clinical risk factors for arrhythmias were scored: age, angina pectoris (AP), history of myocardial infarction (MI), history of congestive heart failure (CHF), history of stroke, diabetes mellitus (fasting glucose level ≥7.0 mmol/L or use of insulin or oral glucose lowering medication), and renal dysfunction (serum creatinine level > 170 μmol/L). All patients were screened for hypertension (blood pressure ≥140/90 mmHg or blood pressure lowering medication), hypercholesterolemia (plasma cholesterol level ≥5.5 mmol/L or use of cholesterol-lowering medication), smoking status, and chronic obstructive pulmonary disease (defined as a FEV1 < 70% of age and gender predictive value or medication use. Venous blood samples for C-Reactive Protein (CRP) and N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP) were routinely performed at the outpatient clinic. In all patients beta-blockers were prescribed prior to surgery to obtain perioperative heart rates of 60-70 beats per minute[10]. After the visit to the outpatient-clinic patients were prescribed with beta-blockers and antiplatelet and/or anticoagulant medication. On admission to the hospital, all patients received beta-blockers.

Preoperative transthoracic echocardiogram

Preoperatively, a routine transthoracic echocardiogram (TTE) was performed in all patients at the outpatient clinic. Using a handheld Acuson Cypress Ultrasound System with a 7V3c transducer, images were made according to the guidelines of the American Society of Echocardiography[11]. Standard parasternal and apical views were obtained at rest with the patient in the left lateral decubitus position. Left ventricular ejection fraction (LVEF) was calculated using the biplane Simpson's technique[12]. Aortic and valve abnormalities were also assessed and graded. Two physicians, unaware of the clinical information for each patient, performed and analyzed the echocardiography procedures.

ECG monitoring

Patients were continuously monitored with a 10-electrode, 12-lead digital ECG recorder (DR180+ Digital Recorder, NorthEast Monitoring Inc. Massachusetts) for 72 hours perioperatively starting one day before their surgical procedure and continuing until two days after. Recordings were performed in the continuous 12-lead mode with a recording cycle of 10 seconds every minute. Signal bandwidth was 0.05Hz to 150Hz. Electrocardiographic data were initially processed by a technician to exclude artefacts, afterwards analyzed by two physicians unaware of the clinical information for each patient, and then verified for the presence of ischemia and new-onset arrhythmias (AF, VT, SVT, and VF). Standard postoperative 12-lead ECG recordings were made on days 3, 7 and 30, and/or at discharge, and whenever clinically indicated by chest pain or dyspnea complaints.

AF was defined by characteristic absolute irregularity of RR intervals and concurrent loss of identifiable P waves in the ECG recordings[13]. VT was characterized by three or more consecutive QRS complexes with a wide QRS complex at a rate of greater than 100 bpm and duration greater than 30 seconds[14]. SVT was identified as a narrow QRS complex (< 0.12 sec) and a rate greater than 180 bpm[14]. VF was defined as chaotic ventricular electrical discharge with marked variability in QRS cycle length, morphology, and amplitude[14].

Episodes of ischemia were defined as reversible ST-segment changes, lasting at least one minute and shifting from baseline by more than 0.1mV (1mm). ST-segment amplitude was measured 60 ms after the J point. If the J point fell within the T-wave, the ST-segment change was measured 40ms after that point. The baseline ST-segment level was defined as the average ST-segment value during a stable period of at least 20 min duration. The criteria for an ST-depression and ST-elevation were 0.1 mV flat or down sloping morphology with deviated J-point.

Heart Rate Variability (HRV) was evaluated with the time domain indices during the pre-, intra- and post-surgery period. The standard deviation of the normal-to-normal RR intervals (SDNN), the square root of the mean squared differences of successive NN intervals (RMS), the number of normal-to-normal RR intervals that were more than 50 milliseconds different from the preceding RR interval (NN50), and the average RR interval within the specified time period (RRmean) were used to characterize autonomic tone[15].

Long-term outcome

During follow-up, outpatient visits were scheduled every 3 months after discharge. Survival status was determined by contacting the municipal civil service registry. The study endpoint was the composite of cardiac death, MI, unstable angina, and stroke (cardiovascular (CV) events) during long-term follow-up (median 1.7 years; IQR 1.0 – 2.8 years). MI was defined according to the universal definition of myocardial infarction[16]. Cardiovascular death was defined as any death with a cardiovascular cause, including deaths following a cardiac procedure, cardiac arrest, MI, pulmonary embolus, stroke, or sudden death not ascribed to other causes.

Data analysis

Continuous data are expressed as means ± standard deviation (SD) compared using the Student's *t* test. Continuous data with a skewed distribution are expressed as medians with interquartile ranges (IQR) and were compared using the Mann-Whitney *U* test. Categorical data are described as numbers and

percentages and analyzed using the chi-square test or Fisher's exact test as appropriate. Preoperative risk factors for new-onset perioperative cardiac arrhythmias were assessed using uni,- and multivariable logistic regression analyses to evaluate the relation between baseline characteristics and perioperative cardiac arrhythmias. Cardiac risk factors, site of surgery, LVF, and continuous-ECG results were entered during the multivariable analysis. We made three subsequent models adding different variables (e.g. cardiac risk factors, site and type of surgery, LVF, cardiac valve abnormalities, inflammation marker and continuous-ECG results), adjusted all variables so as to reach as unbiased estimate of the effect of perioperative new-onset arrhythmias. The relationship between cardiac arrhythmias and long-term CV events was assessed with multivariate logistic regression analysis. In multivariate analysis, adjustments were made for perioperative new-onset cardiac arrhythmias, perioperative myocardial ischemia, cardiac risk factors, site and type of surgery, cardiac valve abnormalities, inflammation marker and LVF. Odds ratios (OR) and hazard ratios (HR) are given with 95% confidence intervals (CI). For all tests, a p-value of less than 0.05 (two-sided) was considered significant. All analyses were performed using SPSS 15.0 statistical software (SPSS Inc., Chicago, Illinois).

Results

Study population

The baseline clinical characteristics and medication use of the 513 included patients undergoing elective abdominal aortic aneurysm repair (n=254), peripheral artery bypass surgery (n=111) and carotid artery surgery (n=148) are listed in **Table 1**. The mean age at baseline was 68.6 ± 9.5 years and 77% were male.

Table 1. Baseline Characteristics

	All (n=513)	**No arrhythmia (n=458)**	**Arrhythmia (n=55)**	**p-value**
Age, years	68.6 ± 9.5	68.6 ± 9.5	72.6 ± 9.6	0.03
Males – no. (%)	397 (77)	350 (76)	47 (86)	0.13
History of MI – no. (%)	143 (28)	126 (28)	17 (31)	0.60
History of AP – no. (%)	87 (17)	79 (17)	8 (15)	0.71
History of CHF – no. (%)	39 (8)	32 (7)	7 (13)	0.17
Diabetes mellitus – no. (%)	109 (21)	96 (21)	13 (24)	0.65
Renal dysfunction – no. (%)	39 (8)	32 (7)	7 (13)	0.17
History of stroke – no. (%)	192 (37)	179 (39)	13 (24)	0.03
Hypertension – no. (%)	262 (51)	235 (51)	27 (49)	0.76
COPD – no. (%)	185 (36)	163 (36)	22 (40)	0.52
Smoking – no. (%)	393 (77)	352 (77)	41 (75)	0.70
BMI – kg/m^2	23.8 ± 7.8	24.3 ± 7.0	19.1 ± 11.8	<0.001
Medication use				
Beta-blockers – no. (%)	468 (91)	417 (91)	51 (93)	0.68
Statins – no. (%)	430 (84)	388 (85)	42 (76)	0.11
Antiplatelet therapy – no. (%)	388 (76)	350 (76)	38 (69)	0.23
Oral anticoagulants – no. (%)	72 (14)	61 (13)	11 (20)	0.18
Calcium channel blocking agents – no. (%)	133 (26)	121 (26)	12 (22)	0.46
ACE-inhibitors – no. (%)	147 (29)	131 (29)	16 (29)	0.94
Type of surgery				
Open AAA repair – no. (%)	131 (26)	112 (25)	19 (35)	0.03
Endovascular AAA repair – no. (%)	123 (24)	105 (23)	18 (33)	
Lower extremity bypass surgery – no. (%)	111 (22)	99 (22)	12 (22)	
Carotid endarterectomy – no. (%)	100 (20)	97 (21)	3 (6)	
Carotid artery stenting – no. (%)	48 (9)	45 (10)	3 (6)	

New-onset cardiac arrhythmias

Continuous-ECG monitoring started on average 12.6 ± 7.4 hours prior to surgery. New-onset arrhythmias occurred in 55 (11%) patients: AF, VT, SVT and VF occurred in 3.7%, 6.6%, 1.2% and 0.2% respectively. Supraventricular tachyarrhythmias occurred in 4% of the patients and ventricular tachyarrhythmias in 7% respectively. Arrhythmias were detected postoperatively in 53% of the 55 patients, the rest were detected prior to (29%) and during (18%) surgery. New-onset cardiac arrhythmias developed 8.3 (IQR 0.9-10.2) hours post surgery. The vast majority of patients with cardiac arrhythmias (97%) were asymptomatic. Symptomatic patients or those with detected ECG abnormalities started with medical therapy adjusted for heart rate control (e.g. beta-blockers and digoxin). Patients with new-onset AF received oral anticoagulant therapy next to antiplatelet medication. Those patients undergoing peripheral artery bypass surgery were also started on oral anticoagulants. All but 3 patients with new-onset cardiac arrhythmias returned to sinus rhythm at 30 days postoperatively, confirmed by standard ECG.

Risk factors for perioperative cardiac arrhythmias

Patients with cardiac arrhythmias were significantly older, as shown in **Table 1**. Preoperative use of beta-blockers was similar in patients with and without arrhythmias (93% versus 91%, p=0.68). The prevalence of smoking was similar in those with cardiac arrhythmias. Baseline NT-proBNP was significantly higher (median 391 versus 179 pg/mL, p<0.001) and there was a higher prevalence of LVEF lower than 40% in patients with perioperative cardiac arrhythmias as compared to those without (24% versus 12%, p=0.02, **Table 2)**. Patients with perioperative arrhythmias had significantly more cardiac valve abnormalities. The time domain HRV indices during the preoperative recording period were also higher in patients with perioperative cardiac arrhythmias (**Table 2**). Patients with perioperative cardiac arrhythmias also had a significantly higher inflammation status, reflected by a higher level of CRP (median 8 versus 4 mg/L, p=0.006).

As shown in **Table 3**, in multivariate analysis only increased age and reduced LVEF were independent risk factors associated with an increased risk of perioperative new-onset arrhythmias (OR 1.04, 95% CI 1.00-1.08, p=0.05 and OR 2.37, 95% CI 1.04-5.40, p=0.04 respectively).

Table 2. Preoperative laboratory markers, TTE and continuous-ECG results.

	All (n=513)	No arrhythmia (n=458)	Arrhythmia (n=55)	p-value
Laboratory markers				
CRP, mg/L	4 (2-10)	4 (2-9)	8 (2.5-19.5)	0.006
NT-proBNP, pg/mL	199 (89-476)	179 (80-431)	391 (142-1223)	<0.001
LVEF				
LVEF ≤40% - no. (%)	70 (14)	57 (12)	13 (24)	0.02
LVEF >40% - no. (%)	443 (86)	401 (88)	42 (76)	
Mitral valve*				
Normal – no. (%)	329 (64)	310 (68)	19 (35)	<0.001
Abnormal – no. (%)	48 (9)	39 (9)	9 (16)	
Aortic valve*				
Normal – no. (%)	334 (65)	312 (68)	22 (40)	<0.001
Abnormal – no. (%)	43 (8)	37 (8)	6 (11)	
Continuous-ECG				
Preoperative ischemia – no. (%)	37 (7)	30 (7)	7 (13)	0.10
Ischemia – no. (%)	100 (20)	83 (18)	17 (31)	0.02
Preoperative HRV				
SDNN	36.8 (27.1-48.0)	36.7 (27.1-47.5)	37.6 (25.6-53.5)	0.51
RMS	23.6 (16.1-35.7)	23.4 (16.0-34.8)	27.1 (17.1-47.2)	0.05
NN50	7.9 (4.0-22.1)	7.8 (4.0-20.6)	11.5 (4.6-44.0)	0.07
RRmean	924 (812-1038)	924 (810-1037)	928 (821-1134)	0.30

* Data were available of 73% of patients.

Table 3. Risk factors for arrhythmias.

	Model I		Model II		Model III	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Age	1.04 (1.00 – 1.07)	0.03	1.04 (1.00 – 1.08)	0.05	1.04 (1.00 – 1.08)	0.05
Gender	1.81 (0.83 – 3.96)	0.14	1.67 (0.70 – 3.99)	0.25	1.68 (0.70 – 4.02)	0.25
Ischemic Heart Disease	1.12 (0.63 – 1.98)	0.70	0.66 (0.32 – 1.34)	0.25	0.66 (0.32 – 1.35)	0.25
CHF	1.94 (0.81 – 4.64)	0.14	1.35 (0.42 – 4.31)	0.62	1.37 (0.43 – 4.40)	0.59
Diabetes Mellitus	1.17 (0.60 – 2.26)	0.65	0.85 (0.37 – 1.93)	0.70	0.86 (0.38 – 1.95)	0.71
Renal Failure	1.94 (0.81 – 4.64)	0.14	1.19 (0.43 – 3.27)	0.74	1.23 (0.44 – 3.44)	0.69
Stroke	0.48 (0.25 – 0.92)	0.03	1.22 (0.50 – 2.96)	0.66	1.25 (0.51 – 3.04)	0.63
CRP; (1 mg/L increase)	1.06 (0.99 – 1.13)	0.09	1.03 (0.96 – 1.10)	0.47	1.03 (0.96 – 1.11)	0.44
Type of surgery						
Open AAA repair	1.00	0.05	1.00	0.10	1.00	0.09
Endovascular AAA repair	1.01 (0.50 – 2.03)		0.62 (0.28 – 1.41)		0.59 (0.25 – 1.37)	
Lower extremity surgery	0.72 (0.33 – 1.55)		0.63 (0.27 – 1.49)		0.62 (0.26 – 1.47)	
Carotid endarterectomy	0.18 (0.05 – 0.64)		0.15 (0.03 – 0.64)		0.14 (0.03 – 0.62)	
Carotid artery stenting	0.39 (0.11 – 1.39)		0.20 (0.04 – 1.13)		0.19 (0.03 – 1.08)	
Reduced LVEF			2.29 (1.02 – 5.16)	0.05	2.37 (1.04 – 5.40)	0.04
Mitral valve abnormalities			2.34 (0.91 – 6.04)	0.08	2.35 (0.91 – 6.10)	0.08
Aortic valve abnormal			0.96 (0.38 – 2.45)	0.93	0.96 (0.38 – 2.44)	0.93
Preoperative ischemia					0.81 (0.34 – 1.92)	0.63

Cardiac arrhythmias and myocardial ischemia during continuous-ECG

Transient myocardial ischemia was detected in 100 (19%) patients; in 9 as ST-elevation and 91 as ST-depression. Patients with cardiac arrhythmias also had a significantly higher incidence of myocardial ischemia, compared to patients without cardiac arrhythmias, during continuous-ECG registration (31% versus 18%, p=0.02, **Table 2**). In a minority of cases (10/55, 18%) arrhythmia was preceded by ischemia with a median time of 6.1 hours (IQR 3.2–23.8). In the majority of cases arrhythmia was not preceded by ischemia, while a small portion developed arrhythmia prior to an ischemic event. There were no significant differences in potassium level between patients with versus those without arrhythmias (median 4.6 versus 4.5 mmol/L).

Long-term outcome

A total of 87 (17%) patients died during the mean follow-up period of 2 years; 61 (70%) were due to cardiovascular causes. The combined endpoint for CV events occurred in 98 (19%) patients, including 21 of 55 (38%) patients with perioperative arrhythmia and 77 of 458 (17%) in those without arrhythmia. The detection of perioperative arrhythmias was associated with an increased risk in the incidence of death from cardiovascular causes, myocardial infarction, unstable angina, and stroke (**Figure 1**). After correction for cardiac risk factors, site and type of surgery, inflammation marker, cardiac valve abnormalities and LVEF, perioperative new-onset arrhythmias were still found to be associated with long-term cardiovascular events, irrespective of the presence of perioperative myocardial ischemia (HR 2.2, 95% CI 1.3–3.8, p=0.004, **Table 4**). Patients who developed new-onset supraventricular tachyarrhythmias had the highest risk of developing cardiovascular events during long-term follow-up, while the HRs for patients with ventricular tachyarrhythmias did not reach significant difference compared to patients without arrhythmias (HR 3.0, 95% CI 1.5-6.2 and HR 1.7, 95% CI 0.9-3.6 respectively).

Table 4. Multivariate analyses for cardiovascular event-free survival during long-term follow-up.

	HR (95%CI)	*p-value*
Age	1.03 (1.01 – 1.06)	0.01
Gender	0.91 (0.54 – 1.53)	0.71
Ischemic Heart Disease	1.76 (1.10 – 2.81)	0.02
Congestive Heart Failure	1.27 (0.64 – 2.53)	0.49
Diabetes Mellitus	0.86 (0.50 – 1.48)	0.58
Renal Failure	1.13 (0.59 – 2.19)	0.71
Stroke (TIA and/or ischemic CVA)	1.98 (1.17 – 3.34)	0.01
CRP prior to surgery (cutoff 10.0 mg/L)	1.05 (1.01 – 1.10)	0.01
Type of surgery		
Open AAA repair	1.00	<0.001
Endovascular AAA repair	0.32 (0.16 – 0.63)	
Lower extremity bypass surgery	0.59 (0.34 – 1.03)	
Carotid endarterectomy	0.09 (0.03 – 0.26)	
Carotid artery stenting	0.48 (0.19 – 1.19)	
Reduced LVEF	1.51 (0.88 – 2.59)	0.13
Mitral valve abnormalities	0.87 (0.51 – 1.50)	0.62
Aortic valve abnormalities	1.23 (0.71 – 2.13)	0.46
Perioperative myocardial ischemia	2.23 (1.39 – 3.58)	0.001
Perioperative new-onset cardiac arrhythmias	2.20 (1.28 – 3.77)	0.004

Discussion

Principal findings

The current study shows that new-onset perioperative arrhythmias are common after vascular surgery, often asymptomatic, and more often found among elderly patients and those with reduced LVEF. No consistent relationship between the timing of new-onset arrhythmias and transient ischemic events was observed. Occurrence of arrhythmias is an independent predictor of increased risk for CV events and death.

In the context of literature

The pathophysiology of new-onset arrhythmias after non-cardiac surgery is complex and they may bring about severe CV complications. It has been proposed that patients who develop perioperative arrhythmias may already possess a preoperative electrophysiological substrate for this arrhythmia[5, 6]. However, studies of cardiothoracic surgery patients without evidence of substrate suggest that arrhythmia risk factors also include advanced age, male gender, myocardial ischemia, electrolyte disorders, valvular heart disease, a heightened inflammatory response invoked by the surgical procedure, a history of cardiac arrhythmias, and direct manipulation during the surgical procedure[6, 17-19]. In a study by Steinberg et al., there was a 3.1% incidence of VT in 382 patients undergoing CABG procedure in which the number of bypass grafts, indicating myocardial ischemia, was an independent factor predicting VT[19].

In the general non-surgical population, the pathologic and electrophysiologic substrate for VT after MI has been well characterized[20]. Inhomogeneous scarring results in slowed conduction channels leading to the development of re-entrant VT[21]. Tachyarrhythmias may reduce cardiac output, and increase myocardial oxygen consumption, producing myocardial ischemia[20-22]. In the current study, however, there was no detectable relationship in time between arrhythmias and onset of ischemia: minority (10/55=18%) of arrhythmias were preceded by ischemia.

How does cardiothoracic surgery differ from general vascular surgery? The cardiothoracic surgery procedure itself has made estimation of arrhythmia prevalence difficult, since there's obviously direct irritation of the pericardium or myocardium, which cannot account for the observed incidence of arrhythmias in non-cardiac surgery. These data are scarce. Our estimated prevalence matches prior summaries of the literature by Walsh et al.[3]. More recently, Polanczyk et al. conducted a study of 4181 patients undergoing non-cardiac surgery and found that AF and SVT occurred most frequently, usually postoperatively[2]. However, in Polanczyk's study ECG-data were restricted to periodical performances in the recovery room, day 1, 3, and 5 after surgery. Use of continuous-ECG strengthens the current findings. In a study by Hollenberg et al. initiating factors for postoperative arrhythmias in non-cardiac surgery patients are transient imbalance (i.e. cardiac ischemia, catecholamine excess, electrolyte abnormalities)[22]. Knotzer er al. found that sepsis, age, and a history or presence of CHF were independent predictors of tachyarrhythmias in 987 cardiac surgery patients[7].

The pathophysiological causes of elevated filling pressure have been attributed to the fact that increased ventricular diastolic wall stretch augments synthesis and release of BNP and NT-proBNP[23]. The current study found that increased natriuretic peptides levels are associated with arrhythmias. Circulating BNP and NT-proBNP levels are increased in heart failure in proportion to disease severity, but could also be observed in arrhythmias, myocardial ischemia, and more[23]. However our data show no relationship between a previous history of CHF and arrhythmias, even though reduced LVEF is a significant factor. A possible explanation is that in case of left ventricular dysfunction, myocardial stretch can induce myocyte depolarization, changing action potential, causing abnormal impulses by stretch-activated channel currents and may thus trigger the onset of arrhythmias[24].

Implications

The reported incidence and prevalence of perioperative arrhythmias varies among different studies, depending on patient population profile, type of surgery, arrhythmia definition and detection methods[1, 3, 22]. The incidence particularly

depends on the type of cardiac monitoring, with better estimates obtained using continuous-ECG[3]. In a study by Mathew et al. it was noted that most episodes of perioperative arrhythmias (76.8%) are diagnosed using continuous-ECG, and reduces to 17.5% by use of intermittent 12-lead ECG and only 12.8% by physical examination[8]. Use of continuous-ECG and longer monitoring in this study has enhanced the detection of perioperative arrhythmias (AF, SVT, VT and VF) since we aimed to assess potential preoperative risk factors for and the prognostic influence of arrhythmias. A major finding in the current study is that patients with arrhythmias were independently associated with a two-fold increased risk of poor CV outcome, irrespective of the presence of ischemia.

More than 30 years ago Goldman et al. published a prospective series of 916 patients undergoing major non-cardiac surgery of whom 4% developed postoperative supraventricular arrhythmia and concluded that the onset thereof is often transient and the importance is to correct the cause of arrhythmia[25]. As reported by Brathwaite and Weissman, concluded that arrhythmias were more a marker for increased mortality and morbidity[1].

Patients at risk of arrhythmias may benefit from medication like antiplatelet and/or anticoagulant therapy, beta-blockers and statin therapy. Several trials have shown that there is an under use of cardio-protective medication[26, 27]. The anti-ischemic and anti-arrhythmic properties of beta-blockers could diminish the incidence of perioperative arrhythmias[10]. Antiplatelet therapy is the cornerstone for preventing ischemic events resulting from coronary atherosclerotic disease[28]. Anticoagulant therapy might be indicated for prevention of cardiocerebrovascular diseases in a variety of conditions that include AF[29]. Holmes et al. concluded that the combined use of antithrombotic therapy is associated with significant bleeding hazards[28]. In the current study, patients with new-onset AF received oral anticoagulant therapy and antiplatelet medication. At admission in the hospital all patients received beta-blockers. Further and larger studies will have to investigate the true impact of this antithrombotic regiment on perioperative arrhythmias.

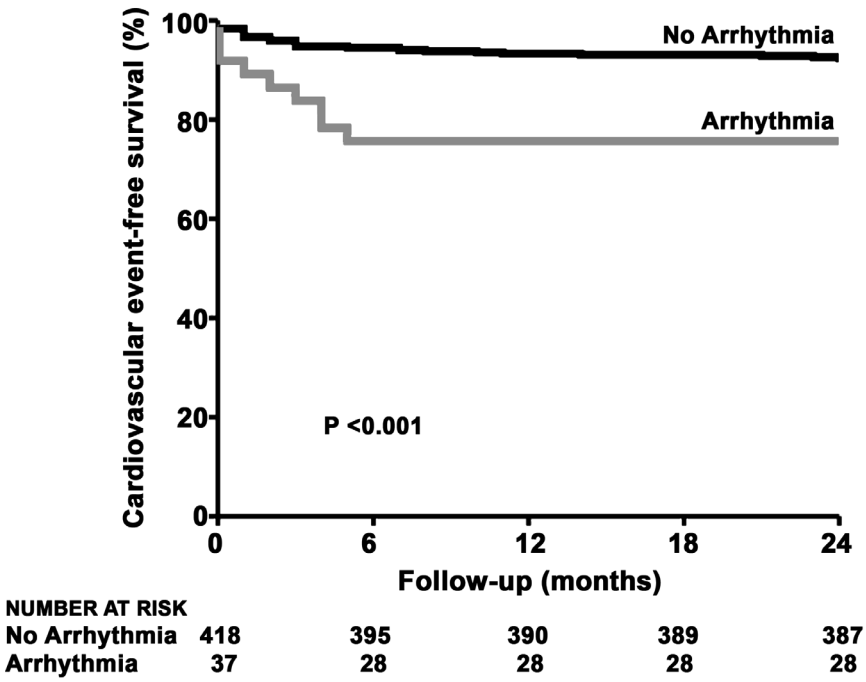
Limitations

A major limitation in our study is the fact that there is a relatively small amount of new-onset perioperative arrhythmias. It is for this reason that we conducted the current study combining all new-onset arrhythmias together. Despite this combination the findings clearly require confirmation in independent and larger patient cohorts. The reader should not conclude that arrhythmias are “alike”. It is for this reason that we did try to do a sub-analysis, yet these groups were too small to make a prediction model for arrhythmias. Continuous-ECG monitoring for a longer period of time during vascular surgery may decrease the potential underestimation of the true prevalence of arrhythmias and may be warranted, which could ensure that asymptomatic and paroxysmal cases are not missed.

Conclusions

New-onset perioperative arrhythmias are common after vascular surgery; the elderly and those with diminished LVF are at higher risk. The appearance of arrhythmias is an independent predictor of CV events, irrespective of the presence of myocardial ischemia. The use of perioperative continuous-ECG monitoring to screen for arrhythmias increases the number of patients identified with arrhythmic events, and may help to improve management of patients at risk for subsequent CV events.

Figure 1: Long-term survival of vascular surgery patients with and without new-onset perioperative cardiac arrhythmias.



Reference

1. Brathwaite, D. and C. Weissman, The new onset of atrial arrhythmias following major noncardiothoracic surgery is associated with increased mortality. Chest, 1998. **114**(2): p. 462-8.
2. Polanczyk, C.A., Goldman L., Marcantonio E.R., et al., Supraventricular arrhythmia in patients having noncardiac surgery: clinical correlates and effect on length of stay. Ann Intern Med, 1998. **129**(4): p. 279-85.
3. Walsh, S.R., Tang T., Wijewardena C., et al., Postoperative arrhythmias in general surgical patients. Ann R Coll Surg Engl, 2007. **89**(2): p. 91-5.
4. Schouten, O., J.J. Bax, and D. Poldermans, Preoperative cardiac risk assessment in vascular surgery patients: seeing beyond the perioperative period. Eur Heart J, 2008. **29**(3): p. 283-4.
5. Walsh, S.R., Oates J.E., Anderson J.A., et al., Postoperative arrhythmias in colorectal surgical patients: incidence and clinical correlates. Colorectal Dis, 2006. **8**(3): p. 212-6.
6. Hogue, C.W., Jr., Creswell L.L., Gutterman D.D., et al., Epidemiology, mechanisms, and risks: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. Chest, 2005. **128**(2 Suppl): p. 9S-16S.
7. Knotzer, H., Mayr A., Ulmer H., et al., Tachyarrhythmias in a surgical intensive care unit: a case-controlled epidemiologic study. Intensive Care Med, 2000. **26**(7): p. 908-14.
8. Mathew, J.P., Fontes M.L.., Tudor I.C., et al., A multicenter risk index for atrial fibrillation after cardiac surgery. Jama, 2004. **291**(14): p. 1720-9.
9. Bender, J.S., Supraventricular tachyarrhythmias in the surgical intensive care unit: an under-recognized event. Am Surg, 1996. **62**(1): p. 73-5.
10. Fleisher, L.A., Beckman J.A., Brown K.A., et al., ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the ACC/AHA Task Force on Practice Guidelines (Writing Committee). Circulation, 2007. **116**(17): p. e418-99.
11. Lang, R.M., Bierig M., Devereaux R.B., et al., Recommendations for chamber quantification. Eur J Echocardiogr, 2006. **7**(2): p. 79-108.
12. Quinones, M.A., Otto C.M., Stoddard M., et al., Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr, 2002. **15**(2): p. 167-84.
13. Estes, N.A., 3rd, Halperin J.L., Calkins H., et al., ACC/AHA/Physician Consortium 2008 Clinical Performance Measures for Adults with Nonvalvular AF or Atrial Flutter: a report of the ACC/AHA Task Force on Performance Measures and the Physician Consortium for Performance Improvement (Writing Committee) Developed in Collaboration with the Heart Rhythm Society. J Am Coll Cardiol, 2008. **51**(8): p. 865-84.
14. Zipes, D.P., Camm A.J., Borggrefe M., et al., ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the ACC/AHA Task Force and the ESC Committee for Practice Guidelines (Writing Committee). J Am Coll Cardiol, 2006. **48**(5): p. e247-346.
15. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the ESC and the North American Society of Pacing and Electrophysiology. Circulation, 1996. **93**(5): p. 1043-65.
16. Thygesen, K., J.S. Alpert, and H.D. White, Universal definition of myocardial infarction. Eur Heart J, 2007. **28**(20): p. 2525-38.
17. Ascione, R., Reeves B.C., Santo K., et al., Predictors of new malignant ventricular arrhythmias after coronary surgery: a case-control study. J Am Coll Cardiol, 2004. **43**(9): p. 1630-8.
18. Echahidi, N., Pibarot P., O'Hara G., et al., Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. J Am Coll Cardiol, 2008. **51**(8): p. 793-801.
19. Steinberg, J.S., Gaur A., Sciacca R., et al., New-onset sustained ventricular tachycardia after cardiac surgery. Circulation, 1999. **99**(7): p. 903-8.
20. de Bakker, J.M., van Capelle F.J., Janse M.J., et al., Reentry as a cause of ventricular tachycardia in patients with chronic ischemic heart disease: electrophysiologic and anatomic correlation. Circulation, 1988. **77**(3): p. 589-606.
21. de Bakker, J.M., van Capelle F.J., Janse M.J., et al., Slow conduction in the infarcted human heart. 'Zigzag' course of activation. Circulation, 1993. **88**(3): p. 915-26.

22. Hollenberg, S.M. and R.P. Dellinger, Noncardiac surgery: postoperative arrhythmias. Crit Care Med, 2000. **28**(10 Suppl): p. N145-50.
23. Omland, T. and T.A. Hagve, Natriuretic peptides: physiologic and analytic considerations. Heart Fail Clin, 2009. **5**(4): p. 471-87.
24. De Mello, W.C., Cell swelling, impulse conduction, and cardiac arrhythmias in the failing heart. Opposite effects of angiotensin II and angiotensin (1-7) on cell volume regulation. Mol Cell Biochem, 2009.
25. Goldman, L., Supraventricular tachyarrhythmias in hospitalized adults after surgery. Clinical correlates in patients over 40 years of age after major noncardiac surgery. Chest, 1978. **73**(4): p. 450-4.
26. Bhatt, D.L., Steg P.G., Ohman E.M., et al., International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. Jama, 2006. **295**(2): p. 180-9.
27. Hoeks, S.E., Scholte op Reimer W.J., Schouten O., et al., Statin use in the elderly: results from a peripheral vascular survey in The Netherlands. J Vasc Surg, 2008. **48**(4): p. 891-5; discussion 895-6.
28. Holmes, D.R., Jr., Kereiakes D.J., Kleiman N.S., et al., Combining antiplatelet and anticoagulant therapies. J Am Coll Cardiol, 2009. **54**(2): p. 95-109.
29. Conway, D.S. and G.Y. Lip, Comparison of outcomes of patients with symptomatic peripheral artery disease with and without atrial fibrillation (the West Birmingham Atrial Fibrillation Project). Am J Cardiol, 2004. **93**(11): p. 1422-5, A10.

4

Prognosis of transient new-onset atrial fibrillation during vascular surgery.

European Journal of Vascular and Endovascular Surgery 2009;38(6):683-8

Tamara A. Winkel
Olaf Schouten
Sanne E. Hoeks
Hence J.M. Verhagen
Jeroen J. Bax
Don Poldermans

Abstract

Background: Chronic atrial fibrillation (AF) in the non-surgical setting is associated with cardiovascular events. However, the prognosis of transient new-onset AF during vascular surgery is unknown.

Objective: To study the prognosis of new-onset AF during vascular surgery using continuous electrocardiographic monitoring (continuous-ECG).

Methods: 317 patients, all in sinus rhythm, scheduled for major vascular surgery were screened for cardiac risk factors. Continuous-ECG recordings for 72 hours and standard ECG on days 3, 7, and 30, were used to identify new-onset AF. Cardiac troponin-T (cTnT) was measured routinely after surgery. Study endpoint was the composite of cardiac death, myocardial infarction, unstable angina, and stroke (cardiovascular events) at 30-days after surgery and during late follow-up. Median follow-up was 12 (interquartile range 2 – 28) months.

Results: New-onset AF was noted in 15(4.7%) patients. All but three patients returned spontaneously to sinus rhythm. The composite endpoint of cardiovascular events within 30-days and during late follow-up occurred in 34(11%) and 62(20%) patients respectively. Multivariate regression analysis showed that new-onset AF was associated with perioperative (HR 6.0, 95%CI 2.4–15) and late cardiovascular events (HR 4.2, 95%CI 2.1–8.8).

Conclusion: New-onset AF during vascular surgery is associated with an increased incidence of 30-day and late cardiovascular events.

Introduction

Cardiovascular complications are a major cause for morbidity and mortality in patients undergoing non-cardiac vascular surgery[1]. It is estimated that after non-cardiac surgery 2-10% of patients develop cardiac arrhythmias of which atrial fibrillation is the most common form[2-5]. Atrial fibrillation is facilitated by electrolyte disturbances, hypoxia, and acidosis. Postoperative atrial fibrillation is associated with a prolonged hospital stay, as well as neurological, and cardiac complications and increased health care costs. It was estimated that after cardiac surgery atrial tachyarrhythmias increased costs with $ 6356 per patient[6]. Patients with recurrent episodes of preoperative atrial fibrillation are probably at the greatest risk for this adverse outcome.

The impact of new-onset AF in the perioperative period after vascular surgery is ill defined. Importantly, the incidence of postoperative atrial fibrillation is closely related to the extensiveness of cardiac rhythm monitoring. Up to now, detection of cardiac arrhythmias was most frequently performed with intermittent and/or daily electrocardiographic (ECG) monitoring and based on patients' complaints. However, this might be insufficient to detect the true incidence of new-onset AF and it's impact on perioperative and long-term outcome after vascular surgery. It must be held into account that perioperative new-onset AF is often short-lived and asymptomatic making detection difficult.

Therefore, the purpose of this study was to assess the incidence and impact of perioperative new-onset AF in vascular surgery patients using continuous ECG registration for the first 48-hours after surgery.

Methods

Study population

The study population consisted of 409 patients undergoing elective abdominal aortic aneurysm repair or peripheral artery bypass surgery at the Erasmus Medical Center in Rotterdam, the Netherlands, during the period 2004 to 2009. Patients with a history of cardiac arrhythmias (n=28), cardiac pacemaker (n=6), left ventricular hypertrophy (n=33) and left or right bundle branch block (n=25) were excluded. The hospital's ethical committee approved the study.

Preoperative cardiovascular screening

We determined the cardiac risk score for each patient in our dataset, and one point was assigned to each of the following characteristics: advanced age (> 70 years), history of myocardial infarction (MI), history of angina pectoris, history of congestive heart failure, history of stroke, diabetes mellitus (fasting glucose level ≥ 7.0 mmol/L or use of insulin or oral glucose lowering medication), and renal insufficiency (serum creatinine >170 umol/l). Based on the number of these risk factors, patients were stratified into low-risk (no risk factors), intermediate-risk (1 or 2 risk factors), and high-risk (≥ 3 risk factors) categories[7]. Furthermore, all patients were screened for hypertension (blood pressure ≥ 140/90 mmHg or blood pressure lowering medication), hypercholesterolemia (plasma cholesterol level ≥5.5 mmol/L or use of cholesterol-lowering medication), smoking status, and chronic obstructive pulmonary disease (defined as a FEV1 < 70% of age and gender predictive value or medication use) [8].

Detection of atrial fibrillation

Patients were continuously monitored with a 10-electrode, 12-lead digital ECG recorder (DR180+ Digital Recorder, NorthEast Monitoring Inc. Massachusetts), starting 1 day before surgery and continuing up to 2 days after. Continuous-ECG recordings were started one day prior to surgery, depending on the time of admission of the patient at the vascular surgery ward. Recordings were performed in the continuous 12-lead mode with a recording length of 10 seconds every

minute. The frequency response was 0.05 – 150Hz. Electrocardiographic data were initially processed by a technician and analyzed by 2 experienced cardiologists who were blinded to the patient's clinical data. After excluding all artifacts, the ambulatory electrocardiography recordings were analyzed for new-onset AF. On the ECG, AF is characterized by the replacement of consistent P waves with rapid oscillations or fibrillatory waves that vary in amplitude, shape, and timing, associated with an irregular, frequently rapid ventricular response when atrioventricular conduction is intact [9]. Continuous-ECG recordings were analyzed off-line. Postoperatively standard ECG's were made routinely on day 3,7 and 30, and/or at discharge and whenever clinically indicated by chest pain or dyspnea complaints.

Perioperative outcome

The perioperative endpoint was the composite of cardiac death, MI, unstable angina pectoris, and stroke (cardiovascular events) within 30 days after surgery. After surgery, cardiac troponin T (cTnT) levels were routinely measured on postoperative days 1, 3, 7, 30 and/or at discharge and whenever clinically indicated by chest pain complaints or ECG changes consistent with myocardial ischemia or infarction. Myocardial infarction was defined as the presence of 2 out of the following 3 criteria: (1) Characteristic ischemic symptoms lasting > 20 minutes, (2) electrocardiographic changes including acute ST elevation followed by appearance of Q waves or loss of R waves, or new left bundle branch block, or new persistent T wave inversion for at least 24 hours, or new ST segment depression which persists > 24 hours, and (3) a positive troponin T, i.e. >0.10 ng/ml with characteristic rise and fall [10]. Cardiovascular death was defined as any death with a cardiovascular cause, including those deaths following a cardiac procedure, cardiac arrest, MI, pulmonary embolus, stroke, or sudden deaths not ascribed to other causes [11].

Long-term outcome

During follow-up, outpatient visits were scheduled every 3 months after discharge. Long-term study endpoints were cardiovascular events, i.e. cardiac death, MI, unstable angina pectoris, and stroke. Cardiac death was defined as death caused by acute myocardial infarction, cardiac arrhythmias, congestive heart failure, or sudden death. Survival status was ascertained by contacting the civil service registry.

Data analysis

Continuous data are expressed as means ± standard deviation (SD) and compared using the Student's *t* test. Categorical variables are described as numbers and percentages and analyzed using the chi-square test or Fisher's exact test as appropriate. The association of new-onset AF with short and long-term prognosis was assessed via multivariate Cox regression analysis. All co-variables associated with perioperative cardiovascular complications (P-value < 0.20 in univariate analysis) were included in the multivariate model. The number of outcome events in the study was limited. Therefore, to avoid over fitting, and to enable assessment of the relation between clinical risk factors and the composite endpoint, we used the risk score described by Boersma et al.[7] In multivariate analysis, adjustments were made for risk factors, cardiac risk score, site of surgery and open or endovascular procedure. Hazard ratios (HR) are given with 95% confidence intervals (CI). For all tests, a p-value of less than 0.05 (two-sided) was considered significant. All analyses were performed using SPSS 15.0 statistical software (SPSS Inc., Chicago, Illinois).

Results

Patient characteristics

A total of 317 patients undergoing abdominal aortic aneurysm repair (n=216) or peripheral arterial bypass surgery (n=101) were analyzed. Their mean age was 68.6 ± 9.5 years and 79% were male. According to the cardiac risk score 23% of patients had low cardiac risk, 54% intermediate cardiac risk and 23% high cardiac risk. The baseline clinical characteristics are listed in Table 1. Patients who developed new-onset AF were significantly older (p= 0.02). Except for age, there were no significant differences in baseline characteristics between the two groups.

New-onset atrial fibrillation

Continuous-ECG monitoring started 12.1 ± 7.2 hours prior to surgery. During 20,775 patient-hours of continuous 12-lead ECG monitoring (65.5 ± 20.2 h/patient), 13 (4%) patients developed new-onset AF. In all but one continuous-ECG recording, new-onset AF occurred postoperatively. Additionally, in 2 patients new-onset AF was noted on standard ECG's between day 3 and 7 after surgery. The vast majority of patients (80%) were without clinical symptoms. In three patients signs of worsening of heart failure symptoms were present and were treated by additional diuretics and digoxin therapy. All patients were on perioperative beta-blocker therapy as well as low molecular heparins. All but three patients with new-onset AF returned to sinus rhythm at 30 days postoperatively, confirmed on standard ECG.

There were no significant differences in the type of anaesthesia or the duration of anaesthesia between the two groups. In the group of patients with new-onset AF 80% had general anaesthesia, as compared to 61% in those without new-onset AF (p=0.80). The mean duration of anaesthesia did not differ between the two groups (4.5 versus 4.3 hours, p=0.63).

Cardiovascular outcome

In total, 63 (19.9%) patients experienced cTnT release within 30 days after surgery. A total of 70 patients developed myocardial ischemia during continuous-ECG monitoring. Eight patients with perioperative new-onset AF also had myocardial ischemia detection.

Table 1. Baseline characteristics

	All (n=317)	**No AF (n=302)**	**New-onset AF (n=15)**
Age, years ± SD	68.6 ± 9.5	68.3 ± 9.5	74.4 ± 8.9
Males – no. (%)	250 (79)	237 (79)	13 (85)
Cardiovascular risk factors – no. (%)			
History of myocardial infarction	100 (32)	97 (32)	3 (20)
History of angina pectoris	60 (19)	59 (20)	1 (7)
History of congestive heart failure	24 (8)	22 (7)	2 (13)
Diabetes mellitus	63 (20)	61 (20)	2 (13)
Renal dysfunction	31 (10)	28 (9)	3 (20)
History of TIA or CVA	48 (15)	44 (15)	4 (27)
Hypertension	153 (48)	144 (48)	9 (60)
COPD	133 (42)	129 (43)	4 (27)
Medication – no. (%)			
Beta-blockers	305 (96)	291 (96)	14 (93)
Statins	261 (82)	249 (83)	12 (80)
Antiplatelet therapy	217 (68)	207 (69)	10 (67)
Oral anticoagulants	48 (15)	44 (15)	4 (27)
ACE-inhibitors	86 (27)	81 (27)	5 (33)
Calcium channel blocking agents	82 (26)	76 (25)	6 (40)
Site of surgery – no. (%)			
Abdominal aorta	216 (68)	205 (68)	11 (63)
Endovascular	95	91	4
Open	121	114	7
Lower extremity artery	101 (32)	97 (32)	4 (27)

AF= atrial fibrillation; TIA = transient ischemic attack; CVA = cerebrovascular accident; COPD = chronic obstructive pulmonary disease; ACE = angiotensin converting enzyme

The incidence of myocardial ischemia in patients with new-onset AF was significantly higher compared to those without new-onset AF (53% versus 21%, p=0.01). New-onset AF was preceded by myocardial ischemia in half of the cases. Seven patients with new-onset AF had the combination of cTnT release and myocardial ischemia detection.

A nonfatal MI and cardiac death was noted in respectively 21 (6.6%) and 12 (3.8%) patients. One patient experienced a nonfatal perioperative stroke. The incidence of the composite perioperative outcome was noted in 34 (10.7%) patients. In univariate analysis new-onset AF was associated with an increased risk of perioperative cardiovascular events (HR 4.9, 95% confidence interval (CI) 2.0 – 11.9, p< 0.001, **table 2**). After correcting for risk factors, type and site of surgery, multivariate regression analysis showed that new-onset AF was still associated with perioperative cardiovascular events (HR 6.0, 95% CI 2.4 – 15.0, p< 0.001, **table 2**).

Table 2. Multivariate Cox regression analysis for perioperative cerebro-cardiovascular outcome.

	Univariate			Multivariate		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Perioperative Arrhythmia	4.9	2.0 - 12	<0.001	6.0	2.4 – 15	<0.001
Clinical cardiac risk						
Low	1					
Intermediate	2.4	0.7 – 8.3	0.16	3.0	0.9 – 10	0.08
High	5.7	1.7 - 20	0.006	7.7	2.2 – 27	0.002
Other risk factors						
Male	0.8	0.4 – 2.0	0.78			
Hypertension	2.1	1.0 – 4.2	0.04	2.0	1.0 – 4.0	0.06
COPD	1.4	0.7 – 2.8	0.31			
Surgery						
Aortic	1		0.01	1		
Peripheral	0.3	0.1 – 0.8		0.2	0.1 – 0.5	0.001
Type of surgery						
Open	1		0.11	1		
Endovascular	0.5	0.2 – 1.2		0.2	0.1 – 0.6	0.001

Within a median follow-up of 12 months (interquartile range 2 – 28 months) after surgery 35 (11.0%) patients experienced a nonfatal MI, 9 (2.8%) unstable angina pectoris, 4 (1.3%) stroke, and 34 (10.7%) died due to a cardiac cause. In total, the combined endpoint of long-term cardiovascular events occurred in 62 (19.6%) patients. In univariate analysis perioperative new-onset atrial fibrillation was associated with an increased risk of long-term cardiovascular events (HR 4.4, 95% CI 2.1 – 8.8, p= 0.001, **figure 1**). This association between perioperative AF and long-term prognosis persisted when other cardiovascular risk factors, type and site of surgery were added to the multivariate Cox regression model (HR 4.2, 95% CI 2.1 – 8.8, p= 0.001, **table 3**).

Table 3. Multivariate Cox regression analysis for long-term cerebro-cardiovascular outcome.

	Univariate			Multivariate		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
New-onset atrial fibrillation	4.4	2.1 – 8.8	<0.001	4.2	2.1 – 8.8	<0.001
Clinical cardiac risk						
Low	1					
Intermediate	3.7	1.3 – 10	0.02	4.0	1.4 – 11	0.01
High	9.2	3.2 – 26	<0.001	10.7	3.7 – 31	<0.001
Other risk factors						
Male	1.3	0.7 – 2.5	0.43			
Hypertension	1.9	1.2 – 3.3	0.01	1.7	1.0 – 2.9	0.04
COPD	1.4	0.8 – 2.3	0.20			
Surgery						
Aortic	1		0.26	1		
Peripheral	0.7	0.4 – 1.3		0.5	0.3 – 0.8	0.01
Type of surgery						
Open	1		0.05	1		0.001
Endovascular	0.5	0.3 – 1.0		0.3	0.2 – 0.6	

Discussion

The current study shows that transient and predominantly asymptomatic, new-onset atrial fibrillation during vascular surgery is associated with an increased risk for perioperative and long-term cardiovascular events. Patients with new-onset AF had an almost five-fold increased risk for perioperative cardiovascular complications. This risk persisted in the first year after surgery as patients with new-onset AF experienced a four-fold increased risk for late complications.

Atrial fibrillation is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of mechanical function. Factors affecting haemodynamic function during AF are loss of synchronous atrial mechanical activity, irregular ventricular response, tachycardia, and impaired coronary arterial blood flow[12]. This may result in a decreased cardiac output, especially when diastolic ventricular filling is impaired by conditions such as hypertension and diabetes mellitus. However, most of the pathophysiological pathways and consequences of AF are investigated in the non-surgical population and after cardiac surgery[6, 12, 13]. The relationship between AF and impaired cardiac outcome after non-cardiac surgery is less well studied. It might be hypothesized that a sustained state of atrial fibrillation after vascular surgery results in a prolonged period of suboptimal left ventricular function and coronary oxygen perfusion abnormalities leading to a cardiac oxygen demand/supply mismatch resulting in myocardial infarction. Both heart failure and myocardial infarction are strong predictors of adverse postoperative outcome[14, 15]. In the current study there was a clear association between atrial fibrillation and myocardial ischaemia as shown by an increased incidence of troponin T release. However, the relation in time could not be assessed as troponin T release can only be assessed at intervals, preventing the understanding of the exact time relation between AF and myocardial ischemia. Furthermore, in our study new-onset AF was preceded by myocardial ischemia in half of the cases.

The majority of studies performed to detect the impact of atrial fibrillation on postoperative outcome were performed in patients undergoing cardiothoracic surgery. In these studies the incidence of new-onset atrial fibrillation is as high as 40%[6]. In the non-cardiothoracic surgical setting the risk for perioperative new-onset atrial fibrillation is significantly lower. As reported by Christians et al., the incidence of new-onset atrial fibrillation in an unselected group of 13,696 patients undergoing elective non-cardiac surgery was as low as 0.37%[5]. In more selected patient populations, such as surgical ICU patients, the incidence of new-onset atrial fibrillation might be as high as 9% as reported by Brathwaite et al[4]. Importantly, in this surgical ICU study, patients with new-onset AF also had an increased risk for mortality. Valentine et al. studied ICU patients after open aortic surgical procedure and revealed a similar incidence of 10% new-onset AF[3]. It should be noticed that these patients were followed with continuous ECG monitoring for a mean of 6 ± 8 days. This high incidence of postoperative new-onset AF after aortic surgery has recently been reconfirmed by Noorani et al.[16] in a group of 200 patients. Those with AF (10%) had an increased risk for cardiac failure and a longer hospital stay. In the study by Noorani et al. no relation was found between AF and prognosis, but it was a retrospective study with a discontinuous fashion of ECG monitoring. In the current study, patients were followed by continuous-ECG for 72 hours and a standard ECG on days 3 and 7. This might explain the lower incidence of new-onset AF observed in our study. Furthermore, intermediate risk surgical patients, i.e. endovascular aneurysm repair and peripheral bypass surgery, were included in the current study. This might have affected the incidence of new-onset atrial fibrillation. Another possible explanation for the lower incidence of new-onset AF might be the use of perioperative beta-blocker therapy in nearly all patients in the current study.

New-onset postoperative AF deserves attention, as it is associated with poor outcome.

It warrants more specific evaluation of the cause of AF and a more rigorous screening for postoperative AF should be considered. Advanced age was a preoperative predictor of new-onset AF. As the average age of patients scheduled

for vascular surgery is increasing, the incidence of AF after vascular surgery is likely to increase. Therefore, development of easy-to-use monitoring devices, which would enable a longer continuous monitoring period, is important.

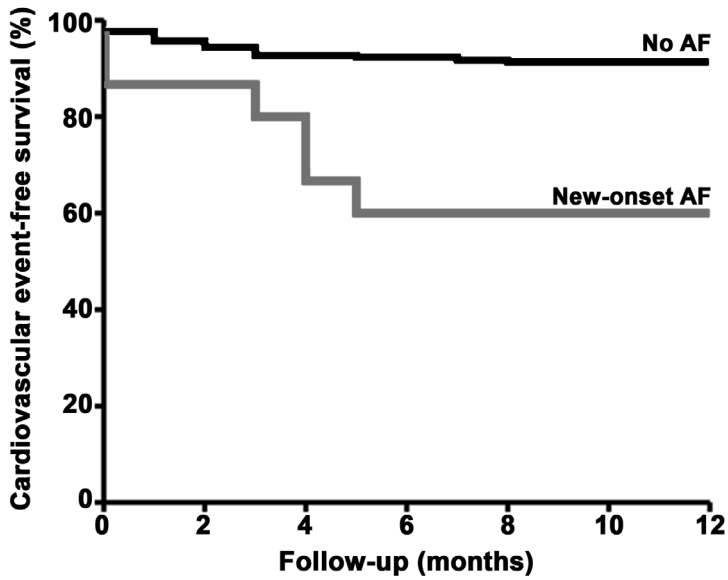
As was found in the current study atrial fibrillation after non-cardiac surgery is often transient and causes little clinical complaints as only 3 /15 (20%) patients required additional medical therapy because of a worsening of heart failure symptoms. It should be appreciated that in the current study nearly all patients were on perioperative beta-blocker therapy and that it was continued after surgery intravenously or as a suppository when oral medication was not feasible. Current guidelines do not provide a clear strategy for asymptomatic transient AF after non-cardiac surgery. As stated in the 2006 ACC/AHA/ESC guidelines administration of AV nodal blocking agents is recommended to achieve rate control in patients who develop postoperative AF[12]. Furthermore it is considered reasonable to (1) restore sinus rhythm by pharmacological cardioversion with ibutilide or direct-current cardioversion in patients who develop postoperative AF as advised for non-surgical patients, (2) administer anti-arrhythmic medications in an attempt to maintain sinus rhythm in patients with recurrent or refractory postoperative AF, as recommended for other patients who develop AF, and (3) administer antithrombotic medication in patients who develop postoperative AF, as recommended for non-surgical patients. Whether these guidelines are also applicable to patients with transient new-onset postoperative AF remains to be investigated.

Limitations

In the present study continuous ECG recordings were only performed for 48 hours after surgery. A prolonged registration could have resulted in an increased number of patients with AF similar to prolonged registrations at the surgical ICU studies. Also, analysis was done off-line, which prevented the assessment of a potential benefit of timely intervention.

Conclusion

New-onset atrial fibrillation after vascular surgery is a common cardiac arrhythmia, often asymptomatic, but associated with a poor perioperative and long-term outcome.



NUMBER AT RISK			
No AF	250	201	146
New-onset AF	9	6	5

Figure 1. Long-term outcome after vascular surgery of patients with new-onset perioperative atrial fibrillation (n=15) and patients without new-onset atrial fibrillation (n=302). Multivariate regression analysis showed that patients with new-onset AF had a four-fold increased risk for late cardiovascular events (HR 4.2, 95%CI 2.1 – 8.8).

References

1. Welten GM, Schouten O, Hoeks SE, Chonchol M, Vidakovic R, van Domburg RT, Bax JJ, van Sambeek MR, Poldermans D. Long-term prognosis of patients with peripheral arterial disease: a comparison in patients with coronary artery disease. Journal of the American College of Cardiology 2008;51(16): 1588-1596.
2. Walsh SR, Tang T, Wijewardena C, Yarham SI, Boyle JR, Gaunt ME. Postoperative arrhythmias in general surgical patients. Annals of the Royal College of Surgeons of England 2007;89(2): 91-95.
3. Valentine RJ, Rosen SF, Cigarroa JE, Jackson MR, Modrall JG, Clagett GP. The clinical course of new-onset atrial fibrillation after elective aortic operations. Journal of the American College of Surgeons 2001;193(5): 499-504.
4. Brathwaite D, Weissman C. The new onset of atrial arrhythmias following major noncardiothoracic surgery is associated with increased mortality. Chest 1998;114(2): 462-468.
5. Christians KK, Wu B, Quebbeman EJ, Brasel KJ. Postoperative atrial fibrillation in noncardiothoracic surgical patients. American journal of surgery 2001;182(6): 713-715.
6. Mitchell LB, Exner DV, Wyse DG, Connolly CJ, Prystai GD, Bayes AJ, Kidd WT, Kieser T, Burgess JJ, Ferland A, MacAdams CL, Maitland A. Prophylactic Oral Amiodarone for the Prevention of Arrhythmias that Begin Early After Revascularization, Valve Replacement, or Repair: PAPABEAR: a randomized controlled trial. Jama 2005;294(24): 3093-3100.
7. Boersma E, Poldermans D, Bax JJ, Steyerberg EW, Thomson IR, Banga JD, van De Ven LL, van Urk H, Roelandt JR. Predictors of cardiac events after major vascular surgery: Role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. Jama 2001;285(14): 1865-1873.
8. Fabbri L, Pauwels RA, Hurd SS. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: GOLD Executive Summary updated 2003. Copd 2004;1(1): 105-141; discussion 103-104.
9. Estes NA, 3rd, Halperin JL, Calkins H, Ezekowitz MD, Gitman P, Go AS, McNamara RL, Messer JV, Ritchie JL, Romeo SJ, Waldo AL, Wyse DG, Bonow RO, DeLong E, Goff DC, Jr., Grady K, Green LA, Hiniker A, Linderbaum JA, Masoudi FA, Pina IL, Pressler S, Radford MJ, Rumsfeld JS. ACC/AHA/Physician Consortium 2008 Clinical Performance Measures for Adults with Nonvalvular Atrial Fibrillation or Atrial Flutter: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and the Physician Consortium for Performance Improvement (Writing Committee to Develop Clinical Performance Measures for Atrial Fibrillation) Developed in Collaboration with the Heart Rhythm Society. J Am Coll Cardiol 2008;51(8): 865-884.
10. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. Eur Heart J 2007;28(20): 2525-2538.
11. Cannon CP, Battler A, Brindis RG, Cox JL, Ellis SG, Every NR, Flaherty JT, Harrington RA, Krumholz HM, Simoons ML, Van De Werf FJ, Weintraub WS, Mitchell KR, Morrisson SL, Brindis RG, Anderson HV, Cannom DS, Chitwood WR, Cigarroa JE, Collins-Nakai RL, Ellis SG, Gibbons RJ, Grover FL, Heidenreich PA, Khandheria BK, Knoebel SB, Krumholz HL, Malenka DJ, Mark DB, McKay CR, Passamani ER, Radford MJ, Riner RN, Schwartz JB, Shaw RE, Shemin RJ, Van Fossen DB, Verrier ED, Watkins MW, Phoubandith DR, Furnelli T. American College of Cardiology key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes. A report of the American College of Cardiology Task Force on Clinical Data Standards (Acute Coronary Syndromes Writing Committee). J Am Coll Cardiol 2001;38(7): 2114-2130.

12. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC, Jr., Jacobs AK, Adams CD, Anderson JL, Antman EM, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Zamorano JL. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). Journal of the American College of Cardiology 2006;48(4): 854-906.
13. Falk RH. Atrial fibrillation. N Engl J Med 2001;344(14): 1067-1078.
14. Hammill BG, Curtis LH, Bennett-Guerrero E, O'Connor CM, Jollis JG, Schulman KA, Hernandez AF. Impact of heart failure on patients undergoing major noncardiac surgery. Anesthesiology 2008;108(4): 559-567.
15. Landesberg G. The pathophysiology of perioperative myocardial infarction: facts and perspectives. Journal of cardiothoracic and vascular anesthesia 2003;17(1): 90-100.
16. Noorani A, Walsh SR, Tang TY, Sadat U, Cooper DG, Callaghan CJ, Varty K, Gaunt ME. Atrial fibrillation following elective open abdominal aortic aneurysm repair. International journal of surgery (London, England) 2009;7(1): 24-27.

5

Prognosis of atrial fibrillation in patients with symptomatic peripheral arterial disease: data from the REduction of Atherothrombosis for Continued Health (REACH) Registry.

European Journal of Vascular and Endovascular Surgery 2010;40(1):9-16

Tamara A. Winkel
Sanne E. Hoeks
Olaf Schouten
Uwe Zeymer
Tobias Limbourg
Iris Baumgartner
Deepak L. Bhatt
Ph. Gabriel Steg
Shinya Goto
Joachim Röther
Patrice P. Cacoub
Hence J.M. Verhagen
Jeroen J. Bax
Don Poldermans
On behalf of the REACH registry investigator

Abstract

Background: Atrial Fibrillation (AF) is a significant risk factor for cardiovascular (CV) mortality. The aim of this study is to evaluate the prognostic implication of AF in patients with peripheral arterial disease (PAD).

Methods: The International Reduction of Atherothrombosis for Continued Health (REACH) Registry included 23 542 outpatients in Europe with established coronary artery disease, cerebrovascular disease (CVD), PAD, and/or ≥ 3 risk factors. Of these, 3753 patients had symptomatic PAD. Cardiovascular risk factors were determined at baseline. Study endpoint was a combination of cardiac death, non-fatal myocardial infarction (MI), and stroke (CV events) during 2 years of follow-up. Cox regression analysis adjusted for age, gender and other risk factors (congestive heart failure, coronary artery revascularization, CABG, MI, hypertension, stroke, current smoking and diabetes) was used.

Results: Of 3753 PAD patients, 392 (10%) were known with AF. Patients with AF were older and had a higher prevalence of CVD, diabetes, and hypertension. Long-term cardiovascular mortality occurred in 5.6% of patients with AF and 1.6% in those without AF ($p<0.001$). Multivariable analyses showed that AF was an independent predictor of late cardiovascular events (HR 1.5; 95% CI 1.09-2.0).

Conclusion: AF is common in European patients with symptomatic PAD and is independently associated with a worse 2-year cardiovascular outcome.

Introduction

Atherothrombosis is a progressive, generalized disorder, that affects large- and medium-sized arteries throughout the arterial tree, with many clinically acute or chronic manifestations [1]. In the peripheral arteries, atherothrombosis can contribute to the progression of peripheral arterial disease (PAD) producing intermittent claudication, as well as ischemic necrosis and, potentially, loss of the limb. Occurrence of an arterial ischaemic event due to atherothrombosis implies that a similar pathological process may already affect other arterial territories [2, 3]. Patients with a first ischemic event are at high risk of developing further atherothrombotic events. The prevalence of additional risk factors, like atrial fibrillation (AF), increases the risk of atherothrombotic events, as shown in the AF sub-study of the REACH Registry [4, 5].

Atrial fibrillation is gaining attention from the medical community as its epidemiological weight is increasing [6]. AF is the most common cardiac arrhythmia in clinical practice, with over 4.5 million in Europe. Most patients with AF are over 65 years of age and present with many co-morbidities, in particular, hypertension (37%), heart failure (23%), coronary artery disease (18%) and diabetes (15%) [7]. The prevalence of AF is estimated to increase due to the aging general population [6, 7]. AF is a major cause of morbidity, being associated with left ventricular dysfunction, decreased exercise tolerance and quality of life [8], as well as a two-fold increased risk in cardiac mortality [7]. In the Copenhagen City Heart Study a 60% increase in hospital admissions for AF independent of changes in known risk factors was reported during the last 10 to 20 years [9]. Much of the morbidity and mortality associated with AF is attributed to the thrombo-embolic complications, resulting in increased risk of cardiovascular death [4], as well as ischaemic stroke [7]. Goto et al. reported worse 1-year cardiovascular events in patients with atherothrombosis and AF [4].

The aim of the analysis in this article was to evaluate the prevalence and prognostic implication of AF among European patients with symptomatic PAD, focusing on risk factor profiles, medication use, and 2-year rates of cardiovascular (CV) death, myocardial infarction (MI), and stroke in AF and non-AF patients. Data were based on the REduction of Atherothrombosis for Continued Health (REACH) Registry, which is a large scale, prospective, international cohort of stable subjects with or at high risk of atherothrombotic complications [3, 10].

Methods

Database of the REACH Registry

Full details of the rationale and design of the REACH Registry have been described elsewhere [10]. In brief, it is an international, prospective, observational registry designed to provide up to 24 months of clinical follow-up of over 68 000 outpatients from approximately 5000 sites in 44 countries; recently extended to provide up to 48 months of clinical follow-up [3]. Patients enrolled were aged 45 years or over with at least one of the following four criteria: documented symptomatic (1) coronary artery disease (CAD; angina, MI, or angioplasty/stent/bypass), (2) cerebrovascular disease (CVD; ischemic stroke, or TIA), (3) peripheral arterial disease (PAD; historical or current intermittent claudication associated with ABI <0.9), or (4) at least three pre-defined atherothrombotic risk factors [10]. Patients already in a clinical trial, hospitalized patients, or those who might have difficulty returning for a follow-up visit were excluded. Subjects were recruited consecutively, mainly by general practitioners (42%) and internists (32%) [3]. They were evaluated at baseline for a range of demographic, medical and laboratory characteristics, prior to being re-evaluated annually for up to 48 months post-baseline to ascertain whether they experienced any clinical events or hospitalizations. The institutional review board in each participating country approved the study design and all patients included in the analysis provided signed, informed consent. In this manuscript we will be focusing on the difference in AF and non-AF patients with symptomatic PAD in the European population, which included 23 542 stable outpatients.

Definition of AF

All patients were classified based on presence or absence of AF, at the time of enrolment [4]. If participating physicians could not confirm whether patients had a history of AF, the patients were classified as “unknown” and excluded from this analysis.

Patients with AF were also stratified using the CHADS2 risk score in which one point is assigned to patients with a history of congestive heart failure, hypertension, diabetes mellitus, age≥75 years, and two points for a history of stroke or transient ischemic attack.[11]

Study outcomes

There were two primary study outcomes. The first was a combined endpoint of non-fatal stroke, non-fatal MI, and cardiovascular death assessed at 21 ± 3 months from enrolment. The second was a combined endpoint of cardiovascular death, non-fatal stroke, non-fatal MI, vascular interventions, and hospitalizations for atherothrombotic events at two years of follow-up. The limb outcome and individual clinical events described constituted the pre-defined secondary endpoints of the study. Events were not adjudicated; however, reports of ischemic stroke and TIA had to be sourced from a neurologist or hospital to ensure a reliable diagnosis.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) compared using the Mann-Whitney-Wilcoxon test. Categorical variables are expressed as numbers and percentages and analyzed using the $\chi 2$ test. A p-value of less than 0.01 was considered statistically significant (for tables 1, 2 and 3) and no allowance for multiple hypothesis testing was made. The relationship between a history of AF and the combined endpoint at 2-years of follow-up was assessed with multivariate Cox regression analyses, correcting for age, gender, and risk factors (congestive heart failure, coronary artery revascularization, CABG, MI, hypertension, stroke, current smoking and diabetes). Hazard Ratios (HR) are given with 95% confidence intervals (CI). A p-value of less than 0.05 (two-sided) was considered significant. All analyses were performed using SAS v.9 statistical software (SAS Institute Inc, Cary, NC).

Results

The study population consisted of 23 542 European patients with atherothrombosis. Of these, 3753 patients had symptomatic PAD. Baseline information regarding a history of AF was available from 3655 patients and represents the analysis sample. The baseline characteristics and medication use are listed in **Table 1**. The mean age at baseline was 67.7 ± 9.6 years and 75.1% of the PAD patients were male. The prevalence of AF in the PAD patient group was 10.4% (n= 392). Patients with AF were significantly older, more often had a history of angina pectoris, myocardial infarction, ischemic stroke, transient ischemic attack (TIA), congestive heart failure (CHF), aortic valve stenosis, CVD, diabetes, hypertension, and included a lower prevalence of smokers.

In general, patients with AF received more medication as compared to those without AF. Use of antithrombotics was high among patients with AF, with approximately 96% receiving at least one antithrombotic agent. Significantly more patients with AF used non-steroid anti-inflammatory drugs, beta-blockers, nitrates, diuretics, and ACE-inhibitors. There were no differences between statin and calcium channel blocker use in AF versus non-AF patients. Approximately half (52.3%) of the patients with AF were treated with oral anticoagulants and 42.6% received aspirin (**Table 1**). As is shown in **Table 2**, patients with a history of AF and no use of anticoagulant agents more often had a history of current smoking.
Also in the current analyses it was calculated that patients with AF had a significantly higher CHADS2 risk score as compared to those without AF (mean CHADS2 score in AF versus non-AF patients; 2.1 ± 1.4 versus 1.9 ± 1.3, general linear model $p<0.001$).

Study outcomes
As shown in **Table 3**, the presence of AF at baseline was associated with higher rates of 2-year adverse CV outcomes (combined CV death, MI, and stroke). The all-cause (7.7%) and CV mortality (5.6%) rates of patients with AF were substantially higher than in non-AF patients (2.5% and 1.6% respectively; p-

value<0.001). In the two years after the baseline visit, there was a significantly higher incidence of congestive heart failure (16.8% versus 5.1%, respectively), unstable angina (11.6% versus 7.0%, respectively), and bleeding requiring hospitalization and transfusion (2.7% versus 1.4%, respectively) in patients with AF compared to those without AF. Worsening of claudication related to PAD was not more evident in the AF versus non-AF patients (27.1% versus 27.4%, p=0.89, respectively). On the other hand, during the 2-year follow-up period patients with AF more often underwent amputations affecting the lower limb as compared to those without AF (4.8% versus 2.1%, p<0.01, respectively). There were no differences between the two groups in combined endpoint and/or revascularization during follow-up (patients with AF 27.1% versus non-AF 23.7%, p=0.13, respectively).

The combined endpoint of CV events occurred in 49 (12.5%) patients with a previous history of AF and 196 (6.0%) patients in those without AF (**Table 3**). Patients with AF also had a higher incidence of the CV events and/or hospitalization for atherothrombotic events than those without AF (37.0% versus 25.5%, p-value<0.001, **Table 3**). As shown in **Figure 1**, the presence of AF at baseline was associated with a significantly higher rate of CV events during two years of follow-up. In multivariable analyses, after adjusting for age, gender and risk factors, AF was an independent predictor of long-term CV events (HR 1.48; 95% CI 1.09-2.02, **Table 4**). Other risk factors that were associated with 2-year CV events were: age, diabetes, congestive heart failure, current smoking and stroke.

Discussion

This study demonstrates that AF is a common condition in European patients with symptomatic PAD and could indicate patients with extensive atherothrombosis. Furthermore, AF is an independent predictor of late adverse outcome with a 1.5-fold increase of cardiovascular mortality in patients with PAD.

Incidence, prevalence, and risk factors associated with AF

The prevalence of AF is 0.4% to 1% in the general population [6, 12]. In the coming years this prevalence will likely increase due to the ageing of the general population, a rising prevalence of cardiovascular disease, and more frequent diagnosis of AF through use of more specific ambulatory monitoring devices [7]. Furthermore, it has to be noticed that the prevalence of AF is an underestimation of this type of arrhythmia since a great proportion of patients are asymptomatic [7]. The ATRIA study assembled a contemporary cohort of 17 974 patients with non-transient AF and found that AF affects 1 in 25 adults 60 years or older and nearly 1 in 10 adults 80 years or older [6]. However, in patients with established atherothrombotic disease, like PAD [13, 14], the prevalence and incidence of AF is likely higher [7, 15], as previously demonstrated in the AF sub-study of the REACH Registry [4]. This high prevalence of AF in PAD patients is also confirmed in the current European focused AF sub-study as we observed a prevalence of 10.4%. When comparing the baseline characteristics of the ATRIA study [6] and the REACH Registry population, it is evident that the current patients have more atherothrombotic risk factors. These data supported the concept that the prevalence of AF is higher in patients with symptomatic atherothrombosis [4]. This process could also be vise versa i.e. due to acute thromboembolic occlusions or progression of the atherothrombotic process which enhances the obstruction of blood flow to the peripheral arteries and could cause intermittent claudication [2, 16]. However, it is hard to define which process precedes the other since these will often be present simultaneously. The Framingham heart study demonstrated that gender, age, diabetes, hypertension, congestive heart failure, and cardiac valve disease were independent risk factors for AF [17]. Previous studies have also

identified non-cardiac precipitants for AF, e.g. obesity [18, 19], thyrotoxicosis [20-22], alcohol use [20, 23], severe infections [20, 24], and pulmonary pathology [20-22]. These general and pathophysiology risk factors have also been confirmed in the current data, where PAD patients with AF were significantly older, more often had a history of angina pectoris, myocardial infarction, congestive heart failure, aortic valve stenosis, CVD, diabetes, and hypertension.

Identification of AF patients at increased risk of adverse outcome

Patients with lone AF were initially thought to have a good prognosis with respect to thromboembolism and mortality, but more recent data suggest that it is associated with higher mortality [6, 24]. Our data, along with previously published AF sub-study of the REACH Registry [4], demonstrated that AF is an independent predictor of long-term CV events in patients with PAD. Goto et al. assessed the distribution of the CHADS2[11] score in patients with and at high risk of atherothrombosis and its relation to cerebrovascular outcomes [11, 25]. They concluded that in patients with AF, CV events, especially non-fatal stroke, and the combined end point of CV death/MI/stroke, were more frequent in the higher CHADS2 score subgroup (the rate of CV death/MI/stroke varied from 3.9% in the CHADS2 score 0 group to 12.4% in the CHADS2 score 6 group) [4]. In the current study the calculated CHADS2 risk score was also significantly differing between the two groups, with a higher CHADS2 score in those patients with AF as compared to those without AF.

Management of patients with AF

Managing patients with AF and the associated conditions is a major challenge. Restoration and maintenance of sinus rhythm in patients with AF is clearly an important therapeutic goal [26], in combination with antithrombotic therapy to decrease the rate of embolic complications caused by AF. The efficacy, safety, and shortcomings of current antithrombotic therapies for patients with AF are an ongoing discussion. Recent clinical trials comparing rhythm and rate control have suggested that effective anticoagulation and heart rate control is not inferior to rhythm control [6, 26]. Current guidelines recommend warfarin for patients who have

AF and are at risk of stroke [7]. The combination of antiplatelet and anticoagulant therapy (triple therapy) is often used in patients with established atherothrombotic disease and AF [7, 27]. However, the WAVE trial randomized patients with PAD to receive oral anticoagulant (OAC) plus antiplatelet therapy or antiplatelet therapy alone and found that the combination of an OAC and antiplatelet therapy was not more effective than antiplatelet therapy alone in preventing major cardiovascular complications and was associated with an increase in life-threatening bleeding [28, 29]. The use of combined therapy is expected to become more prominent, yet is also associated with a significantly increased bleeding risk [27]. The rate of major bleeding complications may be kept acceptably low even in elderly AF patients, provided a careful management of anticoagulation [30]. Our data, however, show that only half of PAD patients with AF received oral anticoagulants. This confirms earlier studies showing an under treatment in AF patients [3, 4]. In the study from REACH on patients with AF in the global population by Goto et al., the use of oral anticoagulants was low even in patients at high risk of stroke [4]. An explanation for this low use of oral anticoagulants in the REACH population was coupled to the markedly high background use of antiplatelet agents [4]. In the current results of the REACH data, 2-year CV-outcomes confirms that patients with AF more often had bleeding requiring hospitalization, which could be speculated to be associated with using combined therapy.

In a more recent non-inferiority trial by Connolly et al. the new oral direct thrombin inhibitor dabigatran, administered at a dose of 150 mg in patients with AF, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage as compared with warfarin [31]. These results could likely increase the intake of these new thrombin inhibitors since these are less cumbersome than vitamin-K antagonists [31].

Patients with PAD should receive beta-blockers, statins, and most commonly an antiplatelet agent [32]. However, as is also shown in the current study patients with PAD are largely under treated.

Limitations

There are several limitations to these data. Firstly, there are no data on the classification of AF (paroxysmal, persistent, or chronic), duration of AF, or use of antiarrhythmic agents available. The specification of the AF classification could partly help explain the therapeutic regiments. Furthermore, no laboratory markers were tested at baseline, which could have helped to make more specifications in a predictive model for risk factors for AF, e.g. inflammation markers and N-terminal pro-B-type Natriuretic Peptide. Also, due to the exclusion of patients without an apparent or certain history of AF by participating physicians it could well be that patients with AF and PAD have been excluded these analyses, with the possibility of underestimating the true prevalence of AF in European PAD patients.

Conclusion

Atrial fibrillation is common in European patients with symptomatic peripheral arterial disease and is independently associated with a worse 2-year cardiovascular outcome. Current guidelines for AF management should be observed to manage the increased risk of cardiovascular morbidity and mortality.

Table 1. Baseline characteristics.

	With AF n=392	Without AF n=3263	p-value
Age, years	71.6 ± 9.1	67.2 ± 9.6	<0.001
Female, %	25.6	24.8	0.74
BMI (kg/m^2)	27.4 ± 4.4	27.1 ± 4.5	0.29
Current smoker, %	18.6	29.2	<0.001
Previous history of			
Smoking, %	65.0	78.2	<0.001
Stable angina, %	40.4	27.2	<0.001
Unstable angina, %	15.6	9.8	<0.001
Myocardial Infarction, %	33.2	24.9	<0.001
Coronary angioplasty/stenting, %	20.5	16.3	<0.05
Coronary artery bypass graft, %	19.6	15.5	<0.05
TIA, %	20.2	13.5	<0.001
Ischemic stroke, %	19.0	14.1	<0.01
Diabetes, %	43.4	36.5	<0.01
Hypertension (despite therapy for minimally 3 months), %	61.0	52.0	<0.001
Hypercholesterolemia (in treatment), %	60.2	64.9	0.07
Congestive heart failure, %	43.5	11.2	<0.001
Aortic valve stenosis, %	11.2	3.5	<0.001
Asymptomatic carotid stenosis (≥70%), %	22.9	15.1	<0.01
Carotid surgery, %	7.2	6.6	0.65
Abdominal aortic aneurysm, %	8.9	6.0	<0.05
Previous history of PAD			
ABI < 0.9, %	89.5	90.2	0.70
Lower limb graft, %	46.4	51.0	0.09
Lower limb amputation, %	11.2	10.8	0.78
Medications			
ASA, %	42.6	61.5	<0.001
Other antiplatelet agent, %	20.2	34.4	<0.001
ASA and other antiplatelet agent, %	7.9	10.8	0.08
Oral anticoagulants, %	52.3	10.1	<0.001
At least 1 antithrombotic agent, %	95.9	92.1	<0.01
Oral anticoagulant and ASA, %	8.4	2.5	<0.001
NSAIDs, %	13.0	7.5	<0.001
Statins, %	60.7	62.6	0.47
Calcium channel blockers, %	31.1	33.0	0.45
Beta blockers, %	48.0	38.3	<0.001
Nitrates, %	34.7	21.4	<0.001
Diuretics, %	62.8	40.1	<0.001
ACE-Inhibitors, %	73.0	60.6	<0.001

TIA= Transient Ischemic Attack, PAD= Peripheral Arterial Disease, ABI= Ankle Brachial Index, ASA= Acetyl Salicylic Acid, NSAID= Non-Steroidal Anti-Inflammatory Drug, ACE= Angiotensin Converting Enzyme, BMI= Body Mass Index

Table 2. Comparison between patients with atrial fibrillation and the use of oral anticoagulants.

	AF + Yes anticoagulants n=222	**AF + No anticoagulants n=205**	**p-value**
Age, years	72.3 ± 8.6	71.4 ± 9.6	0.17
Female, %	27.5	22.5	0.24
BMI (kg/m^2)	27.4 ± 4.3	27.2 ± 4.5	0.45
Current smoker, %	12.0	27.7	<0.001
Previous history of			
Smoking, %	51.4	40.5	<0.05
Stable angina, %	35.9	42.8	0.15
Unstable angina, %	19.6	13.0	0.07
Myocardial Infarction, %	32.9	34.5	0.73
Coronary angioplasty/stenting, %	21.3	19.5	0.65
Coronary artery bypass graft, %	19.9	19.5	0.92
TIA, %	20.5	19.5	0.79
Ischemic stroke, %	22.1	15.8	0.10
Hypertension (despite therapy for minimally 3 months), %	58.1	63.4	0.26
Hypercholesterolemia (in treatment), %	56.8	60.5	0.43
Congestive heart failure, %	47.5	36.9	<0.05
Aortic valve stenosis, %	11.2	10.8	0.91
Asymptomatic carotid stenosis (≥70%), %	22.2	21.5	0.89
Carotid surgery, %	7.2	7.4	0.95
Abdominal aortic aneurysm, %	7.3	9.6	0.43
Previous history of PAD			
ABI < 0.9, %	89.3	89.7	0.91
Lower limb graft, %	50.0	42.4	0.12
Lower limb amputation, %	11.7	12.2	0.88
Medications			
ASA, %	16.2	70.7	<0.001
Other antiplatelet agent, %	9.5	32.2	<0.001
Oral anticoagulants, %	100	0	
At least 1 antithrombotic agent, %	100	91.2	<0.001
NSAIDs, %	9	17.1	<0.05
Statins, %	59.0	59.0	1.00
Calcium channel blockers, %	28.4	35.6	0.11
Beta blockers, %	46.8	44.4	0.61
Nitrates, %	32.0	40.5	0.07
Diuretics, %	66.2	60.0	0.18
ACE-Inhibitors, %	59.9	56.6	0.49

TIA= Transient Ischemic Attack, PAD= Peripheral Arterial Disease, ABI= Ankle Brachial Index, ASA= Acetyl Salicylic Acid, NSAID= Non-Steroidal Anti-Inflammatory Drug, ACE= Angiotensin Converting Enzyme, BMI= Body Mass Index

Table 3. Long-term clinical outcome (2-year follow-up).

	Yes AF n=392	No AF n=3263	p-value
Cardiovascular death, %	5.6	1.6	<0.001
Non-fatal stroke, %	4.1	2.8	0.16
Non-fatal MI, %	4.6	1.8	<0.001
CV events	12.5	6.0	<0.001
CV events and hospitalization	37.0	25.5	<0.001

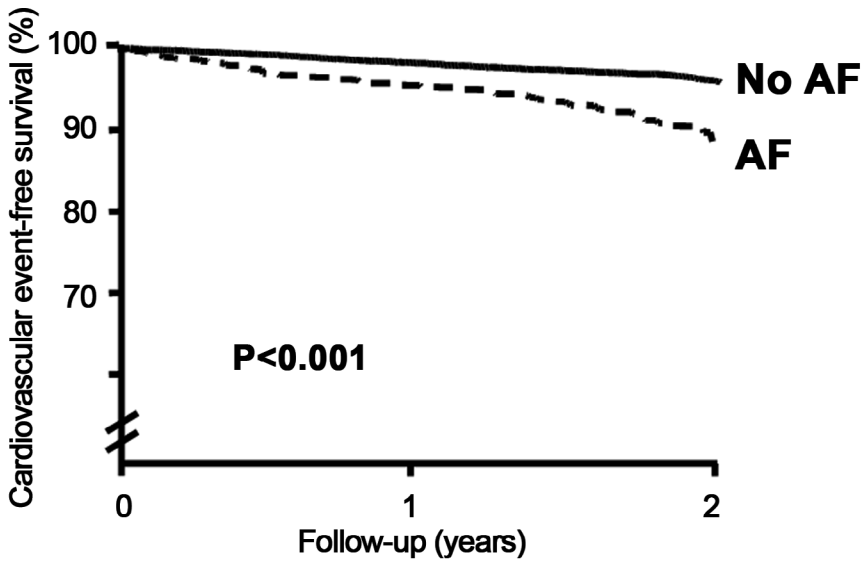
MI= Myocardial Infarction

Combined endpoint= cardiovascular (CV) events (cardiovascular death, non-fatal stroke, non-fatal MI)

Table 4. Multivariate analyses for long-term cardiovascular (CV) events, adjusting for age, gender and risk factors (diabetes, hypertension, congestive heart failure, coronary artery revascularization, CABG, stroke, current smoking and myocardial infarction).

	Hazard Ratio (95% Confidence Interval)
Atrial Fibrillation	1.48 (1.09 – 2.02)
Age	1.03 (1.01 – 1.04)
Female	0.98 (0.75 – 1.28)
Diabetes	1.44 (1.14 – 1.82)
Hypertension	1.06 (0.78 – 1.45)
Congestive Heart Failure	1.73 (1.30 – 2.30)
Coronary angioplasty/stenting	0.76 (0.54 – 1.08)
CABG	1.13 (0.81 – 1.57)
Ischemic stroke	2.20 (1.70 – 2.84)
Myocardial Infarction	1.25 (0.94 – 1.67)
Current smoking	1.43 (1.09 – 1.88)

Figure 1: CV events (cardiovascular death, MI, and stroke) occurred in 12.5% of PAD patients with AF compared to 6.0% in those without AF (p<0.001).



References

1. Conway DS, Lip GY. Comparison of outcomes of patients with symptomatic peripheral artery disease with and without atrial fibrillation (the West Birmingham Atrial Fibrillation Project). Am J Cardiol 2004;93(11):1422-5, A10.
2. Drouet L. Atherothrombosis as a systemic disease. Cerebrovasc Dis 2002;13 Suppl 1:1-6.
3. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA 2006;295(2):180-9.
4. Goto S, Bhatt DL, Rother J, et al. Prevalence, clinical profile, and cardiovascular outcomes of atrial fibrillation patients with atherothrombosis. Am Heart J 2008;156(5):855-63, 63 e2.
5. Montalescot G. Value of antiplatelet therapy in preventing thrombotic events in generalized vascular disease. Clin Cardiol 2000;23 Suppl 6:VI-18-22.
6. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. Jama 2001;285(18):2370-5.
7. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). J Am Coll Cardiol 2006;48(4):854-906.
8. Lane DA, Lip GY. Quality of life in older people with atrial fibrillation. J Interv Card Electrophysiol 2009;25(1):37-42.
9. Friberg J, Buch P, Scharling H, Gadsbphioll N, Jensen GB. Rising rates of hospital admissions for atrial fibrillation. Epidemiology 2003;14(6):666-72.
10. Ohman EM, Bhatt DL, Steg PG, et al. The REduction of Atherothrombosis for Continued Health (REACH) Registry: an international, prospective, observational investigation in subjects at risk for atherothrombotic events-study design. Am Heart J 2006;151(4):786 e1-10.
11. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. Jama 2001;285(22):2864-70.
12. Frykman V, Frick M, Jensen-Urstad M, Ostergren J, Rosenqvist M. Asymptomatic versus symptomatic persistent atrial fibrillation: clinical and noninvasive characteristics. J Intern Med 2001;250(5):390-7.
13. Cacoub PP, Bhatt DL, Steg PG, Topol EJ, Creager MA. Patients with peripheral arterial disease in the CHARISMA trial. Eur Heart J 2009;30(2):192-201.
14. Steg PG, Bhatt DL, Wilson PW, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. Jama 2007;297(11):1197-206.
15. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. Arch Intern Med 1995;155(5):469-73.
16. Ouriel K. Peripheral arterial disease. Lancet 2001;358(9289):1257-64.
17. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. Jama 1994;271(11):840-4.
18. Dublin S, French B, Glazer NL, et al. Risk of new-onset atrial fibrillation in relation to body mass index. Arch Intern Med 2006;166(21):2322-8.
19. Frost L, Hune LJ, Vestergaard P. Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. Am J Med 2005;118(5):489-95.
20. Aberg H. Atrial fibrillation. A review of 463 cases from Philadelphia General Hospital from 1955 to 1965. Acta Med Scand 1968;184(5):425-31.
21. Davidson E, Weinberger I, Rotenberg Z, Fuchs J, Agmon J. Atrial fibrillation. Cause and time of onset. Arch Intern Med 1989;149(2):457-9.
22. Petersen P, Godtfredsen J. Atrial fibrillation--a review of course and prognosis. Acta Med Scand 1984;216(1):5-9.
23. Mukamal KJ, Tolstrup JS, Friberg J, Jensen G, Gronbaek M. Alcohol consumption and risk of atrial fibrillation in men and women: the Copenhagen City Heart Study. Circulation 2005;112(12):1736-42.

24. Kozlowski D, Budrejko S, Lip GY, et al. Lone Atrial Fibrillation - What Do We Know? Heart 2009.
25. Laguna P, Martin A, Del Arco C, Millan I, Gargantilla P. Differences among clinical classification schemes for predicting stroke in atrial fibrillation: implications for therapy in daily practice. Acad Emerg Med 2005;12(9):828-34.
26. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 2008;358(25):2667-77.
27. Holmes DR, Jr., Kereiakes DJ, Kleiman NS, Moliterno DJ, Patti G, Grines CL. Combining antiplatelet and anticoagulant therapies. J Am Coll Cardiol 2009;54(2):95-109.
28. Anand S, Yusuf S, Xie C, et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. N Engl J Med 2007;357(3):217-27.
29. The effects of oral anticoagulants in patients with peripheral arterial disease: rationale, design, and baseline characteristics of the Warfarin and Antiplatelet Vascular Evaluation (WAVE) trial, including a meta-analysis of trials. Am Heart J 2006;151(1):1-9.
30. Poli D, Antonucci E, Grifoni E, Abbate R, Gensini GF, Prisco D. Bleeding risk during oral anticoagulation in atrial fibrillation patients older than 80 years. J Am Coll Cardiol 2009;54(11):999-1002.
31. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361(12):1139-51.
32. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation 2006;113(11):e463-654.

6

Aortic surgery complications evaluated by an implanted continuous electrocardiography device: a case report.

submitted

Tamara A. Winkel
Jan-Peter van Kuijk
Ellen V. Rouwet
Michiel T. Voûte
Mirko de Melis
Hence J.M. Verhagen
Don Poldermans

Abstract

Introduction: Cardiac arrhythmias are a major cause for morbidity and mortality in patients undergoing non-cardiac vascular surgery.

Report: An implantable loop recorder (Reveal® XT) was used for continuous heart rhythm monitoring to detect perioperative arrhythmias in a 69-year-old man undergoing major vascular surgery for an infected aortobifemoral prosthesis. The Reveal® detected several episodes of asymptomatic new-onset atrial fibrillation postoperatively, associated with elevated serum levels of troponin-T and NT-proBNP.

Discussion: Continuous heart rhythm monitoring with assessment of serum cardiac biomarkers allows early identification and treatment of patients at high risk of perioperative cardiovascular complications, in particular cardiac arrhythmias.

Introduction

Cardiovascular complications are a major cause for morbidity and mortality in vascular surgery patients.[1] In addition to ischemic complications, up to 20% of patients develop cardiac arrhythmias postoperatively, of which atrial fibrillation (AF) is the most common form. Consequences of cardiac arrhythmias include sudden cardiac death, congestive heart failure (CHF), and stroke.[2] Due to their asymptomatic and atypical character, the majority of these perioperative arrhythmias are missed, and, hence, undertreated.[2] We hypothesize that continuous heart rhythm monitoring can identify patients with cardiac arrhythmias, and present the relation with cardiac serum biomarkers in this case report.

Case report

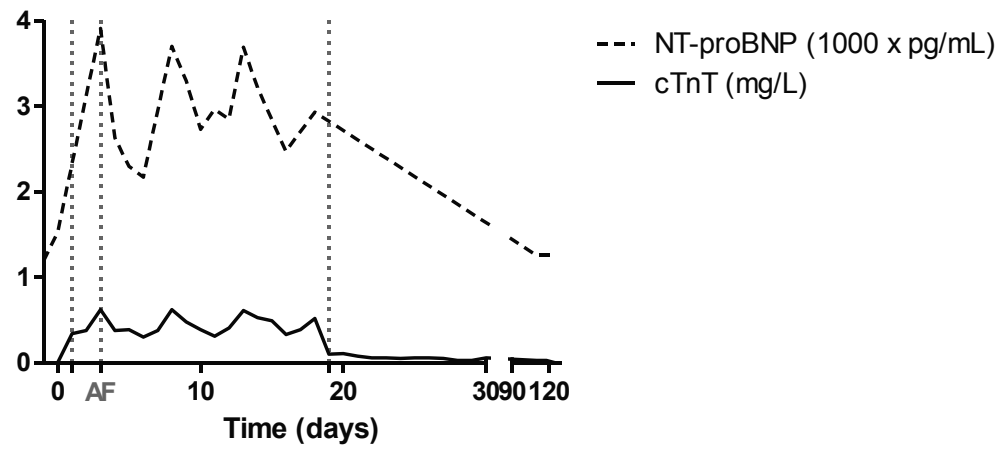
A 69-year old man presented with an infected prosthetic aortobifemoral graft. His medical history was positive for cardiovascular risk factors, including diabetes, hypertension, coronary artery reconstruction, and an aortic bifurcation graft for occlusive arterial disease. He was admitted with fever and blood cultures positive for Streptococcus anginosus. CT-angiography revealed an intimate connection between the aortic graft and the duodenum accompanied by fluid collections, consistent with prosthesis infection. The decision was made to remove the infected graft. The patient had no history of arrhythmias and at preoperative work-up, his ECG showed normal sinus rhythm (SR). Dobutamine echocardiography demonstrated a reduced left ventricular ejection fraction (LVEF 30-40%), septal hypokinesia, no stress-inducible ischemia. Preoperative serum cardiac troponin-T (cTnT) was within normal limits, whereas n-terminal pro-b-type natriuretic peptide (NT-proBNP) was elevated (1191 pg/mL).

Two days prior to surgery, an implantable loop recorder (ILR; Reveal® XT, Medtronic Inc., Minneapolis, MN) was implanted subcutaneously for continuous heart rhythm monitoring. To detect myocardial ischemia continuous 12-lead ECG monitoring (Holter) was performed. Prior to surgery the Reveal® device was read, showing no arrhythmias. The infected aortic prosthesis was removed with venous patch angioplasty of the common femoral arteries. Since there were no signs of

acute limb ischemia, in the presence of partially patent iliac arteries, no central reconstruction was performed during the index procedure.
The first day after surgery, the patient developed new-onset paroxysmal AF, not responding to chemical cardioversion with amiodarone. He was converted electrically, after removal of the Holter monitor, at days 1 and 3 after surgery. At the end of day 3, the patient developed peritonitis requiring a relaparotomy with partial duodenectomy and duodenojejunostomy. After a prolonged septic period and ICU stay, the patient eventually recovered. Due to ongoing ischemia of the right foot, a below the knee amputation was performed 4 months after the index procedure.

Although postoperative Holter and standard 12-lead ECG recording showed no signs of myocardial ischemia, serum levels of cTnT peaked at days 3, 8, 13, and 18 postoperatively to a maximum of 0.62 µg/L in the absence of chest pain (**Figure 1**). Postoperative levels of NT-proBNP showed a similar pattern. Interestingly, Reveal® showed that episodes of AF were paralleled by peaks in serum cTnT and NT-proBNP levels. The last episode of paroxysmal AF was detected 19 days after the index surgery and the patient returned to SR afterwards. Despite electrical cardioversion, the Reveal® recordings remained of good quality.

Figure 1. Perioperative biomarker measurement and detection of AF.



Discussion

This case shows that continuous heart rhythm monitoring has excellent recording quality and will improve the detection of perioperative arrhythmias.

The incidence of arrhythmias depends on the type of cardiac monitoring, with better estimates being obtained using continuous monitoring. In a study by Mathew et al., it was noted that continuous ECG monitoring diagnoses 76.8% of perioperative arrhythmias, whereas intermittent 12-lead ECG or physical examination detect only 17.5% and 12.8%, respectively.[5] In our case, continuous monitoring was performed with an ILR. The Reveal® device is easily implanted in a subcutaneous pocket in a left parasternal position at the level of the 4th or 5th intercostal space, in less than 30 minutes. The device can be left in situ up to three years after implantation and sustains electrocardioversion.

Strikingly, the episodes of AF were paralleled with increased levels of cTnT and NT-proBNP. With respect to the underlying pathophysiological mechanism we suggest that subclinical myocardial ischemia, as revealed by increased serum cTnT, induces cardiomyocyte contractile dysfunction resulting in cardiomyocyte stretch and release of NT-proBNP. Furthermore, cardiomyocyte stretch is associated with myocyte depolarization during diastole, changing the action potential and causing abnormal impulses by stretch-activated channel currents, which may trigger arrhythmias.[5] Transient and asymptomatic new-onset AF during vascular surgery has been shown to be associated with a five-fold increased risk for perioperative and long-term cardiovascular events.[1]

In conclusion, continuous heart rhythm monitoring with assessment of cardiac biomarkers allows early identification and treatment of patients at high risk of perioperative cardiovascular complications, in particular cardiac arrhythmias.

References

1. Schouten O, Hoeks SE, Goei D, Bax JJ, Verhagen HJ, Poldermans D. Plasma N-terminal pro-B-type natriuretic peptide as a predictor of perioperative and long-term outcome after vascular surgery. *J Vasc Surg*. 2009;49:435-41; discussion 41-2.
2. Winkel TA, Schouten O, Hoeks SE, Verhagen HJ, Bax JJ, Poldermans D. Prognosis of transient new-onset atrial fibrillation during vascular surgery. *Eur J Vasc Endovasc Surg*. 2009;38:683-8.
3. Lorentzen JE, Nielsen OM, Arendrup H, Kimose HH, Bille S, Andersen J, et al. Vascular graft infection: an analysis of sixty-two graft infections in 2411 consecutively implanted synthetic vascular grafts. *Surgery*. 1985;98:81-6.
4. Boersma E, Poldermans D, Bax JJ, Steyerberg EW, Thomson IR, Banga JD, van De Ven LL, van Urk H, Roelandt JR. Predictors of cardiac events after major vascular surgery: Role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. *JAMA* 2001;285(14): 1865-1873.
5. Mathew J, Hunsberger S, Fleg J, Mc Sherry F, Williford W, Yusuf S. Incidence, predictive factors, and prognostic significance of supraventricular tachyarrhythmias in congestive heart failure. Chest 2000;118(4):914-22.

7

Perioperative heart rate variability and the prognosis of vascular surgery patients.

submitted

Tamara A. Winkel
Olaf Schouten
Sanne E. Hoeks
Michiel T. Voûte
Niels Ravensbergen
Roger Kessels
Mirko de Melis
Michel Chonchol
Hence J.M. Verhagen
Jeroen J. Bax
Don Poldermans

Abstract

*Objectives***:** This study sought to examine whether perioperative measurements of heart rate variability (HRV) add additional prognostic information to an established cardiac risk index for cardiovascular outcome in vascular surgery patients.

Background: A depressed HRV is a predictor of mortality after acute myocardial infarction (MI). Vascular surgery patients are at increased risk of cardiovascular morbidity and mortality due to underlying coronary artery disease. However, in the perioperative setting these cardiovascular events are often atypical and/or asymptomatic. Perioperative cardiac screening of vascular surgery patients using cardiac troponin T (cTnT) and continuous 12-lead electrocardiography (ECG) monitoring might help to timely identify asymptomatic patients experiencing a postoperative cardiac event. The clinical and prognostic value of HRV in patients undergoing non-cardiac vascular surgery is ill-defined.

Methods: In a prospective study of 495 vascular surgery patients, cardiac risk factors, and medication use were assessed preoperatively. New-onset cardiac arrhythmias, myocardial ischemia and HRV were assessed by 72-hour ECG monitoring, starting 1 day before to 2 days after surgery. Troponin T was measured on postoperative day 1, 3, 7, and before discharge. Cardiovascular events included cardiac death, non-fatal MI, unstable angina, and stroke at 30 days and long-term follow-up (median 2.4 years).

Results: A total of 44 (9%) and 91 (18%) of patients developed a cardiovascular event at 30-day and during the follow-up period. Multivariate analysis revealed that depressed HRV measurements (SDNN: the standard deviation of all normal R-R intervals) were correlated with 30-day (odds ratio [OR] 1.03, 95% confidence interval [CI] 1.01 to 1.08) and long-term cardiac events (hazard ratio [HR] 1.02, 95% CI 1.01 to 1.04), irrespective of the cardiac risk score, preoperative cardioprotective therapy, and type of surgery.

Conclusions: Perioperative decrease in HRV is an independent predictor of 30-day and late cardiovascular events in patients undergoing non-cardiac vascular surgery. Perioperative continuous ECG monitoring, with calculation of the HRV, helps to identify this high-risk group at increased risk of cardiovascular events.

Introduction

Cardiovascular complications are a major cause of morbidity and mortality in patients undergoing non-cardiac vascular surgery[1]. Several preoperative cardiac risk stratification scores use only patient's prior medical history and the preoperative clinical status to predict morbidity and mortality or to identify those with the need for preoperative stress testing[2-3]. However, the patient's outcome not only depends on preoperative risk factors and type of surgical procedure performed, but also on perioperative events occurring within 30 days after surgery[4] (e.g. new-onset cardiac arrhythmias and myocardial ischemia). However, in the perioperative setting it is difficult to rely on the patient's symptoms for the detection of cardiac events as symptoms might very well be atypical, clinically silent, transient, unpredictable or absent, secondary to residual anaesthetic effects, administration of analgesic agents and competing somatic stimuli such as incisional pain[5].

Postoperative cardiac screening of vascular surgery patients using cardiac troponin T (cTnT) and their prognostic values have been shown in several studies[6-7]. In addition to biomarker measurements the use of continuous 12-lead electrocardiography (ECG) monitoring might also help to identify asymptomatic patients experiencing a perioperative cardiac event. ECG monitoring is most often used to identify cardiac arrhythmias and myocardial ischemia, however, the heart rate variability (HRV), provides a vast amount of additional data on the overall health of the cardiac muscle. By starting the ECG recording preoperatively and in an on-line fashion patient's at high-risk for preoperative arrhythmia, ischemia, HRV change and consequently cardiovascular events could de timely identified. HRV is a quantitative marker for the sympathetic and vagal activity. Depressed HRV as a parameter of the patient's autonomic function was shown to be another predictor of future cardiac events (e.g. cardiac death, congestive heart failure, and all-cause mortality) in patients with acute myocardial infarction (MI) and unstable angina[8]. Because depressed HRV and increased heart rate may trigger ischemic events, an improvement of the HRV by use of beta-blockers may be a potential mechanism of

cardioprotection.[6] However, the prognostic value of HRV in surgical patients has been evaluated only in a small number of patients as a predictor of short-term[9] and one-year mortality[4].

Therefore, we conducted the current study to examine whether perioperative measurements of HRV provide additional prognostic information to an established cardiac risk index for cardiovascular outcome in vascular surgery patients.

Methods

Study population

The study population consisted of 495 patients undergoing vascular surgery at the Erasmus Medical Center in Rotterdam, the Netherlands, during the period December 2004 to March 2010. Patients with a history of cardiac arrhythmias, cardiac pacemaker or implantable cardioverter defibrillator, preoperative cTnT release and procedures that precluded continuous ECG monitoring were excluded. The hospital's ethical committee approved the study.

Preoperative cardiovascular screening

We determined the cardiac risk score for each patient in our dataset, and one point was assigned to each of the following characteristics: advanced age (>70 years), angina pectoris (AP), history of MI, congestive heart failure (CHF), stroke (transient ischemic attack [TIA] and/or cerebral vascular accident [CVA]), diabetes mellitus (fasting glucose level ≥7.0 mmol/L or use of insulin or oral glucose lowering medication), and renal dysfunction (serum creatinine level > 170 μmol/L). Based on the number of these risk factors, patients were stratified into low-risk (no cardiac risk factors), intermediate-risk (1 or 2 risk factors), and high-risk (≥ 3 risk factors) categories.[2] All patients were screened for hypertension (blood pressure ≥140/90 mmHg or blood pressure lowering medication), hypercholesterolemia (plasma cholesterol level ≥5.5 mmol/L or use of cholesterol-lowering medication), smoking status, and chronic obstructive pulmonary disease (COPD). Left ventricular ejection fraction (LVEF) was calculated preoperatively using a transthoracic echocardiogram (handheld Acuson Cypress Ultrasound System with a 7V3c transducer)[11-12]. Venous blood samples for C-Reactive Protein (CRP), cardiac troponin T (cTnT), and N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP) were routinely performed at the outpatient clinic. In all patients guidelines for perioperative cardiac care were followed for perioperative cardiac management[13].

ECG monitoring

Patients were continuously monitored with a 10-electrode, 12-lead digital ECG recorder (DR180+ Digital Recorder, NorthEast Monitoring Inc., Massachusetts) for 72 hours perioperatively, starting one day before their surgical procedure and continuing until two days after. Recordings were performed in the continuous 12-lead mode with a 10-seconds strip saved every minute. Signal bandwidth was 0.05Hz to 150Hz. Electrocardiographic data were initially processed by a technician to exclude artefacts, afterwards analyzed by two physicians unaware of the clinical information for each patient, and then verified for the presence of new-onset myocardial ischemia (episodes of ischemia were defined as reversible ST-segment changes, lasting at least one minute and shifting from baseline by more than 0.1mV [1mm]) and cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia, sustained ventricular tachycardia, and/or ventricular fibrillation[14-15]). Standard postoperative 12-lead ECG recordings were made on days 3, 7 and 30, and/or at discharge, and whenever clinically indicated by chest pain or dyspnea complaints.

Assessment of perioperative heart rate variability

Heart Rate Variability (HRV) was evaluated with the time domain indices, analyses of short-term 5-min recordings, during the pre-, intra- and postoperative period. The average heart rate variability of all the 5-min recordings was calculated for each period (the pre-, intra- and postoperative time span). The standard deviation of the normal-to-normal RR intervals (SDNN), the square root of the mean squared differences of successive NN intervals (RMSSD), the number of normal-to-normal RR intervals that were more than 50 milliseconds different from the preceding RR interval (NN50), and the average RR interval within the specified time period (RR-mean) were used to characterize autonomic tone[16].

Cardiac Troponin T measurement

After surgery, cTnT levels were routinely measured on postoperative days 1, 3, 7, 30 and/or before discharge, and whenever clinically indicated by chest pain complaints or ECG changes consistent with myocardial ischemia or infarction. The cTnT level was measured using a whole blood rapid test by an electrochemiluminescence immuneassay (TropT version 2, Roche Diagnostics GmbH, Mannheim, Germany). The lower limit of cTnT detection was 0.01 ng/mL and the upper limit of detection was 25 ng/mL, with the limit of quantification set at 0.03 ng/mL. If cTnT release occurred, measurements were repeated every day until the level returned to baseline.

Cardiovascular outcome

During follow-up, outpatient visits were scheduled every 3 months after discharge. Survival status was determined by contacting the municipal civil service registry. The study endpoint was the composite of cardiac death, MI, unstable angina, and stroke (cardiovascular events) at 30-days and during long-term follow-up (median 2.4 years; IQR 1.4 – 3.5 years). Myocardial infarction was defined according to the universal definition of MI[17]. Cardiovascular death was defined as any death with a cardiovascular cause, including deaths following a cardiac procedure, cardiac arrest, MI, pulmonary embolus, stroke, or sudden death not ascribed to other causes.

Data analysis

Categorical data are described as numbers and percentages and continuous data are expressed as means ± standard deviation (SD). Continuous data with a skewed distribution (HRV time domain variables) are expressed as medians with interquartile ranges (IQR) and were compared using the Mann-Whitney *U* test. SDNN time domain was divided in tertiles to explore the prognostic value. Binary logistic regression analysis was used to evaluate the association of perioperative HRV indices on 30-day clinical cardiac outcome. The relationship between perioperative HRV, and long-term cardiovascular events was assessed with the multivariate Cox regression analysis. In multivariate analyses, adjustments were

made for gender, cardiac risk index (low, intermediate, high), type of surgery (endovascular and open repair) and cardioprotective medication (beta-blocker, statin, and oral antiplatelet therapy). These covariates were chosen on the basis of clinical plausibility. Odds and hazard ratios (OR and HR) are given with 95% confidence intervals (CI). For all tests, a p-value of less than 0.05 (two-sided) was considered significant. All analysis was performed using SPSS 15.0 statistical software (SPSS Inc., Chicago, Illinois).

Results

Study population

The baseline clinical characteristics and medication use of the 495 included patients undergoing elective abdominal aortic aneurysm repair (n=251), lower extremity bypass surgery (n=103) and carotid artery surgery (n=141) are listed in **table 1**. The mean age at baseline was 68.6 ± 9.4 years and 77% were male. Preoperative cardiac risk index and cardioprotective medication use is also listed in **table 1**. The preoperative cardiac risk was assessed and showed that 19% had a low-risk, 56% an intermediate-risk, and 25% a high-risk.

Table 1. Baseline Characteristics of Study Population

	All (n=495)
Age, years	68.6 ± 9.4
Males – no. (%)	380 (77)
History of MI – no. (%)	133 (27)
History of AP – no. (%)	84 (17)
History of CHF – no. (%)	36 (7)
Diabetes mellitus – no. (%)	105 (21)
Renal dysfunction – no. (%)	40 (8)
History of stroke – no. (%)	180 (36)
Hypertension – no. (%)	261 (53)
COPD – no. (%)	178 (36)
Smoking – no. (%)	387 (78)
BMI – kg/m^2	23.0 ± 8.6
Cardiac Risk Index	
Low-risk (0 risk factors) – no. (%)	92 (19)
Intermediate-risk (1 to 2 risk factors) – no. (%)	278 (56)
High-risk (≥ 3 risk factors) – no. (%)	125 (25)
Medication use	
Beta-blockers – no. (%)	454 (92)
Statins – no. (%)	419 (85)
Antiplatelet therapy – no. (%)	384 (77)
Oral anticoagulants – no. (%)	60 (12)
Calcium channel blocking agents – no. (%)	128 (26)
ACE-inhibitors – no. (%)	138 (28)
Type of surgery	
Open AAA repair – no. (%)	132 (27)
Endovascular AAA repair – no. (%)	119 (24)
Lower extremity bypass surgery – no. (%)	103 (21)
Carotid endarterectomy – no. (%)	95 (19)
Carotid artery stenting – no. (%)	46 (9)

ECG monitoring and cTnT release

Continuous-ECG monitoring started on average 12.4 ± 7.5 hours prior to surgery. As shown in **table 2**, perioperative new-onset arrhythmias and myocardial ischemia occurred in 54 (11%) and 93 (19%; ST-elevation n=9 and ST-depression n=84) patients respectively. The vast majority of patients with cardiac arrhythmias and/or myocardial ischemia (97%) were asymptomatic. Postoperative cTnT release occurred in 76 (15%) patients, however, in only 12 (2%) patients a combination of myocardial ischemia, arrhythmias and cTnT release was observed. Symptomatic patients or those with detected ECG abnormalities, e.g. new-onset arrhythmia or ischemia, received oral anticoagulant therapy next to antiplatelet medication, and/or preoperative cardioprotective medication dose was adjusted.

Table 2. Preoperative laboratory markers, TTE and continuous-ECG results.

	All (n=495)
Laboratory markers	
CRP, mg/L	4 (2-10)
NT-proBNP, pg/mL	182 (83-430)
LVEF	62 (13)
LVEF ≤ 40% - no. (%)	421 (87)
LVEF > 40% - no. (%)	
Continuous-ECG	
Ischemia - no. (%)	93 (19)
New-onset arrhythmia - no. (%)	54 (11)
Postoperative cTnT release – no. (%)	76 (15)
Ischemia, Arrhythmia and cTnT release – no. (%)	12 (2)

Perioperative HRV

In **table 3** the perioperative HRV time domain analyses during the pre, intra, and postoperative period is listed. HRV was highest before the surgical procedure and lowest during surgery (SDNN 37 ms, 31 ms, and 33 ms before, during, and after surgery, respectively [p<0.001]). Postoperative HRV (SDNN, RMSSD, and RR-mean respectively) decreased significantly compared to preoperative calculations.

Table 3. Course of the perioperative HRV time domain indices.

	Preoperative	Intra-operative	Postoperative	P-value
SDNN	37 (27 – 48)	31 (24 – 44)	33 (23 – 46)	<0.001
RMSSD	24 (16 – 35)	19 (13 – 32)	21 (14 – 36)	<0.001
NN50	8 (4 – 21)	7 (4 – 18)	7 (4 – 18)	0.37
RR-mean	929 (815 – 1045)	940 (825 – 1069)	854 (759 – 982)	<0.001

Long-term outcome

A total of 80 (16%) patients died during the mean follow-up period of 2.4 years; 57 (71%) were due to cardiovascular causes. The combined endpoint for cardiovascular events at 30-days and long-term occurred in 44 (9%) and 91 (18%) patients, respectively. As shown in **table 4 and 5**, the postoperative SDNN and RR-mean were significantly lower in those patients developing cardiovascular events at 30-days and long-term, as compared to patients without events. Additionally. **table 6** shows that long-term cardiovascular events were more often observed in patients at high cardiac risk, with an increased preoperative inflammation status (increased CRP), worse LVEF and higher NT-proBNP, and undergoing high-risk surgery (more specifically open AAA repair). Patients with cardiovascular events developed more cardiac arrhythmias, ischemia and cTnT release. We investigated the predictive value of both significant postoperative time domain variables SDNN and RR-mean. **Figure 1** shows that long-term cardiovascular events occurred in 27%, 16%, and 11% of patients across the SDNN tertiles. Patients in the lowest SDNN tertile were independently associated with an increased risk in the incidence of cardiovascular events (**figure 1**; p=0.001). Multivariate analysis adjusted for preoperative risk factors (gender, cardiac risk index and type of surgery) and cardioprotective therapy (included beta-blocker, statin and antiplatelet therapy) and postoperative RR-mean revealed that depressed HRV measurements (postSDNN) were correlated with 30-day (odds ratio [OR] 1.03, 95% confidence interval [CI] 1.00 to 1.06) and long-term cardiac events (hazard ratio [HR] 1.02, 95% CI 1.01 to 1.04, respectively). When correcting for above mentioned risk factors, medication use, left ventricular function, and perioperative risk factors (myocardial ischemia, cardiac arrhythmias, and cTnT release), a depressed postoperative SDNN calculations was still found to be

associated with 30-day (odds ratio [OR] 1.03, 95% confidence interval [CI] 1.00 to 1.06) and long-term cardiac events (hazard ratio [HR] 1.02, 95% CI 1.01 to 1.04, respectively). Other factors also independently associated with cardiovascular outcome were detection of myocardial ischemia, cardiac arrhythmias and cTnT release.

Table 4. 30-day cardiovascular events

	Preoperative			Intraoperative			Postoperative		
	No events n=451	Events n=44	P	No events n=451	Events n=44	p	No events n=451	Events n=44	P
SDNN	37 (27–48)	34 (27-42)	.33	32 (24–45)	30 (19–42)	.18	34 (24–47)	25 (19–34)	.001
RMSSD	23 (16–35)	27 (19-35)	.29	19 (14-32)	19 (12-38)	.88	21 (14–36)	20 (13–34)	.52
NN50	8 (4-20)	9 (4-27)	.16	7 (4–17)	11 (4–20)	.17	7 (4–19)	10 (4–16)	.85
RR-mean	930 (816-1045)	923 (790-1041)	.69	944 (824-1070)	933 (829-1067)	.71	869 (763–989)	815 (691–883)	.01

Table 5. Long-term cardiovascular events

	Preoperative			Intraoperative			Postoperative		
	No events n=404	Events n=91	P	No events n=404	Events n=91	p	No events n=404	Events n=91	P
SDNN	38 (28–49)	33 (27-43)	.02	32 (24–45)	29 (21–42)	.10	35 (25–48)	27 (19–36)	<.001
RMSSD	24 (16–35)	21 (17-36)	.85	19 (14-31)	20 (12-37)	.85	21 (13-33)	20 (12-37)	.29
NN50	8 (4-20)	7 (4-27)	.77	7 (4–18)	9 (4–18)	.43	7 (4–17)	9 (4–18)	.71
RR-mean	930 (819-1046)	906 (803-1033)	.33	942 (825-1071)	940 (827-1054)	.69	870 (765-989)	824 (727-951)	.04

Figure 1. Long-term cardiovascular events and SDNN.

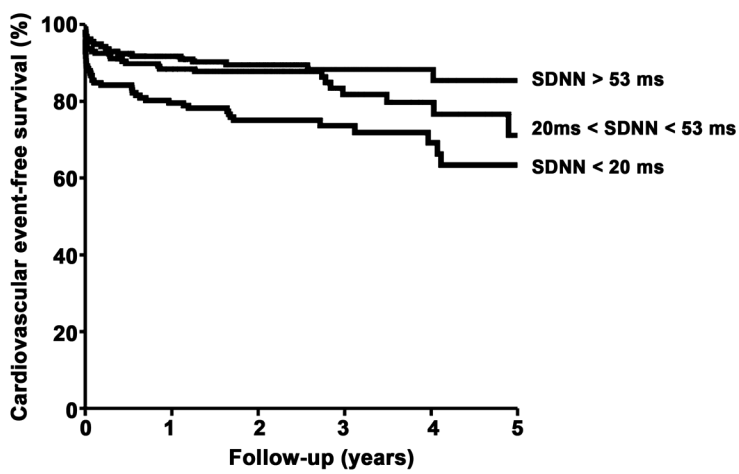


Table 6. Long-term cardiovascular events in relation to pre, and perioperative risk factors.

	No events (n=404)	Events (n=91)	p-value
Males – no. (%)	308 (76)	71 (78)	0.72
Cardiac Risk Index			0.002
Low-risk (0 risk factors) – no. (%)	82 (20)	10 (11)	
Intermediate-risk (1 to 2 risk factors) – no. (%)	233 (58)	46 (50)	
High-risk (≥ 3 risk factors) – no. (%)	89 (22)	35 (39)	
Medication use			
Beta-blockers – no. (%)	368 (91)	85 (93)	0.47
Statins – no. (%)	336 (83)	82 (90)	0.10
Antiplatelet therapy – no. (%)	315 (78)	68 (75)	0.50
Preoperative laboratory markers			
CRP, mg/L	4 (1-8)	7 (3-25)	< 0.001
NT-proBNP, pg/mL	149 (75-354)	447 (217-1075)	< 0.001
LVEF			0.001
LVEF ≤40% - no. (%)	41 (10)	21 (23)	
LVEF >40% - no. (%)	363 (90)	70 (77)	
Type of surgery			< 0.001
Open AAA repair – no. (%)	87 (21)	45 (50)	
Endovascular AAA repair – no. (%)	104 (26)	15 (16)	
Lower extremity bypass surgery – no. (%)	83 (21)	20 (22)	
Carotid endarterectomy – no. (%)	91 (22)	4 (4)	
Carotid artery stenting – no. (%)	39 (10)	7 (8)	
Perioperative laboratory marker			
Postoperative cTnT release– no. (%)	26 (6)	50 (55)	< 0.001
Continuous-ECG			
Ischemia – no. (%)	50 (12)	43 (47)	< 0.001
New-onset arrhythmia – no. (%)	32 (8)	22 (24)	< 0.001

Discussion

Principal findings

Depressed HRV, especially postoperatively, is strongly associated with higher 30-day and long-term cardiovascular events, independent of preoperative cardiac risk score, cardioprotective medication and type of surgery, in patients undergoing non-cardiac vascular surgery procedures.

In the context of literature

The first observation that HRV could be used as a predictor of mortality after acute MI was published in 1978[18]. Since then the usefulness of HRV for the identification of patients at high risk of mortality after (acute) MI[19-21] and CHF[22-23] has been confirmed in several studies. Bigger et al. found that decreased HRV predicted both mortality and arrhythmic events with greater sensitivity and specificity than conventional predictors such as LVEF[24]. Increased sympathetic or decreased parasympathetic tone are reflected in decreased indices of HRV, while decreased sympathetic and increased parasympathetic nervous activity are reflected in increased indices of HRV[25]. HRV is not only a subject of many physiologically oriented investigations[26], but has also gained widespread interest among clinical investigators and its potential clinical value. Kop et al. demonstrated in 19 male patients with stable coronary disease that decreases in frequency domain HRV measures occur as early as 10 min before the ischemic event and is pronounced in the 4 min before ST-depression, implying that activity induced changes in sympathicovagal balance are involved in triggering myocardial ischemia[20]. In a prospective study by Nolan and colleagues 433 outpatients with CHF showed that the annual mortality rate in SDNN subgroups was 5.5% for > 100 ms, 12.7% for the 50 to 100 ms, and 51.4% for < 50ms[22]. Similar results were found by Rich et al. reporting 100 stable patients who initially had elective coronary angiography, and SDNN < 50 ms being associated with an 18-fold 1-year mortality compared with patients with an SDNN > 50 ms[27]. The beat of the healthy heart varies as a result of many factors, including exercise, physical, and mental stress[25]. Furthermore, the intervals between normal sinus beats vary periodically because of respiration,

blood pressure regulation, thermoregulation, actions of the renin angiotensin system, circadian rhythms, and several unknown factors[25]. There are two approaches to the measurement of HRV: analysis of the time, which was used in the current study, or in the frequency domain. Time domain indexes are relatively easy to calculate, with two classes of variables to be measured. One based on interbeat variables (e.g. SDNN which has also been called the cycle length variability) and the other based on comparisons of the lengths of adjacent cycles (e.g. NN50, RMSSD)[25]. These variables are independent of long-term trends and lack intra-individual variability over time making measurement of HRV useful in assessing the function of the autonomic nervous system, and could also be valuable in evaluating surgical stress during the non-cardiac perioperative period[8,25]. Ushiyama et al. analyzed the relationship between HRV and surgical stress in 24 patients undergoing digestive surgery and concluded that in 7 patients with postoperative complications, HRV indices (SDNN and heart rate variability index) were significantly lower than in those without complications ($p<0.05$) and that HRV indices could provide useful information with respect to surgical stress[28]. In the current study similar conclusions can be drawn, where postoperative HRV indices were significantly lower in those patients with postoperative cardiovascular events. Another conclusion that can be drawn from the current results is that the HRV index is an independent predictor of 30-day and long-term cardiovascular events, irrespective of the preoperative risk factors, medication use, type of surgery and perioperative development of ischemia, arrhythmia and cTnT release.

Clinical implications

An important observation in this study was that patients developing 30-day and long-term cardiovascular events were associated with a depressed postoperative HRV index. The combination of preoperative cardiac risk factors with perioperative ECG monitoring, HRV indices and biomarker measurements are all feasible monitoring and detection methods for a patient undergoing vascular surgery which can easily be used in daily clinical practice. However, larger studies will be needed to link therapeutic consequences (e.g. statins and/or beta-blockers) aimed at increasing the HRV, consequently reducing the risk of cardiovascular events,

mortality or both. Feringa et al. showed that higher statin doses were significantly associated with higher SDNN, leading them to conclude that in situations of decreased HRV and increased myocardial oxygen demand, statins may exert an anti-ischemic effect by modulating the autonomic nervous system[6]. Atenolol in post-MI patients[29] and angiotensin-converting enzyme (ACE) inhibitors in CHF patients[30] have both shown to increase HRV, and also improve survival in high-risk patients. Furthermore, with an on-line ECG device capable of long-term continuous monitoring pharmacological manipulations on HRV could become a routine therapeutic consideration for clinicians, especially in high-risk patients.

Limitations

There are important differences between the type of heart rhythm recordings used for physiological studies and those used for clinical studies, where standard ambulatory ECGs are much less stationary and furthermore where the different processes modulating the heart rate are much less easily distinguishable. Malik et al. found that arbitrary short-term recordings are not sufficient, only when the total circadian variation of autonomic nervous activity was integrated did practically acceptable values of sensitivity and specificity emerge[8]. In addition, all HRV data in our study were calculated from Holter recordings, a time-consuming process and not suitable for daily routine. However, there are commercially available continuous ECG devices that perform HRV analyses automatically. Also, carotid surgery patients were included in the current study which have been associated with heart rate change secondary to baroreceptor reflexes and might have confounded the HRV. Nevertheless, the HRV index differed significantly between patients with 30-day and long-term cardiovascular events, in uni, and multivariate analyses.

Conclusions

Depressed perioperative HRV is an independent predictor of 30-day and late cardiovascular events in vascular surgery patients and add incremental prognostic information to an established cardiac risk score. Perioperative continuous ECG monitoring, with calculation of the HRV, helps to identify this high-risk group at increased risk of cardiovascular events and death.

References

1. Hertzer NR, Beven EG, Young JR, O'Hara PJ, Ruschhaupt WF, 3rd, Graor RA, Dewolfe VG, Maljovec LC. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. *Ann Surg* 1984;199:223-33.
2. Boersma E, Poldermans D, Bax JJ, Steyerberg EW, Thomson IR, Banga JD, van De Ven LL, van Urk H, Roelandt JR. Predictors of cardiac events after major vascular surgery: Role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. *Jama* 2001;285:1865-73.
3. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, Ludwig LE, Pedan A, Goldman L. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999;100:1043-9.
4. Filipovic M, Jeger RV, Girard T, Probst C, Pfisterer M, Gurke L, Studer W, Seeberger MD. Predictors of long-term mortality and cardiac events in patients with known or suspected coronary artery disease who survive major non-cardiac surgery. *Anaesthesia* 2005;60:5-11.
5. Devereaux PJ, Goldman L, Yusuf S, Gilbert K, Leslie K, Guyatt GH. Surveillance and prevention of major perioperative ischemic cardiac events in patients undergoing noncardiac surgery: a review. *Cmaj* 2005;173:779-88.
6. Feringa HH, Schouten O, Karagiannis SE, Brugts J, Elhendy A, Boersma E, Vidakovic R, van Sambeek MR, Noordzij PG, Bax JJ, Poldermans D. Intensity of statin therapy in relation to myocardial ischemia, troponin T release, and clinical cardiac outcome in patients undergoing major vascular surgery. *J Am Coll Cardiol* 2007;50:1649-56.
7. Schouten O, Dunkelgrun M, Feringa HH, Kok NF, Vidakovic R, Bax JJ, Poldermans D. Myocardial damage in high-risk patients undergoing elective endovascular or open infrarenal abdominal aortic aneurysm repair. *Eur J Vasc Endovasc Surg* 2007;33:544-9.
8. Malik M, Camm AJ. Heart rate variability and clinical cardiology. *Br Heart J* 1994;71:3-6.
9. Fleisher LA, Pincus SM, Rosenbaum SH. Approximate entropy of heart rate as a correlate of postoperative ventricular dysfunction. *Anesthesiology* 1993;78:683-92.
10. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van Weel C, Zielinski J. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;176:532-55.
11. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, St John Sutton M, Stewart W. Recommendations for chamber quantification. *Eur J Echocardiogr* 2006;7:79-108.
12. Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* 2002;15:167-84.
13. Poldermans D, Bax JJ, Boersma E, De Hert S, Eeckhout E, Fowkes G, Gorenek B, Hennerici MG, Iung B, Kelm M, Kjeldsen KP, Kristensen SD, Lopez-Sendon J, Pelosi P, Philippe F, Pierard L, Ponikowski P, Schmid JP, Sellevold OF, Sicari R, Van den Berghe G, Vermassen F, Hoeks SE, Vanhorebeek I, Vahanian A, Auricchio A, Bax JJ, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, McGregor K, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas P, Widimsky P, De Caterina R, Agewall S, Al Attar N, Andreotti F, Anker SD, Baron-Esquivias G, Berkenboom G, Chapoutot L, Cifkova R, Faggiano P, Gibbs S, Hansen HS, Iserin L, Israel CW, Kornowski R, Eizagaechevarria NM, Pepi M, Piepoli M, Priebe HJ, Scherer M, Stepinska J, Taggart D, Tubaro M. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: The Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur Heart J* 2009.

14. Estes NA, 3rd, Halperin JL, Calkins H, Ezekowitz MD, Gitman P, Go AS, McNamara RL, Messer JV, Ritchie JL, Romeo SJ, Waldo AL, Wyse DG, Bonow RO, DeLong E, Goff DC, Jr., Grady K, Green LA, Hiniker A, Linderbaum JA, Masoudi FA, Pina IL, Pressler S, Radford MJ, Rumsfeld JS. ACC/AHA/Physician Consortium 2008 Clinical Performance Measures for Adults with Nonvalvular Atrial Fibrillation or Atrial Flutter: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and the Physician Consortium for Performance Improvement (Writing Committee to Develop Clinical Performance Measures for Atrial Fibrillation) Developed in Collaboration with the Heart Rhythm Society. *J Am Coll Cardiol* 2008;51:865-84.
15. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, Smith SC, Jr., Jacobs AK, Adams CD, Antman EM, Anderson JL, Hunt SA, Halperin JL, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). *J Am Coll Cardiol* 2006;48:e247-346.
16. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996;93:1043-65.
17. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *Eur Heart J* 2007;28:2525-38.
18. Wolf MM, Varigos GA, Hunt D, Sloman JG. Sinus arrhythmia in acute myocardial infarction. *Med J Aust* 1978;2:52-3.
19. Kleiger RE, Miller JP, Bigger JT, Jr., Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987;59:256-62.
20. Kop WJ, Verdino RJ, Gottdiener JS, O'Leary ST, Bairey Merz CN, Krantz DS. Changes in heart rate and heart rate variability before ambulatory ischemic events(1). *J Am Coll Cardiol* 2001;38:742-9.
21. Malik M, Farrell T, Cripps T, Camm AJ. Heart rate variability in relation to prognosis after myocardial infarction: selection of optimal processing techniques. *Eur Heart J* 1989;10:1060-74.
22. Nolan J, Batin PD, Andrews R, Lindsay SJ, Brooksby P, Mullen M, Baig W, Flapan AD, Cowley A, Prescott RJ, Neilson JM, Fox KA. Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). *Circulation* 1998;98:1510-6.
23. Wijbenga JA, Balk AH, Meij SH, Simoons ML, Malik M. Heart rate variability index in congestive heart failure: relation to clinical variables and prognosis. *Eur Heart J* 1998;19:1719-24.
24. Bigger JT, Jr., Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation* 1992;85:164-71.
25. Stein PK, Bosner MS, Kleiger RE, Conger BM. Heart rate variability: a measure of cardiac autonomic tone. *Am Heart J* 1994;127:1376-81.
26. Malliani A, Lombardi F, Pagani M. Power spectrum analysis of heart rate variability: a tool to explore neural regulatory mechanisms. *Br Heart J* 1994;71:1-2.
27. Rich MW, Saini JS, Kleiger RE, Carney RM, teVelde A, Freedland KE. Correlation of heart rate variability with clinical and angiographic variables and late mortality after coronary angiography. *Am J Cardiol* 1988;62:714-7.
28. Ushiyama T, Mizushige K, Wakabayashi H, Nakatsu T, Ishimura K, Tsuboi Y, Maeta H, Suzuki Y. Analysis of heart rate variability as an index of noncardiac surgical stress. *Heart Vessels* 2008;23:53-9.
29. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis* 1985;27:335-71.
30. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med* 1991;325:293-302.

8

Sudden death during follow-up after new-onset ventricular tachycardia's in vascular surgery patients.

accepted for publication

Tamara A. Winkel
Michiel T. Voûte
Mirko de Melis
Sanne E. Hoeks
Olaf Schouten
Roger Kessels
Hence J.M. Verhagen
Don Poldermans

Abstract

Background and aim: Vascular surgery patients are at increased risk for late sudden cardiac death. Identification of patients at risk during surgery offers the opportunity for focused therapy.

Methods: We monitored 483 vascular surgery patients, without a documented history of arrhythmias, to identify perioperative new-onset ventricular tachyarrhythmia's (VT) and myocardial ischemia using a continuous electrocardiographic (ECG) device for 72 hours. Cardiac risk factors, left ventricular ejection fraction (LVEF), medical therapy, inflammation status, and perioperative ischemia in relation to arrhythmia were noted in all. During follow-up event based outcomes analysis was used to describe survival.

Results: New-onset perioperative VT was detected in 33 (6.8%) patients. A higher percentage of patients experiencing perioperative VT had reduced LVEF than those without VT (24% versus 12%; p=0.04). Additionally, less patients experiencing VT were receiving statins than those without (70% versus 85%; p=0.02). Patients experiencing VT had a higher incidence of myocardial ischemia (30% versus 18%, p=0.10). Perioperative VT was preceded by ischemia in only 60% of the cases. The overall cohort survival was 83% at 24 months follow-up (IQR 1.1-1.3). Survival among patients experiencing VT was less than in those without (79% versus 92%; p=0.02). After adjusting for gender, cardiac risk factors and type of surgery, new-onset perioperative VT was associated with sudden cardiac death (HR 2.6; 95% CI 1.1-5.8).

Conclusion: Perioperative VT is associated with late sudden cardiac death and decreased survival. Continuous perioperative ECG is an effective method to identify perioperative VT and may allow improved management of vascular surgery patients.

Introduction

Sudden death is among the most common causes of death in developed countries. Sudden cardiac death accounts for more deaths each year, and it is estimated that more than 3 million people die yearly from sudden cardiac death worldwide[1]. The incidence of sudden cardiac arrest in the general Dutch population is 9.2 per 10,000 inhabitants[2]. This can be extrapolated to approximately 40 sudden cardiac arrests per day in the Netherlands[3]. In Dutch patients who had undergone 24hr ambulatory electrocardiography monitoring for various indications, 3.7% of the patients experienced sudden death within 2 years after electrocardiography[4]. The majority (80 to 85%) of such sudden cardiac deaths are caused by acute ventricular arrhythmia (VT), which can be triggered by acute coronary events, which may occur in persons without known cardiac disease or in association with structural heart disease[1, 5].

Patients undergoing vascular surgery are at increased risk of cardiac events, such as cardiac arrhythmias and myocardial infarction (MI)[6]. The use of perioperative continuous electrocardiography (continuous-ECG) monitoring to screen for the presence of ischemia and arrhythmia, increases the number of patients identified with arrhythmic events, and may help to improve management of patients at risk for subsequent cardiac events[7]. The significant influence of an increased incidence and detection of perioperative myocardial ischemia and arrhythmias in vascular surgery patients has been described previously[8]. In this study we tried to identify vascular surgery patients at risk of developing new-onset perioperative VT, registered with continuous-ECG, and late sudden cardiac death.

Methods

Study population

The prospective study cohort consisted of 483 patients undergoing vascular surgery at the Erasmus Medical Center in Rotterdam, the Netherlands, during the period December 2004 to October 2009. Patients with a history of cardiac arrhythmias, cardiac pacemaker and/or implantable cardioverter defibrillator (ICD) were excluded. Procedures that precluded continuous Holter-ECG monitoring were excluded. The hospital's ethical committee approved the study.

Preoperative cardiac screening

The relationship between patient characteristics and the risk of adverse cardiac outcome was determined at the outpatient clinic, as previously described by Boersma et al.[9]. We determined the cardiac risk score for each patient in our dataset and one point was assigned to each of the following characteristics: advanced age (> 70 years), history of MI, angina pectoris (AP), congestive heart failure (CHF), stroke (transient ischemic attack (TIA) and/or cerebral vascular accident (CVA)), diabetes mellitus (fasting glucose level ≥ 7.0 mmol/L or use of insulin or oral glucose lowering medication), and renal insufficiency (serum creatinine >170 umol/l)[9]. Based on the number of these risk factors, patients were stratified into low-risk (no risk factors), intermediate-risk (1 or 2 risk factors), and high-risk (≥ 3 risk factors) categories[9]. Venous blood samples for C-Reactive Protein (CRP), N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP), low density lipoprotein (LDL), and high density lipoprotein (HDL) were routinely performed at the outpatient clinic. A preoperative echocardiographic assessment of the left ventricle ejection fraction (LVEF) was performed in all patients at the outpatient clinic. On admission to the hospital, all patients received beta-blockers.

ECG monitoring

Patients were continuously monitored with a 10-electrode, 12-lead digital ECG recorder (DR180+ Digital Recorder, NorthEast Monitoring Inc. Massachusetts) for 72 hours perioperatively, starting one day before their surgical procedure and

continuing until two days after. Electrocardiographic data were analyzed for ischemia and new-onset ventricular tachyarrhythmias (VT; sustained ventricular tachycardia and ventricular fibrillation (VF)). Sustained ventricular tachycardia was characterized by three or more consecutive QRS complexes with a wide QRS complex at a rate of greater than 100 bpm and duration greater than 30 seconds[7]. VF was defined as chaotic ventricular electrical discharge with marked variability in QRS cycle length, morphology, and amplitude[7]. Episodes of ischemia were defined as reversible ST-segment changes, lasting at least one minute and shifting from baseline by more than 0.1mV (1mm). The baseline ST-segment level was defined as the average ST-segment value during a stable period of at least 20 min duration. The criteria for an ST-depression and ST-elevation were 0.1 mV flat or down sloping morphology with deviated J-point[10]. Standard postoperative 12-lead ECGs were made on days 3, 7 and 30, and/or at discharge, and whenever clinically indicated.

Cardiac Troponin-T measurement

After surgery, cTnT levels were routinely measured on postoperative days 1, 3, 7, 30 and/or before discharge, and/or whenever clinically indicated by chest pain complaints or ECG changes consistent with myocardial ischemia or infarction. The cTnT level was measured using a whole blood rapid test by an electrochemiluminescence immuneassay (TropT version 2, Roche Diagnostics GmbH, Mannheim, Germany). The lower limit of cTnT detection was 0.01 ng/mL and the upper limit of detection was 25 ng/mL, with the limit of quantification set at 0.03 ng/mL. If cTnT release occurred, measurements were repeated every day until the level returned to baseline value.

Outcomes

During follow-up, outpatient visits were scheduled every 3 months after discharge. The study endpoint was sudden cardiac death. Sudden cardiac death was defined as 1) a witnessed natural death attributable to cardiac causes, heralded by abrupt loss of consciousness, within one hour of onset of acute symptoms, or 2) an unwitnessed, unexpected death of someone seen in a stable medical condition <24

hours previously with no evidence of a non-cardiac cause[11-12]. Cardiac death was defined as any death with a cardiac cause, including deaths following a cardiac procedure, cardiac arrest, MI, pulmonary embolus, stroke, or sudden death not ascribed to other causes[13]. The composite of cardiac death, MI, unstable angina, and stroke was considered as cardiac events. Survival status was determined by contacting the municipal civil service registry, by use of electronic medical records and contacting the patient's general practitioner.

Data analysis

Continuous data are expressed as mean ± standard deviation (SD) compared using the Student's *t* test. Continuous data with a skewed distribution are expressed as medians with interquartile ranges (IQR) and were compared using the Mann-Whitney *U* test. Categorical data are described as numbers and percentages and analyzed using the chi-square test or Fisher's exact test as appropriate. The relationship between new-onset perioperative VT and sudden cardiac death was assessed with multivariate Cox regression analysis. In multivariate analysis, adjustments were made for gender, cardiac risk index (prior history of MI, CHF, stroke, AP, renal dysfunction, diabetes, and age) and type of surgery. In addition, a cumulative two-year survival curve for vascular surgery patients experiencing VT and without perioperative VT was determined by the Kaplan-Meier method and compared using the log-rank test. Odds ratios (OR) and hazard ratios (HR) are given with 95% confidence intervals (CI). For all tests, a p-value of less than 0.05 (two-sided) was considered significant. All analyses were performed using SPSS 15.0 statistical software (SPSS Inc., Chicago, Illinois). Continuous-ECG recordings and the data were analyzed off-line thus did not influence perioperative treatment management.

Results

Study population

The baseline clinical characteristics and medication use of the 483 included patients undergoing elective abdominal aortic aneurysm repair (n=241), peripheral artery bypass surgery (n=101) and carotid artery surgery (n=141) are listed in **Table 1**. The mean age at baseline was 68.6 ± 9.5 years and 76% were male. The preoperative cardiac risk was assessed and showed that 18% had a low-risk, 57% an intermediate-risk, and 25% a high-risk.

Risk factors for perioperative cardiac arrhythmias

Patients with new-onset VT were significantly older, as shown in **Table 1**. Twenty-four percent of patients with perioperative VT had a LVEF lower than 40%, as compared to 12% of those without new-onset VT (p=0.04). Patients with perioperative VT had elevated NT-proBNP levels (36 versus 21 pg/mL, p=0.02). A significantly lower percentage of patients developing perioperative VT were treated with statins (70% versus 85%, p=0.02), however neither their baseline inflammation status (preoperative CRP 6 versus 4 mg/L) nor LDL (46.8 versus 48.6 mg/dL) or HDL (23.4 versus 23.4 mg/dL) differed from patients without perioperative VT. Chronic beta-blocker therapy was used in 88% (388/441) of those patients receiving preoperative beta-blocker therapy.

New-onset perioperative VT

Continuous-ECG monitoring started on average 12.4 ± 7.6 hours prior to surgery. New-onset perioperative VT occurred in 33 (6.8%) patients: sustained ventricular tachycardia and VF occurred in 6.6% and 0.2% respectively. The vast majority of patients with cardiac arrhythmias (97%) were asymptomatic. All but 1 patient with new-onset VT returned to sinus rhythm at 30 days postoperatively, confirmed by standard 12-lead ECG. As shown in **table 1**, significantly more patients undergoing aortic aneurysm repair experienced perioperative VT (open 30% versus endovascular 43%), as compared to those undergoing carotid artery operation

carotid endarterectomy 6% and carotid stenting 3%) and peripheral artery bypass procedure (open 18%).

Table 1. Baseline characteristics.

	No perioperative VT (n=450)	Perioperative VT (n=33)	p-value
Age, years	68.4 ± 9.5	72.1 ± 8.1	0.03
Males – no.(%)	340 (76)	29 (88)	0.11
History of myocardial infarction – no.(%)	115 (26)	13 (39)	0.09
History of angina pectoris – no.(%)	74 (16)	5 (15)	0.85
History of congestive heart failure – no.(%)	29 (6)	5 (15)	0.06
Diabetes mellitus – no.(%)	94 (21)	7 (21)	0.97
Renal dysfunction – no.(%)	32 (7)	4 (12)	0.29
History of stroke (TIA and/or CVA) – no.(%)	172 (38)	6 (18)	0.02
Medication use			
Beta-blockers – no. (%)	409 (91)	32 (97)	0.23
Statins – no. (%)	383 (85)	23 (70)	0.02
Antiplatelet therapy – no. (%)	349 (78)	24 (73)	0.52
Oral anticoagulants – no. (%)	53 (12)	4 (12)	0.95
Calcium channel blocking agents – no. (%)	117 (26)	9 (27)	0.87
ACE-inhibitors – no. (%)	123 (27)	10 (30)	0.71
Left ventricular ejection fraction (LVEF)			
LVEF < 40% – no. (%)	54 (12)	8 (24)	0.04
LVEF ≥ 40% – no. (%)	309 (69)	13 (39)	
Laboratory measurements			
CRP, mg/L	4 (2-9)	6 (3-13)	0.18
NT-proBNP, pg/mL	21 (9-50)	36 (15-88)	0.02
LDL, mmol/L	2.7 ± 1.0	2.6 ± 0.7	0.85
HDL, mmol/L	1.3 ± 0.4	1.3 ± 0.3	0.61
Type of surgery			
Open AAA repair – no. (%)	118 (26)	10 (30)	0.03
Endovascular AAA repair – no. (%)	99 (22)	14 (43)	
Lower extremity bypass surgery – no. (%)	95 (21)	6 (18)	
Carotid endarterectomy – no. (%)	93 (21)	2 (6)	
Carotid artery stenting – no. (%)	45 (10)	1 (3)	

Echocardiographic data (LVEF) were available of 80% of the patients.

VT and myocardial ischemia during continuous Holter-ECG

Transient myocardial ischemia was detected in 93 (19.3%) patients; in 9 as ST-elevation and 84 as ST-depression. Patients with new-onset VT had a higher but non-significant incidence of myocardial ischemia, compared to patients without VT, during continuous-ECG registration (30% versus 18%, p=0.10, **Table 2**). New-onset perioperative VT was preceded by myocardial ischemia in 60% of the cases. Patients developing new-onset VT and myocardial ischemia had significantly higher postoperative heart rates (median heart rate 80 versus 68, p=0.04). Perioperative cTnT release occurred in 75/483 (16%) patients. In patients experiencing perioperative VT, cTnT release occurred non-significantly more as compared to those not experiencing VT (24% versus 15% respectively, p=0.15). Also, cTnT and myocardial ischemia was detected more often in those patients undergoing elective aneurysm repair (p<0.001) as compared to carotid artery surgery and peripheral bypass procedures.

Table 2. Events and new-onset VT.

	No VT n=450	**Yes VT n=33**	**p-value**
Myocardial ischemia – no. (%)	83 (18)	10 (30)	0.10
Preoperative heart rate (bpm)	68 ± 12	66 ± 11	0.34
Postoperative heart rate (bpm)	73 ± 13	74 ± 12	0.65
Sudden cardiac death – no. (%)	45 (10)	7 (21)	0.05
Cardiovascular events – no. (%)	78 (17)	12 (36)	0.01
Death – no. (%)	71 (16)	9 (27)	0.09

Outcomes

A total of 80 (17%) patients died during the follow-up period (median follow-up of 2.0 years (IQR 1.1-3.1)); 56 (70%) were due to cardiac causes. Sudden cardiac death (n=52) occurred in significantly more patients with perioperative VT, compared to those without VT during vascular surgery (21% versus 10%, p=0.045 respectively, **Table 2**). The median onset of perioperative VT to the occurrence of sudden cardiac death was 19 days. As shown in the Kaplan-Meier curve, the detection of perioperative VT was associated with an increased risk of sudden

cardiac death (**Figure 1**). In univariate analysis, the development of new-onset perioperative VT was independently associated with a significant 2.4-fold increased risk of long-term sudden cardiac death. After correction for gender, cardiac risk factors, and type of surgery, new-onset perioperative VT was still found to be independently associated with long-term sudden cardiac death and all-cause mortality (HR 2.57; 95% CI 1.14-5.79 and HR 2.06; 95% CI 1.02-4.19, respectively, **Table 3**).

Table 3. Multivariate analyses.

	Sudden cardiac death HR (95% CI)	Cardiac events HR (95% CI)	All-cause mortality HR (95% CI)
Male sex	0.69 (0.37 – 1.28)	0.91 (0.55 – 1.50)	0.88 (0.52 – 1.49)
Cardiac risk index			
Low-risk	1	1	1
Intermediate-risk	1.65 (0.68 – 4.04)	1.76 (0.88 - 3.50)	1.28 (0.82 – 3.37)
High-risk	2.82 (1.11 – 7.17)	3.26 (1.60 – 6.67)	1.66 (0.82 – 3.37)
Type of surgery	1.40 (0.75 – 2.61)	1.73 (1.05 – 2.84)	1.08 (0.66 – 1.75)
New-onset perioperative VT	2.57 (1.14 – 5.79)	2.66 (1.43 – 4.92)	2.06 (1.02 – 4.19)

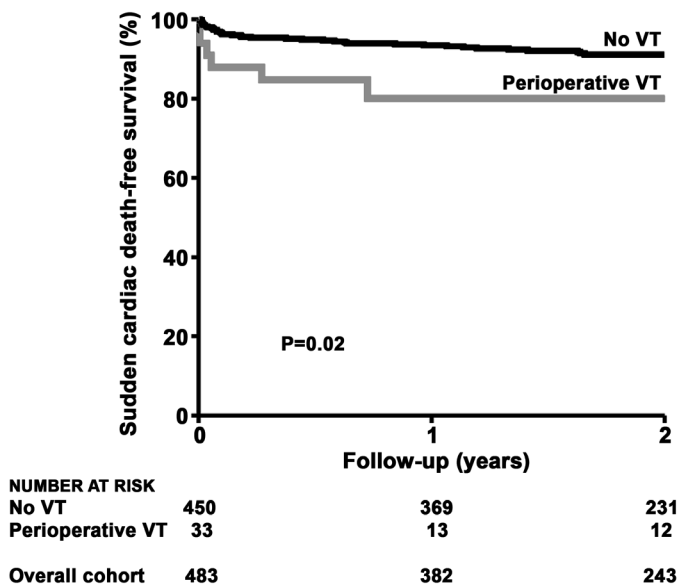


Figure 1. Kaplan-Meier analysis shows the survival of patients with new-onset perioperative VT compared to those not experiencing VT at a median follow-up of 24 months (IQR 1.1-3.1).

Discussion

The use of perioperative continuous-ECG monitoring to screen for the presence of ischemia and arrhythmia, helps to identify patients at risk for late sudden cardiac death. More patients with new-onset VT (incidence 6.8%) had a reduced LVEF and fewer patients received statin therapy preoperatively. The identification of new-onset VT in patients undergoing vascular surgery was related with a 2.6-fold increased risk in late sudden cardiac death.

Sudden death from cardiac causes accounts for approximately 50% of all deaths from cardiovascular diseases and 20% of all deaths[2, 14-15]. In the current study population, the incidence of sudden cardiac death was 10.8% (52/483). When looking into the patients with perioperative VT this incidence of sudden cardiac death was higher (21%). Since a large proportion of sudden cardiac death victims have no warning symptoms, it would be essential to identify the patients at high-risk of long-term sudden death. Despite decades of investigation, the ability to stratify the risk for sudden cardiac death is imperfect at best, as evidenced by the fact that, even among patients with no risk factors, sudden death occurs at a rate just less than 1% per year; patients with ≥ 3 risk factors appear to have event rates that approach 5% per year, whereas even survivors of prior sudden death have a rate of subsequent sudden death of approximately 10% per year[16]. In the latter mentioned study by Maron et al., the risk factors for sudden death were assessed in 506 patients with hypertrophic cardiomyopathy and implanted with an implantable cardioverter-defibrillator (ICD). Their conclusion was that ICD interventions for life-threatening ventricular tachyarrhythmia's were frequent and highly effective in restoring normal rhythm, and that a single marker of high risk for sudden death may be sufficient to justify consideration for prophylactic defibrillator implantation[16]. In the current study, patients with increased cardiac risk factors (prior history of MI, angina pectoris, stroke, CHF, diabetes mellitus, renal dysfunction and age higher than 70 years) were also associated with a significantly increased risk of sudden cardiac death (e.g. patients with a high-risk had a HR of 2.82 for sudden cardiac death), and could thus be indicated for prophylactic ICD. In

the most recently published randomized controlled trial by Steinbeck et al.[17], however, patients with an acute MI had no improved survival after prophylactic ICD placement, compared to those treated medically only. The main difference between Steinbeck's study population and that from the current study is the fact that all Steinbeck's patients had an acute MI prior to being randomized to an ICD. In previously published studies[18-20] reporting that the use of ICD reduces mortality in high-risk populations with ischemic disease, patients were recruited more than one year after the index MI. Hohnloser et al. conducted the DIMAMIT (Defibrillator IN Acute MI Trial) and concluded that prophylactic ICD therapy did not reduce overall mortality in high-risk patients with a recent MI (enrolled 6 to 40 days after an acute MI), even though it was associated with a reduction in the rate of death due to arrhythmia that was offset by an increase in the rate of death due to non-arrhythmic causes[21].

In the current study population the majority of patients were treated optimally with medical therapy. However it is notable that a lower percentage of patients who experienced VT were receiving preoperative statin therapy (70%) compared to those who did not experience arrhythmias (85%) even though baseline CRP levels were not different between these groups. A previous study by Vyas et al. concluded that statin use in patients with an ICD were associated with fewer VT/VF episodes and a 28% reduction in risk of a first VT/VF episode[22]. It could be hypothesized that the patients developing perioperative new-onset VT, in the current study, could benefit from statin use and that some of the patients, especially those with VT prior to MI may benefit form an ICD implant to prevent sudden cardiac death. In the end, the choice whether to pursue an ICD comes down to whether the individual patients and their physicians perceive that the risk of sudden death outweighs the risk of device placement. In the current study population 45 out of 52 patients who died due to sudden cardiac death were not identified with perioperative VT. By extending the ECG monitoring period with an implantable monitoring device recording online, the chances of capturing more episodes of new-onset VT increase, especially those presenting outside the 72 hour ECG window, which in turn could enhance detection of those at highest risk of sudden death.

Study limitations

Larger studies will make a better understanding of the triggers for ventricular arrhythmias and better risk stratification algorithms. This study has limitations which include a relatively small cohort which likely precludes a fully characterization of the relationship between perioperative ventricular arrhythmias and sudden cardiac death.

In conclusion, perioperative VT during vascular surgery procedures is associated with late sudden cardiac death and decreased survival. Continuous perioperative ECG is an effective method to identify perioperative VT and may allow improved management of patients undergoing vascular operations.

References

1. Josephson M, Wellens HJ. Implantable defibrillators and sudden cardiac death. *Circulation*. 2004;109:2685-91.
2. Gorgels AP, Gijsbers C, de Vreede-Swagemakers J, Lousberg A, Wellens HJ. Out-of-hospital cardiac arrest--the relevance of heart failure. The Maastricht Circulatory Arrest Registry. *Eur Heart J*. 2003;24:1204-9.
3. Straus SM, Bleumink GS, Dieleman JP, van der Lei J, Stricker BH, Sturkenboom MC. The incidence of sudden cardiac death in the general population. *J Clin Epidemiol*. 2004;57:98-102.
4. Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J. QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. *Circulation*. 1991;83:1888-94.
5. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Engl J Med*. 2001;345:1473-82.
6. Schouten O, Bax JJ, Poldermans D. Preoperative cardiac risk assessment in vascular surgery patients: seeing beyond the perioperative period. *Eur Heart J*. 2008;29:283-4.
7. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). *J Am Coll Cardiol*. 2006;48:e247-346.
8. Feringa HH, Karagiannis S, Vidakovic R, Noordzij PG, Brugts JJ, Schouten O, et al. Comparison of the incidences of cardiac arrhythmias, myocardial ischemia, and cardiac events in patients treated with endovascular versus open surgical repair of abdominal aortic aneurysms. *Am J Cardiol*. 2007;100:1479-84.
9. Boersma E, Poldermans D, Bax JJ, Steyerberg EW, Thomson IR, Banga JD, et al. Predictors of cardiac events after major vascular surgery: Role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. *Jama*. 2001;285:1865-73.
10. Bjerregaard P, El-Shafei A, Kotar SL, Labovitz AJ. ST segment analysis by Holter Monitoring: methodological considerations. *Ann Noninvasive Electrocardiol*. 2003;8:200-7.
11. Myerburg RJ, Castellanos A. Language and interpretation of clinical trial outcomes: alternates, surrogates, and composites. *Heart Rhythm*. 2004;1:538-9.
12. Priori SG, Aliot E, Blomstrom-Lundqvist C, Bossaert L, Breithardt G, Brugada P, et al. Task Force on Sudden Cardiac Death of the European Society of Cardiology. *Eur Heart J*. 2001;22:1374-450.
13. Cannon CP, Battler A, Brindis RG, Cox JL, Ellis SG, Every NR, et al. American College of Cardiology key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes. A report of the American College of Cardiology Task Force on Clinical Data Standards (Acute Coronary Syndromes Writing Committee). *J Am Coll Cardiol*. 2001;38:2114-30.
14. Myerburg RJ, Interian A, Jr., Mitrani RM, Kessler KM, Castellanos A. Frequency of sudden cardiac death and profiles of risk. *Am J Cardiol*. 1997;80:10F-9F.
15. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: epidemiology, transient risk, and intervention assessment. *Ann Intern Med*. 1993;119:1187-97.
16. Maron BJ, Spirito P, Shen WK, Haas TS, Formisano F, Link MS, et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. *JAMA*. 2007;298:405-12.
17. Steinbeck G, Andresen D, Seidl K, Brachmann J, Hoffmann E, Wojciechowski D, et al. Defibrillator implantation early after myocardial infarction. *N Engl J Med*. 2009;361:1427-36.
18. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med*. 1999;341:1882-90.

19. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med*. 1996;335:1933-40.
20. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346:877-83.
21. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med*. 2004;351:2481-8.
22. Vyas AK, Guo H, Moss AJ, Olshansky B, McNitt SA, Hall WJ, et al. Reduction in ventricular tachyarrhythmias with statins in the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II. *J Am Coll Cardiol*. 2006;47:769-73.

PART II

Perioperative serum biomarker

9

Perioperative asymptomatic cardiac damage after endovascular abdominal aneurysm repair is associated with poor long-term outcome.

Journal of Vascular Surgery 2009;50(4):749-54

Tamara A. Winkel
Olaf Schouten
Jan-Peter van Kuijk
Hence J.M. Verhagen
Jeroen J. Bax
Don Poldermans

Abstract

Background: Endovascular abdominal aortic aneurysm (AAA) repair is associated with a decreased incidence of perioperative cardiac complications compared to open repair. However, endovascular AAA repair is not associated with long-term survival benefit. The aim of the current study was to assess the impact of perioperative asymptomatic cardiac damage after endovascular AAA repair on long-term prognosis.

Methods: In 220 patients undergoing elective endovascular AAA repair routine sampling of cardiac troponin T (cTnT) and ECG recording was performed on days 1, 3, and day 7 if the patient remained in the hospital. Elevated cTnT was defined as serum concentrations ≥ 0.01 ng/ml. Asymptomatic cardiac damage was defined as cTnT release without symptoms or ECG changes. The median follow-up was 2.9 years and survival status was obtained by contacting the civil service registry.

Results: A total of 24/220 patients had cTnT release, median 0.08 ng/ml, of who 20 (83%) were asymptomatic and without ECG changes. Patients with asymptomatic cardiac damage had a mortality rate of 49% [corrected] after 2.9 years vs 15% [corrected] for patients without perioperative cardiac damage ($P < .001$). Also after adjustment for clinical risk factors and medication use applying multivariate Cox regression analysis, asymptomatic cardiac damage was associated with a 2.3-fold increased risk for death (95% confidence interval, 1.1-5.1). Statin use was associated with a reduced long-term risk for death (hazard ratio, 0.5; 95% confidence interval, 0.3-0.9).

Conclusion: Asymptomatic cardiac damage in patients undergoing endovascular AAA repair is associated with poor long-term outcome. Routine perioperative cardiac screening after endovascular AAA repair might be warranted.

Introduction

Endovascular abdominal aneurysm (AAA) repair is associated with less perioperative cardiac complications compared to open abdominal aortic aneurysm repair. While (a)symptomatic cardiac damage occurs in up to 25% of patients undergoing open repair, the incidence of (a)symptomatic cardiac damage in endovascular repair is around 10%, even in those at high cardiac risk[1-3].

Despite this perioperative cardiac advantage of endovascular AAA repair the early benefits of endovascular repair dissipates within 2 years as has been shown in both the DREAM and EVAR-1 trials[4, 5]. While aneurysm related death free survival in DREAM and EVAR was better in patients treated endovascular, all-cause mortality was similar in both groups. Cardiac frail patients are less likely to survive the stress of open repair than the relatively safe endovascular repair. Consequently several studies have suggested that long-term outcome after successful AAA repair is related primarily to the presence and extent of underlying coronary artery disease and not to treatment modality[6, 7].

However, if patients are screened rigorously after endovascular AAA repair a substantial proportion of patients will be identified who experience asymptomatic cardiac damage as assessed by cardiac tropopin T measurements[1, 2]. Cardiac troponin T is a sensitive and specific marker for myocardial injury[8]. However, the impact of elevations of cardiac troponin T without clinical evidence of myocardial ischemia and persistent electrocardiographic abnormalities are unknown.

If asymptomatic cardiac troponin T release after endovascular treatment is associated with poor long-term outcome it might be used to identify those patients who benefit from aggressive follow-up and medical treatment after endovascular AAA repair. Therefore, we performed the current study with the aim to assess the prognostic value of asymptomatic cardiac troponin T release in patients undergoing endovascular AAA repair.

Methods

The study population consisted of 220 patients undergoing elective endovascular abdominal aneurysm repair during the period January 2003 to November 2008. These patients were identified in a prospectively maintained database of all patients undergoing vascular surgery at Erasmus MC, Rotterdam, the Netherlands. The Medical Ethics Committee of the Erasmus MC approved the study.

Prior to surgery, a detailed cardiac history was obtained and patients were screened for hypertension (blood pressure >140/90 mmHg, or medical therapy to control hypertension) and diabetes mellitus (fasting glucose level > 7.0 mmol/L, or medication to control diabetes). The presence of coronary artery disease was indicated by a previous myocardial infarction, previous coronary intervention, or present stable angina pectoris. Other cardiovascular risk factors scored in all patients included a history of CVA or TIA, age over 70 years, chronic heart failure, and chronic obstructive pulmonary disease (defined as a FEV1 < 70% of age and gender predictive value or medication use). Preoperative creatinine values were routinely obtained in all patients. Using the MDRD formula (186 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.212 if African)) the glomerular filtration rate was estimated (eGFR). Patients were subsequently categorized as having no renal impairment (eGFR > 90 mL/min/1.73 m^2), mild renal impairment (> 60, $\leq$ 90 mL/min/1.73 m^2), moderate renal impairment (> 30, $\leq$ 60 mL/min/1.73 m^2) and severe renal impairment (< 30 mL/min/1.73 m^2).

Additional cardiac stress testing

Preoperative stress testing at our institution is done based on the number of cardiac risk factors identified at preoperative screening. Patients without cardiac risk factors usually do not undergo additional cardiac stress testing. As is shown in the DECREASE II trial patients with 1 or 2 also do not need additional cardiac stress testing[9]. Patients with 3 or more risk factors all undergo additional testing. Since some patients included in the current study underwent EVAR in the period that DECREASE II was not yet completed there were also some patients with 1 or

2 risk factors that underwent additional cardiac stress testing. Since we did not have stress test results of all patients, we did not perform an analysis between preoperative stress testing and postoperative outcome.

Troponin measurement

At our institution troponin T levels are routinely measured in patients undergoing major vascular surgery on postoperative day 1, 3, and if patients are still in hospital on day 7 and whenever clinically indicated by ECG changes, consistent with myocardial ischemia or infarction. Routinely ECGs are recorded preoperatively and on day 1, 3, and on day 7 if the patient remained in the hospital, and 30 after surgery. Troponin T level was measured using a whole blood rapid test (TropT version 2, Roche Diagnostics, Mannheim, Germany). Only patients with asymptomatic cardiac troponin T release, i.e. without ischemic symptoms or new ECG abnormalities, were included in the current study.

Endpoint

In January 2009 a follow-up was performed of all patients who survived major vascular surgery for at least 30 days. The primary endpoint chosen for the present study was all-cause mortality in order to avoid misclassification among cardiac, arrhythmic and non-cardiac mortality. Information about patients' vital status was requested by approaching the Office of Civil Registry.

Statistical analysis

Dichotomous variables were compared by means of Fisher's exact test, and continuous variables were compared by means of Kruskal–Wallis test. The Kaplan–Meier method was used to evaluate the prognostic value of asymptomatic troponin release with respect to survival. Differences in survival curves were compared by the log-rank test. Univariable Cox proportional hazard regression models were used to assess the independent association between troponin release, baseline clinical characteristics, and all-cause mortality. In order to avoid model over-fitting we applied a clinical risk model used in the DECREASE studies[9, 10]. In this model 1 point is assigned for the following risk factors: age over 70 years,

myocardial infarction, angina pectoris, heart failure, diabetes mellitus, renal dysfunction, history of cerebrovascular accident or transient ischemic attack. Patients with no risk factors are considered low-risk patients, those with 1 or 2 risk factors intermediate risk patients, and those with $\geq$ 3 risk factors high risk patients. Multivariable regression models were constructed by backward stepwise deletion of the least significant characteristics. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) are reported. For all tests, a P value of <.05 was considered significant. All analyses were performed using SPSS statistical software (SPSS Inc., Chicago, Illinois, version 15.0).

Results

Patient characteristics

A total of 220 patients undergoing endovascular abdominal aortic aneurysm repair were included in the study. The majority of patients were males (88%) and the mean age was 72.9 ± 7.4 years. General anesthesia was used in 102 patients (47%). According to cardiac risk score 14% of patients had low cardiac risk, 60% intermediate cardiac risk and 26% high cardiac risk. A total of 24 (10.9%) patients developed troponin T release within 30 days after surgery. Of these patients 4 (17%) had symptomatic troponin T release and/or ECG changes while 20 (83%) patients had asymptomatic troponin release without ECG changes. Baseline differences between patients with asymptomatic troponin T release and patients without troponin T release are shown in **table 1**.

Table 1: Baseline clinical characteristics.

	All patients N=216	**Troponin + N=20**	**Troponin – N=196**	**p-value**
Male – no. (%)	190 (88)	18 (90)	172 (88)	.77
Age – mean, years (SD)	73 (7.4)	77 (6.6)	73 (7.4)	<.01
Myocardial infarction – no. (%)	74 (34)	6 (30)	68 (35)	.81
Angina – no. (%)	53 (25)	6 (30)	47 (24)	.55
Heart failure – no. (%)	19 (9)	3 (15)	16 (8)	.30
TIA or CVA – no. (%)	30 (14)	5 (25)	25 (13)	.13
Diabetes – no. (%)	26 (12)	2 (10)	24 (12)	.77
Renal dysfunction – no. (%)	23 (11)	5 (25)	18 (9)	.03
Hypertension – no. (%)	122 (57)	10 (50)	112 (57)	.54
COPD – no. (%)	59 (27)	6 (30)	53 (27)	.78
Previous CABG or PCI – no. (%)	40 (19)	1 (5)	39 (20)	.13
Beta-blocker use – no. (%)	187 (87)	15 (75)	172 (88)	.11
Statins – no. (%)	125 (58)	9 (45)	116 (59)	.22
Glomerular filtration rate* (mL/min/1.73 m^2)				<.01
< 30 – no. (%)	10 (5)	4 (20)	6 (3)	
≥ 30, <60 – no. (%)	41 (19)	7 (35)	34 (17)	
≥ 60, <90 – no. (%)	110 (51)	6 (30)	104 (53)	
≥ 90 – no. (%)	55 (26)	3 (15)	52 (27)	

**estimated using the MDRD formula; TIA = transient ischemic attack; CVA = cerebrovasular accident; COPD = chronic obstructive pulmonary disease*

Patients who experienced asymptomatic troponin T release were more likely to have preoperative renal dysfunction; 11/20 (55%) of patients with postoperative asymptomatic troponin T release had an estimated GFR < 60 mL/min/1.73 m^2 compared to 40/196 (20%) of patients without postoperative troponin T release (P<.01). A total of 22 patients were admitted to the Post Anesthesia Care Unit or Intensive Care Unit postoperatively. Of these, in only 2 patients the ICU stay was longer than one day.

Long-term prognosis of patients with asymptomatic cardiac damage

The median follow-up was 2.9 years (interquartile range 0.9 – 4.3 years). A total of 46 (21%) patients died during follow-up. As shown in **figure 1** asymptomatic troponin T release was significantly associated with poor long-term survival in patients undergoing endovascular AAA repair. In univariate analysis patients with asymptomatic troponin T release had a 3.6-fold increased risk (95% CI 1.8 – 7.2) for mortality during follow-up.

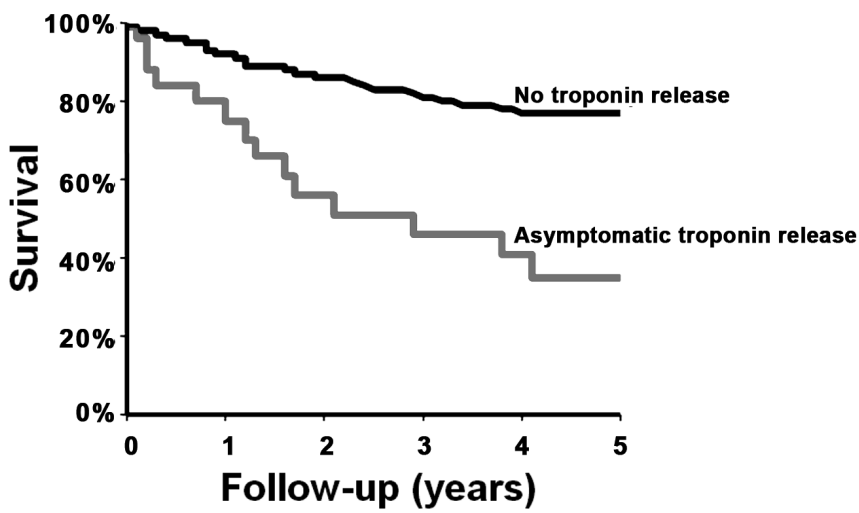


Figure 1. Long-term survival of patients without perioperative troponin release and patients with asymptomatic troponin release.

Other variables that were associated with poor long-term outcome in univariate analysis included a history of ischemic heart disease (HR 1.6, 95% 0.9 - 2.9), heart failure (HR 2.4, 95% 1.1 - 5.2), renal failure (HR 2.3, 95% 1.1 - 4.8), and age over 70 years (HR 2.1, 95% 1.1 - 4.3). Importantly, also in multivariate analysis asymptomatic cardiac troponin release was still associated with a 2.3 (95% CI 1.1 – 5.1) fold increased risk for all-cause mortality during a median follow-up of 2.9 years (**table 2**).

Table 2. Multivariate Cox regression analysis for all-cause death*

	HR	95% CI	p-value
Perioperative troponin release	2.33	1.07 – 5.07	.03
Age, per year increase	1.05	1.01 – 1.10	.02
Ischemic heart disease	1.88	0.99 – 3.55	.05
GFR < 60 mL/min/1.73 m^2	1.81	0.92 – 3.56	.09
Statin use	0.47	0.25 – 0.90	.02

**adjusted for age, gender, diabetes, stroke, COPD, hypertension; GFR = glomerular filtration rate.*

Long-term prognosis of patients with asymptomatic cardiac damage and renal dysfunction

A recurring discussion is whether asymptomatic cardiac troponin T release in patients with renal dysfunction has any clinical relevance. Therefore we performed a separate analysis of patients with an estimated GFR < 60 mL/min/1.73 m^2. Of 51 patients with an estimated GFR < 60 mL/min/1.73 m^2, 11 had asymptomatic cardiac troponin release. As shown in **figure 2** asymptomatic troponin T release in these patients was associated with a 3.0-fold (95% CI 1.2 - 7.5) increased risk for long-term mortality. Also in multivariate analysis we found a significant 2.8-fold (95% CI 1.1 – 7.3) increased risk for mortality when adjusted for the presence of ischemic heart disease, age over 70 years and congestive heart failure.

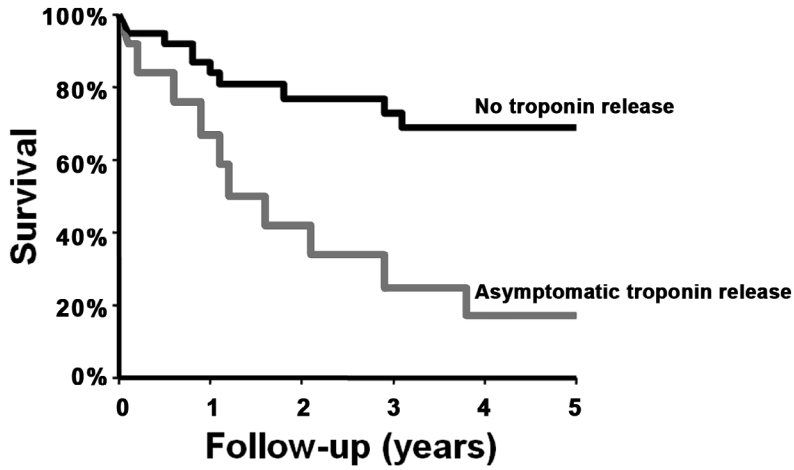


Figure 2. Long-term survival of patients with a eGFR < 60 mL/min/1.73 m^2 with and without asymptomatic perioperative troponin release.

Impact of statin therapy on long-term outcome

A total of 41% of patients were not on statin therapy at the time of discharge from the hospital. During follow-up patients statin use at hospital discharge was associated with a decrease in all-cause mortality compared to patients not on statins (HR 0.52, 95% CI 0.29-0.94, **figure 3**). Also after adjustment for clinical baseline characteristics and perioperative troponin release statin use was associated with improved outcome (HR 0.47, 95% 0.25 – 0.90).

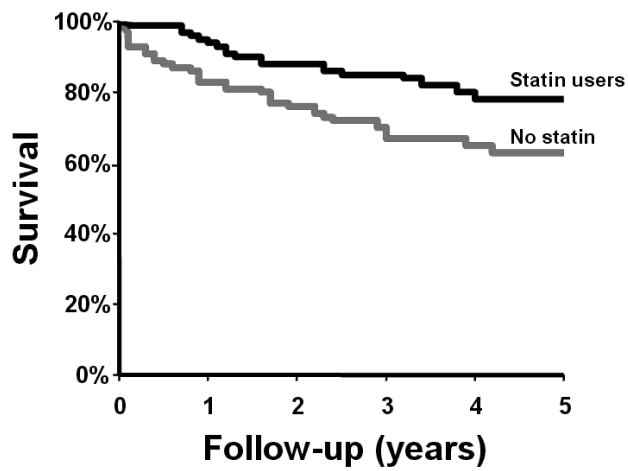


Figure 3: Long-term survival in statin users and non-users after endovascular AAA repair.

Discussion

The current study shows a strong association between perioperative asymptomatic cardiac troponin T release and poor long-term outcome after endovascular AAA repair. Despite the relative low surgical stress of endovascular repair approximately 10% of patients suffer asymptomatic myocardial damage that would not have been detected without routine postoperative cardiac troponin T measurements.

While the perioperative benefits of endovascular AAA repair are widely accepted, the long-term benefit of endovascular AAA repair is less well established. Though previous studies suggest a potential cardiac event free survival benefit for patients undergoing endovascular AAA repair, these patients are still considered to be at high risk for cardiac events compared to the general population. The compromised long-term survival of endovascular AAA repair patients might be explained by the high prevalence of symptomatic and asymptomatic underlying coronary artery disease. As was already shown 25 years ago by Hertzer et al., only 6% of patients with an abdominal aortic aneurysm have a normal coronary artery tree while 36% have severe coronary artery disease[11]. More recent series using functional tests such as dobutamine stress echocardiography confirmed these findings. As has been shown previously the impact of the presence and extent of coronary artery disease seems to have much greater impact on long-term survival of patients with AAA than is the choice of treatment modality[6].

The finding of approximately 10% of patients undergoing endovascular AAA experiencing cardiac troponin T release is in line with previously published work. In a previous smaller study we found an incidence of perioperative myocardial injury after endovascular AAA repair of 10.2% in a group of 49 unselected patients[12]. Also in 55 endovascular AAA repair patients at high clinical cardiac risk, based on traditional cardiac risk factors, the incidence of perioperative myocardial injury is relatively low (13%)[7]. Other authors confirmed these findings. Abraham et al. found an incidence of 10% in patients undergoing elective endovascular AAA repair[1]. It is remarkable that none of these patients had clinical signs of ischemia and would

thus have been missed if no routine cardiac troponin T measurement had been performed. These findings are in line with the results of the current study as 77% of patients with troponin release were asymptomatic. The concealed cardiac damage might also explain the low incidence of ischemic cardiac complications reported in other studies and randomized trials. For example the DREAM trial showed an incidence of cardiac complications in the endovascular group of 5.3% of which 66% was classified as being not severe[13]. It should be noted that patients undergoing EVAR are usually hospitalized for only 2 or 3 days postoperatively. It might be argued that the true incidence of myocardial damage is even higher than reported in the current study as troponin was only measured during hospitalization.

Almost 100% of patients with an acute coronary syndrome have cardiac troponin release as a consequence of the ischemic cardiac event[8]. Indeed troponin I and T are cardiac isoforms and solely expressed in cardiac muscles, making it a very sensitive marker for myocardial injury. However, there are several other conditions that might trigger troponin release. These conditions include among others: sepsis, systemic inflammatory response syndrome, pulmonary embolism, acute and chronic heart failure, and end-stage renal disease[8]. The cause of troponin release in these conditions is not clarified. A transient leakage of troponins of the cystosolic pool might possibly be an explanation for troponin release into the bloodstream, in particular in case of pulmonary embolism or after physical exercise.

The current study supports the observations in patients undergoing major, open vascular surgery. In a study of 447 patients by Landesberg et al. even minor elevations of cardiac troponin during the first three postoperative days were associated with a 2-fold increased risk for long-term mortality after major vascular surgery[14]. In a study by Kertai et al., including 393 patients undergoing open aortic or infrainguinal vascular surgery this 2-fold increased risk for patients with asymptomatic troponin release was confirmed[15]. In a study by de Virgilio et al. patients undergoing endovascular aneurysm repair with an asymptomatic rise in CK-MB or troponin there was a clear trend for an increased risk for long-term mortality ($p=.09$)[16]. Importantly, it should be noted that this study started in 1996, a

time where troponin essays were less sensitive. This is reflected in the lower incidence of patients with troponin release compared to our study (6% vs 11%).

Patients undergoing endovascular abdominal aortic aneurysm repair with renal dysfunction are considered to be at high risk for long-term events. In a study by Azizzadeh et al. in 398 patients, a reduced GFR was associated with a significantly increased risk for long-term mortality[17]. The meaning of troponin release in patients with renal dysfunction is a matter of recurrent debate. As mentioned patients with end-stage renal disease often have levels of troponin above the 99th percentile. It should be noted that also in the current study patients with renal dysfunction more frequently had postoperative asymptomatic troponin release. For these patients the pattern of troponin release is of particular interest. Patients with renal dysfunction might have elevated troponins before the actual cardiac damage occurs. Therefore in the presence of a classical pronounced rise and fall of troponin levels in these patients, they still should be considered as having a cardiac event[18]. The current study showed that new-onset perioperative troponin release in patients with moderate renal dysfunction, i.e. an estimated GFR < 60 mL/min/1.73 m^2, is associated with a poor long-term prognosis. Therefore asymptomatic perioperative troponin release in patients with renal dysfunction should not be considered a relative harmless condition.

The optimal treatment of patients with asymptomatic troponin release is still ill-defined. As with all vascular surgical patients statins and aspirin should be prescribed[19, 20]. In the non-operative setting patients with non ST elevation myocardial infarctions are usually prescribed aggressive antiplatelet therapy, such as clopidogrel[21]. Whether it would also improve long-term outcome in patients with marginally elevated levels of troponin T after endovascular AAA repair remains to be determined.

The true incidence of myocardial damage may be even higher than reported in the current study

as troponin was only measured during hospitalization and many patients are discharged within 2-3 days postoperatively. In fact, in the current study the median length of stay was 3 days. Subsequently, in some patients troponin release might have been missed after the third postoperative day.

In conclusion, perioperative asymptomatic troponin T release in patients undergoing endovascular AAA repair is a marker for poor long-term survival, even in those with renal dysfunction. While only 10% of patients experience asymptomatic troponin T release, 55% of deaths during 2.9 years of follow-up occurred in this group of patients. Stringent follow-up and adherence to secondary prevention guidelines in these patients is of utmost importance.

References

1. Abraham N, Lemech L, Sandroussi C, Sullivan D, May J. A prospective study of subclinical myocardial damage in endovascular versus open repair of infrarenal abdominal aortic aneurysms. J Vasc Surg 2005;41(3):377-80; discussion 80-1.
2. Schouten O, Dunkelgrun M, Feringa HH, et al. Myocardial damage in high-risk patients undergoing elective endovascular or open infrarenal abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg 2007;33(5):544-9.
3. Le Manach Y, Perel A, Coriat P, Godet G, Bertrand M, Riou B. Early and delayed myocardial infarction after abdominal aortic surgery. Anesthesiology 2005;102(5):885-91.
4. Blankensteijn JD, de Jong SE, Prinssen M, et al. Two-year outcomes after conventional or endovascular repair of abdominal aortic aneurysms. N Engl J Med 2005;352(23):2398-405.
5. Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial. Lancet 2005;365(9478):2179-86.
6. Schouten O, van Waning VH, Kertai MD, et al. Perioperative and long-term cardiovascular outcomes in patients undergoing endovascular treatment compared with open vascular surgery for abdominal aortic aneurysm or iliaco-femoro-popliteal bypass. The American journal of cardiology 2005;96(6):861-6.
7. Schouten O, Lever TM, Welten GM, et al. Long-term cardiac outcome in high-risk patients undergoing elective endovascular or open infrarenal abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg 2008;36(6):646-52.
8. Korff S, Katus HA, Giannitsis E. Differential diagnosis of elevated troponins. Heart (British Cardiac Society) 2006;92(7):987-93.
9. Poldermans D, Bax JJ, Schouten O, et al. Should major vascular surgery be delayed because of preoperative cardiac testing in intermediate-risk patients receiving beta-blocker therapy with tight heart rate control? Journal of the American College of Cardiology 2006;48(5):964-9.
10. Boersma E, Poldermans D, Bax JJ, et al. Predictors of cardiac events after major vascular surgery: Role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. Jama 2001;285(14):1865-73.
11. Hertzer NR, Beven EG, Young JR, et al. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. Ann Surg 1984;199(2):223-33.
12. Feringa HH, Karagiannis S, Vidakovic R, et al. Comparison of the incidences of cardiac arrhythmias, myocardial ischemia, and cardiac events in patients treated with endovascular versus open surgical repair of abdominal aortic aneurysms. Am J Cardiol 2007;100(9):1479-84.
13. Prinssen M, Verhoeven EL, Buth J, et al. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. N Engl J Med 2004;351(16):1607-18.
14. Landesberg G, Shatz V, Akopnik I, et al. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. J Am Coll Cardiol 2003;42(9):1547-54.
15. Kertai MD, Boersma E, Klein J, Van Urk H, Bax JJ, Poldermans D. Long-term prognostic value of asymptomatic cardiac troponin T elevations in patients after major vascular surgery. Eur J Vasc Endovasc Surg 2004;28(1):59-66.
16. de Virgilio C, Tran J, Lewis R, et al. Factors affecting long-term mortality after endovascular repair of abdominal aortic aneurysms. Arch Surg 2006;141(9):905-9; discussion 9-10.
17. Azizzadeh A, Sanchez LA, Miller CC, 3rd, et al. Glomerular filtration rate is a predictor of mortality after endovascular abdominal aortic aneurysm repair. J Vasc Surg 2006;43(1):14-8.
18. Freda BJ, Tang WH, Van Lente F, Peacock WF, Francis GS. Cardiac troponins in renal insufficiency: review and clinical implications. Journal of the American College of Cardiology 2002;40(12):2065-71.
19. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45 Suppl S:S5-67.

20. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Journal of the American College of Cardiology 2006;47(6):1239-312.
21. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Journal of the American College of Cardiology 2007;50(7):e1-e157.

10

Prognosis of vascular surgery patients using a quantitative assessment of troponin-T release; is the crystal ball still clear?

accepted for publication

Tamara A. Winkel
Olaf Schouten
Sanne E. Hoeks
Michiel T. Voûte
Michel Chonchol
Dustin Goei
Willem-Jan Flu
Jan-Peter van Kuijk
Jan Lindemans
Hence J.M. Verhagen
Jeroen J. Bax
Don Poldermans

Abstract

Background: Cardiac troponin-T (cTnT) assays with increased sensitivity might increase the number of positive tests. Using the area under the curve (AUC) with serial sampling of cTnT an exact quantification of the myocardial damage size can be made. We compared the prognosis of vascular surgery patients with integrated cTnT-AUC values to continuous and standard 12-lead electrocardiography (ECG) changes.

Methods: 513 patients were monitored. cTnT sampling was performed on postoperative day 1, 3, 7, 30 and/or at discharge or whenever clinically indicated. Daily measurements of cTNT were performed, until baseline was achieved. CTnT-AUC was quantified and divided in tertiles. All-cause mortality and cardiac events (cardiac death and myocardial infarction) were noted during follow-up.

Results: 81/513 (16%) patients had cTnT release. After adjustment for gender, cardiac risk factors, and site and type of surgery, those in the highest cTnT-AUC tertile were associated with a significantly worse cardiac outcome and long-term mortality (HR 20.2; 95% CI 10.2-40.0 and HR 4.0; 95% CI 2.0-7.8 respectively). Receiver operator analyis showed that the best cut-off value for cTnT-AUC was <0.01 days*ng/mL for predicting long-term cardiac events and all-cause mortality.

Conclusion: In vascular surgery patients quantitative assessment of cTnT strongly predicts long-term outcome.

Introduction

Patients undergoing major vascular surgery are at high risk of cardiovascular morbidity and mortality due to underlying coronary artery disease[1]. It is estimated that the incidence of perioperative myocardial infarction (MI) is up to 5 to 10% in unselected patient populations[2]. However, in the perioperative setting it is difficult to rely on patients' symptoms for the detection of cardiac events as symptoms might very well be atypical or absent, due to residual anaesthetic effects, administration of analgesic agents and competing somatic stimuli such as incisional pain[3].

Postoperative cardiac screening of vascular surgery patients using cardiac troponin T (cTnT) and continuous 12-lead electrocardiography (ECG) monitoring might help to timely identify asymptomatic patients experiencing a postoperative cardiac event. While ECG changes are often transient and continuous ECG monitoring time consuming, cardiac troponins are biomarkers highly sensitive for the detection of a perioperative MI. Furthermore, the half-life of cardiac troponins is 6 hours, which enhances the chance of detection. Importantly, recent studies using highly sensitive troponin assays have demonstrated that low-level troponin elevations (>0.03 ng/mL) are common in high cardiac risk patients postoperatively, often with no evidence of ECG changes of ischemia[4]. CTnT assays detect low levels of troponin; however, the detection level has significantly improved, indicating that more patients with troponin release are identified. The clinical implications of these measurements are lacking, therefore a quantitative measurement of cTnT was studied.

However, besides the strong association between cardiac risk and perioperative ischemia characterized by cTnT release, and its influence on short, and long-term outcome, little is known on the measurement of this serum marker within the first 30 days postoperatively. Therefore, the present study was conducted to establish the additional prognostic and possible therapeutic consequences of cTnT area under the curve (cTnT-AUC) in patients undergoing elective vascular surgery.

Methods

Study population

The study population consisted of 513 unique patients undergoing vascular surgery at the Erasmus Medical Center in Rotterdam, the Netherlands, during the period December 2004 to November 2009. Patients with a history of cardiac arrhythmias, cardiac pacemaker, preoperative cTnT release, and procedures that precluded continuous-ECG monitoring were excluded. The hospital's ethical committee approved the study.

Preoperative risk assessment

We determined the cardiac risk score for each patient in our dataset, and one point was assigned to each of the following characteristics[2]: advanced age (> 70 years), history of myocardial infarction (MI), angina pectoris (AP), congestive heart failure (CHF), of stroke (transient ischemic attack and/or cerebral vascular accident), diabetes mellitus (fasting glucose level ≥ 7.0 mmol/L or use of insulin or oral glucose lowering medication), and renal insufficiency (serum creatinine >170 umol/l). Based on the number of these risk factors, patients were stratified into low-risk (no risk factors), intermediate-risk (1 or 2 risk factors), and high-risk (≥ 3 risk factors) categories[2]. All patients were screened for hypertension (blood pressure ≥140/90 mmHg or blood pressure lowering medication), hypercholesterolemia (plasma cholesterol level ≥5.5 mmol/L or use of cholesterol-lowering medication), smoking status, and chronic obstructive pulmonary disease (COPD[5]). In all patients beta-blockers were prescribed prior to surgery to obtain perioperative heart rates of 60-70 beats per minute[6]. After the visit to the outpatient clinic patients were prescribed with beta-blockers, statins and antiplatelet and/or anticoagulant medication.

ECG monitoring

Patients were continuously monitored with a 10-electrode, 12-lead digital ECG recorder (DR180+ Digital Recorder, NorthEast Monitoring Inc. Massachusetts) for 72 hours perioperatively initiated one day before and was continued until 48h after the surgical procedure. Recordings were performed in the continuous 12-lead mode with a recording cycle of 10 seconds every minute. Signal bandwidth was 0.05Hz to 150Hz. Electrocardiographic data were initially processed by a technician to exclude artifacts, and then analyzed for the presence of myocardial ischemia. Standard postoperative 12-lead ECGs were made on days 3, 7 and 30, and/or at discharge, and whenever clinically indicated. Using 12-lead ECG, patients with a perioperative MI were categorized into acute ST-segment elevation MI (STEMI; defined by the presence of ST-segment elevation ≥ 0.1mV in unipolar leads and confirmed by elevated cTnT above 0.03 ng/mL[7-8]) and non-ST-segment elevation MI (non-STEMI; defined by an elevation of cTnT above 0.03 ng/mL, on at least one occasion within 24 hours after the ischemic index event, with a rise or fall during subsequent sampling[7-8]).

Episodes of ischemia on continuous-ECG were defined as reversible ST-segment changes, lasting at least one minute and shifting from baseline by more than 0.1mV (1mm). ST-segment amplitude was measured 60 ms after the J point. If the J point fell within the T-wave, the ST-segment change was measured 40ms after that point[9]. The baseline ST-segment level was defined as the average ST-segment value during a stable period of at least 20 min duration. The criteria for an ST-depression and ST-elevation were 0.1 mV flat or down sloping morphology with deviated J-point[10].

Cardiac Troponin-T measurement

After surgery, cTnT levels were routinely measured on postoperative days 1, 3, 7, 30 and/or before discharge, and/or whenever clinically indicated by chest pain complaints or ECG changes consistent with myocardial ischemia or infarction. On average there were five cTnT measurements per patient. The cTnT level was measured using a whole blood rapid test by an electrochemiluminescence

immuneassay (TropT version 2, Roche Diagnostics GmbH, Mannheim, Germany). The lower limit of cTnT detection was 0.01 ng/mL and the upper limit of detection was 25 ng/mL, with the limit of quantification set at 0.03 ng/mL. If cTnT release occurred, measurements were repeated every day until the level returned to baseline value. Absolute cTnT levels were noted, peak value of cTnT was measured, and the release pattern was presented as AUC (days*ng/mL).

Long-term outcome

During follow-up outpatient visits were scheduled every 3 months after discharge. Survival status was determined by contacting the municipal civil service registry. The endpoints of the study were all-cause mortality and adverse cardiac events (cardiac death, MI, and unstable angina) during long-term follow-up (2.0 years; interquartile ranges (IQR) 1.1 – 3.1 years). MI was defined as the presence of 2 out of the following 3 criteria: (1) typical chest pain complaints, (2) electrocardiographic changes including acute ST-elevation followed by appearance of Q waves or loss of R waves, or new left bundle branch block, or new persistent T wave inversion for at least 24 hours, or new ST-segment depression which persists > 24 hours, and (3) a positive troponin T, i.e. > 0.10 ng/mL with characteristic rise and fall[8]. Cardiac death was defined as any death with a cardiovascular cause, including deaths following a cardiac procedure, cardiac arrest, MI, pulmonary embolus, stroke, or sudden death not ascribed to other causes[11]. No patients were lost to follow-up.

Data analysis

Continuous data are expressed as means ± standard deviation (SD) compared using the Student's *t* test. Continuous data with a skewed distribution are expressed as medians with IQR, compared using the Mann-Whitney *U* test. Categorical data are described as numbers and percentages and analyzed using the chi-square test or Fisher's exact test as appropriate. The trapezoidal rule was used to calculate the cTnT-AUC values for each patient profile from the concentrations of cTnT in the first 30 days after surgery. To facilitate the analyses with cTnT-AUC, cTnT levels were divided in tertiles (AUC1; 0.29 days*ng/mL [0.13 – 0.33], AUC2; 0.89 days*ng/mL [0.62 – 1.56] and AUC3; 8.67 days*ng/mL [5.99 – 23.12]). CTnT levels within the normal range were used as reference and an AUC1 to AUC3 represent those with an increasing cTnT-AUC. Gender, cardiac risk factors (prior history of MI, CHF, stroke, AP, renal dysfunction, diabetes, and age), and type and site of surgery were entered during the multivariable analysis. Estimates of the C-statistic for the Cox regression models were calculated and covariate adjusted receiver-operating-characteristic (ROC) plots were generated for models both with and without cTnT. The increased discriminative value of the cTnT-AUC level was examined to establish the change in the predictive survival probabilities for cardiac events and all-cause mortality (cTnT-AUC ROC). The relationship between cTnT-AUC and long-term cardiac events and all-cause mortality were assessed with Cox proportional hazards models. In addition, a cumulative one-year survival curve for vascular surgery patients with and without cTnT release was determined by the Kaplan-Meier method and compared using the log-rank test. Hazard ratios (HR) are given with 95% confidence intervals (CI). For all tests, a p-value of less than 0.05 (two-sided) was considered significant. All analyses were performed using SPSS 15.0 statistical software (SPSS Inc., Chicago, Illinois).

Results

The baseline clinical characteristics of the 513 included patients are listed in **Table 1.** The mean age at baseline was 69 ± 10 years and 77% were male. The preoperative cardiac risk was assessed and showed that 17% had a low-risk, 56% an intermediate-risk, and 27% a high-risk.

Perioperative outcome

During the first 30 days after surgery 20/513 (4%) patients died, of which 19/20 (95%) were due to cardiac causes. Thirteen out of the 20 patients with perioperative death experienced perioperative cTnT release. During the first 30 days after surgery cTnT abnormal levels were detected in 81/513 (16%) patients, of which 64 (79%) also had postoperative ECG changes. A total of 8 patients were classified as having a STEMI (10%) and 56 (69%) as non-STEMI (**Table 2**). Only 6/81(7%) patients had typical chest pain complaints. The median cTnT level was 0.11 ng/mL (IQR: 0.06 – 0.64). An elevated cTnT level was detected in 38% of patients undergoing an open AAA repair, 7% of those undergoing endovascular AAA repair, 17% in the lower extremity revascularization group, and 2% in those undergoing carotid endarterectomy. A total of seven patients underwent coronary artery revascularization during the perioperative period. The median cTnT-AUC was 0.89 days*ng/mL (IQR 0.33-6.02). As shown in **Table 1**, patients in the highest cTnT-AUC tertile were significantly older, more often had a history of MI, CHF, renal dysfunction, and more often underwent high-risk vascular surgery procedures. Patients with a STEMI were more often situated in the highest cTnT-AUC ($p<0.001$, **Table 2**) tertile.

Table 1. Baseline characteristics and cTnT-AUC

	All	No cTnT	AUC1	AUC2	AUC3	p-value
	n=513	n=432	n=27	n=27	n=27	
Age, years	68.9 ± 9.5	68.5 ± 9.6	68.7 ± 10.1	72.5 ± 7.6	72.6 ± 7.3	0.04
Males – no. (%)	397 (77)	327 (76)	22 (82)	23 (85)	25 (93)	0.14
History of MI – no. (%)	143 (28)	107 (25)	10 (37)	13 (48)	13 (48)	0.003
History of angina pectoris – no. (%)	87 (17)	70 (16)	5 (19)	5 (19)	7 (26)	0.61
History of CHF – no. (%)	39 (8)	27 (6)	1 (4)	5 (19)	6 (22)	0.002
Diabetes mellitus – no. (%)	109 (21)	87 (20)	7 (26)	8 (30)	7 (26)	0.54
Renal dysfunction – no. (%)	39 (8)	21 (5)	2 (7)	7 (26)	9 (33)	<0.001
History of stroke – no. (%)	192 (37)	167 (39)	7 (26)	9 (33)	9 (33)	0.53
Hypertension – no. (%)	262 (51)	217 (50)	13 (48)	15 (56)	17 (63)	0.58
COPD – no. (%)	185 (36)	144 (33)	9 (33)	17 (63)	15 (56)	0.002
Smoking – no. (%)	393 (77)	332 (77)	21 (78)	18 (67)	22 (82)	0.60
Preoperative cardiac risk						0.001
Low risk (no risk factors)	89 (17)	83 (19)	3 (11)	1 (4)	2 (7)	
Intermediate risk (1 or 2 risk factors)	288 (56)	247 (57)	18 (67)	12 (44)	11 (41)	
High risk (≥ 3 risk factors)	136 (27)	102 (24)	6 (22)	14 (52)	14 (52)	
Medication						
Beta-blockers – no. (%)	468 (91)	389 (90)	26 (96)	26 (96)	27 (100)	0.17
Statins – no. (%)	430 (84)	357 (83)	24 (89)	26 (96)	23 (85)	0.25
Antiplatelet therapy – no. (%)	388 (76)	323 (75)	25 (93)	19 (70)	21 (78)	0.18
Oral anticoagulants – no. (%)	72 (14)	62 (14)	2 (7)	5 (19)	3 (11)	0.65
ACE inhibitors – no. (%)	147 (29)	122 (28)	8 (30)	7 (26)	10 (37)	0.78
Diuretics – no. (%)	122 (24)	97 (23)	4 (15)	12 (44)	9 (33)	0.03
Site and type of surgery						<0.001
Open AAA repair – no. (%)	131 (26)	81 (19)	13 (48)	18 (67)	19 (70)	
Endovascular AAA repair – no. (%)	123 (24)	114 (26)	3 (11)	3 (11)	3 (11)	
Lower artery bypass– no. (%)	111 (22)	92 (21)	9 (33)	5 (19)	5 (19)	
Carotid endarterectomy – no. (%)	100 (19)	97 (23)	2 (7)	1 (4)	0 (0)	
Carotid artery stenting – no. (%)	48 (9)	48 (11)	0 (0)	0 (0)	0 (0)	

Table 2. Events and cTnT-AUC

	All	No cTnT	AUC1	AUC2	AUC3	p-value
	n=513	n=432	n=27	n=27	n=27	
STEMI – no. (%)	8 (2)	0 (0)	0 (0)	2 (7)	6 (22)	<0.001
Non-STEMI – no. (%)	56 (11)	0 (0)	12 (44)	17 (63)	17 (63)	<0.001
Cardiovascular events – no. (%)	97 (19)	43 (10)	15 (56)	16 (59)	23 (85)	<0.001
All-cause mortality – no. (%)	87 (17)	55 (13)	7 (26)	10 (37)	15 (56)	<0.001

Long-term outcome

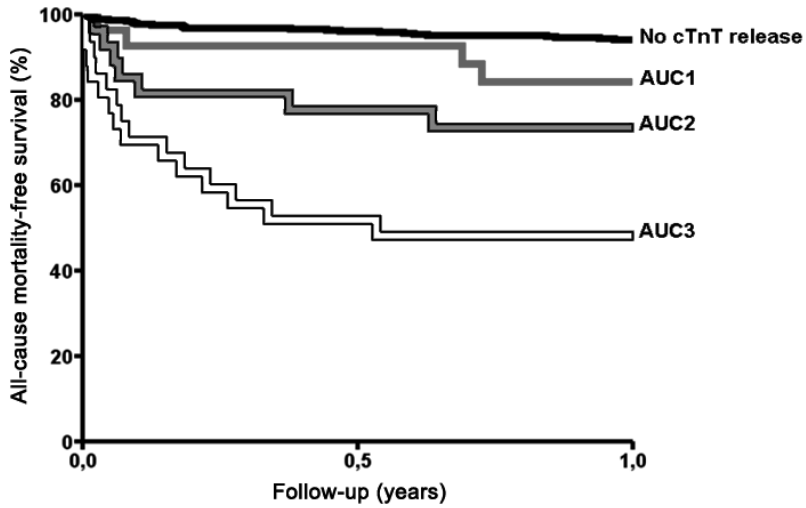
During a median follow-up of two years (IQR 1.1 – 3.1), 87 (17%) patients died. **Table 2** shows that patients with higher cTnT levels had a significantly higher incidence of mortality as compared to patients without cTnT release (32/81 (40%) versus 55/432 (13%); p<0.001) and cardiac events (54/81 (67%) versus 43/432 (10%); p<0.001). Cardiac events and long-term mortality occurred more often in those in the highest cTnT-AUC tertile as compared to those in the lowest or intermediate cTnT-AUC tertiles. In univariate analysis an increased cTnT-AUC was associated with an increased risk of long-term cardiac events and all-cause mortality (**Figure 1**, log-rank p-value < 0.001). The additional value of cTnT-AUC for predicting the combined endpoint of cardiac events and all-cause mortality on top of gender, cardiac risk factors and type and site of surgery, as compared to those without cTnT release, is portrayed in **figure 2**. As shown in **table 3** and **4**, those in the highest cTnT-AUC tertile were associated with a significantly worse cardiac outcome and long-term mortality (HR 20.2; 95% CI 10.2-40.0 and HR 4.0; 95% CI 2.0-7.8 respectively). When using cTnT-AUC as a continuous variable in multivariate analyses this was still found to be a significant predictor of late cardiac events and all-cause mortality (HR 1.07, 95% CI 1.05-1.09) and HR 1.02, 95% CI 1.00-1.04 respectively). C-statistic analyses showed that the best cut-off value for cTnT-AUC was <0.01 days*ng/mL for predicting long-term cardiac events and all-cause mortality. Patients with a cTnT-AUC ≥ 0.01 days*ng/mL had significantly more events during the long-term follow-up. A sub analyses with the addition of postoperative ECG changes and clinical symptoms to the model did not improve the prediction of cardiac events (cTnT-AUC C-statistic 0.82; cTnT-AUC, ECG changes and chest pain C-statistic 0.82 respectively) nor all-cause mortality (C-statistic 0.73 and 0.73 respectively).

Table 3. Uni -and multivariate analyses for the predictive value of gender, cardiac risk factors, site and type of surgery, and cTnT release on cardiovascular outcome.

	Univariate	**Mulitvariate**
	HR (95% CI)	**HR (95% CI)**
Gender	1.16 (0.67 – 1.99)	0.74 (0.44 – 1.24)
Prior history of MI	2.25 (1.42 – 3.57)	1.13 (0.72 – 1.78)
Prior history of CHF	2.99 (1.50 – 5.94)	1.43 (0.77 – 2.63)
Prior history of stroke	0.83 (0.52 – 1.33)	1.78 (1.09 – 2.92)
AP	1.58 (0.92 – 2.73)	1.26 (0.75 – 2.10)
Renal dysfunction	2.99 (1.50 – 5.94)	0.93 (0.50 – 1.72)
Diabetes	0.95 (0.55 – 1.65)	0.64 (0.38 – 1.09)
Age	1.03 (1.01 – 1.06)	1.03 (1.01 – 1.06)
Site and type of surgery		
Open AAA	1.00	1.00
EVAR	0.28 (0.15 – 0.52)	0.82 (0.42 – 1.58)
Lower extremity artery bypass	0.51 (0.29 – 0.91)	1.19 (0.69 – 2.04)
Carotid endarterectomy	0.08 (0.03 – 0.22)	0.18 (0.06 – 0.57)
Carotid artery stenting	0.32 (0.13 – 0.76)	0.82 (0.31 – 2.20)
cTnT release		
No cTnT release	1.00	1.00
AUC 1	11.31 (4.97 – 25.72)	7.84 (4.09 – 15.03)
AUC 2	13.16 (5.74 – 30.17)	7.08 (3.54 – 14.15)
AUC 3	52.02 (17.19 – 157.45)	20.15 (10.16 – 39.96)

Table 4. Uni -and multivariate analyses for the predictive value of gender, cardiac risk factors, site and type of surgery, and cTnT release on all-cause mortality.

All-cause mortality	**Univariate**	**Mulitvariate**
	HR (95% CI)	**HR (95% CI)**
Gender	1.06 (0.61 – 1.84)	0.76 (0.45 – 1.31)
Prior history of MI	1.65 (1.02 – 2.69)	1.09 (0.68 – 1.76)
Prior history of CHF	2.36 (1.15 – 4.87)	1.57 (0.81 – 3.05)
Prior history of stroke	0.51 (0.30 – 0.86)	0.69 (0.38 – 1.26)
AP	1.02 (0.56 – 1.89)	0.86 (0.48 – 1.54)
Renal dysfunction	2.70 (1.33 – 5.50)	1.68 (0.88 – 3.18)
Diabetes	0.54 (0.28 – 1.04)	0.56 (0.30 – 1.04)
Age	1.04 (1.01 – 1.07)	1.04 (1.02 – 1.07)
Site and type of surgery		
Open AAA	1.00	1.00
EVAR	0.49 (0.27 – 0.89)	0.69 (0.38 – 1.26)
Lower extremity artery bypass	0.46 (0.24 – 0.86)	0.79 (0.44 – 1.40)
Carotid endarterectomy	0.07 (0.02 – 0.24)	0.19 (0.05 – 0.68)
Carotid artery stenting	0.34 (0.13 – 0.86)	0.88 (0.30 – 2.55)
cTnT release		
No cTnT release	1.00	1.00
AUC 1	2.40 (0.97 – 5.94)	1.89 (0.83 – 4.31)
AUC 2	4.03 (1.76 – 9.25)	2.04 (0.97 – 4.33)
AUC 3	8.57 (3.81 – 19.26)	3.96 (2.01– 7.78)



No. at risk			
No cTnT release	432	398	356
AUC 1	27	22	20
AUC 2	27	20	17
AUC 3	27	14	12

Figure 1. Long-term mortality occurred more often in those in the highest cTnT AUC tertile as compared to those in the lowest or intermediate cTnT-AUC tertiles.

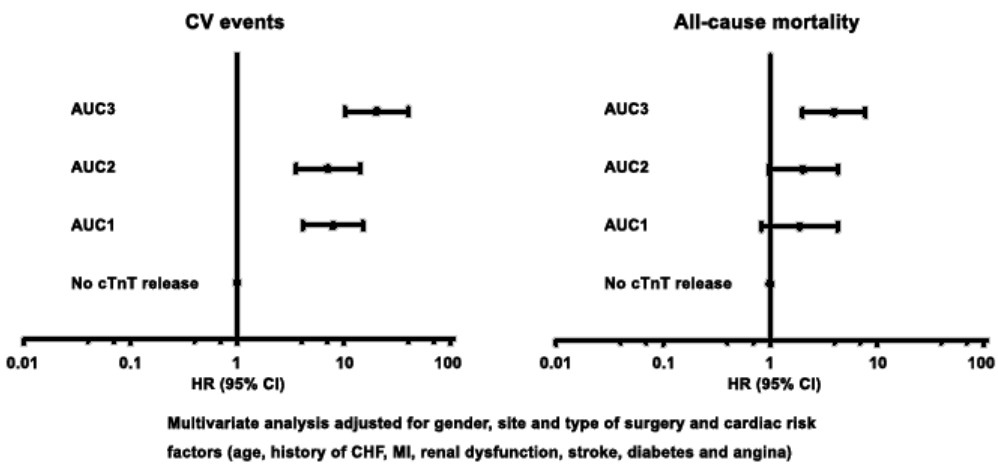


Figure 2. Multivariate analyses shows that increasing cTnT-AUC is associated with an increased risk of CV events and long-term all-cause mortality.

Discussion

This study shows that perioperative cTnT levels > 0.01 ng/mL as well as gradual increasing circulating levels of cTnT, presented as the cTnT-AUC, have a graded relationship with the incidence of cardiac events and all-cause mortality on long-term follow-up of such vascular surgery patients.

With the use of conventional assays of troponin, the prevalence of detectable concentrations of cTnT in the general population is approximately 0.7%[12]. Approximately 7% of cTnT exists freely in the cardiac myocyte cytoplasm[13] and has an increased precision at the lower end of the reference range. The mechanisms responsible for the release of very low levels of cTnT in patients with stable coronary artery disease (CAD) could include transient, clinically silent ischemic episodes and small-vessel occlusions, inflammatory processes, cardiomyocyte apoptosis, reduced renal clearance, and increased myocardial strain due to pressure or volume overload[14]. In the current study, patients with more cardiac risk factors were prone to develop perioperative cTnT release and had more events during the long-term follow-up. By introducing high-sensitivity cTnT (hs-cTnT) assays a greater number of patients will be detected and the first question arises whether minor changes in very low levels still remain strong predictors of events than are conventional and/or absolute levels and second whether serial testing of cTnT would enhance the prognostic value of the assay. In a study by Omland et al., 3679 patients with stable CAD were followed for a median time of 5.2 years and it was concluded that also hs-cTnT concentrations were significantly associated with the incidence of cardiac death and heart failure[15]. In the current study this was also the case for the lowest cTnT-AUC (AUC1) tertile being associated with a 8-fold increased risk of cardiac events as compared to those without cTnT release. Furthermore, the current analyses showed that the detection of cTnT in low levels indicates a higher detection of cardiac events and all-cause mortality on the long-term outcome.

In a study by Miller et al., serial cTnT samples were collected in 172 patients with CHF (New York Heart Association class III to IV)[16]. They concluded that elevations in cTnT, even when using a low threshold of 0.01 ng/mL, were highly associated with an increased risk of events, particularly with frequent or persistent cTnT elevations of ≥ 0.01 ng/mL[16]. We sought to elaborate on the hypothesis that an increased cTnT-AUC emerging from serial measurements of cTnT would provide incremental risk stratification information in addition to gender, cardiac risk factors, and type and site of surgery, in predicting adverse cardiac events and mortality. These findings might lead to an understanding of what types and timing of intervention might be effective in the management of these at-risk patients. In patients with chest pain complaints suspected for acute coronary syndrome early detection using ECG could offer the opportunity of timely thrombolysis. In a study of 3027 patients, of whom 362 were randomized to prehospital versus hospital thrombolysis, a significant resolution of ST-segment elevation was achieved due to timely intervention[17]. This setting is significantly different to the immediate postoperative period in which patients are recovering from surgery, where systemic thrombolysis is commonly not feasible. In addition the vast majority of patients are asymptomatic, stressing the importance of objective detection of myocardial damage. The optimal intervention in patients with immediate postoperative ST-segment changes has not been clarified yet. The early warning by standard assessment of cTnT levels in the perioperative period with short time intervals, for example, on day 1,2 and 3 postoperatively, and ECG abnormalities offers the opportunity to stratify the patient to intensified therapy. Despite multiple studies assessing the significance of perioperative myocardial ischemia measured by ECG monitoring[18-20], the study by Muehlschlegel et al. showed that none of the ECG criteria for myocardial injury predicted mortality, however, cTnT levels independently predicted 5-year mortality[21]. Similar results have been found in the current analyses, in which this is also the case, being that there is no additional predictive value of postoperative ECG changes and clinical symptoms on top of increasing cTnT-AUC. Importantly however, as is also shown in the current study, postoperative ischemia is silent in the majority of cases, making it difficult to detect[19]. Landesberg and colleagues found that long-duration (>2hr) of silent

subendocardial ischemia, using continuous 12-lead ECG, is predictive of postoperative cardiac complications[22-23]. Patients who developed an MI had more than 5-fold longer episodes of ischemia, and the cumulative ischemia duration was more than 7-fold longer, compared with patients with ischemia but no MI[22-23]. This indicates that timely intervention might improve postoperative outcome.

Limitations

Potential limitations of the current study merit consideration. First, is there an optimal cut-off value of cTnT-AUC and hs-cTnT that could aid clinicians in distinguishing patients at most risk of CV events and mortality? With the current study findings one could say that the mere presence of a cTnT-AUC is associated with an increased incidence of long-term CV events. Second, in the majority of cases continuous-ECG recordings were stopped by the time that cTnT release occurred. Continuous-ECG monitoring for a longer period of time may increase the potential detection of myocardial ischemia and those patients with perioperative ECG changes, which could ensure that asymptomatic and paroxysmal cases are not missed. Third, cTnT measurements were not done in a continuous online fashion, but were performed at fixed times or when clinical symptoms indicated myocardial damage. Finally, although medication at discharge was recorded, no data on medication during the follow-up period were available.

In conclusion, the present study shows that in vascular surgery patients an increased cTnT-AUC, as compared to the detection of ischemia on ECG, strongly predicts late mortality and cardiovascular events. Furthermore, patients with an increased perioperative cTnT-AUC should be highlighted, investigated and treated aggressively in an attempt to reduce late cardiovascular events or death after vascular surgery.

References

1. Hertzer NR, Beven EG, Young JR, O'Hara PJ, Ruschhaupt WF, 3rd, Graor RA, et al. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. *Ann Surg*. 1984;199:223-33.
2. Boersma E, Poldermans D, Bax JJ, Steyerberg EW, Thomson IR, Banga JD, et al. Predictors of cardiac events after major vascular surgery: Role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. *Jama*. 2001;285:1865-73.
3. Devereaux PJ, Goldman L, Yusuf S, Gilbert K, Leslie K, Guyatt GH. Surveillance and prevention of major perioperative ischemic cardiac events in patients undergoing noncardiac surgery: a review. *Cmaj*. 2005;173:779-88.
4. van Kuijk JP, Flu WJ, Voûte MT, Poldermans D, Schouten O. Asymptomatic perioperative cardiac damage: long-term prognosis. *Future Cardiol*. 2009;5:417-20.
5. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2007;176:532-55.
6. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *Circulation*. 2007;116:e418-99.
7. Giannitsis E, Steen H, Kurz K, Ivandic B, Simon AC, Futterer S, et al. Cardiac magnetic resonance imaging study for quantification of infarct size comparing directly serial versus single time-point measurements of cardiac troponin T. *J Am Coll Cardiol*. 2008;51:307-14.
8. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *Eur Heart J*. 2007;28:2525-38.
9. Bottiger BW, Motsch J, Teschendorf P, Rehmert GC, Gust R, Zorn M, et al. Postoperative 12-lead ECG predicts peri-operative myocardial ischaemia associated with myocardial cell damage. *Anaesthesia*. 2004;59:1083-90.
10. Bjerregaard P, El-Shafei A, Kotar SL, Labovitz AJ. ST segment analysis by Holter Monitoring: methodological considerations. *Ann Noninvasive Electrocardiol*. 2003;8:200-7.
11. Cannon CP, Battler A, Brindis RG, Cox JL, Ellis SG, Every NR, et al. American College of Cardiology key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes. A report of the American College of Cardiology Task Force on Clinical Data Standards (Acute Coronary Syndromes Writing Committee). *J Am Coll Cardiol*. 2001;38:2114-30.
12. Wallace TW, Abdullah SM, Drazner MH, Das SR, Khera A, McGuire DK, et al. Prevalence and determinants of troponin T elevation in the general population. *Circulation*. 2006;113:1958-65.
13. Freda BJ, Tang WH, Van Lente F, Peacock WF, Francis GS. Cardiac troponins in renal insufficiency: review and clinical implications. *J Am Coll Cardiol*. 2002;40:2065-71.
14. Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, et al. A sensitive cardiac troponin T assay in stable coronary artery disease. *N Engl J Med*. 2009;361:2538-47.
15. Omland T, Hagve TA. Natriuretic peptides: physiologic and analytic considerations. *Heart Fail Clin*. 2009;5:471-87.
16. Miller WL, Hartman KA, Burritt MF, Grill DE, Jaffe AS. Profiles of serial changes in cardiac troponin T concentrations and outcome in ambulatory patients with chronic heart failure. *J Am Coll Cardiol*. 2009;54:1715-21.
17. Kudenchuk PJ, Maynard C, Cobb LA, Wirkus M, Martin JS, Kennedy JW, et al. Utility of the prehospital electrocardiogram in diagnosing acute coronary syndromes: the Myocardial Infarction Triage and Intervention (MITI) Project. *J Am Coll Cardiol*. 1998;32:17-27.

18. Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, Tateo IM. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. *N Engl J Med*. 1990;323:1781-8.
19. Mangano DT, Hollenberg M, Fegert G, Meyer ML, London MJ, Tubau JF, et al. Perioperative myocardial ischemia in patients undergoing noncardiac surgery--I: Incidence and severity during the 4 day perioperative period. The Study of Perioperative Ischemia (SPI) Research Group. *J Am Coll Cardiol*. 1991;17:843-50.
20. Raby KE, Barry J, Creager MA, Cook EF, Weisberg MC, Goldman L. Detection and significance of intraoperative and postoperative myocardial ischemia in peripheral vascular surgery. *JAMA*. 1992;268:222-7.
21. Muehlschlegel JD, Perry TE, Liu KY, Nascimben L, Fox AA, Collard CD, et al. Troponin is superior to electrocardiogram and creatinine kinase MB for predicting clinically significant myocardial injury after coronary artery bypass grafting. *Eur Heart J*. 2009;30:1574-83.
22. Landesberg G, Mosseri M, Wolf Y, Vesselov Y, Weissman C. Perioperative myocardial ischemia and infarction: identification by continuous 12-lead electrocardiogram with online ST-segment monitoring. *Anesthesiology*. 2002;96:264-70.
23. Landesberg G, Mosseri M, Zahger D, Wolf Y, Perouansky M, Anner H, et al. Myocardial infarction after vascular surgery: the role of prolonged stress-induced, ST depression-type ischemia. *J Am Coll Cardiol*. 2001;37:1839-45.

PART III

Perioperative and long-term risk reduction

11

Reducing cardiac risk in non-cardiac surgery: evidence from the DECREASE studies.

European Heart Journal supplements 2009;11(supplement A):A9-A14

Don Poldermans
Olaf Schouten
Jeroen J. Bax
Tamara A. Winkel

Abstract

Ischaemic cardiac events are a major cause of perioperative morbidity and mortality in non-cardiac surgery; 10–40% of the perioperative deaths are due to myocardial infarction (MI). Drugs that influence myocardial oxygen balance (e.g. beta-blockers) or improve plaque stability (e.g. statins) would be expected to reduce perioperative MI. Evidence for the benefit of beta-blockers in high-risk patients undergoing noncardiac surgery comes from various studies including the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) study, in which perioperative bisoprolol significantly reduced short- and long-term cardiac death and MI. DECREASE IV found that bisoprolol also significantly reduced 30-day cardiac death and MI in intermediate-risk patients, with a non-significant trend towards a beneficial effect of fluvastatin XL. DECREASE III showed that in high-risk patients undergoing major vascular surgery, fluvastatin XL reduced myocardial ischaemia and the combined endpoint of cardiovascular death and MI. DECREASE II showed that patients identified as intermediate risk on the basis of clinical assessment did not need pre-operative echocardiographic cardiac stress testing, provided that they received bisoprolol to maintain tight heart rate control. DECREASE V found that in high-risk patients with extensive stress-induced ischaemia, coronary revascularization (added to tight heart rate control with bisoprolol) did not produce any additional reduction in death and MI.

Introduction

Ischaemic heart disease (IHD) leading to angina pectoris, myocardial infarction (MI), and chronic heart failure is one of the most important health issues confronting western societies. For example, angina pectoris affects up to 20% of men older than 74 years.[1] Overall, the prognosis of patients with IHD is poor; 5.5% of men with angina pectoris will die due to cardiovascular causes within 2 years of diagnosis.[1] However, prognosis also varies greatly and is related to the presence and treatment of underlying co-morbidities such as diabetes, hypertension, smoking, and hyperlipidaemia.

Treatment of patients with known coronary artery disease (CAD) and IHD is focused not only on symptomatic management, but also on improving prognosis, i.e. preventing acute cardiovascular events and the development of left ventricular (LV) dysfunction. Lifestyle changes (smoking cessation, diet, and exercise) are required, along with pharmacological management.

For example, in stable angina pectoris, management may include anti-platelet agents, statins, angiotensin-converting enzyme (ACE) inhibitors for patients with coincident ACE inhibitor indications, and beta-blockers. Beta-blockers reduce oxygen demand by reducing heart rate, contractility, and blood pressure. ESC guidelines recommend them as first-line anti-anginal agents for their effects on ischaemic symptoms.[1] They also state that they should be used for their long-term preventative benefits in all post-MI patients (discussed subsequently) and in those with LV dysfunction. The guidelines state that, for tolerability, beta1-selective agents such as bisoprolol, metoprolol, and atenolol should be preferred. To achieve 24 h efficacy with once-daily dosing, they suggest using a beta1-selective agent with a long half-life (e.g. bisoprolol) or a formulation providing an extended plasma concentration profile (e.g. metoprolol succinate).

Beta-blockers also play a pivotal part in the management of post-MI patients, in whom long-term beta-blockade reduces the risk of death by about 23%.[2] Current ESC guidelines therefore recommend that beta-blockers should be used long-term in all patients who have recovered from an acute MI (in the absence of

contraindications).[3] Normally, treatment will start before the patient leaves hospital and continue indefinitely.

With the benefits of beta-blockers in IHD well-established, attention has turned in the last decade to another situation in which they can prevent ischaemia and save lives: non-cardiac surgery. Cardiac complications are the commonest cause of death following major surgery, with MI accounting for 10–40% of post-operative fatalities.[4] Exact data on post-operative outcomes in Europe are scarce. Given that some 40 million surgical procedures are performed annually in Europe and in a large survey from the Netherlands, the incidence of perioperative MI and death is 1 and 0.3%, respectively; it is estimated that about 400 000 of non cardiac surgical patients suffer an MI each year and about 133 000 die from cardiovascular causes.[5]

The high prevalence of cardiac events associated with noncardiac surgery reflects the high prevalence of underlying CAD in the general population, upon which the additional stresses of surgery are overlaid. The pathophysiology of perioperative MI is complex, but may include myocardial oxygen demand/supply mismatch associated with tachycardia, hypertension, and pain. Coronary plaque instability and subsequent rupture may also be involved. Thus, drugs that influence plaque stability and myocardial oxygen balance would be expected to reduce the incidence and severity of perioperative MI.

The guidelines of the American Heart Association/American College of Cardiology (AHA/ACC)[6] focus largely on betablockers as the most extensively researched pharmacological approach to reducing perioperative cardiac risk in non-cardiac surgery. Beta-blockers improve myocardial oxygenation by decreasing heart rate and myocardial contractility,[6] and this may explain their beneficial effects on cardiac events in high-risk patients undergoing non-cardiac surgery. A recent meta-analysis of 15 studies in 1077 high-risk patients indicated that betablockade could reduce the risk of perioperative cardiac death or non-fatal MI by 67%.[7] There is also evidence (albeit less extensive) for a beneficial role of statins. Non-pharmacological measures include surgical and anaesthetic techniques and preoperative revascularization.

This review briefly summarizes the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) series of studies (Table 1).[8–13] These randomized controlled trials have made a significant contribution to our understanding of how to prevent ischaemic events in patients undergoing non-cardiac surgery, using evidence-based evaluation and management strategies.

Table I Summary of key findings of the Duth Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) series of studies

Trial	Risk category	Conclusion
DECREASE I	High	In high-risk patients undergoing non-cardiac surgery, perioperative beta-blokkade with bisoprolol significantly reduces cardiac death and MI in the short- and long-term
DECREASE II	Low, intermediate, high	Patients identified as intermediate risk on the basis of a simple clinical assessment do not need pre-operative echocardiographic cardiac stress testing, provided that they receive bisoprolol to maintain resting heart rate at 60-65 b.p.m.
DECREASE III	High	In high-risk patients undergoing major vascular surgery, fluvastatin XL significantly reduces myocardial ischemia and the combined endpoint of cardiovascular death and MI
DECREASE IV	Intermediate	In intermediate-risk patients, bisoprolol significantly reduces cardiac death and MI, with a non-significant trend towards a benificial effect of fluvastatin XL
DECREASE V	High	In high-risk patients with extensive stress-induced ischaemia, coronary revascularization (added to tight heart rate control with bisoprolol) does not produce any additional reduction in death and MI and delays surgery

DECREASE: evidence for beta-blockade in high-risk patients

The first major study establishing a benefit of beta-blockers in reducing cardiac mortality in non-cardiac surgery was DECREASE.[8,9] This study selected a high-risk group of patients with proven CAD undergoing vascular surgery (a high-risk procedure). A total of 1351 patients were screened, 846 of whom had one or more cardiac risk factors. Of these, 173 had stress-induced ischaemia during dobutamine echocardiography and 112 of these were randomized to bisoprolol (n =

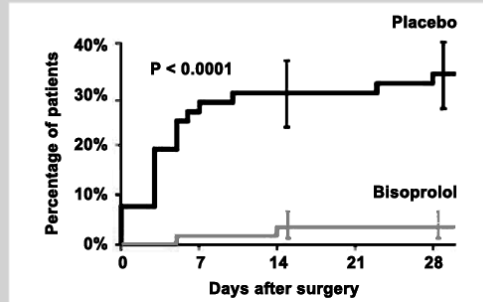


Figure 1 DECREASE showed that in high-risk patients undergoing non-cardiac surgery, perioperative β-blockade with bisoprolol significantly reduced the combined primary endpoint of cardiac death and myocardial infarction. Reproduced with permission from Poldermans *et al.*[9]

59) or standard care alone (n = 53). Bisoprolol was dosed at 5–10 mg once daily, starting at least 1 week before surgery (average 37 days) and continuing for 30 days post-operatively.

In the bisoprolol group, 2 patients (3.4%) died of cardiac causes within 30 days, compared with 9 patients (17%) who received standard care (P = 0.02) (Figure 1). Nine patients (17%) in the standard care group had a non-fatal MI, compared with none in the bisoprolol group (P = 0.001). The primary endpoint, the combined incidence of cardiac deaths and non-fatal MI, occurred in 3.4% in the bisoprolol group and in 34% in the standard care group (P = 0.001). During a 2-year follow-up, long-term administration of bisoprolol produced a significant three-fold reduction in cardiac death and MI (12% for bisoprolol vs. 32% in the standard care group).[8]

As noted in the AHA/ACC guidelines, not all studies show a benefit of perioperative beta-blockade in non-cardiac surgery. Negative results have been reported from some studies with metoprolol.[14,15] However, the AHA guidelines state that 'the weight of evidence—especially in aggregate—suggests a benefit to perioperative beta-blockade during non-cardiac surgery in highrisk patients.[6] Issues raised by the very recent Perioperative Ischemic Evaluation (POISE) with extended-release metoprolol succinate[16] are discussed below.

DECREASE IV: evidence for beta-blockade in intermediate-risk patients

The AHA/ACC guidelines divide patients undergoing non-cardiac surgery into various risk categories, based on clinical predictors established in observational studies.[17,18] With regard to intermediate-risk patients, the 2007 AHA/ACC recommendations (Table 2) state only that beta-blockade 'might be reasonable'. A firm recommendation could not be made on the basis of the available evidence, despite the fact that intermediate-risk patients represent the vast majority of surgical patients evaluated for cardiac risk in everyday practice. However, the issue of whether beta-blockade is beneficial in intermediate-risk patients has recently been addressed by the DECREASE IV study.[12,19]

DECREASE IV evaluated the effect of bisoprolol and fluvastatin on 30-day cardiac outcome in intermediate-risk patients after elective non-cardiac surgery. Patients were assessed as intermediate risk if they had one or two risk factors on the Revised Cardiac Risk Index Score (one point for each of high-risk surgery, CAD, heart failure, stroke, diabetes mellitus, renal failure). Patients had to be both beta-blocker- and statin-naive, which meant that 45 000 patients had to be screened in order to randomize the final cohort of 1066 patients. The mean age of the patients was 64 years, and 60% were male. About 5% had a history of angina or MI, and 11% had diabetes. This meant that they were at much lower risks than those included in previous studies.

Table 2 Summary of ACC/AHA recommendations on patients selection for perioperative beta-blockade

Potential candidates for perioperative β-blockade	Strenght of Recommendation
Patients already receiving β-blockers	Recommended
Vascular surgery in patients with ischaemia on pre-operative testing	Recommended
Vascular surgery in patients with coronary disease	Reasonable
Vascular surgery in patients with multiple clinical risk factors	Reasonable
Intermediate or high-risk surgery in patients with coronary disease or multiple clinical risk factors	Reasonable
Intermediate or high-risk surgery in patients with a single clinical risk factor	Might be reasonable
Vascular surgery in low-risk patients	Might be reasonable

Based on Fleisher *et al.*[6]

Prior to surgery, patients were randomized to bisoprolol, fluvastatin, the combination or control therapy. Medication was started at a median 34 days before surgery. The starting dose of bisoprolol was 2.5 mg daily, titrated to a perioperative heart rate of 50– 70 b.p.m. Fluvastatin was prescribed at a fixed daily dose of 80 mg. The primary endpoint was the composite of cardiac death and MI at 30 days after surgery.

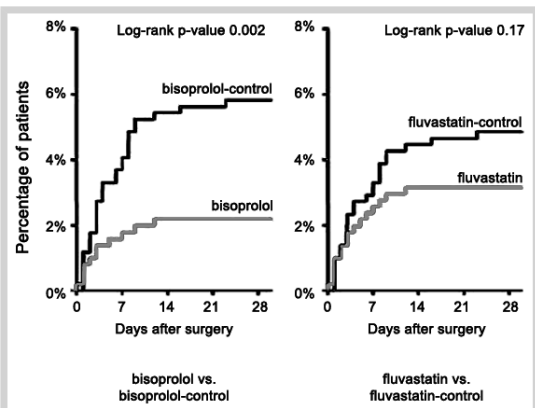


Figure 2 DECREASE IV showed that in intermediate risk patients undergoing non-vascular surgery, bisoprolol or bisoprolol plus fluvastatin significantly reduced 30-day cardiac death and myocardial infarction. Fluvastatin alone showed a non-significant trend towards an improved outcome.
Reproduced with permission from Dunkelgrun *et al.*[19]

This endpoint occurred in 43 (4.0%) patients: 5 (1.9%) on bisoprolol, 11 (4.1%) on fluvastatin, 6 (2.2%) on the combination, and 21 (7.8%) on double control. The beneficial effect of bisoprolol on the primary endpoint was statistically significant [hazard ratio (HR) 0.34; 95% confidence interval (CI): 0.17–0.67; P = 0.002]. Patients receiving fluvastatin had a lower incidence of the primary endpoint than fluvastatin controls (HR 0.65; 95% CI 0.35–1.20), but statistical significance was not reached (P = .17) (Figure 2). The beneficial effects of bisoprolol were not modified by fluvastatin (P-value for heterogeneity 0.26).

DECREASE III: evidence for statins in high-risk patients

Statins may act to prevent perioperative cardiac events in noncardiac surgery by stabilizing coronary plaques, due to their pleiotropic anti-inflammatory effects. The 2007 AHA/ACC guidelines state that 'the evidence accumulated thus far suggests a protective effect of perioperative statin use on cardiac complications during non-cardiac surgery', but note that most of the evidence is observational. A meta-analysis of 12 retrospective and three prospective trials found a 44% reduction in mortality with statins, when both cardiac and non-cardiac surgeries were included.[20]

Recently, the evidence for a beneficial effect of statins has been augmented by DECREASE III, a large randomized controlled trial. This shows that extended-release fluvastatin significantly reduces myocardial ischaemia and the combined endpoint of cardiovascular death and MI in high-risk patients undergoing major vascular surgery.[11]

DECREASE III included 500 statin-naive patients randomized to receive either placebo (n = 247) or fluvastatin (n = 253)-extended release at a dose of 80 mg once daily—on top of beta-blocker therapy (73% on bisoprolol). The primary endpoint was myocardial ischaemia, as assessed by a combination of continuous ECG monitoring in the first 72 h and then intermittent troponin-T measurements and further ECGs until the end of follow-up (30 days).

There was a clear reduction in the primary endpoint in the fluvastatin group. One month after surgery, 27 patients in the fluvastatin group (10.9%) had experienced

myocardial ischaemia, compared with 47 (18.9%) in the placebo group (OR 0.55; 95% CI 0.34–0.88, P = 0.013). The number needed to treat to prevent one patient experiencing myocardial ischaemia was 12.5. Similarly, the combined secondary endpoint of cardiac death or non-fatal MI occurred in 12 (4.8%) patients of those taking fluvastatin, compared with 25 (10.0%) of those on placebo (OR 0.47; CI 0.24–0.94).

DECREASE II: evidence that, with tight heart rate control, non-invasive cardiac testing is unnecessary in intermediate-risk patients

Current guidelines of the ACC/AHA recommend non-invasive cardiac testing to detect CAD in all patients about to undergo major vascular surgery.[6] However, non-invasive testing often delays surgery and carries its own risks. The success of bisoprolol in DECREASE therefore raises an important clinical question: given the protection offered by beta-blockade, is pre-operative echocardiographic stress testing necessary in all patients? DECREASE II was conducted to answer this question in intermediate-risk patients scheduled for major vascular surgery.[10]

DECREASE II included 1476 patients assessed according to a standard set of clinical criteria. Those assessed as low risk (0 risk factors; 24%) were given beta-blocker therapy if they were not already receiving it and proceeded to surgery without further testing. Highrisk patients (three or more risk factors; 23%) were referred for further cardiac testing. The remaining 770 patients were categorized as intermediate risk (one to two risk factors) and were randomly assigned to cardiac testing or no cardiac testing.

All patients were prescribed perioperative beta-blockers. Those already receiving beta-blockers continued their medication and those without beta-blockers started on bisoprolol 2.5 mg once daily at the screening visit. Beta-blocker dose was adjusted at admission and on the day before surgery to achieve a resting HR of 60–65 b.p.m. After discharge, patients continued on betablockade to maintain resting HR at the same level.

Intermediate-risk patients randomized to no testing had an incidence of cardiac death or MI similar to those who had undergone testing (1.8 vs. 2.3%, P = 0.62).

The upper limit of the 95% CI of the absolute risk difference in favour of cardiac testing was 1.2%, which indicates that the no-testing strategy was non-inferior to the testing strategy. Patients assigned to pre-operative testing waited an average of 3 weeks longer for their surgery (53 days between screening and surgery vs. 34 days in the no-testing group; P = 0.001). This implies that pre-operative echocardiography can be safely omitted among intermediate-risk patients reducing the delay to surgery and beta-blockers should be prescribed aiming at tight heart rate control. Tight heart rate control is important, as poor heart rate control predicted a worse outcome at 30 days.

DECREASE V: evidence that, with tight heart rate control, pre-operative revascularization is not necessary in high-risk patients

The DECREASE V pilot study[13] was designed to determine whether prophylactic coronary revascularization improves postoperative outcomes in high-risk patients with multiple risk factors and extensive stress-induced ischaemia. It screened 1880 patients scheduled for major vascular surgery. Of these, 343 were identified as high risk (three or more risk factors), all of whom received stress testing. Mild or no ischaemia was found in 242 of the high-risk patients. The remaining 101 patients, who had extensive stress-induced ischaemia, were randomized to revascularization (n = 49) or no revascularization (n = 52). All patients received bisoprolol to maintain tight heart rate control.

Among these high-risk patients with extensive stress-induced ischaemia, those assigned to revascularization had a 30-day outcome similar to those without. The composite endpoint of death or MI occurred in 33% of the revascularization group and in 27% of the no-revascularization group (P = 0.48). Two-year follow-up also showed no difference between the groups (Figure 3). Moreover, pre-operative cardiac workup delayed surgery, and two patients died between revascularization and operation. The findings of DECREASE V are consistent with those of the Coronary Artery Revascularization Prophylaxis (CARP) study.[21]

On the basis of these findings, the 2007 AHA/ACC guidelines6 note that ‘the usefulness of pre-operative coronary revascularization is not well-established in

high-risk ischaemic patients'. They therefore restrict their recommendations for pre-operative revascularization to patients with a range of additional specific indications.

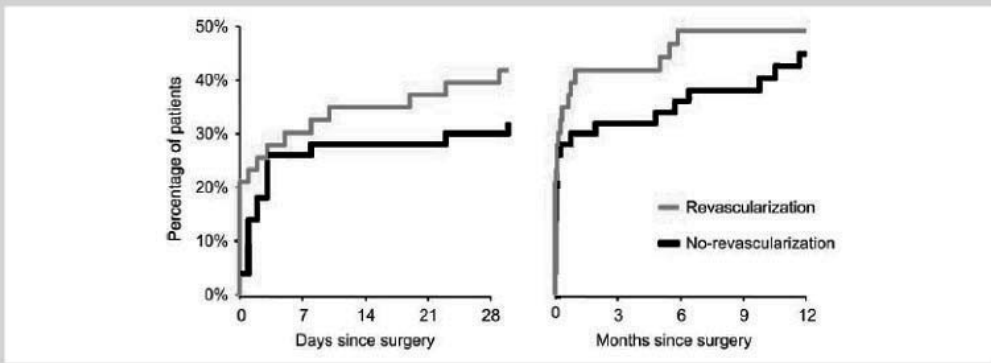


Figure 3 DECREASE V showed that pre-operative revascularization did not improve the outcome (composite endpoint: incidence of all-cause death or MI) for high-risk patients undergoing vascular surgery. Reproduced with permission from Poldermans *et al.*[13]

Stroke and perioperative beta-blockade: evidence from combined analysis of the DECREASE studies

Concerns have been raised recently by POISE with extended-release metoprolol succinate in patients undergoing non-cardiac surgery.[16] This showed that although metoprolol reduced the risk of cardiac events (cardiac death and non-fatal MI), it increased the risk of severe stroke and overall death. In contrast, in an analysis of all 3889 patients in the DECREASE trials, there was no evidence of any increase in perioperative stroke.[22] The overall incidence of perioperative stroke was significantly lower in the DECREASE trials compared with POISE: 0.46 vs. 0.98%, P = 0.006. Among beta-blocker users, the incidence was 0.5% in the DECREASE trials and 1.0% in the POISE study. In the DECREASE trials, all strokes were of ischaemic origin. Patients were more likely to have a perioperative stroke if they already had a history of stroke, but there was no association with either bisoprolol therapy.

The reasons for the different findings regarding stroke in the DECREASE series of studies and POISE remain the subject of debate.[23] However, it should be noted that the doses of metoprolol succinate used in POISE were high. A 100 mg dose

was given 2–4 h before surgery, 100 mg during 6 h after surgery, and 200 mg daily starting 12 h after surgery for 30 days thereafter.

Thus, at the day of surgery, the patients received up to 400 mg, which is the maximum recommended therapeutic dose for metoprolol succinate. Moreover, the 100 mg starting dose in POISE was two to eight times the recommended starting dose in other indications. In contrast, in the DECREASE trials, the average dose of bisoprolol was 2.5 mg once daily, only 12.5% of the maximum recommended therapeutic dose.

When beta-blockers are started could also be important. In the DECREASE trials, the low-dose bisoprolol regimen started at least 30 days prior to surgery, whereas in POISE, metoprolol was started 2–4 h before surgery. It is therefore reasonable to recommend that doses of beta-blockers used in non-cardiac surgery should be low (2.5 mg daily for bisoprolol as in the DECREASE trials and 25–50 mg daily for metoprolol succinate). Additionally, the drug should be started 30 days prior to surgery.

Conclusions

DECREASE and other randomized controlled trials provide a firm foundation for the use of beta-blockers to prevent perioperative ischaemic events in high-risk patients (and probably also intermediate-risk patients). Evidence for a beneficial effect of statins is also accumulating. Moreover, tight heart rate control with beta-blockade appears to enable us to dispense with routine non-invasive pre-operative testing in intermediate-risk patients and prophylactic coronary revascularization in high-risk patients. Thus, many patients could proceed to surgery earlier, which has important clinical and economic implications. Although many questions still remain to be answered, it is clear that, in future, new strategies in pharmacological therapy should markedly reduce the heavy burden of cardiac events associated with noncardiac surgery today.

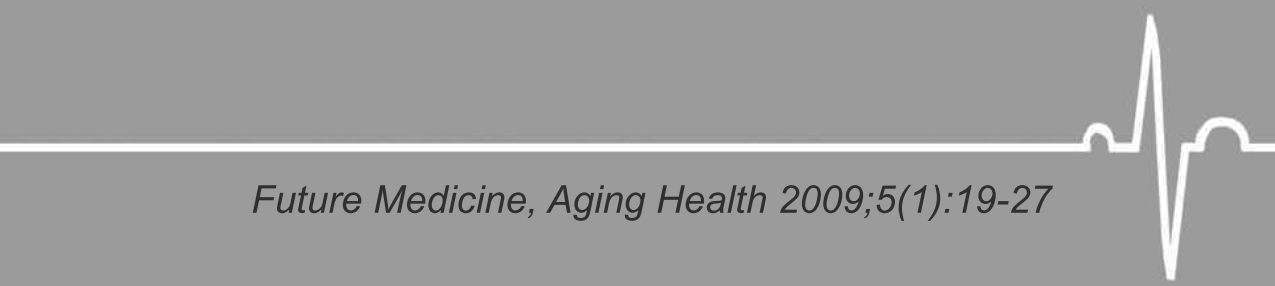
References

1. Fox K, Garcia MA, Ardissino D, Buszman P, Camici PG, Crea F, Daly C, De Backer G, Hjemdahl P, Lopez-Sendon J, Marco J, Morais J, Pepper J, Sechtem U, Simoons M, Thygesen K, Priori SG, Blanc JJ, Budaj A, Camm J, Dean V, Deckers J, Dickstein K, Lekakis J, McGregor K, Metra M, Osterspey A, Tamargo J, Zamorano JL. Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J 2006;27:1341–1381.
2. Freemantle N, Urdahl H, Eastaugh J, Hobbs FD. What is the place of betablockade in patients who have experienced a myocardial infarction with preserved left ventricular function? Evidence and (mis)interpretation. Prog Cardiovasc Dis 2002;44:243–250.
3. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, Dallongeville J, De Backer G, Ebrahim S, Gjelsvik B, Herrmann-Lingen C, Hoes A, Humphries S, Knapton M, Perk J, Priori SG, Pyorala K, Reiner Z, Ruilope L, Sans-Menendez S, Scholte op Reimer W, Weissberg P, Wood D, Yarnell J, Zamorano JL, Walma E, Fitzgerald T, Cooney MT, Dudina A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Funck-Brentano C, Filippatos G, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Altiner A, Bonora E, Durrington PN, Fagard R, Giampaoli S, Hemingway H, Hakansson J, Kjeldsen SE, Larsen ML, Mancia G, Manolis AJ, Orth-Gomer K, Pedersen T, Rayner M, Ryden L, Sammut M, Schneiderman N, Stalenhoef AF, Tokgozoglu L, Wiklund O, Zampelas A. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Eur Heart J 2007;28:2375–2414.
4. Auerbach AD, Goldman L. Beta-blockers and reduction of cardiac events in noncardiac surgery: clinical applications. JAMA 2002;287:1445–1447.
5. Boersma E, Kertai MD, Schouten O, Bax JJ, Noordzij P, Steyerberg EW, Schinkel AF, van Santen M, Simoons ML, Thomson IR, Klein J, van Urk H, Poldermans D. Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee cardiac risk index. Am J Med 2005;118:1134–1141.
6. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, Freeman WK, Froehlich JB, Kasper EK, Kersten JR, Riegel B, Robb JF, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Buller CE, Creager MA, Ettinger SM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Ornato JP, Page RL, Tarkington LG, Yancy CW. ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) Developed in Collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. J Am Coll Cardiol 2007;50:1707–1732.
7. Schouten O, Shaw LJ, Boersma E, Bax JJ, Kertai MD, Feringa HH, Biagini E, Kok NF, Urk H, Elhendy A, Poldermans D. A meta-analysis of safety and effectiveness of perioperative beta-blocker use for the prevention of cardiac events in different types of noncardiac surgery. Coron Artery Dis 2006;17:173–179.
8. Poldermans D, Boersma E, Bax JJ, Thomson IR, Paelinck B, van de Ven LL, Scheffer MG, Trocino G, Vigna C, Baars HF, van Urk H, Roelandt JR. Bisoprolol reduces cardiac death and myocardial infarction in high-risk patients as long as 2 years after successful major vascular surgery. Eur Heart J 2001;22: 1353–1358.
9. Poldermans D, Boersma E, Bax JJ, Thomson IR, van de Ven LL, Blankensteijn JD, Baars HF, Yo TI, Trocino G, Vigna C, Roelandt JR, van Urk H. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. N Engl J Med 1999;341: 1789–1794.

10. Poldermans D, Bax JJ, Schouten O, Neskovic AN, Paelinck B, Rocci G, van Dortmont L, Durazzo AE, van de Ven LL, van Sambeek MR, Kertai MD, Boersma E. Should major vascular surgery be delayed because of preoperative cardiac testing in intermediate-risk patients receiving beta-blocker therapy with tight heart rate control? J Am Coll Cardiol 2006;48:964–969.
11. Poldermans D, Schouten O, Benner R, van Urk H, Verhagen HJ, Khan N, Feringa H, Dunkelgrun M, Bax JJ, Boersma E. Fluvastatin XL use is associated with improved cardiac outcome after major vascular surgery. Results from a randomized placebo controlled trial: DECREASE III. Circulation 2008;118:S792. Abstract 2886.
12. Schouten O, Poldermans D, Visser L, Kertai MD, Klein J, van Urk H, Simoons ML, van de Ven LL, Vermeulen M, Bax JJ, Lameris TW, Boersma E. Fluvastatin and bisoprolol for the reduction of perioperative cardiac mortality and morbidity in high-risk patients undergoing non-cardiac surgery: rationale and design of the DECREASE IV study. Am Heart J 2004;148:1047–1052.
13. Poldermans D, Schouten O, Vidakovic R, Bax JJ, Thomson IR, Hoeks SE, Feringa HH, Dunkelgrun M, de Jaegere P, Maat A, van Sambeek MR, Kertai MD, Boersma E. A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery: the DECREASE V Pilot Study. J Am Coll Cardiol 2007;49:1763–1769.
14. Yang H, Raymer K, Butler R, Parlow J, Roberts R. The effects of perioperative beta-blockade: results of the Metoprolol after Vascular Surgery (MaVS) study: a randomized controlled trial. Am Heart J 2006;152:983–990.
15. Juul AB, Wetterslev J, Gluud C, Kofoed-Enevoldsen A, Jensen G, Callesen T, Norgaard P, Fruergaard K, Bestle M, Vedelsdal R, Miran A, Jacobsen J, Roed J, Mortensen MB, Jorgensen L, Jorgensen J, Rovsing ML, Petersen PL, Pott F, Haas M, Albret R, Nielsen LL, Johansson G, Stjernholm P, Molgaard Y, Foss NB, Elkjaer J, Dehlie B, Boysen K, Zaric D, Munksgaard A, Madsen JB, Oberg B, Khanykin B, Blemmer T, Yndgaard S, Perko G, Wang LP, Winkel P, Hilden J, Jensen P, Salas N. Effect of perioperative beta blockade in patients with diabetes undergoing major non-cardiac surgery: randomised placebo controlled, blinded multicentre trial. BMJ 2006;332:1482.
16. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Malaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008;371:1839–1847.
17. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, Ludwig LE, Pedan A, Goldman L. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999;100: 1043–1049.
18. L'Italien GJ, Paul SD, Hendel RC, Leppo JA, Cohen MC, Fleisher LA, Brown KA, Zarich SW, Cambria RP, Cutler BS, Eagle KA. Development and validation of a Bayesian model for perioperative cardiac risk assessment in a cohort of 1,081 vascular surgical candidates. J Am Coll Cardiol 1996;27:779–786.
19. Dunkelgrun M, Boersma E, Gemert AK-V, van Poorten F, Kalkman C, Schouten O, Siphanto W, Goei D, Hoeks S, Winkel T, Bax J, Thomson I, Poldermans D. 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. Circulation 2008;118:S906–S907. Abstract 4536.
20. Hindler K, Shaw AD, Samuels J, Fulton S, Collard CD, Riedel B. Improved postoperative outcomes associated with preoperative statin therapy. Anesthesiology 2006;105:1260–1272, quiz 89–90.
21. McFalls EO,Ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F, Pierpont G, Santilli S, Rapp J, Hattler B, Shunk K, Jaenicke C, Thottapurathu L, Ellis N, Reda DJ, Henderson WG. Coronary-artery revascularization before elective major vascular surgery. N Engl J Med 2004;351:2795–2804.
22. Poldermans D, Schouten O, Hoeks SE, Dunkelgrun M, van Lier F, Durazzo AE, Bax JJ, Boersma E. Perioperative stroke in non-cardiac surgery; the impact of prophylactic beta-blocker therapy. Circulation 2008;118:S758. Abstract 2637.
23. Fleisher LA, Poldermans D. Perioperative beta blockade: where do we go from here? Lancet 2008;371:1813–1814.

12

Bisoprolol in patients with chronic heart failure undergoing non-cardiac surgery.



Future Medicine, Aging Health 2009;5(1):19-27

Willem-Jan Flu
Tamara A Winkel
Jeroen J. Bax
Don Poldermans

Summary

Although considerable improvements in the treatment of chronic heart failure [CHF] have been made, CHF still remains a strong risk factor in patients undergoing major non-cardiac surgery. Adequate treatment of CHF in the perioperative setting is of great importance in the reduction of postoperative morbidity and mortality. Beta-blockers have beneficial effects towards CHF in which heart rate reduction plays a pivotal role. Randomized studies have shown that long acting beta-blockers, such as bisoprolol, seem to be the agents of preference in the reduction of cardiovascular and all-cause mortality. Titration according to tolerance and relatively low dosage of beta-blockers is of utmost importance to obtain a tight heart rate control and prevent adverse side effects. It is concluded that adequate bisoprolol treatment is beneficial in the perioperative setting in patients with or without CHF.

Introduction

Chronic heart failure is a clinical syndrome in which the ability of the ventricles to fill with or eject blood is impaired due to a variety of structural or clinical cardiac disorders. In the Western world the main causes of CHF are: 1) coronary artery disease, 2) hypertension, 3) dilated cardiomyopathy and 4) valvular heart disease. Chronic heart failure can be considered as a large health problem with major clinical impact. In the US a total of 5 million patients are diagnosed with CHF with an incidence of 550.000 new patients each year [1]. In the "European Society of Cardiology [ESC] guidelines for diagnosing and treatment of chronic heart failure" an estimated 0.4%-2% prevalence of CHF is noted. Furthermore, it is suggested that the prevalence of patients with symptomatic CHF is similar to the prevalence of patients with asymptomatic CHF, which may lead to an underestimation of the extent CHF in the general population [2-5]. The prognosis of patients with diagnosed CHF is poor. Half of the patients will die within 4 years and of the patients diagnosed with severe CHF, more than 50% will die within one year [6]. The main risk factors for CHF are: 1) hypertension, 2) older age, 3) diabetes mellitus, 4) obesity and 5) coronary artery disease. Chronic heart failure is diagnosed based upon a combination of clinical criteria first described in the Framingham study [7]. Most definitions of CHF focus on the presence of heart failure symptoms (i.e. shortness of breath at rest or during exertion and fatigue) and physical signs of fluid retention [8]. Chronic heart failure often presents without symptoms and when symptoms are present, they can be difficult to interpret. Therefore, a clinical suspicion must be confirmed by more objective test such as: echocardiographic examination, chest X-ray, ECG, and laboratory testing such as B-type natriuretic peptide.

The effect of CHF on postoperative outcome was first described by Kazmers et al, who concluded that survival rates are reduced in patients with an impaired left ventricular ejection fraction [LVEF] of 35% or less [9]. Hernandez et al showed that patients with CHF undergoing major non-cardiac surgery suffer substantial morbidity and mortality, despite advances in perioperative care [10]. Therefore,

preoperative risk stratification is of great importance to predict cardiac outcome in patients requiring major non-cardiac surgery. Multiple risk indexes have been developed over the years, such as the risk stratification models by Goldman and Detsky [11, 12]. The Lee index (or revised Goldman index) is generally considered to be the most relevant index in the prediction of cardiac risk. In preoperative risk stratification, based on the Lee index, CHF is considered as a strong risk factor in patients undergoing major non-cardiac surgery, with a large impact on postoperative cardiovascular outcome leading to a significant increase in morbidity and mortality [13]. Boersma et al not only focussed on the preoperative risk indexes estimating cardiac death, but they also developed a simple risk-index that accounts for significant clinical risk factors and medication use to predict perioperative all-cause mortality. By summing individual scores derived from the given predictors (myocardial infarction, angina pectoris, CHF, stroke, diabetes mellitus, renal dysfunction and age over 70 years) and with the use of the total risk score, the patient's probability of perioperative mortality can be estimated [14, 15].

In the past, major surgery was rarely carried out in elderly subjects. However, nowadays many major surgical interventions are performed in elderly populations at high risk for heart failure. Coupled to the growing prevalence of CHF and the elderly population is the increase in surgical procedures, amounting to nearly 40 million per year in Europe. Over 10 million major non-cardiac surgical interventions are performed each year, with the largest group of patients aged > 65 years. Although previous studies emphasize ischemic heart disease as the most important risk factor for perioperative complications, heart failure is equally important [10]. Therefore, adequate treatment of CHF in the perioperative setting is of pivotal importance to reduce morbidity and mortality after major non-cardiac surgery. Hammill et al noted that improvements in perioperative care are needed for adequate treatment of the patient population with CHF undergoing major non-cardiac surgery [16]. The present article reviews the current use of beta-blockers in patients with CHF undergoing major non-cardiac surgery, focussing on the use of bisoprolol in the perioperative setting.

Introduction to the compound

Bisoprolol, a selective beta 1-adrenoreceptor antagonist without intrinsic sympathomimetic (no partial agonist) or membrane stabilizing (local anaesthetic) activities [17] is widely used for the treatment of hypertension, angina pectoris and CHF. In comparison with other beta 1-adrenoceptor antagonists (e.g. atenolol, metoprolol), bisoprolol proved to be the compound with the highest β1-selectivity in all in vitro and in vivo experiments and in all animal species investigated [18-21]. Administration of bisoprolol to patients with CHF led to significant reductions in morbidity and mortality and symptomatic improvement. The survival benefits were associated with hemodynamic improvements such as increases in left ventricular function with a reverse remodelling of the left ventricle, reduction in heart rate, increases in heart rate variability, reduction in hormonal activation and a modest improvement in exercise capacity [22, 23]. Routinely, the agent is given orally in doses ranging from 1.25 – 10mg daily to patients with CHF.

Pharmacodynamics, pharmacokinetics and metabolism

When orally administered, bisoprolol is almost completely absorbed and due to an only minimal first-pass metabolism the bioavailability is 90% [24]. Bisoprolol, around 30% protein bound, is rapidly and widely distributed in the body with peak plasma concentrations occurring 2-4 hours after oral administration [24]. The total clearance of bisoprolol is around 15 L/h. Bisoprolol is a long-acting agent with a half-life of 10-11 hours [24] which is slightly prolonged in patients with CHF [25]. In the liver 50% of bisoprolol is metabolised to pharmacologically inactive metabolites [24, 26]. Half of the agent is eliminated via renal excretion as unchanged substance [24, 26]. Due to its balanced clearance bisoprolol can be given to all patients, even if they suffer from a seriously impaired renal or liver function [24, 26]. However, it is recommended not to exceed a daily dose of 10 mg in patients with hypertension or angina pectoris and concomitant terminal liver or renal failure [24, 26].

Bisoprolol and chronic heart failure

A meta-analysis performed by Frigerio et al noted that beta-blocker treatment, on top of existing CHF treatment (i.e. ACE inhibitors), leads to an increased LVEF and has a beneficial effect on the enlargement and functional deterioration of the left ventricle, the main mechanisms of heart failure progression [27]. According to the European and American guidelines for treatment of CHF, beta-blockers should be considered as a treatment option for all patients (NYHA class II-IV) with stable, mild, moderate and severe heart failure with ischemic or non-ischemic cardiomyopathies and a reduced LVEF (Class of recommendation I, level of evidence A). Unless contraindicated beta-blockers should be added to standard treatment with angiotensin-converting enzyme-inhibitors [ACE-inhibitors] and diuretics [1, 6, 8]. Following an acute myocardial infarction long term beta-blockade is recommended, in addition to ACE-inhibitory therapy, in patients with impaired systolic function and symptomatic or asymptomatic heart failure (Class of recommendation I, level of evidence B) [1, 6, 8]. To assess the mechanisms contributing to the beneficial effect of beta-blockers Flannery et al evaluated thirty-five controlled clinical trials of beta-blockade in CHF, which included 22.926 patients [28]. They identified a clear relation between 1) heart rate reduction due to beta-blockade, 2) change in LVEF and 3) all-cause mortality, concluding that the level of heart rate reduction is of great importance for the clinical benefits of beta-blocker therapy in CHF [28].

In the randomized double-blind placebo controlled Cardiac Insufficiency Bisoprolol Study [CIBIS], subgroup analyses were performed evaluating bisoprolol treatment in patients with CHF, in addition to standard diuretic and vasodilator (ACE inhibitors in 90% of cases) therapy. This study showed that a progressively increasing dose of bisoprolol, starting from 1.25 mg once daily up to 5 mg once daily, led to a significant reduction of hospital admission for CHF. Although bisoprolol treatment conferred functional benefit in patients with CHF, no mortality reduction was demonstrated in this trial [29]. The CIBIS II trial, in which 2647 patients were enrolled, showed a 34% reduction in all cause mortality and a reduction in sudden deaths by

44% with bisoprolol treatment compared with placebo, together with significant reductions in all-cause hospitalizations and admissions for CHF [23]. Simon et al evaluated whether patients' survival in the CIBIS II trial was related to the tolerated dose of bisoprolol. They concluded that bisoprolol significantly reduced the risk of mortality for all tolerated dose levels (34% with low doses of 1.25 / 2.5 / 3.75 mg per day (Hazard Ratio [HR] 0.66, 95% confidence interval [95%CI] 0.48-0.92), 67% with moderate doses of 5 or 7,5 mg per day (HR 0.33, 95%CI 0.21-0.51) and 41% with a high dose of 10 mg per day (HR 0.59, 95%CI 0.40-0.89). Hospitalizations were also significantly reduced at all tolerated dose levels. Furthermore, a significantly increased risk of mortality was noted after withdrawal of bisoprolol [30]. In the CIBIS III study it is stated that initiation of CHF treatment with the beta-blocker bisoprolol may be as efficacious and safe as the initiation with the ACE inhibitor enalapril [31]. The patients in the CIBIS III study were older than patients in the CIBIS II study (mean age 72 years old). Up to now, clinical trials have not yet evaluated hard clinical outcome and safety profile of treatment initiation with bisoprolol, compared with enalapril, in the elderly population. Therefore, a more careful up-titration is required in the elderly population to prevent worsening of CHF events [32]. The CIBIS II and CIBIS III trial were conducted in patients with CHF and a low LVEF. The effect of bisoprolol on patients with CHF and a preserved LVEF remains to be elucidated in randomized clinical trials.

Chronic heart failure and major non-cardiac surgery

Chronic heart failure is one of the most common conditions requiring evaluation and treatment in the perioperative period. Preoperative heart failure has been identified as a risk factor for a variety of cardiac complications after surgery and is the most frequently encountered postoperative cardiac complication as well. CHF occurs in 1 to 6 percent of patients undergoing major non-cardiac surgery. In patients with existing cardiac conditions such as coronary artery disease, prior CHF, or valvular heart disease, the risk is higher (6 to 25%). This risk may be further increased for patients with 1) diabetes mellitus, 2) renal insufficiency, 3)

high-risk surgery procedures such as vascular surgery [12, 33, 34] and 4) when an excessive volume of fluid is administered during surgery [11, 33].

Patients who are at increased risk of postoperative events may benefit from medical treatment or other preoperative interventions and identification of these patients has been an important goal in preoperative screening strategies. Tools for preoperative screening include cardiac risk scores, resting echocardiography and dobutamine stress echocardiography, which may detect both left ventricular dysfunction and stress-induced myocardial ischemia. Perioperative management of these patients is aimed at maximally improving hemodynamic status and providing intensive postoperative surveillance. Advances in preoperative risk stratification, perioperative management and surgery have led to substantial improvements in outcomes among patients undergoing major vascular surgery over the past 30 years [35]. In 2008, Hammill et al concluded that elderly patients with CHF who undergo major non-cardiac surgery have substantially higher risks of perioperative mortality and hospital readmission than other patients (including those with coronary artery disease) admitted for the same procedure [16]. A study conducted by Xu-Cai et al demonstrated that patients with clinically stable heart failure undergoing elective major non-cardiac surgery were more likely to 1) have longer hospital stays, 2) require hospital readmission and 3) had a substantial long-term mortality [36].

Recent studies showed that an increased plasma level of NT-proBNP or BNP is associated with adverse postoperative outcome. NT-proBNP is increased in patients with left ventricular dilatation caused by fluid overload (e.g. CHF and renal dysfunction), pressure overload (e.g. aortic valve stenosis) and myocardial ischemia, which might explain the strong correlation with adverse postoperative outcome [8]. Several articles have reported the prognostic value of varying NT-proBNP levels as an independent predictor of cardiac complications in patients undergoing major non-cardiac surgery [37-39]. The general assessment of postoperative patients with decompensated heart failure should be focussed on evaluating asymptomatic and unstable myocardial ischemia. The diagnosis of

postoperative myocardial infarction is frequently difficult to make since it often presents atypically and may have a different aetiology compared with non-postoperative myocardial infarction [40]. The evaluation of postoperative myocardial infarction should include cardiac monitoring, electrocardiography, and serial cardiac biomarker measurements [27]. Left ventricular remodelling after myocardial infarction exacerbates left ventricular dysfunction (diastolic and systolic) and causes progressive CHF. Once the aetiology of postoperative decompensated heart failure is diagnosed, treatment should be no different to the management of CHF during a general medical service admission [1, 6, 8].

Multiple studies have been performed to assess the value of beta-blockers in the perioperative setting. In addition to the type of beta-blocker and time of initiation prior to surgery, dose adjustment for adequate heart rate control is of great importance. Raby et al were the first to show positive results with strict heart rate control in 26 patients with preoperative ischemia detected by Holter monitoring undergoing major vascular surgery. The patients were randomized to receive beta-blockade with esmolol or placebo immediately after surgery [41]. Aiming to reduce the postoperative heart rate to 20% below the ischemic threshold markedly reduced postoperative ischemia. Feringa et al demonstrated that tight heart rate control and higher doses of beta-blockers, in this case bisoprolol, were associated with reduced perioperative myocardial ischemia, troponin T release and improved long-term outcome in 272 patients undergoing vascular surgery [42]. Accordingly, the new ACC/ AHA guidelines on perioperative care strongly recommend the achievement and maintenance of a heart rate of 60-65 beats per minute [43]. Redelmeier et al retrospectively studied 37.151 elderly patients undergoing major non-cardiac surgery who were treated with atenolol. They demonstrated that atenolol treatment was associated with greater cardioprotective benefits perioperatively, compared with treatment with short-acting beta-blockers, such as metoprolol tartrate [44]. Despite an increase in beta-blocker prescription worldwide, Hoeks et al demonstrated that there still is an under-use of beta-blockers in patients undergoing vascular surgery, even when patients are considered to be at high-risk for cardiovascular events. Perioperative beta-blockade use was

independently associated with a lower risk of 1-year mortality compared with non-use. Furthermore, perioperative withdrawal of beta-blocker therapy was associated with a higher 1-year mortality [45]. Similar results were obtained by Shammash et al. who concluded that discontinuation of beta-blockers immediately after major vascular surgery could increase the risk of postoperative cardiovascular mortality [46]. Lindenauer et al. conducted a retrospective cohort study of 782.969 patients and concluded that preoperative beta-blocker therapy is associated with a reduced risk of in-hospital death in high-risk (but not in low-risk) patients undergoing major non-cardiac surgery. In this high-risk patient group, safety may be further enhanced by expanding beta-blocker treatment [47]. In 2006, Feringa et al concluded that the use of beta-blockers in patients with severe left ventricular dysfunction undergoing major vascular surgery was associated with a reduced incidence of in-hospital and long-term postoperative mortality [48]. Although multiple studies have been performed, a reference study assessing the benefit of beta-blocker therapy for CHF patients undergoing major non-cardiac surgery could not be identified.

Poldermans et al randomized 112 patients with preoperative dobutamine stress echocardiography and more than 1 cardiac risk factor. Ten percent of the patients in the bisoprolol group were diagnosed with CHF preoperatively. Half of the patients received standard care and patients randomized to the second group received bisoprolol in addition to standard care. The primary endpoint, death from cardiac causes or nonfatal myocardial infarction, occurred in 3.4% of the bisoprolol group and 34% of the standard care patients ($p<0.001$) [49]. By achieving tight heart rate control, bisoprolol treatment reduces myocardial ischemia during surgery with a beneficial effect on postoperative outcome. The optimal treatment would be to start bisoprolol treatment several days to weeks preoperatively [50]. As put forward in the CIBIS III study, initiation of treatment for CHF with the beta-blocker bisoprolol might be as efficacious and safe as the initiation with the ACE inhibitor enalapril [31]. Therefore, patients with CHF in whom elective major non-cardiac surgery is planned could be stabilized with bisoprolol treatment, next to ACE-inhibitory treatment, as recommended by current CHF guidelines [1, 8] prior to surgery. In many patients it is not possible to start treatment with a beta-blocker and ACE inhibitory

treatment simultaneously. The CIBIS III has provided evidence treatment initiation with bisoprolol has a similar impact as treatment initiated with the ACE-inhibitor enalapril [31]. Therefore it may be possible to initiate CHF treatment with bisoprolol, prior to surgery.

Safety and tolerability

Analysing the safety and tolerability of bisoprolol is as important as assessing the beneficial effects of bisoprolol regarding efficacy. The most important side effects, which are to be expected with treatment of bisoprolol, are bradycardia and hypotension, which usually occur dose-dependently. As recommended by CHF guidelines and shown in beta-blocker studies in CHF such as the CIBIS studies, beta-blocker treatment in CHF has to be started with a very low dose (e.g. 1.25 mg bisoprolol), and the up-titration to the target dose or the maximum tolerated dose has to be done strictly according to tolerance [1, 8, 23, 29, 31]. In the elderly population, a more careful up-titration is required to prevent worsening of CHF events [32].

Recently, the results of the POISE trial have caused discussion regarding beta-blocker use in perioperative care [51]. The results show that treatment with the long-acting beta-blocker metoprolol succinate administered at high dosage (100 mg were given 2-4 hours prior to surgery, another 100 mg within 6 hours followed by another 200mg 12-18 hours post surgery; if permitted by heart rate and blood pressure, i.e. up to the maximum recommended therapeutical daily dose of 400 mg at the day of surgery; continued with 200 mg daily for 30 days post surgery) doubled the patients' risk of stroke (from 0.5% to 1%) and increased their overall risk of death by a third (from 2.3% to 3.1%) compared with placebo within 30 days after major non-cardiac surgery was performed. On the other hand, metoprolol succinate did lower the incidence of myocardial infarction by more than a quarter (5.7% to 4.2%), however this benefit was outweighed by the above described increased incidence of stroke and death [51]. In the editorial to the publication of the POISE study, Fleisher and Poldermans compared the POISE trial results with results from the DECREASE trials, in which patients undergoing major non-cardiac

surgery were treated with low-dose bisoprolol starting at least 7 days, but in most cases more than 30 days, before surgery [52]. The incidence of stroke in the DECREASE trials was 0.4%, comparable with placebo, while maintaining a significant reduction in cardiac death and nonfatal myocardial infarction from 34% in the standard-care group to 3.4% in the bisoprolol treated group in the first DECREASE trial [49, 52]. Multiple studies have been performed to evaluate perioperative beta-blocker use and only the POISE trial reported an increased incidence of stroke (POISE: OR 2.17, 95%CI [0.26-3.75] vs. DECREASE: OR 0.79, 95%CI [0.4-3.04]) [53-57]. This is shown in **figure 1**.

Conclusion

CHF is a clinical syndrome in which the ability of the heart to fill with or eject blood is impaired with a great clinical impact and poor prognosis. Over the years, considerable improvements have been made in the treatment of patients with CHF. However, it still remains a strong risk factor in patients undergoing major non-cardiac surgery, with significant impact on postoperative cardiovascular outcome. Adequate treatment of CHF in the perioperative setting is of great importance for the reduction of perioperative morbidity and mortality. Beta-blockers have beneficial effects in CHF, they significantly reduce morbidity and mortality. Their survival benefits are associated with hemodynamic improvements such as increases in left ventricular function with a reverse remodelling of the left ventricle. The reduction in heart rate presumably plays a pivotal role. The ACC/AHA guidelines on perioperative care strongly recommend the achievement and maintenance of a heart rate between 60-65 beats per minute. Since beta-blockers with short half-lives obviously are less effective and may increase the risk of cardiovascular events after sudden withdrawal, long-acting beta-blockers such as bisoprolol seem to be the agents of preference. Randomized studies have established the beneficial effects of bisoprolol in CHF, demonstrating a significant reduction of all-cause mortality in CHF patients treated with bisoprolol compared with those receiving placebo. To obtain tight heart rate control, the highest tolerated dosage of bisoprolol should be given, starting from 1.25 mg to a

maximum of 10 mg daily. A more careful up-titration is required in the elderly population. According to current data, high-risk patients may benefit more from beta-blocker therapy than low-risk patients. It is concluded that adequate bisoprolol treatment could be beneficial in the perioperative setting in patients with or without CHF. Future studies should further evaluate the efficacy of bisoprolol in patients with CHF undergoing major non-cardiac surgery.

Future perspective

In future times an increase of major surgical procedures performed in elderly patients is to be expected. Therefore the clinical impact of CHF will be of an even greater extent in the perioperative setting than today. Proper diagnostics and treatment of CHF therefore is required. Due to its long-acting properties, bisoprolol could be the beta-blocker of preference to obtain proper heart rate control. Bisoprolol can be administered safely and initiation and maintenance treatment can be done safely by primary care physicians.

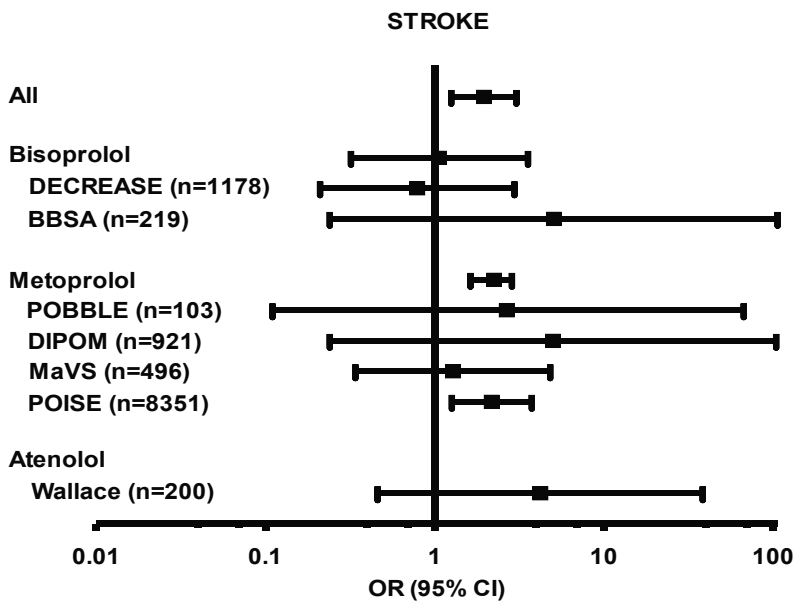


Figure 1. the accociation between perioperative beta-blocker use and stroke. Results of the POBBLE and MaVS trials were conducted in patients undergoing major vascular surgery [49, 51, 53-57].

References

1. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation.* Sep 20 2005;112(12):e154-235.
2. Sutton GC. Epidemiologic aspects of heart failure. *Am Heart J.* Dec 1990;120(6 Pt 2):1538-1540.
3. Davies M, Hobbs F, Davis R, et al. Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study. *Lancet.* Aug 11 2001;358(9280):439-444.
4. Petrie M, McMurray J. Changes in notions about heart failure. *Lancet.* Aug 11 2001;358(9280):432-434.
5. Nielsen OW, Hilden J, Larsen CT, et al. Cross sectional study estimating prevalence of heart failure and left ventricular systolic dysfunction in community patients at risk. *Heart.* Aug 2001;86(2):172-178.
6. Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J.* Jun 2005;26(11):1115-1140.
7. McKee PA, Castelli WP, McNamara PM, et al. The natural history of congestive heart failure: the Framingham study. *N Engl J Med.* Dec 23 1971;285(26):1441-1446.
8. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J.* Oct 2008;29(19):2388-2442.
9. Kazmers A, Cerqueira MD, Zierler RE. Perioperative and late outcome in patients with left ventricular ejection fraction of 35% or less who require major vascular surgery. *J Vasc Surg.* Sep 1988;8(3):307-315.
10. Hernandez AF, Whellan DJ, Stroud S, et al. Outcomes in heart failure patients after major noncardiac surgery. *J Am Coll Cardiol.* Oct 6 2004;44(7):1446-1453.
11. Detsky AS, Abrams HB, Forbath N, et al. Cardiac assessment for patients undergoing noncardiac surgery. A multifactorial clinical risk index. *Arch Intern Med.* Nov 1986;146(11):2131-2134.
12. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med.* Oct 20 1977;297(16):845-850.
13. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation.* Sep 7 1999;100(10):1043-1049.
14. Boersma E, Kertai MD, Schouten O, et al. Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee cardiac risk index. *Am J Med.* Oct 2005;118(10):1134-1141.
15. Kertai MD, Boersma E, Klein J, et al. Optimizing the prediction of perioperative mortality in vascular surgery by using a customized probability model. *Arch Intern Med.* Apr 25 2005;165(8):898-904.
16. Hammill BG, Curtis LH, Bennett-Guerrero E, et al. Impact of heart failure on patients undergoing major noncardiac surgery. *Anesthesiology.* Apr 2008;108(4):559-567.
17. Lancaster SG, Sorkin EM. Bisoprolol. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in hypertension and angina pectoris. *Drugs.* Sep 1988;36(3):256-285.
18. Maack C, Tyroller S, Schnabel P, et al. Characterization of beta(1)-selectivity, adrenoceptor-G(s)-protein interaction and inverse agonism of nebivolol in human myocardium. *Br J Pharmacol.* Apr 2001;132(8):1817-1826.

19. Schliep HJ, Schulze E, Harting J, et al. Antagonistic effects of bisoprolol on several beta-adrenoceptor-mediated actions in anaesthetized cats. *Eur J Pharmacol.* Apr 16 1986;123(2):253-261.
20. Smith C, Teitler M. Beta-blocker selectivity at cloned human beta 1- and beta 2-adrenergic receptors. *Cardiovasc Drugs Ther.* Apr 1999;13(2):123-126.
21. Wellstein A, Palm D, Belz GG. Affinity and selectivity of beta-adrenoceptor antagonists in vitro. *J Cardiovasc Pharmacol.* 1986;8 Suppl 11:S36-40.
22. de Groote P, Delour P, Lamblin N, et al. Effects of bisoprolol in patients with stable congestive heart failure. *Ann Cardiol Angeiol (Paris).* Jul 2004;53(4):167-170.
23. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet.* Jan 2 1999;353(9146):9-13.
24. Leopold G, Kutz K. Bisoprolol: Phamacokinetic Profile *Rev Contemp Pharmacother.* 1987;8:35-43.
25. McGavin JK, Keating GM. Bisoprolol: a review of its use in chronic heart failure. *Drugs.* 2002;62(18):2677-2696.
26. Leopold G. Balanced pharmacokinetics and metabolism of bisoprolol. *J Cardiovasc Pharmacol.* 1986;8 Suppl 11:S16-20.
27. Frigerio M, Roubina E. Drugs for left ventricular remodeling in heart failure. *Am J Cardiol.* Dec 19 2005;96(12A):10L-18L.
28. Flannery G, Gehrig-Mills R, Billah B, et al. Analysis of randomized controlled trials on the effect of magnitude of heart rate reduction on clinical outcomes in patients with systolic chronic heart failure receiving beta-blockers. *Am J Cardiol.* Mar 15 2008;101(6):865-869.
29. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). CIBIS Investigators and Committees. *Circulation.* Oct 1994;90(4):1765-1773.
30. Simon T, Mary-Krause M, Funck-Brentano C, et al. Bisoprolol dose-response relationship in patients with congestive heart failure: a subgroup analysis in the cardiac insufficiency bisoprolol study(CIBIS II). *Eur Heart J.* Mar 2003;24(6):552-559.
31. Willenheimer R, van Veldhuisen DJ, Silke B, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. *Circulation.* Oct 18 2005;112(16):2426-2435.
32. Dobre D, van Veldhuisen DJ, Goulder MA, et al. Clinical effects of initial 6 months monotherapy with bisoprolol versus enalapril in the treatment of patients with mild to moderate chronic heart failure. Data from the CIBIS III Trial. *Cardiovasc Drugs Ther.* Oct 2008;22(5):399-405.
33. Charlson ME, MacKenzie CR, Gold JP, et al. Risk for postoperative congestive heart failure. *Surg Gynecol Obstet.* Feb 1991;172(2):95-104.
34. Mangano DT, Browner WS, Hollenberg M, et al. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. *N Engl J Med.* Dec 27 1990;323(26):1781-1788.
35. Feringa HH, Bax JJ, Schouten O, et al. Beta-blockers improve in-hospital and long-term survival in patients with severe left ventricular dysfunction undergoing major vascular surgery. *Eur J Vasc Endovasc Surg.* Apr 2006;31(4):351-358.
36. Xu-Cai YO, Brotman DJ, Phillips CO, et al. Outcomes of patients with stable heart failure undergoing elective noncardiac surgery. *Mayo Clin Proc.* Mar 2008;83(3):280-288.
37. Rajagopalan S, Croal BL, Bachoo P, et al. N-terminal pro B-type natriuretic peptide is an independent predictor of postoperative myocardial injury in patients undergoing major vascular surgery. *J Vasc Surg.* Oct 2008;48(4):912-917; discussion 917.
38. Yeh HM, Lau HP, Lin JM, et al. Preoperative plasma N-terminal pro-brain natriuretic peptide as a marker of cardiac risk in patients undergoing elective non-cardiac surgery. *Br J Surg.* Aug 2005;92(8):1041-1045.
39. Feringa HH, Bax JJ, Elhendy A, et al. Association of plasma N-terminal pro-B-type natriuretic peptide with postoperative cardiac events in patients undergoing surgery for abdominal aortic aneurysm or leg bypass. *Am J Cardiol.* Jul 1 2006;98(1):111-115.
40. Priebe HJ. Perioperative myocardial infarction--aetiology and prevention. *Br J Anaesth.* Jul 2005;95(1):3-19.
41. Raby KE, Brull SJ, Timimi F, et al. The effect of heart rate control on myocardial ischemia among high-risk patients after vascular surgery. *Anesth Analg.* Mar 1999;88(3):477-482.

42. Feringa HH, Bax JJ, Boersma E, et al. High-dose beta-blockers and tight heart rate control reduce myocardial ischemia and troponin T release in vascular surgery patients. *Circulation.* Jul 4 2006;114(1 Suppl):I344-349.
43. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *Circulation.* Oct 23 2007;116(17):e418-499.
44. Redelmeier D, Scales D, Kopp A. Beta blockers for elective surgery in elderly patients: population based, retrospective cohort study. *Bmj.* Oct 22 2005;331(7522):932.
45. Hoeks SE, Scholte Op Reimer WJ, van Urk H, et al. Increase of 1-year Mortality After Perioperative Beta-blocker Withdrawal in Endovascular and Vascular Surgery Patients. *Eur J Vasc Endovasc Surg.* Jan 2007;33(1):13-19.
46. Shammash JB, Trost JC, Gold JM, et al. Perioperative beta-blocker withdrawal and mortality in vascular surgical patients. *Am Heart J.* Jan 2001;141(1):148-153.
47. Lindenauer PK, Pekow P, Wang K, et al. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. *N Engl J Med.* Jul 28 2005;353(4):349-361.
48. Feringa HH, Bax JJ, Schouten O, et al. Protecting the heart with cardiac medication in patients with left ventricular dysfunction undergoing major noncardiac vascular surgery. *Semin Cardiothorac Vasc Anesth.* Mar 2006;10(1):25-31.
49. Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. *N Engl J Med.* Dec 9 1999;341(24):1789-1794.
50. Poldermans D, Hoeks SE, Feringa HH. Pre-operative risk assessment and risk reduction before surgery. *J Am Coll Cardiol.* May 20 2008;51(20):1913-1924.
51. Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet.* May 31 2008;371(9627):1839-1847.
52. Fleisher LA, Poldermans D. Perioperative beta blockade: where do we go from here? *Lancet.* May 31 2008;371(9627):1813-1814.
53. Brady AR, Gibbs JS, Greenhalgh RM, et al. Perioperative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial. *J Vasc Surg.* Apr 2005;41(4):602-609.
54. Juul AB, Wetterslev J, Gluud C, et al. Effect of perioperative beta blockade in patients with diabetes undergoing major non-cardiac surgery: randomised placebo controlled, blinded multicentre trial. *Bmj.* Jun 24 2006;332(7556):1482.
55. Wallace A, Layug B, Tateo I, et al. Prophylactic atenolol reduces postoperative myocardial ischemia. McSPI Research Group. *Anesthesiology.* Jan 1998;88(1):7-17.
56. Yang H, Raymer K, Butler R, et al. The effects of perioperative beta-blockade: results of the Metoprolol after Vascular Surgery (MaVS) study, a randomized controlled trial. *Am Heart J.* Nov 2006;152(5):983-990.
57. Zaugg M, Bestmann L, Wacker J, et al. Adrenergic receptor genotype but not perioperative bisoprolol therapy may determine cardiovascular outcome in at-risk patients undergoing surgery with spinal block: the Swiss Beta Blocker in Spinal Anesthesia (BBSA) study: a double-blinded, placebo-controlled, multicenter trial with 1-year follow-up. *Anesthesiology.* Jul 2007;107(1):33-44.

13

The effect of statins on perioperative events in patients undergoing vascular surgery.

Acta Chirurgica Belgica 2010; 110(1):28-31

Tamara A. Winkel
Olaf Schouten
Michiel T. Voûte
Sanne E. Hoeks
G.M. Welten
Jeroen J. Bax
Hence J.M. Verhagen
Don Poldermans

Abstract

Despite recent advancements in perioperative care and guideline recommendations, patients undergoing vascular surgery remain at risk for perioperative cardiovascular complications. In this review, the results are summarized of the most recent studies on the effectiveness and safety of perioperative statin use for the prevention of these perioperative cardiovascular complications. Perioperative statin therapy was associated with an improvement in postoperative cardiovascular outcome and a reduction in serum lipid levels and levels of inflammation markers.

Introduction

The number of cardiac patients undergoing surgery is steadily increasing. In Europe, with an overall population of 490 million, a crude estimate of 7 million major surgical procedures are conducted on average annually.[1] After major surgery the incidence of cardiac death is estimated between 0.5% and 1.5%.[1] Although developments in anesthesiologic and surgical techniques, such as locoregional anesthesia and endovascular treatment modalities, have improved postoperative cardiac outcome considerably, perioperative cardiac complications remain a significant problem. The risk of perioperative complications depends on the condition of the patient prior to surgery, the prevalence of co-morbidities, and the magnitude and duration of the surgical procedure.[2] More specifically, patients with atherosclerotic vascular disease who undergo non-cardiac vascular surgery are at high risk of cardiovascular events. Cardiovascular events occur in up to 24% of patients in high-risk cohorts[3] and are related to the high incidence of underlying coronary artery disease (CAD). The reported incidence of postoperative cardiovascular events varies as the majority of events occur asymptomatic.[3]

Perioperative MI may be caused by a sustained myocardial supply/demand imbalance due to tachycardia and increased myocardial contractility.[2] Although the pathophysiology of perioperative MIs is not entirely understood, it is well accepted that coronary plaque rupture, leading to thrombus formation and subsequent vessel occlusion, is considered to be an important cause of acute perioperative coronary syndromes. Surgery itself is a significant stress factor, inducing a catecholamine surge with associated haemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation and consequent hypercoagulability, leading to an increased risk of plaque rupture.[2] Two retrospective autopsy result studies by Dawood et al.[4] and Cohen and Aretz[5] demonstrated that plaque rupture was found in approximately 50% of patients with postoperative MI. Furthermore, Dawood et al. concluded that fatal perioperative MI occurs predominantly in patients with multivessel coronary-artery disease, especially left main and three-vessel disease and that the severity of pre-existing underlying stenosis did not predict the resulting

infarct territory.[4] Perioperative MIs have similar coronary artery pathology to non-operative MIs with regard to coronary plaque haemorrhage, rupture, and thrombus formation and probably occur by a similar mechanism.[4, 5] Unstable plaques have a large lipid core and a thin, weakened fibrous cap infiltrated by macrophages and other inflammatory cells that are vulnerable to disruption. Inflammatory processes in general and monocyte-derived macrophages in particular play a critical role in the progression and destabilization of coronary plaque.[2, 4, 5]

Several trials involving the non-surgical and surgical population have shown a beneficial role of statin therapy on cardiac outcome.[6, 7] These effects are related to a reduction of low-density lipoprotein (LDL) cholesterol levels and inflammation. Reduction in inflammation might, independently of the patients' cholesterol levels, prevent destabilization of coronary plaque induced by the stress of surgery. Recently, the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography III (DECREASE III) trial assessed the effect of statin therapy on the 30-day postoperative outcome in patients undergoing elective vascular surgery.[8]

Statin therapy

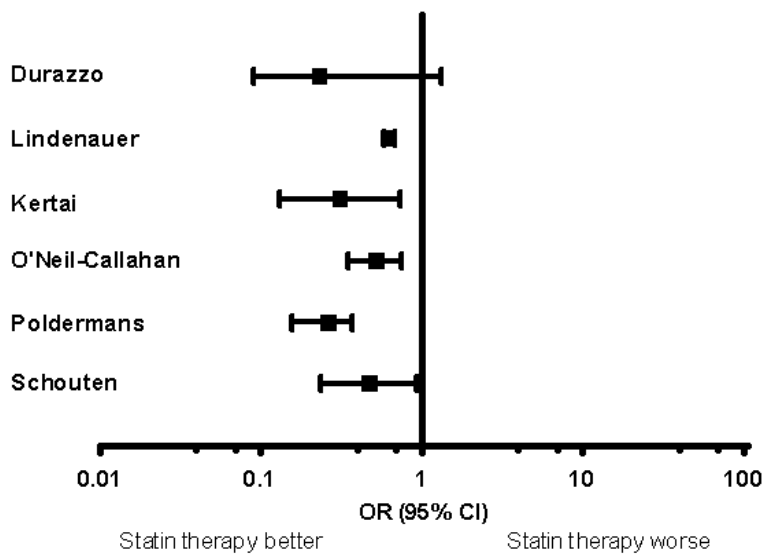
Statins are widely prescribed in patients with or at risk for CAD because of their effectiveness in lowering serum cholesterol concentrations through 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibition (HMG-CoA reductase inhibitors or statins).[1, 9] Reduction of low-density lipoprotein (LDL) cholesterol is one of the primary objectives of cardiovascular disease prevention. Evidence suggests that beyond the lipid-lowering effects, there are the more immediate benefits related to the so-called pleiotropic effects of statins. These pleiotropic effects are thought to include improved endothelial function, enhanced stability of atherosclerotic plaques, decreased oxidative stress, and decreased vascular inflammation. As reported by Naghavi et al. in their extensive review on vulnerable plaques, inflammation is one of the major extrinsic factors involved in the rupture of vulnerable plaques.[10] The pleiotropic effects of statins include several possible

plaque-stabilizing effects such as the increased expression of endothelial nitric oxide synthase, the reduced production of endothelin-1, and the generation of reactive oxygen species, an improvement of the thrombogenic profile, and importantly, a reduction in inflammation via the reduced expression of inflammatory cytokines, chemokines, adhesion molecules, and a lowering of C-reactive protein (CRP) levels; therefore, the perioperative prescription of statins might improve plaque stability. However, the mechanisms by which statins reduce plasma CRP levels remain unknown. Arnaud et al.[11] demonstrated that statins reduce interleukine-6-induced CRP production directly in the hepatocytes via inhibition of protein geranylgeranylation and provides a new molecular explanation for the reduced plasma CRP levels observed in patients treated by statins.[11]

Statins in major surgery

Several studies have addressed the beneficial effects of statin use in patients undergoing non-cardiac surgery, including vascular surgery (Figure 1).

Figure 1.



Durazzo et al. performed the first prospective randomized controlled trial in a small population carried out at a single center.[12] One hundred patients scheduled for vascular surgery were randomized to either 20 mg atorvastatin or placebo. Patients received treatment once a day for 45 days and surgical intervention was performed not earlier than 2 weeks after inclusion. On average statins were prescribed 30 days after randomization. The outcome of this trial was the combined endpoint of cardiac death, non-fatal MI, stroke, or unstable angina pectoris. After 6 months, cardiovascular events occurred in 26.0% of the placebo group, compared to only 8.0% in the statin-users group (p=0.031). Though not powered to assess 30-day postoperative outcome, there was a clear trend for the beneficial effect of statins (OR 0.23, 95%CI 0.09-1.30).[12] Lindenauer performed a large retrospective cohort study of 780,591 patients undergoing major non-cardiac surgery at 329 hospitals throughout the United States. The authors concluded that the 70,159 statin users had a 1.4-fold reduced risk of in-hospital mortality (adjusted OR 0.62; CI 0.58-0.67).[13] Kertai et al. conducted a retrospective study in 510 patients undergoing major vascular surgery and found similar effects of perioperative statins for all-cause and cardiovascular mortality (adjusted OR 0.6; 95% CI 0.5-0.9 and adjusted OR 0.7; 95% CI 0.4-0.9 respectively).[14] They also found the effect of statin to be independent of beta-blocker use.[14] In the observational retrospective study by O'Neil-Callahan et al. data of 1163 patients who underwent non-cardiac vascular surgery was collected and found that patients who were statin-users had a substantially lower perioperative cardiac complication rate than patients without statin use (OR 0.52; 95% CI 0.35-0.77).[15] The protective effect of statin use was similar across different risk group categories and persisted after accounting for the likelihood of statin use in patients with hypercholesterolemia.[15] In a case-control study including 2816 patients undergoing major non-cardiac vascular surgery, perioperative statin use was also associated with a more than 4-fold reduced risk in perioperative mortality (OR 0.22; 95% CI 0.10-0.47).[16] The meta-analysis by Hindler et al. including 12 retrospective and 3 prospective trials (n = 223,010 patients) showed that preoperative statin therapy was associated with 38% and 59% reduction in the risk of mortality after cardiac (1.9% vs. 3.1%; P = 0.0001) and vascular (1.7% vs. 6.1%; P = 0.0001) surgery, respectively. When including non-

cardiac surgery, a 44% reduction in mortality (2.2% vs. 3.2%; P = 0.0001) was observed.[17] In the overview study by Paraskevas et al. any benefit of statins occurs soon after initiating treatment and reduces perioperative morbidity and mortality in patients undergoing non-cardiac vascular surgery.[7]

Prospective placebo-controlled randomized trials cannot be performed in the future due to the obvious ethical restrictions, since all vascular patients should receive statin treatment as secondary prevention of cardiovascular disease. However, the recently reported DECREASE III study is the first adequately powered randomized controlled trial, which could answer the pivotal role of statins in the perioperative period.[8]

DECREASE III study

The recently published DECREASE III trial was a randomized placebo controlled trial that was conducted between 2004 and 2008 at the Erasmus Medical Center, Rotterdam, the Netherlands. All patients older than 40 years of age and scheduled for non-cardiac vascular surgery were eligible for inclusion in the trial. Patients were excluded from the trial if they were currently treated with a statin, had a contraindication for statin therapy, were undergoing surgery that could interfere with continuous 12-lead electrocardiographic (ECG) recording, were undergoing emergency surgery, were undergoing reoperation within 30 days after a previous surgical procedure, had unstable coronary artery disease, or had extensive stress-induced myocardial ischemia suggestive of left main coronary artery disease or its equivalent. Patients were randomly assigned to receive either extended-release fluvastatin (Novartis) at a dose of 80 mg, or an identical-appearing placebo, once daily. The study drug was started at the outpatient clinic on the day of randomization and was continued for at least 30 days after surgery. The primary study outcome was the occurrence of myocardial ischemia, defined as either transient ECG signs of ischemia, release of troponin T, or both. The principal secondary end point was the composite of death from cardiovascular causes and non-fatal MI. The other secondary study outcome was the effect of fluvastatin therapy on levels of biomarkers including lipids, high-sensitivity CRP, and

interleukin-6. Safety outcome measures included serum creatine kinase and alanine aminotransferase levels and development of clinical myopathy and rhabdomyolysis. Blood samples were obtained before randomization, on the day of hospital admission, and on days 1, 3, 7, and 30 after surgery.

Of 1669 patients assessed for trial eligibility, 497 were eventually randomized and included in the study. A total of 250 patients received fluvastatin, and 247 were assigned to placebo, at a median of 37 days before vascular surgery.
The incidence of the myocardial infarction in fluvastatin and placebo allocated groups respectively was 10.8% versus 19.0% (OR 0.55; 95% CI 0.34-0.88). The incidence of the secondary, composite endpoint of cardiac death or non-fatal MI was 4.8% versus 10.1% (OR 0.47; 95% CI 0.24-0.94).
Baseline lipid levels were similar in the two groups (5.40 versus 5.30 mmol/L respectively), this was also the case for baseline LDL, HDL, high-sensitivity CRP and interleukin-6 levels.[8] Fluvastatin treatment was associated with significant decreases in serum lipid levels and inflammatory activity within weeks.

Whether the decrease in inflammation is responsible for the beneficial clinical effects of perioperative statin use is unclear. The DECREASE III findings on the perioperative benefits of statins are in line with those in previous retrospective studies.[7] Furthermore, there was no heterogeneity of effect among patients in subgroups characterized by various baseline characteristics, including cardiac risk, cholesterol levels, type of surgery, and levels of inflammatory markers. One concern with perioperative statin treatment is the necessity of treatment interruption when oral administration is not feasible during the early postoperative period. Because of the unavailability of an intravenous formula of statins and the underappreciated pleiotropic effects of statins, statin withdrawal is also a well-known phenomenon in the immediate postoperative period. Such interruption is potentially hazardous, as sudden withdrawal of statins in the non-surgical setting has been associated with a diminished benefit.[18] This increased postoperative risk associated with the withdrawal of statins was also observed by Le Manach and colleagues.[19] Fluvastatin had to be interrupted in approximately a quarter of the

DECREASE III patients for a median of 2 days, but this did not result in a significant increase in adverse outcome (adjusted OR 1.1, 95% CI 0.48-2.52). The idea behind this is due to treatment with extended-release fluvastatin, which suggests that statins with a prolonged half-life time or with an extended release formula should be preferred and that statins should be restarted after surgery as soon as possible. Another important issue in the perioperative setting is the use of concomitant medical treatment. The risk of myopathy might increase with concomitant drugs that are myotoxic or increase serum statin levels. Besides concomitant medication use, numerous other factors like renal impairment in the perioperative setting might increase the risk of statin induced myopathy.[20] Furthermore, the use of analgesic agents and postoperative pain may mask signs of myopathy. Failure to detect statin-induced myopathy may possibly lead to continued statin treatment and the subsequent development of rhabdomyolysis and acute renal failure. Neither the retrospective study by Schouten et al.[20], nor the recent DECREASE III study[8] observed myopathy or rhabdomyolysis within 30 days after surgery. This was measured with objective laboratory markers (safety endpoints of the DECREASE III study). Considering that the risk of cardiovascular complications is far greater than the risk of statin-induced myopathy and rhabdomyolysis in the perioperative period, the potential benefits of perioperative statin use seem to outweigh the potential hazards. Another recent issue with regard to statins is the concern of an increase in carcinoma. In the large meta-analysis by Baigent et al., the incidence of carcinoma was 6.4% in the statin and control groups, and did not increase any type of carcinoma.[6]

Conclusion

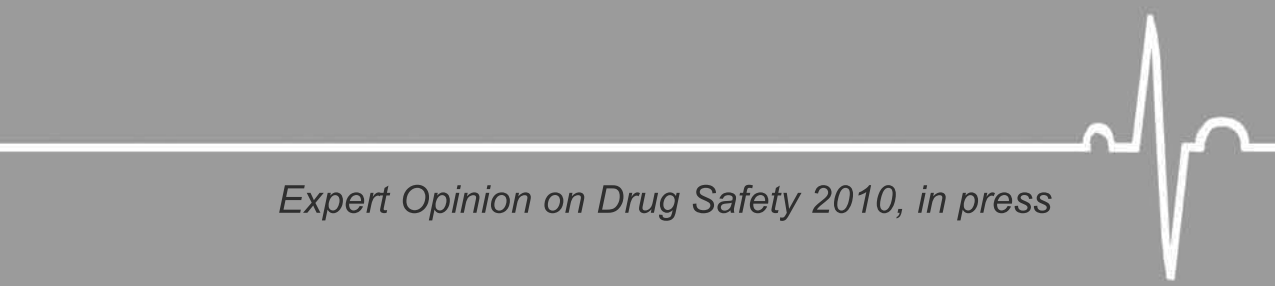
Patients undergoing major vascular surgery should receive statin therapy. It is recommended to start statins in high-risk surgery patients, optimally 30 days and at least one week before surgery and to continue statins perioperatively.

References

1. Poldermans D, Bax JJ, Boersma E, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: The Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). Eur Heart J 2009.
2. Mangano DT. Perioperative cardiac morbidity. Anesthesiology 1990;72(1):153-84.
3. Landesberg G, Shatz V, Akopnik I, et al. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. J Am Coll Cardiol 2003;42(9):1547-54.
4. Dawood MM, Gutpa DK, Southern J, Walia A, Atkinson JB, Eagle KA. Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. Int J Cardiol 1996;57(1):37-44.
5. Cohen MC, Aretz TH. Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. Cardiovasc Pathol 1999;8(3):133-9.
6. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366(9493):1267-78.
7. Paraskevas KI, Liapis CD, Hamilton G, Mikhailidis DP. Can statins reduce perioperative morbidity and mortality in patients undergoing non-cardiac vascular surgery? Eur J Vasc Endovasc Surg 2006;32(3):286-93.
8. Schouten O, Boersma E, Hoeks SE, et al. Fluvastatin and perioperative events in patients undergoing vascular surgery. N Engl J Med 2009;361(10):980-9.
9. Pasternak RC, Smith SC, Jr., Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. J Am Coll Cardiol 2002;40(3):567-72.
10. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part II. Circulation 2003;108(15):1772-8.
11. Arnaud C, Burger F, Steffens S, et al. Statins reduce interleukin-6-induced C-reactive protein in human hepatocytes: new evidence for direct antiinflammatory effects of statins. Arterioscler Thromb Vasc Biol 2005;25(6):1231-6.
12. Durazzo AE, Machado FS, Ikeoka DT, et al. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. J Vasc Surg 2004;39(5):967-75; discussion 75-6.
13. Lindenauer PK, Pekow P, Wang K, Gutierrez B, Benjamin EM. Lipid-lowering therapy and in-hospital mortality following major noncardiac surgery. Jama 2004;291(17):2092-9.
14. Kertai MD, Boersma E, Westerhout CM, et al. Association between long-term statin use and mortality after successful abdominal aortic aneurysm surgery. Am J Med 2004;116(2):96-103.
15. O'Neil-Callahan K, Katsimaglis G, Tepper MR, et al. Statins decrease perioperative cardiac complications in patients undergoing noncardiac vascular surgery: the Statins for Risk Reduction in Surgery (StaRRS) study. J Am Coll Cardiol 2005;45(3):336-42.
16. Poldermans D, Bax JJ, Kertai MD, et al. Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. Circulation 2003;107(14):1848-51.
17. Hindler K, Shaw AD, Samuels J, Fulton S, Collard CD, Riedel B. Improved postoperative outcomes associated with preoperative statin therapy. Anesthesiology 2006;105(6):1260-72; quiz 89-90.
18. Heeschen C, Hamm CW, Laufs U, Snapinn S, Bohm M, White HD. Withdrawal of statins increases event rates in patients with acute coronary syndromes. Circulation 2002;105(12):1446-52.
19. Le Manach Y, Godet G, Coriat P, et al. The impact of postoperative discontinuation or continuation of chronic statin therapy on cardiac outcome after major vascular surgery. Anesth Analg 2007;104(6):1326-33, table of contents.
20. Schouten O, Kertai MD, Bax JJ, et al. Safety of perioperative statin use in high-risk patients undergoing major vascular surgery. Am J Cardiol 2005;95(5):658-60.

14

Safety of fluvastatin in patients undergoing high-risk noncardiac surgery.



Expert Opinion on Drug Safety 2010, in press

Michiel T. Voûte
Tamara A. Winkel
Don Poldermans

Safety of fluvastatin in patients undergoing high-risk noncardiac surgery

Importance of the field: In patients undergoing vascular surgery there is a high incidence of adverse cardiac events, due to sudden coronary plaque rupture. The non-lipid lowering, or pleiotropic effects of statins can help reduce adverse cardiovascular events, associated with vascular surgery.

Areas covered in this review: The evidence for perioperative use of fluvastatin, as well as other statins, in high-risk surgery patients is summarized in this review. Data on pharmacokinetics and metabolism is presented, together with considerations on possible drug interactions in the perioperative period.

What the reader will gain: The reader will gain a comprehensive understanding of the existing safety and efficacy data for fluvastatin and other statins in the perioperative period. The practical considerations of perioperative fluvastatin therapy will be presented, including potential side-effects and management of the early non-oral phase immediately postoperative. Finally, advice on when to initiate therapy and safety recommendations are offered.

Take home message: In patients scheduled for high-risk vascular surgery, fluvastatin improves postoperative outcome, reducing the incidence of myocardial damage by almost 50% in the first 30 days following vascular surgery. In comparison with placebo, fluvastatin was not associated with a rise in liver enzymes or creatine kinase levels. To bridge the non-oral phase, an extended-release formula is recommended.

1. Introduction

Statins are renowned for their ability to reduce low-density lipoprotein (LDL) cholesterol in patients at with hypercholesterolemia.[1-3] Apart from their lipid-modifying properties, other treatment effects of statins, so called pleiotropic effects, have been investigated over the last decade, including anti-inflammatory effects and cardiac risk reduction, among others.[4-6]

Fluvastatin (Lescol®, Novartis Pharmaceuticals, Switzerland) was first tested in humans in 1986 and was approved for clinical use in the USA since December 1993.[7-8]

In this review, we summarize the pharmacology of fluvastatin, evaluate the efficacy and safety in patients undergoing high-risk surgery and comment on possible future developments.

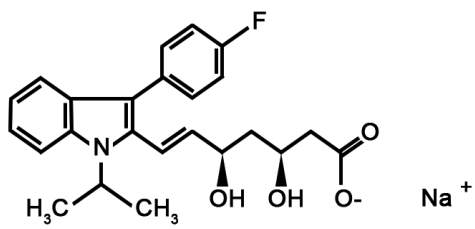
2. Pharmacology

2.1 Pharmacodynamic properties

Fluvastatin sodium is a white to pale yellow, hygroscopic powder. It is soluble in water, ethanol and methanol. Fluvastatin, like all statins, is an inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, an enzyme that is rate-controlling in the mevalonate pathway. Mevalonate is a precursor of sterols, including cholesterol. Inhibition of this enzyme leads to a decrease in cholesterol levels in serum, as well as hepatic cells. This leads to an increase in receptors for low-density lipoprotein (LDL), which clear LDL from the bloodstream, adding to the lipid-lowering effect of fluvastatin.

Additionally, statins has been described to have non-lipid lowering effects, or pleiotropic effects. These effects contribute to the reduction of macrovascular risk that is seen in treated patients. Fluvastatin has been described to improve endothelial function, reducing the expression of adhesion molecules in the peripheral and coronary circulation.[9] Also, by inhibiting the secretion of metallo-proteases by macrophages, fluvastatin may stabilize atherosclerotic lesions, reducing the risk of plaque rupture. Finally, effects on clotting, fybrinolysis and platelet aggregation can prevent extensive thrombus formation on fissured or ruptured plaques.[9]

Box 1. Drug summary.

Drug name	Fluvastatin
Phase	Launched
Approved indication	- Hypercholesterolemia, mixed dyslipidemia - Heterozygous familial hypercholesterolemia in pediatric patients - Secondary prevention of coronary events - Atherosclerosis
Pharmacology description	HMG-CoA reductase inhibitor*
Route of administration	Oral
Chemical structure	 $C_{24}H_{25}FNO_4 \bullet Na$ Mol. wt. 433.46
Pivotal trial(s)	LIPS, LCAS†; ALERT, DECREASE-III§

*HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A

† Key studies supporting approved indications

§ Other large-scale key studies

Acronyms: LIPS, Lescol Intervention Prevention Study; LCAS, Lipoprotein and Coronary Atherosclerosis Study; ALERT, Assessment of LEscol in Renal Transplantation; DECREASE, Dutch Echographic Cardiac Risk Evaluation Applying Stress Echo study group

2.2 Pharmacokinetic properties of fluvastatin

When administered orally, fluvastatin absorption takes place primarily in the small intestine. About 90% of an oral dose is absorbed. Peak concentrations in plasma are reached on average at 0.5 – 1.5 hour in healthy, fasting individuals. Administration with food reduces the rate but not the extent of the absorption. A 50% lower maximum concentration is however reached when taken with food, after twice as much time, when compared to administration 4 hours after a meal.

Fluvastatin endures a substantial first-pass effect in the liver after absorption, with a wide variety in non-hepatic bioavailability of ~ 24% on average (range 9-50%) after a 10mg single dose. Liver metabolism of fluvastatin is saturable, so that the systemic bioavailabilty increases in a non-linear manner after single or multiple doses above 20 mg. Subject to multiple larger doses, the systemic non-hepatic bioavailability can increase to 45-65% in humans.[10-12]

2.3 Pharmacokinetic properties of fluvastatin extended release

The main development rationale for fluvastatin XL was to provide an extended release formulation that allows for once daily dosing of 80 mg of fluvastatin while maintaining low plasma levels. A hydrophilic cellulose matrix, containing the drug, was designed to swell when in contact with intestinal fluids, allowing the drug to diffuse out.[11] The time to peak plasma concentrations was 3-6 hours with fluvastatin XL, within the dose range of 80-320 mg. Steady state concentrations were observed within 7 days with regular daily doses.[13]

2.4 Metabolism and excretion

Fluvastatin is rapidly metabolized by several cytochrome (CYP) P450 isoenzymes, mainly CYP2C9 (75% of metabolism), primarily via hydroxylation. This process lead to forming of three main metabolites, 5-hydroxy fluvastatin, 6-hydroxy fluvastatin and des-isopropyl-fluvastatin. Ex vivo, the 5- and 6-hydroxy metabolites have an inhibitory effect on HMG-CoA (88% and 45% of unmetabolised fluvastatin, respectively), but in vivo there is no clinical relevance to these metabolites due to rapid elimination from the circulation.

Fluvastatin is excreted primarily in bile, and leaves the body in feces. Over 90% of fluvastatin is found in feces as metabolites, and less than 2% present as unchanged drug. Only 5% of radiolabeled fluvastatin is recovered in urine.[10-12]

3. Clinical application of fluvastatin in high-risk surgery

3.1 Clinical efficacy in trials

In a report by Boersma et al. surgical procedures were categorized into low, intermediate and high perioperative cardiac risk.[14] In later guidelines from the European Society of Cardiology (ESC), high-risk surgery was defined as aortic and peripheral vascular surgery, because there is a high probability that the atherosclerotic process is also present in the coronary arteries. Endovascular procedures are considered to be of intermediate cardiac risk, based on data from several randomized trials with open or endovascular aneurysm repair, as is carotid artery endarterectomy.[3]

Few reports have been published on the use of statins in the perioperative period to reduce the risk for a cardiac event after vascular surgery. Only one paper to date has prospectively investigated the effect of fluvastatin on perioperative cardiac events in high-risk surgery patients. The DECREASE-III trial was a large, placebo-controlled trial that assesses the effect of fluvastatin on the 30-day postoperative outcome in vascular surgery patients.[15]

In the DECREASE-III trial, 497 patients (372 male) were enrolled at a median of 37 days prior to vascular surgery. Double-blinded randomization took place between fluvastatin (n=250) and placebo (n=247). No adverse cardiac outcome was reached before surgery. In the first 30 days postoperative, evidence of myocardial ischemia was seen in 27 patients (10.8%) in the fluvastatin group, and 47 patients (19.0%) in the placebo group (P=.016). The secondary endpoint of death from cardiac causes or non-fatal myocardial infarction was reached in 12 patients (4.8%) on fluvastatin and 25 patients (10.1%) on placebo (P=.039). The number needed to treat (NNT) to prevent one occurrence of myocardial ischemia in the first 30 days after vascular surgery was 12; the NNT to prevent one nonfatal MI was 36; and the NNT to prevent one cardiovascular death was 42.[15-16]

4. Safety evaluation

4.1 Side-effects of fluvastatin treatment

Fluvastatin is generally well tolerated in treated patients. Combining all clinical trials, Lawrence et al. found only 1% of patients to withdraw from fluvastatin therapy due to adverse events, attributed to the study medication.[11] Most common are complaints of headache, abdominal symptoms and muscle problems. Statin therapy in general has been reported to lead to myalgia, myositis and myopathy. Although often transient, hepatic abnormalities are also well-known side-effects of statin therapy. Liver function tests should be taken previous to statin administration and regularly thereafter. If a patient has active liver disease or persistent abnormal liver function tests, statin prescription for continous lipid-lowering purposes is contraindicated.[11] No advice is available on statins as prophylaxis for cardiac events in the perioperative period, in patients with liver disease.

Side-effects of fluvastatin in comparison with other statins seem mild. In a pooled analysis by Novartis Pharmaceuticals in 2002, the proportion of the 8951 patients on fluvastatin (20 or 40 mg) or fluvastatin XL (80 mg) that had a CK level more than five times the upper limit of normal was comparable to placebo-treated patients.[17] A large observational study by Bruckert et al. reported on muscular symptoms in general practice with high-dose statin therapy.[18] The rate of muscular symptoms was 5.1% with fluvastatin, compared to 10.9-18.2 % for other statins. However, all these side-effects were recorded when fluvastatin was prescribed in general practice, not surgery patients.

In the high-risk surgery patients from DECREASE-III, general anesthesia prevented monitoring for muscular complaints, but creatine kinase (CK) levels were measured as part of the safety endpoints. In patients treated with fluvastatin, the median CK level was 141 U/L, compared to 113 U/L for placebo (P=.24), and the proportion of patients that had CK levels > 10 times the upper limit of normal (ULN) was 4.0% in the fluvastatin group versus 3.2% in the placebo group (P=.81). Hepatic toxicity was observed without significant differences between groups. The median levels of alanine aminotransferase (ALT) were 24 U/L for the fluvastatin group and 23 U/L for placebo group (P=.43), and only 3.2% of patients had ALT levels > 3 x ULN in the fluvastatin group, compared to 5.3% for placebo (P=.27).[15]

4.2 Safety in special populations

The safety of fluvastatin use in the general population has been subject to research on several occasions. There have been reports on a low incidence of adverse reactions in children and adolescents with familial heterozygous hypercholesterolemia.[19] Animal studies have reported an association of high-dose fluvastatin (12 and 24 mg/kg) with a higher rate of stillbirths and maternal mortality, while a low-dose (2 mg/kg) therapy had no effects on the dam nor the foetus.[20] No data with fluvastatin in pregnant women are available, but statin use should be discontinued in women who become pregnant, and in nursing mothers statin use is strongly discouraged.[21]

With regard to high-risk surgery patients, advanced age and renal insufficiency are common. Age was found not to be of influence on the plasma concentrations for the general population.[10, 22] However, the treatment response measured by LDL-level changes was slightly higher in patients ≥65 years of age, than in patients aged under 65 (30% versus 27%). Subject to the large role of the liver in the metabolism of fluvastatin, renal dysfunction is of no large influence on fluvastatin pharmacokinetics.

4.3 Drug interactions

When prescribing statins, the possibility of drug interactions is important to consider. This may inhibit normal metabolism, leading to increased plasma levels, or increase normal metabolism, via enzyme induction, leading to a decreased treatment effect. Statin toxicity has been reported to cause myalgia or rhabdomyalysis and statin inhibition can lead to under-treatment of dislipidemia and subsequent increased cardiovascular risk.

As mentioned, the metabolism of fluvastatin takes place via the CYP P450 system. Where other statins are metabolized primarily by the CYP3A4 isoenzyme (atorvastatin, lovastatin and simvastatin) or not by the liver at all (pravastatin), fluvastatin is the only statin that is predominantly metabolized by the CYP2C9 isoenzyme (75%), and to a much lesser extent by CYP3A4 (~20%).

There are several known interactions between statins and other drugs that are metabolised by, or are of influence on CYP3A4. Drugs that inhibit this isoenzyme

are antigungals, erythromycin and other macrolides, histamine-2 blockers, cyclosporin, calcium channel blockers and grapefruit juice. All these agents lead to an increase in plasma concentration of statins, and the use of pravastatin or fluvastatin may be preferable, since these are not primarily metabolized by CYP3A4.

Rifampicin, Phenobarbital, carbamazepine and phenytoin are examples of drugs that induce both CYP3A4 and CYP2C9, and therefore lead to increased metabolism of hepatically-metabolized statins.[23] The lipid-lowering effect of statins, including fluvastatin, can be reduced by concomitant use of these drugs.

Warfarin is metabolized by CYP3A4 and CYP2C9, and there have been few reports that patients on fluvastatin/warfarin are potentially at risk for bleeding complications. Careful monitoring of the INR is advised in patients on warfarin, following the start of or any change in statin use (except pravastatin).[24-25]

4.4 Interactions with anesthetic agents

Commonly used agents for general anesthesia may have interactions with statin therapy. Midazolam, a commonly used benzodiazepine, is metabolized in part by the same CYP P450 isoenzyme as most statins, CYP3A4. In theory this could lead to interactions and alterations on the efficacy of either drug or both. However, a recent report showed that statins had no influence on midazolam pharmacokinetics in healthy subjects, dismissing this theory.[26] Among hypnotic agents, propofol is a widespread example, generally used for narcotic induction. It is metabolized primarily by direct glucuronidation in the liver.[27] However, one report suggests that propofol can influence midazolam metabolism by inhibition of CYP3A4. In theory, an interaction between propofol and statins could also be expected based on this report. Finally, narcotic analgesics are used for general anesthesia patients. Fentanyl was introduced in the 1960s, and has been in use ever since. CYP3A4 is the major catalyst in fentanyl metabolism in humans.[28] An interaction with other drugs, metabolized by the same isoenzyme, is hypothesized, but not reported. Alfentanil, a derivate of fentanyl, was investigated in surgery patients with atorvastatin therapy.[29] There was no sign of altered pharmacokinetics of alfentanil.

4.5 Safety considerations of statin withdrawal

Caution in prescribing statin to surgery patients is warranted, in light of the mentioned safety evaluations, but statin withdrawal should be given equal consideration. In the first days directly following surgery, oral medication is often inhibited. Since the pleiotropic effects of statins are often underappreciated, postoperative statin withdrawal is common.[16]

Unfortunately, statin withdrawal can cause a rebound effect, diminishing the treatment benefit of statin administration. Discontinuation of short-acting statins was associated with an increase in inflammatory markers and oxidative stress, and an increase in cardiac events has been observed following acute withdrawal of statins during periods of instability, compared to continuation of statin therapy.[30] In vascular surgery patients, an increased incidence of cardiovascular events was reported, related to statin withdrawal after surgery. In that report, fluvastatin XL was considered a usefull long-acting agent, with a lower rate of adverse cardiac events after withdrawal, than other agents.[31] In guidelines from the European Society of Cardiology the use of a long-acting statin is advised to prevent the withdrawal effect.[3]

5. Use of other statins in high-risk surgery

Apart from DECREASE-III, there have only been four other reports on statin use in patients undergoing vascular surgery.[32-35] Two additional reports discuss the benefit of statin therapy during major noncardiac surgery, including both vascular and nonvascular, or in intermediate risk surgery, excluding vascular surgery entirely.[36-37] From the four reports on statin use during the perioperative period in vascular surgery patients, three were based on retrospective data acquisition, and only one was a prospectively randomized trial.

Poldermans et al. performed a retrospective case-controlled study in 2816 major vascular surgery patients.[32] Cases were all 160 (5.8%) patients who died during perioperative hospital stay, and for each case 2 controls were selected (n=320) from all survivors, stratified according to year and type of surgery. Information on perioperative statin use, cardiac risk factors and other medication was gathered for

all subjects. There were significantly fewer statin users among those that died (8%) than among those that survived (25%, P<.001).[32]

Kertai et al. studied 570 patients who underwent abdominal aortic aneurysm (AAA) surgery.[34] Information on advanced age, medical history, results of dobutamine stress echography, and statin and beta-blocker therapy were collected. They found the incidence of the combined endpoint of perioperative mortality and MI to be significantly lower in statin users than nonusers (3.7% vs. 11.0%). Even after correcting for other covariates, statin therapy was beneficial to AAA-surgery patients (OR: 0.24, 95% confidence interval: 0.10-0.70, P=.01). Beta-blockers were also beneficial to the study population, and a combination of both drugs resulted in the highest relative reduction of the composite endpoint.[34]

The StaRRS study was a retrospective study in 1163 hospitalizations for noncardiac vascular surgery.[35] Patient characteristics, medical history and medication were collected, and perioperative complications, including death, MI, ischemia, congestive heart failure and ventricular tachyarrhythmias were scored. Complications occurred in 9.9% of statin users, and in 16.5% in nonusers (P=.001). Even after correcting for other covariates, statins were associated with a reduction in risk of complications (OR=0.52, P=.001).[35]

Durazzo et al. conducted the first prospective, placebo-controlled, double-blind randomized trial on the effect of statins on cardiovascular event following vascular surgery.[33] They randomized one hundred patients for atorvastatin (n=50) or placebo, on average 30 days before vascular surgery. The combined primary endpoint consisted of death from cardiac cause, nonfatal myocardial infarction, unstable angina and stroke. During the 6-month follow-up period, the incidence of the primary endpoint was 26.0% in the placebo group, compared to 8.0% with atorvastatin. The event-free survival, as a function of time, was significantly higher in patients treated with atorvastatin (P=.018, according to Kaplan-Meier method).[33]

Comparison of the efficacy and safety of fluvastatin and other statins in high-risk surgery patients is inhibited by the lack of comparative studies, and the limited amount of prospectively randomized placebo-controlled trials. Only one prospective RCT was performed using fluvastatin, and one atorvastatin. The rate of cardiac

death or non-fatal MI in DECREASE-III was 4.8%, whereas in the data from Durazzo et al. atorvastatin seemed to be associated with an incidence of 8.0% for the same endpoints.[15, 33] However, there were differences in patients characteristics, distribution of target vessels and years of surgery. More importantly, the incidence of cardiac events in the placebo group was substantially higher in the study by Durazzo et al. (20.0%), compared to DECREASE-III (10.1%).

6. Use of fluvastatin in intermediate-risk surgery

Besides high-risk surgery, the treatment effect of fluvastatin has also been investigated in intermediate-risk surgery patients. DECREASE-IV was a multicenter RCT among 1066 patients undergoing elective nonvascular surgery.[37] In this trial, a trend was observed of reduced cardiac events with fluvastatin therapy in the perioperative period in nonvascular surgery patients. This was not statistically significant, possibly due to under enrollment of the study.[37] However, a recent follow-up study of DECREASE-IV showed that perioperative fluvastatin therapy had a so-called “legacy-effect” in these nonvascular surgery patients. Perioperative fluvastatin, discontinued 30 days after surgery, was associated with a reduction in the incidence of myocardial infarction at long-term follow-up of over thirty months. This suggests that the pleiotropic effects of statin therapy can help reduce the atherosclerotic burden at postoperative hospital discharge. Untreated patients are predisposed to a higher risk of cardiovascular events, compared to patients who did receive perioperative fluvastatin as cardioprotection.

7. Conclusion

The use of fluvastatin as lipid-lowering therapy in the general, non-surgical population has been reported in several studies, and was evaluated in a previous *Expert Opinion* by Lawrence and Reckless.[11] Fluvastatin was described to be effective at lowering total and LDL cholesterol, and to be safe and well-tolerated. Furthermore, drug interactions are low in comparison with other hepatically metabolized statins.

The use of statins in patients undergoing high-risk surgery is aimed at reducing the incidence of perioperative cardiovascular adverse events. Of the few reports on

this subject, fluvastatin was the agent of choice in the largest, prospectively randomized, placebo-controlled trial to date. Compared to placebo, fluvastatin is associated with a significant reduction of myocardial ischemia, myocardial infarction and cardiac death. In terms of safety, no significant adverse reaction was seen on CK-levels or liver enzymes levels, compared to placebo. Fluvastatin seems to be a safe and effective agent, suitable for perioperative treatment in patients undergoing vascular surgery.

8. Expert opinion

Although currently no statin has a particular approved indication for perioperative cardiac prevention, statin are often considered in vascular surgery patients. Not only because of the high incidence of dyslipidemia in this population, but also because of the pleiotropic effects of statin therapy.

Fluvastatin is effective in reducing cardiovascular adverse events in the perioperative period in high-risk surgery patients. Considering the low proportion of patients with side-effects and the extended release formulation, no other available statin is preferential to fluvastatin XL. Unfortunately, no large RCTs have been performed with other statins to provide us with comparable data. For now, the DECREASE-III trial advocates fluvastatin XL administration prior to high-risk surgery.

For adequate implementation of fluvastatin prescription in patients scheduled for surgery, some questions remain.

Is development of a non-oral form of administration warranted?

Surgery patients often have a limited intake immediately after surgery. To bridge these first days, a non-oral form of fluvastatin might be helpful. However, since the acting site of fluvastatin is primarily the liver, where it is metabolized, an intravenous solution may not be optimal. The passage of enteral fluvastatin through the liver is essential to its therapeutic effect. Suppositories may provide a solution, although uptake in the rectum is still not equal to the proximal intestinal tract.

Are there racial differences in the efficacy of fluvastatin?

Although no specific information on fluvastatin is available, racial differences have been reported in the efficacy of lipid-lowering therapy, with evidence that African-Americans are less likely to reach LDL-level goals with statin therapy.[38-39] However, for cardiac events in the perioperative period, no reports on race as a factor have been published. The racial differences in pleiotropic effects of perioperative fluvastatin use for the prevention of perioperative cardiac events are therefore unknown. Since the lipid profile plays an important role in atherosclerotic advancement, only large future studies may reveal that statin therapy is less effective in the prevention of perioperative cardiac events in certain races.

What is the best timing for perioperative statin therapy?

There are some studies of cell cultures and the influence of statins on inflammatory response markers. These show that only 4 hours after simultaneous administration with interleukin (IL)-6, a reduction of C-reactive protein (CRP) release in human hepatic cells was established by statins.[5] An in vitro study found that fluvastatin inhibited IL-6 expression in human vascular smooth muscle cells, even after only 4 hours.[40] The effect substantiated after 8 hours, leading to nearly 50% reduction of IL-6 after 24 hours. In other words, in vitro it seems that fluvastatin has pleiotropic effects after 4-24 hours.

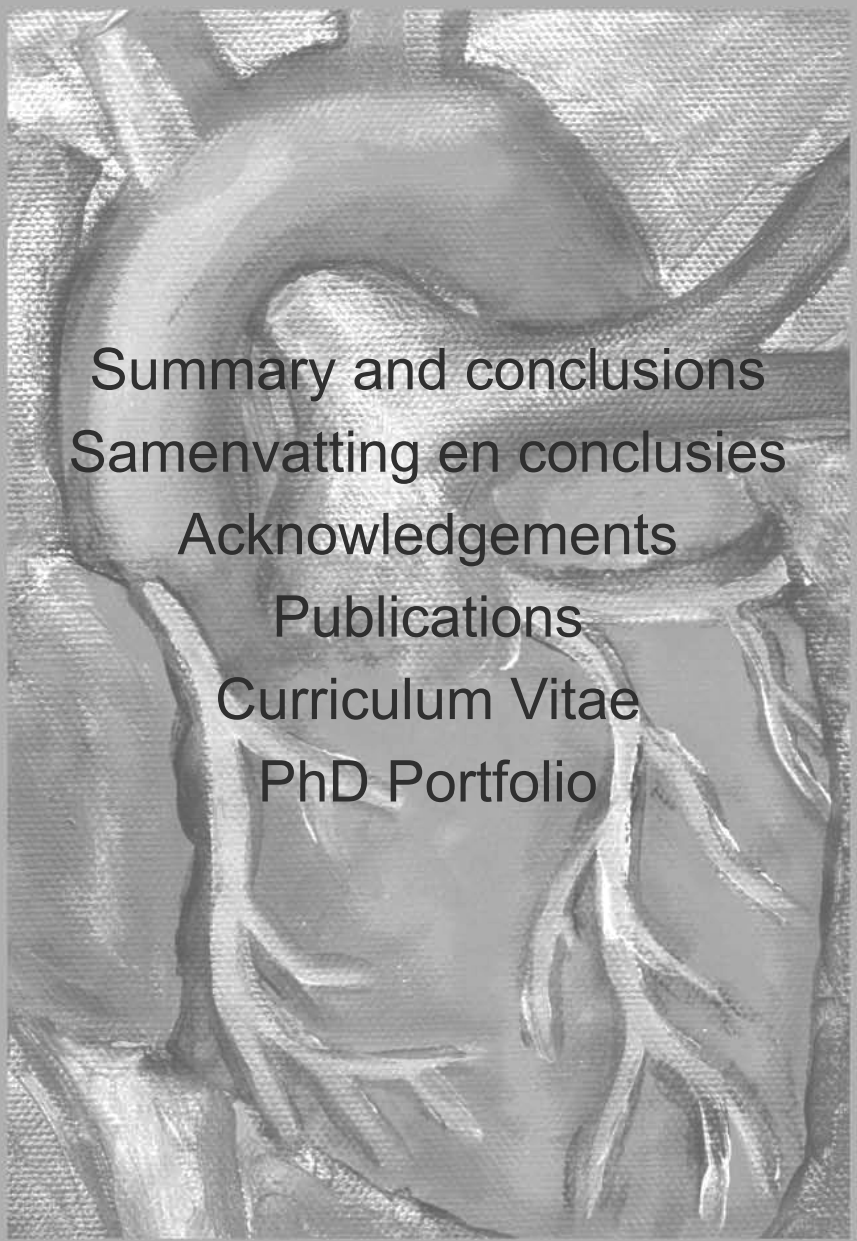
What can be expected for the future?

In DECREASE-III, fluvastatin has proven to reduce cardiovascular events immediately after vascular surgery.[15] The mentioned follow-up study from DECREASE-IV showed additional effects of perioperative fluvastatin at long-term follow-up in intermediate-risk surgery patients. Future studies may reveal a similar legacy effect of perioperative fluvastatin therapy in high-risk surgery patients.

References

1. Gordon DJ, Rifkind BM. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors: a new class of cholesterol-lowering agents. *Ann Intern Med.* Nov 1987;107(5):759-761.
2. Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins. *Circulation.* Aug 20 2002;106(8):1024-1028.
3. Poldermans D, Bax JJ, Boersma E, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: the Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur Heart J.* Nov 2009;30(22):2769-2812.
4. Davignon J, Laaksonen R. Low-density lipoprotein-independent effects of statins. *Curr Opin Lipidol.* Dec 1999;10(6):543-559.
5. Arnaud C, Burger F, Steffens S, et al. Statins reduce interleukin-6-induced C-reactive protein in human hepatocytes: new evidence for direct antiinflammatory effects of statins. *Arterioscler Thromb Vasc Biol.* Jun 2005;25(6):1231-1236.
6. Van Kuijk JP, Flu WJ, Witteveen OP, Voûte M, Bax JJ, Poldermans D. The influence of statins on the expansion rate and rupture risk of abdominal aortic aneurysms. *J Cardiovasc Surg (Torino).* Oct 2009;50(5):599-609.
7. Yuan JN, Tsai MY, Hegland J, Hunninghake DB. Effects of fluvastatin (XU 62-320), an HMG-CoA reductase inhibitor, on the distribution and composition of low density lipoprotein subspecies in humans. *Atherosclerosis.* Apr 1991;87(2-3):147-157.
8. Tse FL, Jaffe JM, Troendle A. Pharmacokinetics of fluvastatin after single and multiple doses in normal volunteers. *J Clin Pharmacol.* Jul 1992;32(7):630-638.
9. Corsini A. Fluvastatin: effects beyond cholesterol lowering. *J Cardiovasc Pharmacol Ther.* Jul 2000;5(3):161-175.
10. Scripture CD, Pieper JA. Clinical pharmacokinetics of fluvastatin. *Clin Pharmacokinet.* 2001;40(4):263-281.
11. Lawrence JM, Reckless JP. Fluvastatin. *Expert Opin Pharmacother.* Nov 2002;3(11):1631-1641.
12. http://www.pharma.us.novartis.com/product/pi/pdf/Lescol.pdf.
13. Sabia H, Prasad P, Smith HT, Stoltz RR, Rothenberg P. Safety, tolerability, and pharmacokinetics of an extended-release formulation of fluvastatin administered once daily to patients with primary hypercholesterolemia. *J Cardiovasc Pharmacol.* May 2001;37(5):502-511.
14. Boersma E, Kertai MD, Schouten O, et al. Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee cardiac risk index. *Am J Med.* Oct 2005;118(10):1134-1141.
15. Schouten O, Boersma E, Hoeks SE, et al. Fluvastatin and perioperative events in patients undergoing vascular surgery. *N Engl J Med.* Sep 3 2009;361(10):980-989.
16. Poldermans D. Statins and noncardiac surgery: current evidence and practical considerations. *Cleve Clin J Med.* Nov 2009;76 Suppl 4:S79-83.
17. Benghozi R, Bortolini M, Jia Y, Isaacsohn JL, Troendle AJ, Gonasun L. Frequency of creatine kinase elevation during treatment with fluvastatin. *Am J Cardiol.* Jan 15 2002;89(2):231-233.
18. Bruckert E, Hayem G, Dejager S, Yau C, Begaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study. *Cardiovasc Drugs Ther.* Dec 2005;19(6):403-414.
19. van der Graaf A, Nierman MC, Firth JC, Wolmarans KH, Marais AD, de Groot E. Efficacy and safety of fluvastatin in children and adolescents with heterozygous familial hypercholesterolaemia. *Acta Paediatr.* Nov 2006;95(11):1461-1466.
20. Hrab RV, Hartman HA, Cox RH, Jr. Prevention of fluvastatin-induced toxicity, mortality, and cardiac myopathy in pregnant rats by mevalonic acid supplementation. *Teratology.* Jul 1994;50(1):19-26.
21. Briggs GG FR, Yaffe SJ. *Drugs in pregnancy and lactation*. 5th ed. Baltimore, Maryland; 1998:630-632.

22. Lye M, Valacio R, Reckless JP, et al. Elderly patients with hypercholesterolaemia: a double-blind study of the efficacy, safety and tolerability of fluvastatin. *Coron Artery Dis.* 1998;9(9):583-590.
23. Chong PH, Seeger JD, Franklin C. Clinically relevant differences between the statins: implications for therapeutic selection. *Am J Med.* Oct 1 2001;111(5):390-400.
24. Kline SS, Harrell CC. Potential warfarin-fluvastatin interaction. *Ann Pharmacother.* Jun 1997;31(6):790.
25. Andrus MR. Oral anticoagulant drug interactions with statins: case report of fluvastatin and review of the literature. *Pharmacotherapy.* Feb 2004;24(2):285-290.
26. Kokudai M, Inui N, Takeuchi K, Sakaeda T, Kagawa Y, Watanabe H. Effects of statins on the pharmacokinetics of midazolam in healthy volunteers. *J Clin Pharmacol.* May 2009;49(5):568-573.
27. Yang LQ, Yu WF, Cao YF, Gong B, Chang Q, Yang GS. Potential inhibition of cytochrome P450 3A4 by propofol in human primary hepatocytes. *World J Gastroenterol.* Sep 2003;9(9):1959-1962.
28. Feierman DE, Lasker JM. Metabolism of fentanyl, a synthetic opioid analgesic, by human liver microsomes. Role of CYP3A4. *Drug Metab Dispos.* Sep 1996;24(9):932-939.
29. McDonnell CG, Malkan D, Van Pelt FD, Shorten GD. Elimination of alfentanil delivered by infusion is not altered by the chronic administration of atorvastatin. *Eur J Anaesthesiol.* Aug 2003;20(8):662-667.
30. Heeschen C, Hamm CW, Laufs U, et al. Withdrawal of statins increases event rates in patients with acute coronary syndromes. *Circulation.* Mar 26 2002;105(12):1446-1452.
31. Schouten O, Hoeks SE, Welten GM, et al. Effect of statin withdrawal on frequency of cardiac events after vascular surgery. *Am J Cardiol.* Jul 15 2007;100(2):316-320.
32. Poldermans D, Bax JJ, Kertai MD, et al. Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. *Circulation.* Apr 15 2003;107(14):1848-1851.
33. Durazzo AE, Machado FS, Ikeoka DT, et al. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. *J Vasc Surg.* May 2004;39(5):967-975; discussion 975-966.
34. Kertai MD, Boersma E, Westerhout CM, et al. A combination of statins and beta-blockers is independently associated with a reduction in the incidence of perioperative mortality and nonfatal myocardial infarction in patients undergoing abdominal aortic aneurysm surgery. *Eur J Vasc Endovasc Surg.* Oct 2004;28(4):343-352.
35. O'Neil-Callahan K, Katsimaglis G, Tepper MR, et al. Statins decrease perioperative cardiac complications in patients undergoing noncardiac vascular surgery: the Statins for Risk Reduction in Surgery (StaRRS) study. *J Am Coll Cardiol.* Feb 1 2005;45(3):336-342.
36. Lindenauer PK, Pekow P, Wang K, Gutierrez B, Benjamin EM. Lipid-lowering therapy and in-hospital mortality following major noncardiac surgery. *JAMA.* May 5 2004;291(17):2092-2099.
37. Dunkelgrun M, Boersma E, Schouten O, et al. Bisoprolol and fluvastatin for the reduction of perioperative cardiac mortality and myocardial infarction in intermediate-risk patients undergoing noncardiovascular surgery: a randomized controlled trial (DECREASE-IV). *Ann Surg.* Jun 2009;249(6):921-926.
38. Yood MU, McCarthy BD, Kempf J, et al. Racial differences in reaching target low-density lipoprotein goal among individuals treated with prescription statin therapy. *Am Heart J.* Oct 2006;152(4):777-784.
39. Krauss RM, Mangravite LM, Smith JD, et al. Variation in the 3-hydroxyl-3-methylglutaryl coenzyme a reductase gene is associated with racial differences in low-density lipoprotein cholesterol response to simvastatin treatment. *Circulation.* Mar 25 2008;117(12):1537-1544.
40. Ito T, Ikeda U, Shimpo M, et al. HMG-CoA reductase inhibitors reduce interleukin-6 synthesis in human vascular smooth muscle cells. *Cardiovasc Drugs Ther.* Mar 2002;16(2):121-126.



Summary and conclusions
Samenvatting en conclusies
Acknowledgements
Publications
Curriculum Vitae
PhD Portfolio

Summary and Conclusions

In 1902, the Dutch physiologist Willem Einthoven published the first ECG recorded with his string galvanometer, for which he was awarded a Nobel Prize. Einthoven never could have imagined the explosion of knowledge his invention would spark. In the ensuing 108 years, several technological advances have been made, including pacemakers, antiarrhythmic drugs, implantable cardioverter defibrillators, radio-frequency ablation, transtelephonic transmission of the ECG, implantable loop recorders (ILR), and much more…

Cardiac complications, such as myocardial infarction (MI) and cardiac arrhythmias, are a major cause of perioperative morbidity and mortality in patients undergoing surgery. Despite the decline in complication rates over the past decades, perioperative adverse cardiac events still remain a significant problem, therefore persisting as an area of clinical interest and concern. Arrhythmias are of special interest, since they can be classified as an adverse event with possible severe consequences, but also as a marker for underlying complications. These include electrolyte abnormalities, hypoxia and cardiac ischemia.

Part One of this thesis takes a close look into perioperative cardiac arrhythmias, in an effort to improve detection and prediction of arrhythmias, and discuss the influence of arrhythmias on the postoperative outcome of vascular surgery patients.

Chapter 1 hypothesizes that in addition to cardiac arrhythmias, an ILR could detect for the presence of myocardial ischemia. Since the ILR is largely used in clinical practice for diagnosing patients with syncope and heart rhythm recording, the expansion of its capabilities with ischemia detection was assessed and further tested in a population with a high-risk of perioperative cardiac events, such as vascular surgery patients. Future and larger studies will have to determine the feasibility of an ILR for ischemia, next to arrhythmia detection. The challenge

remains to find ways to monitor the patient's heart rhythm continuously without using an excessive number of electrodes and lead wires.

Fortunately, ILRs are equipped with a dedicated atrial fibrillation (AF) detection algorithm which is sensitive in detecting the presence of AF with a high specificity, positive and high negative predictive value. **Chapter 2** therefore focuses on continuous heart rhythm monitoring for improved arrhythmia detection. We confirmed that long-term continuous ECG recording with an ILR (Reveal® XT, model 9529, Medtronic Inc., Minneapolis, MN, USA), appeared to improve both the precise detection of AF and the transient asymptomatic character of perioperative cardiac arrhythmias. The use of traditional methods to diagnose AF such as standard surface 12-lead ECG and 72-hour Holter recordings are limited by the short documentation period. This study provides the true incidence of new-onset arrhythmias in patients undergoing major vascular surgery, and states that it is high, varying from 14% with Holter ECG recordings to 36% with an ILR. This chapter promotes the use of long-term continuous heart rhythm monitoring in vascular surgery patients; primarily since longer duration of ECG monitoring enhances detection of arrhythmia and secondly since on-line recordings, as with an ILR, enable quicker therapeutic response.

To predict perioperative arrhythmias, **chapter 3** evaluates traditional cardiac risk factors and several other risk factors, such as myocardial ischemia, inflammation markers, left ventricular function, and medication use, for their association with cardiac arrhythmias. The pathophysiology of arrhythmias is complex and several causal factors may be involved in the development of perioperative cardiac arrhythmias. Elderly and patients with reduced left ventricular function showed new-onset arrhythmias. The left ventricular function was assessed with 1) natriuretic peptide serum measurements, n-terminal pro B-type natriuretic peptide (NT-proBNP), as a good marker for increased ventricular diastolic wall stretch, 2) performance of a transthoracic echocardiography calculating the left ventricular ejection fraction (LVEF). It should be recognized that arrhythmogenesis may be multifactorial; attribution of an arrhythmia to a single predisposing factor may

oversimplify a complex situation. Regardless of their complexity, it is clear that identification and correction of potential predisposing factors is essential for prevention and management of postoperative arrhythmias.

Perioperative arrhythmias may influence the postoperative prognosis of vascular surgery patients. **Chapters 4 and 5** describe the influence of asymptomatic manifestations of AF on postoperative cardiac outcome. The five percent incidence of new-onset AF in 317 patients undergoing major non-cardiac vascular surgery is depicted in **chapter 4** where the conclusion is drawn that these AF episodes are associated with a 6-fold increased risk for perioperative cardiac events, and 4.2-fold increased risk of late cardiovascular events. **Chapter 5** encompasses 3753 European patients with symptomatic peripheral arterial disease (PAD) from the Reduction of Atherothrombosis for Continued Health (REACH) Registry, and also found that this population is at increased risk of 2-year cardiovascular mortality, and that PAD patients with AF have a 1.5-fold increased risk of long-term cardiovascular events.

Chapter 6 emphasizes the benefit of an ILR for the detection and diagnostic value of perioperative arrhythmias. Continuous heart rhythm monitoring with assessment of serum cardiac biomarkers, such as cardiac troponin T (cTnT) and NT-proBNP, allows early identification, treatment and treatment targets of patients at high risk of perioperative cardiovascular complications, in particular cardiac arrhythmias.

In **chapter 7** the additional value of heart rate variability (HRV) as a quantitative marker for the autonomic function is assessed. A depressed perioperative HRV is found to be an independent predictor of perioperative and late cardiovascular events in 495 patients undergoing non-cardiac vascular surgery. It is hypothesized that the use of an on-line ECG device calculating the perioperative HRV, instead of the 72-hour off-line Holter analyses used in this study, is capable of pharmacological manipulations on HRV and could thus become a routine therapeutic consideration for clinicians.

Chapter 8 encompasses detection, prediction and the prognostic value of perioperative arrhythmias. First, it concludes that there is a seven percent incidence of new-onset perioperative ventricular tachyarrhythmia's (VT) in vascular surgery patients. Second, it shows that there is an increased prevalence of a reduced left ventricular function in these patients, and states that fewer of these patients received statins (70% versus 85%, p=0.02), even though their baseline inflammation status did not differ (CRP 6 versus 4 mg/L). Third, patients with new-onset perioperative VT were found to have a 2.6-fold increased risk for long-term sudden cardiac death, even after adjusting for sex, cardiac risk factors and type of surgery. This chapter further states that identification of patients at risk for new-onset VT and subsequent late sudden cardiac death offers the opportunity for focused therapy.

Part Two of this thesis expands focus from cardiac arrhythmias to perioperative damage to the myocardium by any cause using the highly sensitive and specific biomarker, cTnT. The risk of perioperative myocardial damage and cardiac events depends on the condition of the patient prior to surgery, the prevalence of co-morbidities and the magnitude and duration of the surgical procedure. Surgical procedures can be classified to be associated with low-risk (< 1%), intermediate-risk (1-5%), or high-risk (> 5%) for the development of perioperative adverse cardiac events.

In **chapter 9** the influence of asymptomatic cardiac damage, defined as cTnT-release without ECG changes, was assessed in 220 patients undergoing endovascular abdominal aortic aneurysm (AAA) repair and found that 83% of patients with cTnT release were asymptomatic and also described the association between asymptomatic cTnT release and poor long-term outcome after 2.9 years. The use of statin therapy was associated with a reduced risk for long-term mortality. It is advised to perform routine perioperative cardiac screening after endovascular AAA repair.

Recent studies with high-sensitivity cTnT (hs-cTnT) assays have demonstrated that low-level troponin elevations are common in postoperative high cardiac risk patients.

Chapter 10 addresses application of a quantitative assessment of the cTnT area under the curve (AUC) in vascular surgery patients. Especially with future introduction of hs-cTnT assays, cTnT-AUC would give a better estimate of the extent of myocardial damage. Receiver operator curve analysis showed that the best cut-off value for cTnT-AUC was <0.01 days*ng/mL for predicting long-term cardiovascular events and all-cause mortality. After adjustment for risk factors, site and type of surgery and ECG changes, those in the highest cTnT-AUC tertile were associated with a significantly worse cardiovascular outcome and long-term mortality.

Part Three of this thesis discusses treatment possibilities, once the perioperative cardiac risk is assessed. It evaluates several risk reduction strategies, including medical management, in patients with an increased risk for cardiac adverse events.

Chapter 11 is a review of the various Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) studies. Ischemic cardiac events are a major cause of perioperative morbidity and mortality in non-cardiac surgery, where 10–40% of the perioperative deaths are due to myocardial infarction (MI). Therefore, to improve postoperative cardiac outcome after non-cardiac surgery a dual approach is required. Firstly, one must focus on correcting the mismatch of myocardial oxygen supply and demand. Secondly, one must stabilize the coronary artery atheromatous plaque. At present, these needs seem to be best met with a combined medical therapy of cardioselective beta-blockers, statins and, if possible, aspirin.

Chapter 12 describes that chronic heart failure remains a strong risk factor in patients undergoing major non-cardiac surgery and that adequate treatment with long-acting beta-blockers, such as bisoprolol, are the agents of preference and of

great importance in reducing postoperative morbidity and mortality. Titration according to tolerance and relatively low dosage of beta-blockers is of utmost importance to obtain a tight heart rate control and prevent adverse side effects.

Chapter 13 summarizes the most recent studies on the effectiveness and safety of perioperative statin use and once again concluded that statin therapy was associated with an improvement in postoperative cardiovascular outcome and a reduction in serum lipid levels and levels of inflammation markers. In patients scheduled for high-risk vascular surgery, treatment with a statin, such as fluvastatin, improves postoperative outcome, reducing the incidence of myocardial damage by almost 50% in the first 30 days following vascular surgery. In comparison with placebo, statin therapy was not associated with a rise in liver enzymes or creatine kinase levels.

In **chapter 14**, it is advised to bridge the non-oral phase, which commonly occurs after major surgery, with an extended-release formula, such as fluvastatin XL. The safety and efficacy of this specific agent, in both vascular and nonvascular surgery patients, is addressed in this chapter.

In **summary**, this thesis emphasizes that cardiac complications, such as MI and cardiac arrhythmias, are a major cause of perioperative morbidity and mortality in patients undergoing non-cardiac vascular surgery. It is advocated to screen vascular surgery patients perioperatively, by using continuous long-term ECG monitoring, with a 72-hour Holter device or an ILR for a longer duration. This helps detecting not only arrhythmias, but also underlying health conditions, and it contributes to the prognosis of patients. Measurement of cardiac serum biomarkers, i.e. cTnT and NT-proBNP, helps to identify asymptomatic patients experiencing a postoperative cardiac event. Finally, the most important risk reduction strategies – including beta-blocker and statin therapy – and their effect on outcome are evaluated. Optimal medical management is vital in the surgical population and the use of before mentioned medication is strongly recommended.

The results of these studies will hopefully contribute to a better understanding of perioperative cardiac arrhythmias and the use of biomarkers for the improvement of medical management and outcome of non-cardiac surgery patients. Future endeavors should encompass long-term heart rhythm monitoring in patients at high-risk of perioperative cardiac events.

Samenvatting en Conclusies

De Nederlandse fysioloog Willem Einthoven publiceerde in 1902 het eerste, met zijn snaargalvanometer gemeten, elektrocardiogram (ECG). Hiervoor ontving hij de Nobel prijs. Einthoven had nooit kunnen bedenken wat voor explosie aan wetenschap en kennis zijn uitvinding teweeg zou brengen. Sindsdien zijn er met betrekking tot het hartritme diverse technologische ontwikkelingen geweest, zoals pacemakers, anti-aritmica, inwendige cardioverter defibrillatoren, radiofrequentie ablatie therapie, transtelefonische transmissie van een ECG, implanteerbare hartritme monitors (ILR), en nog veel meer…

Cardiale complicaties, zoals hartinfarcten (MI) en hartritmestoornissen, zijn een belangrijke oorzaak van mortaliteit en morbiditeit rond niet-cardiale operaties. In de laatste decennia zijn deze complicaties in aantal afgenomen, maar blijven een significant probleem, waardoor het in de kliniek een interessant gebied met veel vraagstukken blijft. Veel aandacht gaat uit naar hartritmestoornissen, welke als een cardiale complicatie gezien kunnen worden met mogelijk ernstige consequenties. Daarnaast kunnen hartritmestoornissen ook beschouwd worden als voorspellende factor voor onderliggend lijden, zoals perioperatieve elektrolytstoornissen, hypoxie en cardiale ischemie.

In **Deel I** van dit proefschrift wordt ingegaan op perioperatieve hartritmestoornissen, waarbij ook de methoden voor het vaststellen en voorspellen van hartritmestoornissen worden uiteengezet. Tevens is de invloed van hartritmestoornissen op de postoperatieve uitkomst bij vaatchirurgische patiënten onderzocht.

Hoofdstuk 1 beschrijft de toepassing van een implanteerbare hartritme monitor (ILR) voor het vaststellen van myocard ischemie. De ILR wordt in de cardiologie reeds gebruikt om het hartritme te monitoren bij patiënten met onverklaarde collaps en bij verdenking van hartritmestoornissen. De indicatie voor het plaatsen en de

capaciteitsuitbreiding met tevens een detectie van myocard ischemie is onderzocht bij vaatchirurgische patiënten met een vergroot risico op perioperatieve cardiale complicaties. Grotere studies zullen moeten volgen om de vraagstellingen volledig te beantwoorden. Het continu registreren van het hartritme middels een monitor zonder een overvloedige hoeveelheid elektroden en draden vormt een uitdaging.

ILR's hebben een hoge specificiteit en negatief en positief voorspellende waarde voor het vaststellen van boezemfibrilleren. **Hoofdstuk 2** beschrijft een onderzoek naar het continu registreren van het hartritme om de detectie van hartritmestoornissen te verbeteren. In dit onderzoek wordt vastgesteld dat langdurige continue ECG registratie middels een ILR (Reveal® XT, model 9529, Medtronic Inc., Minneapolis, MN, Verenigde Staten) zowel boezemfibrilleren als andere typen van perioperatieve hartritmestoornissen kan detecteren. Het gebruik van traditionele ECG registratie, in de vorm van standaard 12-afleiding ECG en 72-uurs Holter meting, voor het registreren van hartritmestoornissen wordt beperkt door de korte opnameduur. Deze studie laat zien dat de ware incidentie van nieuw ontstane hartritmestoornissen bij vaatchirurgische patiënten hoog blijkt te zijn. Dit varieert van 14% bij het gebruik van Holter ECG registratie tot 36% bij het gebruik van ILR. Het gebruik van langdurige continue hartritme monitoring bij vaatchirurgische patiënten wordt in dit hoofdstuk aanbevolen, aangezien dit zorgt voor een grotere kans om hartritmestoornissen te detecteren. Door het gebruik van een ILR vindt een actuele continue ECG registratie plaats, wat aangrijpingspunten kan bieden voor eventuele doelgerichtere therapie.

In **Hoofdstuk 3** worden de voorspellende waarde en de relatie tot perioperatieve hartritmestoornissen van de traditionele cardiale risicofactoren evenals andere risicofactoren, zoals myocard ischemie, ontstekingsmediatoren, linker ventrikel functie en gebruik van medicatie, onderzocht. De pathofysiologie van hartritmestoornissen is complex en spelen verscheidene factoren een rol bij het ontstaan hiervan. Bij ouderen en patiënten met linker ventrikel dysfunctie worden vaker perioperatieve hartritmestoornissen vastgesteld. De linker ventrikel functie is vastgesteld middels: 1) een serum bepaling van het natriuretische peptide

genaamd n-terminal pro B-type natriuretic peptide (NT-proBNP) wat een goede maat is voor een toegenomen diastolische rek van de ventrikelwand en; 2) het bepalen van de linker ventrikel ejectie fractie met gebruik van een rust echo van het hart. Er wordt benadrukt dat het ontstaan van hartritmestoornissen een multifactoriële aandoening is. Het toewijzen van een enkele oorzaak voor het ontstaan van hartritmestoornissen zou een te simplistische weergave van de situatie zijn. Ongeacht de complexiteit hiervan is het van belang om predisponerende factoren voor hartritmestoornissen te identificeren om postoperatieve hartritmestoornissen te voorkomen en te behandelen.

Perioperatieve hartritmestoornissen kunnen de postoperatieve uitkomst van vaatchirurgische patiënten beïnvloeden. **Hoofdstuk 4 en 5** beschrijven de invloed van asymptomatisch boezemfibrilleren op de postoperatieve uitkomst. De incidentie van nieuw ontstaan boezemfibrilleren, bij 317 patiënten die een niet-cardiale vaatchirurgische procedure ondergingen bleek vijf procent te zijn. Verder blijkt uit het onderzoek in **Hoofdstuk 4** dat het perioperatief vaststellen van nieuw ontstaan boezemfibrilleren geassocieerd is met een zes maal hogere incidentie van perioperatieve cardiale complicaties en een 4,2 maal grotere kans op lange termijn cardiale complicaties. **Hoofdstuk 5** toont de data afkomstig uit de Reduction of Atherothrombosis for Continued Health (REACH) Registry van 3753 Europese patiënten met symptomatisch perifeer vaatlijden. Gedurende een follow-up van 2 jaar hadden deze patiënten, die tevens boezemfibrilleren in de voorgeschiedenis hadden, een 1,5 maal grotere kans op cardiovasculaire complicaties.

Het gebruik van een ILR biedt een unieke kans om perioperatieve hartritmestoornissen te registreren. **Hoofdstuk 6** bestudeert het continu registreren van het hartritme met gebruik van een ILR bij een patiënt met een hoog risico op perioperatieve cardiale complicaties. Hierbij wordt de continue ECG registratie gecombineerd met het bepalen van cardiale biomarkers, zoals cardiale troponine T (cTnT) en NT-proBNP, in het serum. Er wordt een relatie gevonden tussen het biomarker patroon en het ontstaan van perioperatief boezemfibrilleren. Daarnaast

heeft het gebruik van een ILR ook een diagnostische waarde, waarbij patiënten met een vergroot risico op perioperatieve cardiale complicaties zoals hartritmestoornissen gerichter behandeld kunnen worden ofwel de medicamenteuze therapie hierop aangepast kan worden.

In **Hoofdstuk 7** wordt de toegevoegde waarde van de heart rate variability (HRV) naast het continu registreren van het hartritme besproken. De HRV is een kwantitatieve maat voor de functie van het autonome zenuwstelsel. In 495 vaatchirurgische patiënten blijkt het perioperatief vaststellen van een verminderde HRV geassocieerd te zijn met een verhoogd risico op perioperatieve en lange termijn cardiale complicaties. In de huidige studie zijn de 72-uurs Holter analyses off-line verricht. Een meerwaarde voor toekomstige ECG monitors zou het langdurig en on-line registreren van het hartritme zijn, waarbij ook de HRV gemeten wordt. Hieraan kunnen mogelijk therapeutische consequenties worden verbonden.

Hoofdstuk 8 onderzoekt de voorspellende en prognostische waarde van het vaststellen van perioperatieve hartritmestoornissen. De incidentie van nieuw vastgestelde ventriculaire tachycardieën (VT) blijkt bij vaatchirurgische patiënten zeven procent te zijn. Ook wordt beschreven dat bij de patiënten met nieuw vastgestelde VT vaker sprake is van linker ventrikel dysfunctie. Maar 70% van de patiënten met nieuw vastgestelde VT gebruikte preoperatief statines, in vergelijking tot 85% van de patiënten zonder perioperatief VT (p=0.02). Desondanks waren de preoperatieve ontstekingswaarden niet significant verschillend (CRP 6 versus 4 mg/L). Nieuw vastgestelde VT bleek geassocieerd te zijn met een 2,6 maal vergroot risico op acute hartdood op de lange termijn. Perioperatieve nieuw vastgestelde VT bleken na correctie voor geslacht, cardiale risicofactoren en type vaatoperatie, een onafhankelijke voorspeller van acute hartdood op de lange termijn. Dit hoofdstuk concludeert dat er een hoog risico bestaat op het ontwikkelen van nieuw ontstane perioperatieve VT bij vaatchirurgische patiënten. Dit hoofdstuk benadrukt verder dat de identificatie van patiënten met een verhoogd risico voor

het ontwikkelen hiervan en hierdoor een vergroot risico op langetermijns acute hartdood hebben, van belang is voor gerichte therapie.

Deel II van dit proefschrift verlegt de aandacht van hartritmestoornissen naar perioperatieve cardiale complicaties in de vorm van een hartinfarct. Cardiale troponine T (cTnT) is een sensitieve en specifieke maat voor het vaststellen van een hartinfarct en de ernst van de schade aan het hart. Het risico op perioperatieve hartschade en cardiale complicaties is afhankelijk van de preoperatieve conditie van de patiënt en aanwezigheid van cardiale risicofactoren. Ook is het afhankelijk van de grootte en de duur van de operatie. Operaties kunnen onderverdeeld worden in laag-risico (< 1%), middelmatig-risico (1-5%) en hoog-risico (> 5%) voor de patiënt op het ontwikkelen van perioperatieve cardiale complicaties.

In **Hoofdstuk 9** wordt bij 220 patiënten, die een endovasculair herstel van een aneurysma van de abdominale aorta hebben gehad, de invloed van asymptomatsche hartschade op de langetermijns uitkomst onderzocht. Asymptomatische hartschade werd gedefinieerd als postitieve cTnT meting zonder ECG veranderingen, Asymptomatische hartschade werd bij 83% van de patiënten met positieve postoperatieve uitslagen van cTnT vastgesteld. Dit werd geassocieerd met een slechtere uitkomst na 2,9 jaar follow-up. Ook werd vastgesteld dat het gebruik van statines geassocieerd kon worden met een betere uitkomst op de lange termijn. Dit leidde tot het adviseren van routinematig bepalen van cTnT na een endovasculair herstel van een aneurysma aortae abdominalis.
Recente studies met hoge-sensitiviteits cTnT (hs-cTnT) metingen hebben bewezen dat een laag positieve waarde van cTnT een veel voorkomend verschijnsel is bij cardiaal hoog-risico patiënten.

In **Hoofdstuk 10** wordt gebruik gemaakt van de cTnT area under the curve (cTnT-AUC) als maat voor de ernst van de perioperatief opgetreden hartschade. Voor het voorspellen van langetermijns uitkomst en cardiale complicaties heeft de receiver operator curve analyse uitgewezen dat de optimale afkapwaarde voor cTnT-AUC <0.01 dagen*ng/mL was. In een multivariate analyse, na correctie voor cardiale

risicofactoren en type vaatingreep, bleek het hebben van een hoge waarde van cTnT-AUC geassocieerd te zijn met een slechtere langetermijns uitkomst en cardiale complicaties.

Deel III van dit proefschrift bevat een overzicht van verschillende strategieën gericht op reductie van cardiale risico zoals bètablokkers en statine therapie, bij patiënten die op basis van klinische risicofactoren een verhoogd perioperatief cardiaal risico hebben.

Hoofdstuk 11 geeft een overzicht van enkele van de Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) studies. Ischemische cardiale complicaties zijn een belangrijke oorzaak van mortaliteit en morbiditeit rond niet-cardiale operaties. Tien tot 40% van de perioperatieve mortaliteit wordt veroorzaakt door een hartinfarct.Het is daarom van belang om een tweesporen beleid te volgen bij de preventie van perioperatieve cardiale complicaties. Ten eerste dient de behoefte aan zuurstof aan het hart te worden geoptimaliseerd. Ten tweede moet de zogenaamde instabiele coronaire plaque, die op het punt staat te ruptureren, worden gestabiliseerd. Het beste effect bereikt men met een combinatie van bètablokkers, statines en, indien mogelijk, aspirines.

In **Hoofdstuk 12** wordt de perioperatieve behandeling van patiënten met chronisch hartfalen besproken. Hieruit komt naar voren dat deze hoog risico patiënten die een niet-cardiale operatie ondergaan gebaat kunnen zijn bij een behandeling met een bètablokker zoals bisoprolol. Bètablokkers bleken geassocieerd te zijn met een significante reductie in het aantal perioperatieve cardiale complicaties. Ook wordt in dit hoofdstuk benadrukt dat bètablokker therapie met verstand gedoseerd dient te worden. Men moet tijdig beginnen met bètablokkers en de dosis op geleide van bloeddruk en hartslagfrequentie aanpassen. Wanneer bètablokkers tijdig in een lage dosering worden gestart en de dosis, indien nodig, adequaat wordt aangepast, is het risico op een beroerte niet verhoogd terwijl de kans op perioperatieve cardiale complicaties wel verlaagd wordt.

In **Hoofdstuk 13** worden de meest recente studies over de effectiviteit en veiligheid van perioperatief gebruik van statines beschreven. Er wordt een verband gezien tussen statine gebruik en een verlaagde kans op perioperatieve cardiale complicaties. Ook blijkt statine gebruik geassocieerd te zijn met daling van het lipiden spectrum en een vermindering van de ontstekingswaarden in het serum. Bij patiënten die op basis van klinische risicofactoren een verhoogd perioperatief cardiaal risico hebben wordt het gebruik van statines, zoals fluvastatine, geassocieerd met een verbetering van de postoperatieve uitkomst. In de eerste 30 dagen na een vaatchirurgische operatie blijken statines de incidentie van perioperatieve hartschade met bijna 50% te verminderen. In tegen stelling tot placebo's bleken statines niet geassocieerd te zijn met een stijging van de leverenzymen noch de waarden van kreatinine kinase.

In **Hoofdstuk 14** wordt het advies uitgesproken dat het gebruik van een statine met vertraagde afgifte, zoals fluvastatin XL, aan te bevelen is gedurende de perioperatieve periode, vooral gedurende die fase dat patiënten nuchter zijn. Tevens wordt de veiligheid en effectiviteit van fluvastatine zowel bij patiënten die een vaatchirurgische als niet-vaatchirurgische procedure ondergaan besproken.

Dit proefschrift benadrukt dat cardiale complicaties, zoals hartritmestoornissen en een hartinfarct, een belangrijke oorzaak zijn van perioperatieve morbiditeit en mortaliteit rond niet-cardiale vaatoperaties. Het is aanbevolen om het hartritme van vaatchirurgische patiënten tijdens de perioperatieve periode te monitoren middels een continue langdurige ECG registratie (hetzij met een 72-uurs Holter monitor of een ILR apparaat welke langdurig het hartritme kan meten). Op deze manier kunnen zowel hartritmestoornissen als onderliggend hartlijden worden gediagnosticeerd, wat van prognostische waarde is voor het risico op perioperatieve en langetermijns cardiale complicaties en mortaliteit. Het identificeren van patiënten met asymptomatische cardiale complicaties wordt bespoedigd door het meten van cardiale serum biomarkers, zoals cTnT en NT-proBNP. Als laatst wordt het reduceren van het risico op cardiale complicaties middels medicamenteuze therapie, zoals bètablokkers en statines, en hun positief

effect op de uitkomst besproken. Optimale medicamenteuze therapie blijkt in de vaatchirurgische populatie belangrijk te zijn en dient ten gevolge te worden aangeboden.

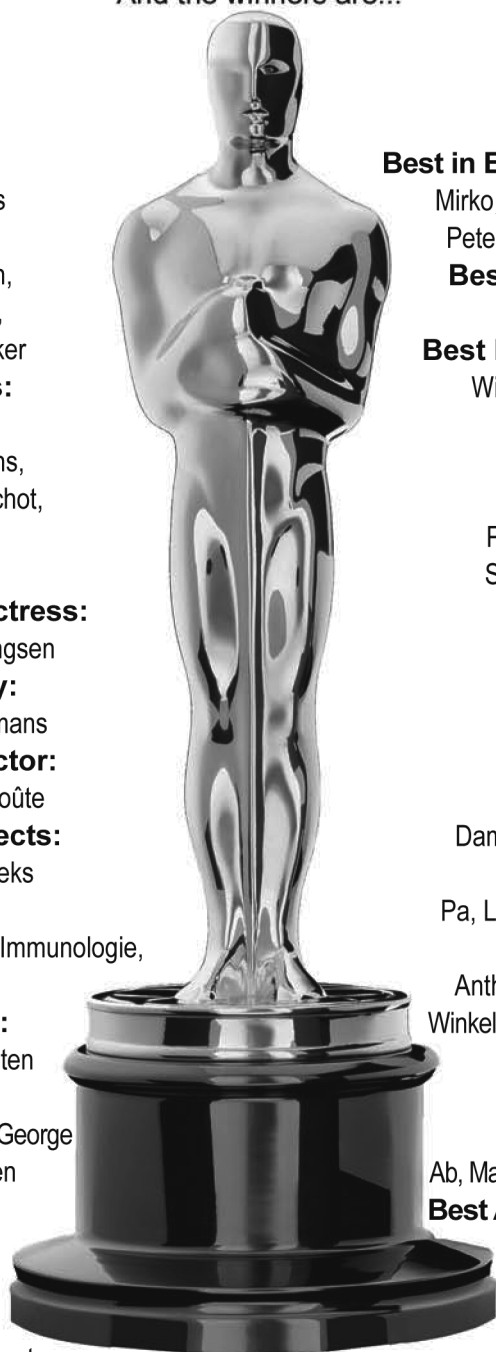
Wij hopen dat wij met deze studies hebben bijgedragen aan het inzicht in de verschillende aspecten van perioperatieve hartritmestoornissen en het gebruik van serum biomarkers ter bevordering van de medicamenteuze therapie en de uitkomst van vaatchirurgische patiënten. In de toekomst zal het langdurig registreren van het hartritme bij patiënten met een hoog risico op cardiale complicaties een aandachtspunt moeten zijn.

'If Shakespeare were alive today; he'd be in Hollywood making movies!'

(Bazaar 1999)

Mijn dank en blijdschap zijn niet goed in woorden uit te drukken, vandaar dat iedereen die in enige vorm heeft bijgedragen aan dit proefschrift een Oscar verdient!

And the winners are...



Best Director:
Prof. dr. Don Poldermans

Academy Board:
Prof. dr. Hence Verhagen,
Prof. dr. ir. Eric Boersma,
Prof. dr. Robert Jan Stolker

Academy Members:
Prof. dr. J.F. Hamming,
Prof. dr. L.J.L.M. Jordaens,
Prof. dr. J.J.B. van Lanschot,
Prof. dr. H. W. Tilanus,
Prof. dr. H.van Urk

Best Supporting Actress:
Nienke Dols, Cecilie Ellingsen

Best Choreography:
Virginie Roeloff - Poldermans

Best Supporting Actor:
Olaf Schouten, Michiel Voûte

Best Statistical Effects:
Dr. Sanne Hendrikx - Hoeks

Best Short Film:
Klinische Experimentele Immunologie,
AKC Trial Lab

Best Script Writers:
Alle deelnemende patiënten

Best Stunt Crew:
Joke, Ellen, Mark, Metz, George
en alle arts-assistenten en
CHIVO's Heelkunde

Best Soundtrack:
Dames van de poli,
Dames van de PKV,
Afdeling 9-Zuid en Margaret

Best in Electrocinematography:
Mirko, Dave, Anneke, Peter Kessel
Peter, Art Pilmeyer, Elizabeth Hoff

Best Surgical Supervisor:
Dr. Jan Oomen

Best Research Department:
Willem-Jan, Dustin, Martin, Gijs
Yvette, Jan-Peter, Frederico
Ruud, Wael, Radosav, Niels

Best Animation:
Pieter, Zarina, Tessa, Brechtje
Stephanie, Jan-Willem, Carlijn
Sanne, Hasan, Jeroen, Mark
en alle overige onderzoekers

Best Art Director:
Steph, Ab, MTV

My Special Effects:
Fee, Steef, Lot, Rosi
Dames van Absoluut, Medibabes

Original Screenplay:
Pa, Link, Dikkie, Inez, Bert, Ruben
oma Ruth, oma Joan
Anthony, Kitty, de gehele families
Winkel, Da Costa Gomez en Capriles
Familie da Costa

Adapted Screenplay:
Annemarie, Carolien, Guido
Ab, Marie-José, mr et mme Beyerman

Best Actor in a Leading Role:
Abe Jongbloed

Best Kiss:
Mi dushi

Publications

- **Winkel T**, Schouten O, Poldermans D. Long-term risk prediction in patients undergoing abdominal aortic aneurysm repair: the ultimate stress test of open repair. Eur J Vasc Endovasc Surg.2008;35(4):420-1.
- **Winkel TA**, Schouten O, van Kuijk JP, Verhagen HJ, Bax JJ, Poldermans D. Perioperative asymptomatic cardiac damage after endovascular abdominal aortic aneurysm repair is associated with poor long-term outcome. J Vasc Surg. 2009 Oct;50(4):749-54.
- **Winkel TA**, Schouten O, Hoeks SE, Verhagen HJ, Bax JJ, Poldermans D. Prognosis of transient new-onset atrial fibrillation during vascular surgery. Eur J Vasc Endovasc Surg. 2009 Dec;38(6):683-8.
- **Winkel TA**, Schouten O, Voûte MT, Hoeks SE, Welten GM, Bax JJ, Verhagen HJM, Poldermans D. The effect of statins on perioperative events in patients undergoing vascular surgery. Acta Chir Belg, 2010, 110, 28-31.
- **Winkel TA**, Schouten O, Hoeks SE, Flu WJ, Hampton D, Kirchhof P, van Kuijk JP, Lindemans J, Verhagen HJM, Bax JJ, Poldermans D. Risk factors and outcome of new-onset cardiac arrhythmias in vascular surgery. Am Heart Journal, 2010; 159(6):1108-15.
- **Winkel TA**, Hoeks SE, Schouten O, Zeymer U, Limbourg T, Baumgartner I, Bhatt DL, Steg PG, Goto S, Rother J, Cacoub PP, Verhagen HJM, Bax JJ, Poldermans D; on behalf of the REACH Registry investigators. Prognosis of atrial fibrillation in patients with peripheral arterial disease: data from the REduction of Atherothrombosis for Continued Health (REACH) Registry. Eur J Vasc Endovasc Surg. 2010;40(1):9-16.
- **Winkel TA**, Voûte MT, de Melis M, Hoeks SE, Schouten O, Kessels R, Verhagen HJ, Poldermans D. Sudden death during follow-up after new-onset ventricular tachycardia's in vascular surgery patients. *Accepted for publication.*

- **Winkel TA**, Schouten O, Hoeks SE, Voûte MT, Chonchol M, Goei D, Flu WJ, van Kuijk JP, Lindemans J, Verhagen HJM, Bax JJ, Poldermans D. Prognosis of vascular surgery patients using a quantitative assessment of troponin-T release; is the crystal ball still clear? *Accepted for publication.*
- Voûte MT, **Winkel TA**, Poldermans D. Safety of fluvastatin in patients undergoing high-risk non-cardiac surgery. Expert Opinion on Drug Safety 2010, in press.
- Flu WJ, **Winkel TA**, Bax JJ, Poldermans D. Bisoprolol in patients with chronic heart failure undergoing non-cardiac surgery. Aging Health 2009;5(1).
- **Winkel TA**, Schouten O, Hoeks SE, Flu WJ, Hampton D, Kirchhof P, van Kuijk JP, Lindemans J, Verhagen HJM, Bax JJ, Poldermans D. Cardiac arrhythmias in vascular surgery patients; the comparison of continuous electrocardiography devices. *Submitted for publication.*
- **Winkel TA**, Schouten O, Hoeks SE, Voûte MT, Ravensbergen N, Chonchol M, de Melis M, Kessels R, Verhagen HJ, Bax JJ, Poldermans D. Perioperative heart rate variability and the prognosis of vascular surgery patients. *Submitted for publication.*
- **Winkel TA**, van Kuijk JP, Rouwet EV, Voûte MT, de Melis M, Verhagen HJ, Poldermans D. Aortic surgery complications evaluated by an implanted continuous electrocardiography device: a case report. *Submitted for publication.*
- Voûte MT, **Winkel TA**, Dunkelgrün M, Hoeks SE, Schouten O, Chonchol M, Kastelein J, Lindemans J, Boersma H, Bax JJ, Verhagen HJM, Poldermans D. The legacy effect of perioperative bisoprolol and fluvastatin treatment on long-term outcome; the link within inflammatory cytokines (follow-up from the DECREASE-IV trial). *Submitted for publication.*
- Flu WJ , van Kuijk JP, Chonchol M, **Winkel TA**, Verhagen HJ, Bax JJ, Poldermans D. Timing of preoperative beta-blocker treatment in vascular surgery patients: influence on postoperative outcome. J Am Coll Card 2010, in press.

- van Kuijk JP, Flu WJ, Chonchol M, Hoeks SE, **Winkel TA**, Verhagen HJ, Bax JJ, Poldermans D. Temporary Perioperative Decline of Renal Function Is an Independent Predictor for Chronic Kidney Disease. Clin J Am Soc Nephrol. May 2010, Epub ahead of print.
- Goei D, Hoeks SE, Boersma E, **Winkel TA**, Dunkelgrun M, Flu WJ, Schouten O, Bax JJ, Poldermans D. Incremental value of high-sensitivity C-reactive protein and N-terminal pro-B-type natriuretic peptide for the prediction of postoperative cardiac events in non-cardiac vascular surgery patients. Coron Artery Dis. 2009;20(3):219-24.
- Poldermans D, Schouten O, Bax JJ, **Winkel TA**. Reducing cardiac risk in non-cardiac surgery: evidence from the DECREASE studies. Eur Heart J supplements 2009;11(supplementA):A9-A14.

  Schouten O, van Kuijk JP, Flu WJ, **Winkel TA**, Welten GM, Boersma E, Verhagen HJ, Bax JJ, Poldermans D; DECREASE Study Group. Long-term outcome of prophylactic coronary revascularization in cardiac high-risk patients undergoing major vascular surgery (from the randomized DECREASE-V Pilot Study). Am J Cardiol. 2009;103(7):897-901.
- Flu WJ, van Kuijk JP, **Winkel T**, Hoeks S, Bax J, Poldermans D. Prevention of acute coronary events in non-cardiac surgery: beta-blocker therapy and coronary revascularization. Expert Rev Cardiovasc Ther. 2009;7(5):521-32.
- Flu WJ, van Kuijk JP, Hoeks SE, Kuiper R, Schouten O, Goei D, **Winkel T**, van Gestel YR, Verhagen HJ, Bax JJ, Poldermans D. Intima media thickness of the common carotid artery in vascular surgery patients: a predictor of postoperative cardiovascular events. An Heart J. 2009;158(2):202-8.
- Goei D, Flu WJ, Hoeks SE, Galal W, Dunkelgrun M, Boersma E, Kuijper R, van Kuijk JP, **Winkel TA**, Schouten O, Bax JJ, Poldermans D. The interrelationship between preoperative anemia and N-terminal pro-B-type natriuretic peptide: the effect on predicting postoperative cardiac outcome in vascular surgery patients. Anesth Analg. 2009 Nov;109(5):1403-8.

- Dunkelgrun M, Hoeks SE, Welten GM, Vidakovic R, **Winkel TA**, Schouten O, van Domburg RT, Bax JJ, Chonchol M, Verhagen HJ, Poldermans D. Anemia as an independent predictor of perioperative and long-term cardiovascular outcome in patients scheduled for elective vascular surgery. Am J Cardiol.2008;101(8):1196-20.
- Galal W, van Gestel YR, Hoeks SE, Sin DD, **Winkel TA**, Bax JJ, Verhagen H, Awara AM, Klein J, van Domburg RT, Poldermans D. The obesity paradox in patients with peripheral arterial disease. Chest 2008;134(5):925-30.
- Dunkelgrun M, Welten GM, Goei D, **Winkel TA**, Schouten O, van Domburg RT, van Gestel YR, Flu WJ, Hoeks SE, Bax JJ, Poldermans D. Association between serum uric acid and perioperative and late cardiovascular outcome in patients with suspected or definite coronary artery diease undergoing elective vascular surgery. Am J Cardiol. 2008;102(7):797-801.
- Schouten O, Lever TM, Welten GM, **Winkel TA**, Dols LF, Bax JJ, van Domburg RT, Verhagen HJ, Poldermans D. Long-term cardiac outcome in high-risk patients undergoing elective endovascular or open infrarenal abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg. 2008;36(6):646-52.

Abstract presentations

- **Winkel TA**, Schouten O, Hoeks SE, Voûte MT, de Melis M, Hampton DR, Kessels R, Verhagen HJM, Poldermans D. Sudden death during follow-up after new-onset ventricular tachycardia's in patients undergoing vascular surgery. (Vascular Annual Meeting, SVS 2010, Boston, MA, USA)
- **Winkel TA**, Voûte MT, Schouten O, de Melis M, Flu WJ, Oomen JPCM, Verhagen HJM, Poldermans D. The comparison of continuous electrocardiography monitoring devices for the detection of new-onset arrhythmias during vascular surgery. (Vascular Annual Meeting, SVS 2010, Boston, MA, USA)
- **Winkel TA**, Voûte MT, Oomen JPCM, Flu WJ, Dunkelgrün M, Goei D, Schouten, Verhagen HJM, Poldermans D. Hartritmestoornissen bij vaatchirurgische patiënten. (Chirurgendagen 2010, Veldhoven, the Netherlands)
- **Winkel TA**, Voûte MT, Oomen JPCM, Flu WJ, Dunkelgrün M, Goei D, Schouten, Verhagen HJM, Poldermans D. Hartritmestoornissen bij vaatchirurgische patiënten. (Vaatdagen 2010, Noordwijkerhout, the Netherlands)
- **Winkel TA**, Hampton DR, Flu WJ, Pietersma A, Schouten O, Oomen JPCM, Verhagen HJM, Poldermans D. The detection of new-onset atrial fibrillation in vascular surgery patients with an implantable continuous electrocardiography monitoring device. (ESC Congress 2009, Barcelona, Spain)
- **Winkel TA**, Hoeks SE, Limbourg T, Zeymer U, Baumgartner I, Bhatt DL, Steg PG, Goto S, Poldermans D. Prognosis of atrial fibrillation in patients with peripheral arterial disease: data from the REduction for Atherothrombosis for Continued Health (REACH) Registry. (ESC Congress 2009, Barcelona, Spain)

- **Winkel TA**, Schouten O, Hoeks SE, Flu WJ, Verhagen HJM, Poldermans D. Risk factors and prognosis of new-onset atrial fibrillation in vascular surgery patients. (Vascular Annual Meeting, SVS2009, Denver, CO, USA)*
- **Winkel TA,** Schouten O, Dunkelgrün M, Welten GMJM, Flu WJ, Welten GMJM, Verhagen HJM, Poldermans D. Veiligheid en effectiviteit van beta-blokker therapie bij patiënten die een oesofagusresectie ondergaan vanwege oesofaguscarcinoom. (Chirurgendagen 2009, Veldhoven, the Netherlands)
- **Winkel TA,** Schouten O, van Kuijk JP, Dunkelgrün M, Goei D, Dols LFC, Welten GMJM, Verhagen HJM, Poldermans D. Perioperatieve asymptomatische cardiale schade na endovasculaire procedure bij abdominale aorta aneurysmata is geassocieerd met een slechtere lange termijnsprognose. (Chirurgendagen 2009, Veldhoven, the Netherlands)
- **Winkel TA,** Pietersma A, van Dam P, Hampton DR, Poldermans D. The use of single lead bipolar electrode during vascular surgery for detection of cardiac arrhythmia and ischemia. (ESC 2008, Munich, Germany)
- **Winkel TA,** Schouten O, Hoeks SE, Dunkelgrün M, Goei D, Dols LFC, Welten GMJM, Verhagen HJM, Poldermans D. NTproBNP als voorspeller van cardiale uitkomst na vaatchirurgische ingreep. (Najaarsvergadering 2008, Ede, the Netherlands)
- **Winkel TA,** van Gestel YRBM, Dunkelgrün M, Schouten O, Goei D, Welten GMJM, Verhagen HJM, Poldermans D. Chronisch onstructief longlijden: een onderschatte cardiale risicofactor bij patiënten met perifeer vaatlijden. (Chirurgendagen 2008, Veldhoven, the Netherlands)
- **Winkel TA,** Schouten O, Goei D, Dunkelgrün M, Welten GMJM, Verhagen HJM, Poldermans D. Incidentie van hartritmestoornissen bij vaatchirurgische patiënten. (Chirurgendagen 2008, Veldhoven, the Netherlands)

** Award winning presentation.*

Curriculum Vitae

Tamara Adele Winkel was born on October 30th, 1979 in Willemstad, Curaçao. After finishing secondary school at the Peter Stuyvesant College in Curaçao, she started Medical School in 1998 at Leiden University, the Netherlands. During her studies she visited the Karolinska Institute in Stockholm (Sweden) and the Harvard Medical School in Boston (MA, USA) as part of a committee promoting an international exchange program for medical students and did several of her clinical rotations in Curaçao. In 2005 she obtained her medical degree. Next, she worked as a surgical resident at the department of surgery of the Slotervaart hospital in Amsterdam (supervisors: Dr. B.J. Dwars and Dr. E.J. Derksen). During the second half of 2007, she started a PhD-project at the Erasmus Medical Center in Rotterdam (supervisor: Prof. dr. D. Poldermans). From December 2009 until February 2010 she was a surgical resident at the Erasmus Medical Center in Rotterdam, after which she continued her PhD-project. July 1st, 2010 she will start her specialization in general surgery at the Maasstad hospital in Rotterdam (supervisors: Dr. E. van der Harst and Prof. dr. J.N.M. IJzermans).

PhD Portfolio Summary

Summary of PhD training and teaching activities

Name PhD student: T.A.Winkel Erasmus MC Department: Anaesthesiology & Vascular Surgery Research School: Erasmus MC	PhD period: July 2007- July 2010 Promotor: Prof. dr. D. Poldermans

PhD training	**Year**	**Workload (Hours/ECTS)**
Courses		
- NIHES 'Principles of research and medicine', 'Regression analysis', 'Classical methods for data-analysis'.	2007-2008	8.5
- COEUR 'Vascular medicine', 'Pathophysiology of ischemic heart disease, 'Cardiovascular Pharmacology', 'Clinical cardiovascular epidemiology', 'Neurovascular and peripheral vascular diseases', 'Arrhythmia research methodology', 'Peripheral and intracranial obstructive vascular disease'.	2007-2009	10.5
- Good Clinical Practice	2007	1.5
- General courses: 'Vascular rounds', 'Statistical analysis', 'Talent course', 'Developments in prognostic modelling and clinical trial update'	2007-2010	1.5
Seminars and workshops		
- Reveal training, Medtronic BRC, Arnhem	2008	0.3
- Journal club	2007-2010	1.0
Presentations		
- National conferences	2007-2010	3.0
- International conferences	2008-2010	6.0
International conferences		
- European Society of Cardiology Congress (Munich, Barcelona, Stockholm)	2008-2010 2009-2010	
- Society of Vascular Surgery (Denver and Boston)		
2. Teaching activities		
	Year	**Workload (Hours/ECTS)**
Lecturing		
- Bed-side teaching	2009	0.1
- Clinical training for nurses	2008-2010	0.1
Supervising practicals and excursions		
- First aid medical students – as examinator	2009-2010	0.5
- MsC students	2008-2010	1.0
Other		
- Organisation COEUR PhD day	2010	1.5