PREOPERATIVE SCREENING AT THE OUTPATIENT CLINIC

Predicting cardiac risk in noncardiac surgery

Peter Noordzij

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PREFACE

THE DUTCH FACTS

Annually, approximately 4% of the Dutch population is scheduled for major noncardiac surgery, with an average perioperative mortality rate of 1.9%.[1] Patients undergoing major noncardiac surgical procedures are at risk for complications during the surgical period, such as pneumonia, infection, myocardial infarction, arrhythmia's or death. It is estimated that out of all perioperative complications, cardiac events are the most frequent contributors to adverse events leading to death. A recent study by Boersma and colleagues, of a 10-year surgical cohort of more than 100,000 Dutch noncardiac surgical patients, showed that at least 30% of mortality during the surgical period was caused by cardiac complications.[2] As a result, more than 3,600 patients die each year due to the cardiac complications of noncardiac surgery in The Netherlands alone.

PATHOFYSIOLOGY OF ADVERSE CARDIAC EVENTS

Perioperative myocardial infarction is the most frequent fatal cardiac complication during noncardiac surgery. In studies that examined cardiac death during the surgical period, authors attributed the cause to myocardial infarction in 66% of cases, and to arrhythmia or heart failure in 34%.[3-10] The pathophysiological mechanisms underlying perioperative myocardial infarction are not completely clear, but seem to be associated with atherogenic coronary artery disease.

Early atherogenesis is characterized by plaque formation, due to accumulation of lipids and recruitment of inflammatory cells in the intima layer of the coronary artery wall. Continuing conditions of dyslipidemia and inflammation of the vessel wall result in a lipid-core, separated from the vessel lumen by a thin fibrous vulnerable endothelial cap. This thin cap is susceptible to rupture due to increased levels of stress hormones during and after surgery.

When the vulnerable coronary plaque ruptures, the liquid lipid core enters the vessel lumen and leads to thrombus formation, (partial) coronary artery occlusion and subsequent myocardial infarction.[11]

In patients with fixed stenotic coronary lesions, due to advanced atherogenesis, the coronary lumen is narrowed. The narrow lumen limits the maximum flow through the vessel in case of increased oxygen demand of the myocardium (e.g. tachycardia in response to pain or bleeding). Insufficient coronary blood flow can induce an oxygen supply and demand mismatch, which results in myocardial ischemia and eventually myocardial infarction.

Figure 1 describes several components during the surgical period that contribute to perioperative myocardial infarction. Surgery and anesthesia related factors initiate inflammatory and hypercoagulable states in the patient (figure 1, left side). Increased levels of circulating inflammatory cells infiltrate the pre-existent atheromatous coronary plaques. The stress state of the patient during surgery induces coronary artery shear stress, and contributes to plaque instability and rupture. Circulating coagulation factors induce thrombus formation at the side of the ruptured plaque, which occludes the vessel and prohibits coronary blood flow. Major increases in blood pressure, heart rate and contractility of the heart caused by

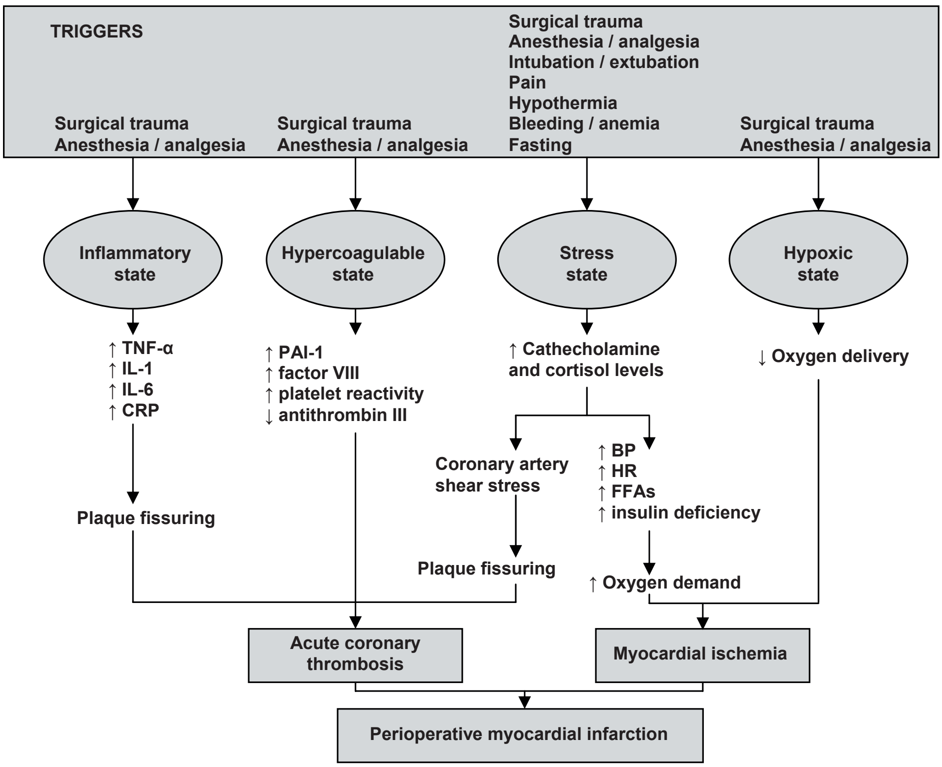

Figure 1. Potential triggers of states associated with perioperative elevations in troponin levels, arterial thrombosis and fatal myocardial infarction

the high stress state of the patient (figure 1, right side), lead to increases in oxygen demand of the myocardium. Insufficient coronary blood flow due to a narrowed lumen induces myocardial oxygen debt and infarction.

It is estimated that half of the perioperative myocardial infarctions are related to sudden plaque rupture, and half to sustained myocardial oxygen supply demand mismatch.[12,13]

IDENTIFYING PATIENTS AT RISK

Preoperative cardiac risk stratification is used to identify patients at increased risk for such perioperative cardiac complications. It reveals important information on the vital status of the patient, the presence and extend of coronary artery disease and other medical risk factors. Being able to identify patients at increased risk for adverse cardiac events provides the perioperative physician with an important tool to make easier treatment decisions that may affect short and long term outcome of the surgical patient.[14]

Patient characteristics and type of surgery

Over the past two decades, several investigators have published clinical indices to estimate the risk of a major perioperative cardiac event in patients undergoing noncardiac surgery.[3-5,15-17] The Revised Cardiac Risk Index of Lee and colleagues, which is in fact a modification of the Multifactorial Risk Index of Goldman and colleagues, is the best validated and most accurate predictive generic risk index at this moment. It consists of 6 equally weighted cardiovascular risk factors: high risk type of surgery (i.e. intraperitoneal, intrathoracic or suprainguinal vascular procedures), ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, preoperative serum creatinine >2.0 mg/dL, and insulin therapy for diabetes mellitus. Table 1 shows the estimated risk of a major perioperative cardiac event based on the number of risk factors met by the patient.[18]

Table 1. Estimated risk of a major perioperative cardiac event based on predictors in the Lee index

No. of risk factors*	Risk of major perioperative cardiac event, % (95% CI)**
0	0.4 (0.1-0.8)
1	1.0 (0.5-1.4)
2	2.4 (1.3-3.5)
≥3	5.4 (2.8-7.9)

* Risk factors include each of the following characteristics: high risk type of surgery (i.e. intraperitoneal, intrathoracic or suprainguinal vascular procedures), ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, preoperative serum creatinine >2.0 mg/dL, and insulin therapy for diabetes mellitus

** Includes cardiac death, nonfatal myocardial infarction, and nonfatal cardiac arrest

Table 2. Clinical predictors of increased perioperative cardiovascular risk*

Major
Unstable coronary syndromes
Acute or recent myocardial infarction with evidence of important ischemic risk by clinical symptoms or non-invasive study **
Unstable or severe angina (Canadian class III or IV) Decompensated heart failure Significant arrhythmias
High grade atrioventricular block
Symptomatic ventricular arrhythmias in the presence of underlying heart disease
Supra ventricular with uncontrolled ventricular rate Severe valvular disease
Intermediate
Mild angina pectoris (Canadian Class I or II)
Previous myocardial infarction by history of pathological Q waves
Compensated or prior heart failure
Diabetes mellitus (particularly insulin dependent)
Renal insufficiency
Minor
Advanced age
Abnormal electrocardiogram (left ventricular hypertrophy, left bundle branch block, ST abnormalities)
Rhythm other than sinus (e.g. atrial fibrillation)
Low functional capacity
History of stroke
Uncontrolled systemic hypertension

* myocardial infarction, heart failure, death
** Recent myocardial infarction defined as > 7 days, ≤ 1 month

The American College of Cardiologists and American Heart Association (ACC/AHA) published guidelines on the perioperative cardiovascular evaluation for noncardiac surgery in 2002.[18] These guidelines were not validated in a study, but were derived from the interpretation of data from various studies and the judgement of the committee members. The committee identified several patient risk factors that are associated with increased risk of adverse outcome (table 2). In addition, they constructed a specific surgical related risk classification (table 3) based on a study by Eagle and colleagues.[6] According to risk, types of procedures were divided into three categories, low, intermediate and high risk surgery.

Preoperative electrocardiography

In addition to patient risk factors and surgery related risk, preoperative non-invasive tests are used to identify the presence and extend of coronary artery disease in patients undergoing noncardiac surgery. In this respect, preoperative electrocardiography is a commonly ordered test by the perioperative physician. In approximately 26% of patients scheduled for noncardiac surgery, electrocardiography testing is used as a marker for cardiac disease and increased perioperative risk.[19] The amount of information used from a preoperative electro-

Table 3. Cardiac risk stratification for noncardiac procedures*

High
Emergent major operations, particularly in the elderly
Aortic and other major vascular surgery
Peripheral vascular surgery
Anticipated prolonged surgical procedures associated with large fluid shifts and/or blood loss
Intermediate
Carotid endarterectomy
Head and neck surgery
Intraperitoneal and intrathoracic surgery
Orthopedic surgery
Prostate surgery
Minor
Endoscopic procedures
Superficial procedures
Cataract surgery
Breast Surgery

* Combined incidence of cardiac death and nonfatal myocardial infarction
High: reported cardiac risk >5%, intermediate: reported cardiac risk <5%, minor: reported cardiac risk <1%

cardiogram for cardiac risk stratification has changed over the last 30 years. The presence of a Q-wave and several sorts of cardiac arrhythmias were part of the Risk Indices of Goldman, Lee and Detsky.[3,4,15] However, more recently these results were questioned by Schein and colleagues, who evaluated the use of routine electrocardiography testing in 18,189 patients undergoing low risk cataract surgery.[20] Preoperative testing, including electrocardiography, did not result in improved risk stratification. The ACC/AHA classified an abnormal preoperative electrocardiogram as a minor predictor of adverse outcome, but data on its prognostic value in addition to other patient characteristics are limited.[18]

Preoperative glucose testing

Diabetes mellitus is strongly associated with cardiovascular disease, and is a well known risk factor for adverse cardiac outcome in noncardiac surgery.[2,3] Preoperative glucose testing is used to screen for asymptomatic type 2 diabetes in patients at risk for the disease (e.g. obesity, and older age). The relationship between diabetes and cardiovascular disease begins early in the progression from normal glucose tolerance to prediabetes.[21,22] Two important studies in the non-surgical population have shown that early medical therapy or lifestyle changes in prediabetic patients reduce cardiac disease.[23,24] Also in the surgical population it seems to become clear that impaired glucose metabolism is associated with adverse clinical outcome.[25-28] However, the relationship between preoperative glucose dysregulation, cardiac disease and perioperative outcome in noncardiac surgical patients has not adequately been defined.

Preoperative HbA_{1c} testing

In diabetes mellitus, glycosylated haemoglobin (HbA_{1c}) is a marker of a patient's glycemic levels over the past 2 to 3 months, and is considered to reflect preoperative diabetic regulation. Stratton and colleagues showed that in patients with known diabetes, the risk of atherosclerotic cardiovascular disease increased with increasing plasma glucose concentration, each 1% increase in HbA_{1c} level was associated with a 14% increase in the incidence of fatal and nonfatal myocardial infarction.[29] Also, tight glycemic control has been shown to result in marked improvement in cardiac survival in hyperglycaemic diabetics with acute coronary syndromes, myocardial infarction and those who have undergone recent cardiac surgery.[25,28] However, the prognostic role of preoperative hyperglycemia reflected by an elevated HbA_{1c} for adverse cardiac events, and its role in perioperative glucose regulation in noncardiac surgery is yet to be determined.

REDUCING CARDIAC RISK

Cardiac risk stratification by preoperative testing should affect the perioperative management of the patient. Perioperative pharmaceutical therapy is a non-invasive strategy to protect the heart during surgery, and prevent cardiac complications. Most of the trials on medical therapy during noncardiac surgery are focussing on perioperative beta-blocker and statin therapy.

Perioperative beta-blockade

Slowing the heart during surgery reduces myocardial oxygen demand. It is hypothesized that due to this reduction in oxygen consumption, the coronary blood flow through pre-stenotic vessels remains sufficient enough to prevent myocardial ischemia. Mangano was among the first to describe the effects of perioperative beta-blockade in patients undergoing high risk surgery[30], and during the following decade many investigators have published studies on this topic. The majority of available evidence has been derived from high risk surgical patients, because they are believed to be at the greatest risk for adverse cardiac events. As a result, recent guidelines on perioperative beta-blocker therapy in noncardiac surgery recommend that, at this moment, a class I evidence level only exists for patients undergoing vascular surgery with inducible myocardial ischemia during preoperative testing.[31] However, the majority of patients are scheduled for low- to intermediate risk surgical procedures.[18] In this surgical population, data on the effect of perioperative beta-blocker is not available, and possible protective effects remain to be defined.

Perioperative statin therapy

A considerable proportion of the surgical population is believed to have undiagnosed, asymptomatic coronary artery disease, characterized by non-blood flow limiting, vulnerable atherosclerotic plaques. Recent studies have suggested that, as a result of the anti-inflammatory action and reversal of endothelial dysfunction, perioperative statin therapy is associated with improved cardiac outcome of high risk noncardiac surgical patients.[32-35] The possible protective effect of statins in the general lower risk surgical population is not know.

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OUTLINE OF THE THESIS

The first chapter of this thesis analyzes perioperative cardiovascular mortality in noncardiac surgery at the Erasmus Medical Center, Rotterdam, The Netherlands. The performance of Lee et al's index in predicting perioperative cardiovascular mortality is validated in a 10-year surgical cohort of patients undergoing noncardiac surgery.

Based on the results of chapter one, the analysis of perioperative mortality risk factors is continued in chapter two. In this chapter, over one million Dutch patients undergoing noncardiac surgery between 1991-2002 were studied. The influence of well known perioperative risk factors in high risk patients was analyzed in the general noncardiac surgical population, and the impact of surgery related risk on perioperative mortality was further clarified. The total cohort was used to derive and validate a newly constructed perioperative risk index to accurately predict all-cause mortality in noncardiac surgery.

Chapter three describes the prognostic value of routine preoperative electrocardiogram testing in patients undergoing noncardiac surgery. All preoperative electrocardiograms made at the Erasmus MC between 1991-2000, were analyzed to determine if their routine use provided additional prognostic information in predicting perioperative mortality in noncardiac surgical patients.

Preoperative electrocardiogram characteristics are further analyzed in chapter four. An electrocardiogram's QTc interval represents the time from onset of ventricular depolarization to completion of repolarization. Prolongation of the QTc interval has been associated with an increased risk of ventricular arrhythmias, which may trigger ventricular fibrillation and cardiac death. The aim of this chapter was to determine whether QTc interval predicts cardiac mortality in patients undergoing noncardiac surgery.

Chapter five describes the role of preoperative glucose testing in patients scheduled for noncardiac surgery to assess the influence of asymptomatic hyperglycemia on perioperative mortality. In a case-control study of surgical patients at the Erasmus MC, the relationship between random preoperative glucose levels and perioperative mortality is analyzed.

Chapter six of this thesis studies the relation between preoperative glucose regulation, perioperative glucose levels and perioperative mortality in diabetic patients undergoing major vascular surgery. In an observational study of 304 patients with diabetes mellitus, the prognostic value of preoperative HbA_{1c} levels for perioperative mortality and adverse cardiac events is estimated.

The final chapter, chapter seven, studies the possible protective effects of perioperative medical therapy in noncardiac surgery. In a case-control study of patients undergoing non-vascular, noncardiac surgery at the Erasmus Medical Center, the relation between perioperative beta-blockade, statin therapy and mortality is evaluated.

CHAPTER ONE

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PERIOPERATIVE CARDIOVASCULAR MORTALITY IN 108,613 NONCARDIAC SURGICAL PROCEDURES: A VALIDATION OF THE LEE CARDIOVASCULAR RISK INDEX IN THE ERASMUS MC 1991-2000 ADMINISTRATIVE DATABASE

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ABSTRACT

Aim: The Lee risk index was developed to predict major cardiac complications in noncardiac surgery. We aimed to retrospectively evaluate the performance of this index in the large cohort of patients who recently underwent noncardiac surgery in our institution. *Methods:* The administrative database of the Erasmus MC, Rotterdam, the Netherlands, contains information on a total of 108613 noncardiac surgical procedures that were performed during 1991-2000. The Lee-index assigns one point to each of the following characteristics: high risk type of surgery, ischemic heart disease, congestive heart failure, cerebrovascular disease, renal insufficiency, and diabetes mellitus. We retrospectively determined the Lee-index for each procedure in our database, and used logistic regression to analyze the relation between the Lee-index and cardiovascular death. Information on clinical characteristics was retrieved from medical records and then classified according to the ninth International Classification of Diseases (ICD-9) system. We should emphasize that the data that we used were not collected for the purposes of this study by clinicians using standardized data collection forms. *Results:* A total of 1877 patients (1.7%) had perioperative death, and 543 (0.5%) had cardiovascular death. The Lee index yielded cardiovascular death rates of 0.3% [255/75352], 0.7% [196/28892], 1.7% [57/3380] and 3.6% [35/969] for scores of 0, 1, 2 and ≥3. Corresponding odds ratios were 1 (reference), 2.0, 5.1 and 11.0, with no overlap for the 95% confidence interval of each score. The C-statistic for the prediction of cardiovascular mortality using the Lee-index was 0.63. If more detailed information regarding the type of surgery was added, then the C-statistic improved to 0.79. *Conclusion:* The Lee index had an admirable performance to predict cardiovascular mortality. However, the simple classification of procedures as high / not high seems suboptimal. Caveats to our analysis include the fact that data are derived from an administrative database, the retrospective nature of the data, the ICD-9 coding of clinical characteristics, and the fact that we evaluated cardiovascular death rather than a broader range of clinical complications. Therefore, prospective studies are warranted to confirm our findings.

INTRODUCTION

Patients undergoing major noncardiac surgery are at high risk of cardiovascular morbidity and mortality. Perioperative myocardial infarction is the most frequent complication in this respect. There is evidence that coronary plaque rupture leading to thrombus formation and subsequent vessel occlusion, is the predominant mechanism, similar to non-surgical settings.[1,2] The clinical importance of perioperative cardiovascular complications is well recognized, and numerous investigators have described the relationship between patient characteristics and the risk of adverse cardiovascular outcome.[3-11] The multivariable cardiovascular risk indices developed by Goldman, Detsky, Eagle and colleagues are most frequently quoted in this respect.[3,7,10] However, most studies evaluating cardiovascular risk in a general surgical population date from the 1970s and 1980s. Since then, there have been important advances in anesthesia, surgery and postoperative care, which might have resulted in improved outcome. Yet, descriptive statistics of contemporary datasets are rare. The current study aims to contribute in this respect, as it presents the characteristics and perioperative outcome of the 108593 patients who underwent noncardiac surgery in the Erasmus MC from 1991 to 2000.

In the 1990s, Lee and colleagues systematically analyzed the risk of major cardiac complications (which include myocardial infarction, pulmonary edema, ventricular fibrillation, and cardiovascular death) in 4315 patients undergoing noncardiac surgery, the largest cohort ever described.[8] As a result, the Lee index was constructed (which in fact is a modification of the Goldman index), and many clinicians and researchers consider this to be the most relevant cardiac risk prediction index. Led by this opinion, we used the Lee index to describe the exposure to cardiovascular risk factors in our cohort. Still, it should be realized, that the patients studied by Lee and colleagues cannot be considered as an average, unselected surgical cohort, as it was dominated by patients undergoing thoracic (12%), vascular (21%), and orthopedic surgery (35%). This fact prompted us to evaluate the performance of the Lee index for perioperative cardiovascular risk prediction in our dataset. We choose cardiovascular mortality, instead of the broader range of clinical complications, as the primary endpoint.

METHODS

Hospital setting, procedures and patients

The Erasmus MC is a metropolitan university hospital, serving a population of approximately 3 million, in the south-western area of the Netherlands, which acts as a tertiary referral center for approximately 30 affiliated hospitals. In the Erasmus MC, between January 1, 1991 and December 31, 2000, 122860 noncardiac surgical procedures were performed in patients above the age of 15 years. We excluded 14267 planned and unplanned procedures that were conducted within 30 days after an initial operation, and analyzed the perioperative course of the remaining 108593 cases.

The number of patients involved in this dataset amounts 75581. Over the 10-year observation period, 20885 patients had multiple surgeries in the Erasmus MC. They were included as many times as they had surgeries. The median span between two successive procedures was 297 days (interquartile range 123 to 677 days; note that the minimum span was 31 days). Thus, we chose operation (and not patient) as unit of analysis, mainly for two reasons. Firstly, this is consistent with clinical practice, as the risk of perioperative complications is assessed in relation to a specific procedure. Secondly, this approach guarantees an optimal utilization of the available information. Dedicated statistical techniques were applied to account for potential dependence among observations (see paragraph on statistical analysis).

Material

For each patient undergoing surgery, a number of data-items are routinely (and prospectively) stored in the computerized hospital information system. First, the surgical techniques are classified by the treating physician according to a standardized national coding system, which was developed in co-operation with the National Health Service and medical insurance companies. This system is used for reimbursement and to record and monitor the experience of surgeons and surgical residents. Using this classification, we grouped surgical procedures into 14 categories. A total of 11969 procedures (11.0%) were classified into multiple categories.

Second, from written information that is provided by the General Practitioner, the referring physician, or the hospital physicians involved in perioperative care, each patient's medical history is classified according to the ninth International Classification of Diseases (ICD-9).[12] The classification and the entry of the data in the electronic database is performed by dedicated administrative personnel who have completed in-depth training on medical data registration. We recorded the following medical conditions: diabetes mellitus (ICD-9 250), myocardial infarction (ICD-9 410, 411, and 412), angina pectoris (ICD-9 413 and 414), heart failure (ICD-9 428), cerebrovascular accident (ICD-9 430), and renal disease (ICD-9 580).

Endpoint definition

The hospital information system also contains data regarding each patient's perioperative course. The vital status at hospital discharge was verified and documented for each patient. The occurrence of perioperative myocardial infarction was also reported, but the protocol did not mandate serial postoperative electrocardiograms, or blood sampling for determination of cardiac enzymes. Consequently, silent ischemic episodes and indistinct events might have been missed. A similar situation occurred with regard to stroke: Clinically apparent strokes were reported, but systematic neurological evaluation and CT-scanning was not performed. In view of these limitations, we chose cardiovascular death as the primary endpoint of our analyses. Events were counted until hospital discharge or 30 days after surgery, whichever day came first.

To obtain the cause of death, two investigators (MDK, DP) independently reviewed all available peri-operative data, but were blind to preoperative characteristics, and aimed to reach consensus. If consensus could not be reached, the opinion of a third, independent investigator (PN) was final. Cardiovascular death was defined as any death with a cardiovascular complication as the primary or secondary cause (according to the definitions of the

World Health Organization), and included deaths following myocardial infarction, cardiac arrhythmia, resuscitation, heart failure, or stroke. Non-cardiovascular death was defined as any death with a principal non-cardiovascular cause, including surgery-related bleeding complications, cancer, trauma and infection. Sudden death in a previously stable patient was considered as cardiovascular.

Data quality and ethical considerations

We should emphasize the fact that the data that we use were collected for administrative purposes, and not for the purposes of this study by clinicians using standardized data collection forms. We designed and undertook this study several years after the last patient was enrolled, and we were not able to verify the completeness nor the correctness of the data. By necessity, we had to rely on the information that was provided by the clinicians taking care of the patients during everyday clinical practice.

This study was approved by the Medical Ethics Committee of the Erasmus MC. However, given the retrospective nature of our study, informed consent could not be obtained from each individual patient.

Statistical analysis

Continuous data are described as median values and corresponding 25th and 75th percentiles, and dichotomous data are described as numbers and percentages. The Lee-index assigns one point to each of the following characteristics: high risk type of surgery (i.e. intraperitoneal, intrathoracic or suprainguinal vascular procedures), ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, preoperative serum creatinine >2.0 mg/dL, and insulin therapy for diabetes mellitus. We calculated the Lee index for each individual patient in our dataset, with this note, that the latter two variables were replaced by renal insufficiency and a history of diabetes, since preoperative creatinine values and data on insulin use were lacking. Univariable logistic regression analyses were then applied to evaluate the relationship between the Lee-index (with individual dummy variables for each score category), the clinical characteristics that are part of this index, and the primary endpoint. Crude, unadjusted odds ratios and corresponding 95% confidence intervals are reported. (Note that we have chosen another endpoint than Lee and colleagues, who considered the composite endpoint of myocardial infarction, pulmonary edema, ventricular fibrillation, or cardiovascular death).

Subsequently, multivariable logistic regression analyses were performed to evaluate if the predictive power of the Lee-index could be improved by adding more detailed information on the type of surgery, according to the classification as recommended by American Heart Association / American College of Cardiology.[13] Also age was taken into account as a potential additional risk determinant. Adjusted odds ratios and corresponding 95% confidence intervals are reported. The performance of risk models was determined by the C-statistic, which indicates how well a model rank-orders patients with respect to their outcomes on a 0.5 (no predictive value) to 1.0 (optimal performance) scale.[14] In our database, we found higher C-indices for multivariable models that added information to the Lee index than for the Lee-index-alone model. However, we did not want to overstretch our data by developing a modified index.

In 1986 Liang and Zeger developed the method of generalized estimation equations to determine regression model parameters - and corresponding standard errors - in datasets with correlated data when the outcome measure of interest is discrete (e.g. binary or count data).[15] Since our dataset involves patients with multiple operations, independence of observations could not be excluded beforehand. Therefore, to examine this phenomenon, all regression analyses were first performed using conventional techniques, and then repeated using of generalized estimation equations, with 'patient' as classification factor. No relevant differences were observed between the parameter estimates as determined according to both methodologies. Hence, we concluded that inter-observation correlation was not a major issue in our dataset. Therefore, we present the results that are based on classical methods.

RESULTS

A total of 52387 surgical procedures were performed in men. Orthopedic surgery (N=12378; 24%), Ear,- Nose-, Throat-surgery (N=9273; 18%), and abdominal surgery (N=8637; 16%) were the most frequent. Among the 56206 procedures in women, gynecological surgery

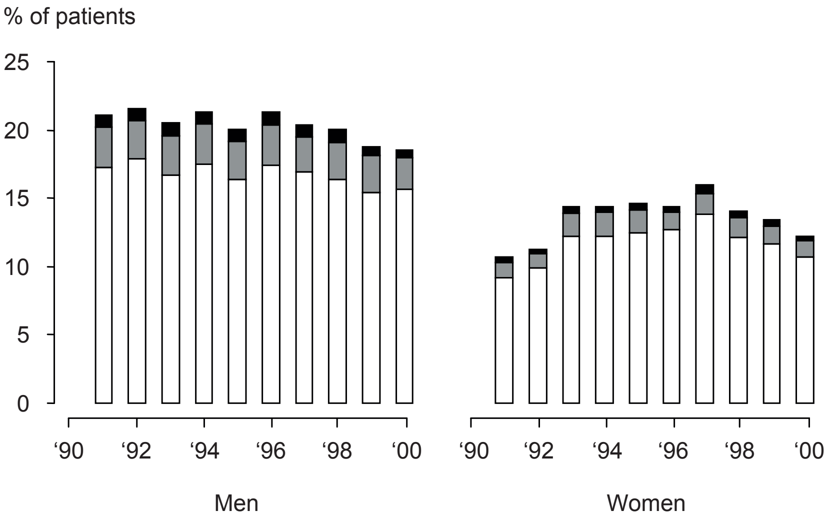

Figure 1. Time trends in the cardiovascular risk profile of the study population
Data indicate the percentage of patients with a score of 1 point (white portion of the bar), 2 points (grey portion) and ≥3 points according to the cardiovascular risk index as developed by Lee and colleagues.[8]

was most common (N=15312; 27%), followed by orthopedic (N=9840; 18%) and abdominal surgery (N=7816; 14%). As a result of a reallocation of patients between hospitals in our region, there were considerable changes in the annual volumes of ophthalmic and gynaecological procedures in the early 1990s. Throughout the study period, the number of men and women undergoing orthopedic surgery gradually increased. The number of patients undergoing abdominal surgery decreased slightly over time.

With a median age of 51 years (25th, 75th percentile: 34, 65 years), men were 7 years older than women (median 44 years, and 25th, 75th percentile: 32, 62 years). As figure 1 demonstrates, the majority of patients had a score of 0 points according to the Lee index. During the study period, no systematic change in the exposure to cardiovascular risk factors, quantified by the Lee index, was observed in men. In women the cardiovascular risk profile slightly worsened in 1993, and remained constant thereafter. This shift was strongly related to the decline in the number of gynecological procedures.

A total of 1877 patients (1.7%) had perioperative death. A cardiovascular complication was the principal cause of death in 405 patients, and the secondary cause in another 138. Thus, 543 patients (0.5% of the sample; 29% of deaths) had cardiovascular death. Patients in whom an autopsy report was available (326 patients; 17% of deaths) were more often labeled as having cardiovascular death than patients in whom no such report was available (37% [122/326] versus 27% [421/1551] patients; P-value <0.001). Infection was the most common non-cardiovascular cause of death (primary cause in 231 patients, and secondary cause in 308 patients; 539 patients in all; 29% of deaths).

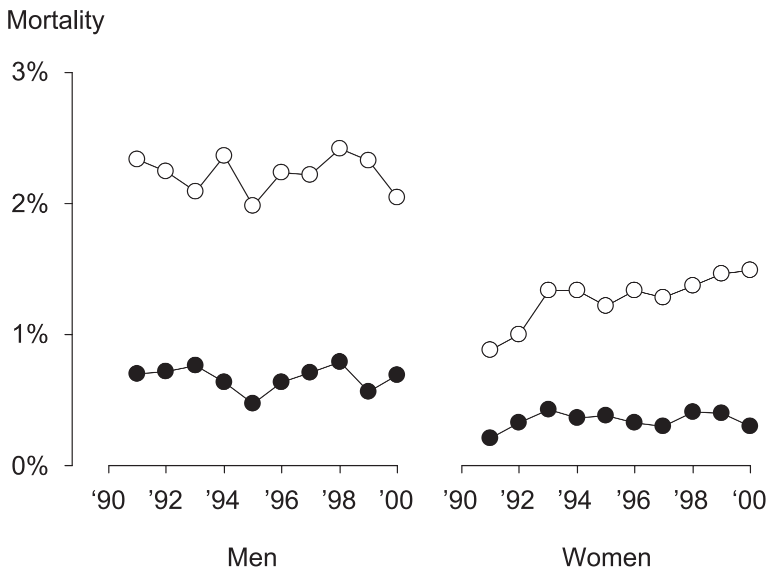

Figure 2. Time trends in the incidence of perioperative all-cause mortality (open circles) and cardiovascular mortality (closed circles)

The incidence of all-cause mortality, as well as cardiovascular mortality was higher in men than in women: 2.2% [1167/52387] versus 1.3% [710/56206] (P-value <0.001), and 0.7% [350/52387] versus 0.3% [193/56206] (P-value <0.001). During the study period, no systematic change in all-cause mortality was observed in men (figure 2). In contrast, all-cause mortality in women increased significantly from 0.9% [55/6280] in 1991 to 1.3% [69/5151] in 1993, and 1.5% [79/5315] in 2000 (71% increase; P-value <0.001). There were no significant changes in cardiovascular mortality over time in either men or in women.

Important differences in the incidence of perioperative cardiovascular death were observed in relation to type of surgery (table 1). Patients undergoing vascular surgery, especially those undergoing aortic surgery, had the highest cardiovascular mortality (1.8%), followed by patients undergoing neuro surgery (1.7%), renal transplant (1.1%) and pul-

Table 1. Perioperative cardiovascular and all-cause death in patients undergoing noncardiac surgery for various indications

Type of surgery	Number of procedures	Cardiovascular death						All-cause death	
		Primary cause		Secondary cause		Total		N	(%)
		N	(%)	N	(%)	N	(%)		
Abdominal	16,453	63	(0.4)	50	(0.3)	113	(0.7)	606	(3.7)
Hepatico, Pancreatico, Billiary	2,752	10	(0.4)	4	(0.1)	14	(0.5)	129	(4.7)
Oesophago-Gastric	11,982	53	(0.4)	44	(0.4)	97	(0.8)	488	(4.1)
Other abdominal	3,714	12	(0.3)	7	(0.2)	19	(0.5)	122	(3.3)
Breast	2,411	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dental	1,225	1	(0.1)	0	(0.0)	1	(0.1)	2	(0.2)
Ear, Nose, Throat	15,291	114	(0.7)	22	(0.1)	136	(0.9)	411	(2.7)
Endocrine	1,029	1	(0.1)	2	(0.2)	3	(0.3)	6	(0.6)
Eye	9,163	1	(0.0)	0	(0.0)	1	(0.0)	11	(0.1)
Gyneacology	15,343	2	(0.0)	1	(0.0)	3	(0.0)	20	(0.1)
Neuro	5,797	87	(1.5)	14	(0.2)	101	(1.7)	381	(6.6)
Orthopedic	22,218	34	(0.2)	9	(0.0)	43	(0.2)	116	(0.5)
Reconstructive	4,157	5	(0.1)	2	(0.0)	7	(0.2)	12	(0.3)
Pulmonary	1,965	14	(0.7)	7	(0.4)	21	(1.1)	86	(4.4)
Renal transplant	711	8	(1.1)	0	(0.0)	8	(1.1)	14	(2.0)
Urologic	11,116	28	(0.3)	10	(0.1)	38	(0.3)	159	(1.4)
Vascular	6,234	90	(1.4)	25	(0.4)	115	(1.8)	277	(4.4)
Aortic - acute	196	21	(10.7)	7	(3.6)	28	(14.3)	57	(29.1)
Aortic - elective	890	29	(3.3)	7	(0.8)	36	(4.0)	72	(8.1)
Carotid endarterectomy	891	4	(0.4)	2	(0.2)	6	(0.7)	18	(2.0)
Peripheral bypass	927	14	(1.5)	2	(0.2)	16	(1.7)	28	(3.0)
Other vascular	3,854	36	(0.9)	13	(0.3)	49	(1.3)	142	(3.7)
Other	9,423	18	(0.2)	13	(0.1)	31	(0.3)	92	(1.0)
Any type	108,593	405	(0.4)	138	(0.1)	543	(0.5)	1,877	(1.7)

Table 2. Univariable relation between the Lee index, demographic and clinical characteristics, and perioperative cardiovascular death

Characteristic		Number of procedures	Number (%) Cardiovascular death		Crude, unadjusted odds ratio (95% CI)
Lee index and components					
Lee index	≥3	969	35	(3.6)	11.0 (7.7, 15.8)
	2	3380	57	(1.7)	5.1 (3.8, 6.7)
	1	28892	196	(0.7)	2.0 (1.7, 2.4)
	0	75352	255	(0.3)	1
Type of surgery *	High	29426	224	(0.8)	1.9 (1.6, 2.3)
	Not high	79167	319	(0.4)	1
History of ischemic heart disease	Yes	3588	77	(2.1)	4.9 (3.9, 6.3)
	No	105005	466	(0.4)	1
History of heart failure	Yes	1377	50	(3.6)	8.2 (6.1, 11.0)
	No	107216	493	(0.5)	1
History of CVA	Yes	500	11	(2.2)	4.6 (2.5, 8.3)
	No	108093	532	(0.5)	1
Renal insufficiency	Yes	1894	31	(1.6)	3.5 (2.4, 5.0)
	No	106699	512	(0.5)	1
Diabetes mellitus	Yes	2001	36	(1.8)	3.8 (2.7, 5.4)
	No	106592	507	(0.5)	1
Detailed data on type of surgery					
Type of surgery †	High risk	1078	63	(5.8)	73.6 (46.9, 115)
	Intermediate risk (A)	40985	371	(0.9)	10.8 (7.4, 15.9)
	Intermediate risk (B)	33275	81	(0.2)	2.9 (1.9, 4.4)
	Low risk	33255	28	(0.1)	1
Laparoscopic procedure	Yes	15318	24	(0.2)	0.3 (0.2, 0.4)
	No	93275	519	(0.6)	1
Emergency surgery	Yes	774	47	(6.1)	14.0 (10.2, 19.0)
	No	107819	496	(0.5)	1
Other potential risk determinants					
Age, years	≥80	5314	77	(1.5)	23.0 (14.8, 35.7)
	70-80	12619	165	(1.3)	20.7 (13.7, 31.1)
	60-70	15742	146	(0.9)	14.6 (9.7, 22.1)
	50-60	15675	91	(0.6)	9.1 (5.9, 14.0)
	40-50	16987	37	(0.2)	3.4 (2.1, 5.6)
	<40	42256	27	(0.1)	1

* According to the Lee index: high risk = intraperitoneal, intrathoracic, and suprainguinal vascular procedures; not high risk = other procedures

† According to the American Heart Association / American College of Cardiology classification: high risk = aortic; intermediate risk = abdominal, ear-, nose-, throat, neuro, orthopedic, pulmonary, renal transplant; urologic, and vascular (excl. aortic and carotid); low risk = breast, carotid, dental, endocrine, eye, gynecology, and reconstructive. Within the intermediate risk group, patients undergoing orthopedic or urologic surgery had significantly lower risk than patients undergoing other types of surgery. Therefore, we labelled orthopedic and urologic procedures as intermediate risk (B), and the remaining procedures as intermediate risk (A).

Table 3. Multivariable relation between the Lee index, type of surgery, clinical characteristics, and perioperative cardiovascular death, based on analyses of 108613 subjects undergoing noncardiac surgery

Characteristic		Odds ratio (95% CI)		
		Lee index only	Lee index and type of surgery	Lee index, type of surgery and clinical characteristics
Model C-statistic		0.63	0.79	0.85
Lee index	≥3	11.0 (7.7, 15.8)		
	2	5.1 (3.8, 6.7)		
	1	2.0 (1.7, 2.4)		
	0	1		
Lee index, excl. type of surgery *	≥3		9.2 (5.5, 15.4)	6.4 (3.8, 10.8)
	2		5.6 (4.0, 7.9)	4.0 (2.9, 5.6)
	1		2.3 (1.8, 3.0)	1.7 (1.3, 2.2)
	0		1	1
Type of surgery †	High risk		35.7 (22.1, 57.6)	20.0 (12.3, 32.5)
	Intermediate risk (A)		10.3 (7.0, 15.2)	10.3 (7.0, 15.1)
	Intermediate risk (B)		2.8 (1.8, 4.3)	2.7 (1.7,4.1)
	Low risk		1	1
Laparoscopic procedure	Yes		0.3 (0.2, 0.4)	0.3 (0.2, 0.4)
	No		1	1
Emergency surgery	Yes		4.6 (3.2, 6.5)	4.4 (3.1, 6.4)
	No		1	1
Age, year	≥80			19.9 (12.8, 31.1)
	70-80			12.6 (8.3, 19.0)
	60-70			8.5 (5.6, 12.9)
	50-60			5.6 (3.6, 8.7)
	40-50			2.5 (1.5, 4.1)
	<40			1

* Index that assigns one point to each of the following characteristics: ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, renal insufficiency, and diabetes mellitus
† According to the Amercian Heart Association / American College of Cardiology classification: high risk = aortic; intermediate risk = abdominal, ear-, nose-, throat, neuro, orthopedic, pulmonary, renal transplant; urologic, and vascular (excl. aortic and carotid); low risk = breast, carotid, dental, endocrine, eye, gynecology, and reconstructive. Within the intermediate risk group, patients undergoing orthopedic or urologic surgery had significantly lower risk than patients undergoing other types of surgery. Therefore, we labelled orthopedic and urologic procedures as intermediate risk (B), and the remaining procedures as intermediate risk (A).

monary surgery (1.1%). Breast, dental, eye and gynecology surgery were associated with cardiovascular mortality rates below 0.1%. A laparascopic technique was applied in 15,318 patients (14%), who had a lower incidence of cardiovascular death than those undergoing open surgery (0.2% versus 0.6%; table 2). The 774 patients (0.7%) who underwent emergency surgery had a higher incidence of cardiovascular death than patients undergoing non-emergency surgery (6.1% versus 0.5%; table 2).

In univariable analyses, the Lee-index and its separate components were associated with an increased risk of cardiovascular death (table 2). The C-statistic for the prediction of cardiovascular mortality using the Lee-index was 0.63. The C-statistic was substantially higher in the subset of 66530 low to intermediate risk procedures (including breast, carotid, dental, endocrine, eye, gynecology, orthopedic, reconstructive and urologic surgery;) than in the remaining 42063 intermediate to high risk procedures (0.68 versus 0.56). If more detailed information regarding the type of surgery was added to the Lee index, then the C-statistic significantly improved to 0.79 (table 3). Additional to the type of surgery, age, had independent prognostic value.

DISCUSSION

Cardiovascular mortality still is a major burden in patients undergoing noncardiac surgery. In the investigated cohort, on average 7 out of 1000 procedures in men and 3 out of 1000 procedures in women had a fatal in-hospital outcome as a result of cardiovascular complications. In contrast, anesthesia related mortality only occurs in approximately 1 out of 250000 procedures.[16] Interestingly, patients who underwent post-mortem examination were considerably more often classified as cardiovascular death than patients in whom no such examination was performed. This suggests that the incidence and impact of cardiovascular complications after noncardiac surgery may be underestimated in clinical practice.

The Lee index (or revised Goldman index) is considered the best currently available cardiac risk prediction index in noncardiac surgery, because it was developed on contemporary data for unselected patients undergoing a wide spectrum of procedures.[17,18] Indeed, the Lee-index showed an admirable performance to predict perioperative cardiovascular mortality. However, in agreement with another investigation,[19] our data also indicated that the Lee-index is probably suboptimal for identifying patients with greater cardiac risk. It should be noticed in this respect, that prior investigations indicated that type of surgery is one of the main determinants of adverse cardiovascular outcome,[13] which was confirmed in our data. In their risk-index, Lee and colleagues only distinguish two surgical subtypes: high risk, including intraperitoneal, intrathoracic and suprainguinal vascular procedures, and remaining procedures (the latter category mainly included orthopedic, abdominal and other vascular procedures; laparoscopic procedures were not included). We found that a more subtle classification, as suggested by the American Heart Association / American College of Cardiology guideline committee,[13] would result in a substantially better risk-discrimination of surgical patients. We realize that the Lee-index was developed for the prediction of 'major cardiac complications' (which include myocardial infarction, pulmonary edema, ventricular fibrillation, and cardiovascular death), and not for the prediction of cardiovascular death only. Still, it is unlikely, that the C-statistics would have shown more favorable values in case we had considered these other events. In general, it is easier to predict the incidence of so-called 'hard' events than 'soft' events.[20] Also, cardiovascular mortality seemed to be the most relevant endpoint in this context.

The American Heart Association / American College of Cardiology guidelines indicate advanced age as a minor predictor of cardiovascular risk.[13] In our data, however, perioperative cardiovascular mortality progressively increased with age. This finding may reflect the broad spectrum of surgical procedures that were included in our analysis as compared to other investigations,[3-11] and, along with that, a large diversity of patients with respect to age. Indeed, elderly patients often have (asymptomatic) coronary disease, which places them at an increased risk of perioperative cardiovascular complications. The modest contribution of the clinical characteristics that form part of the Lee-index, relative to age, might also be the result of under-reporting. Details of the medical history were coded according to the ICD-9 system and subsequently entered in an electronic database by administrative personnel on the basis of written information provided by health-care professionals. These employees are specifically instructed to avoid inappropriate over-diagnosis. As a result, medical conditions might have been overlooked, and, consequently, the relative contribution of these factors to cardiovascular death might have been underestimated.[21] Also, we restricted our analyses to patients who underwent surgery. No information was included from patients who were screened, but did not undergo surgery because the risk was perceived as prohibitive. Obviously, exclusion of patients at risk of adverse cardiovascular outcome might have diluted estimates of relative risk.

The identification of patients at risk of perioperative cardiovascular complications has considerably improved over the recent years. Also, effective risk-reduction strategies have been defined for particular patient categories, such as those undergoing major vascular surgery.[22-25] In general, however, the investigations that successfully aimed at cardiovascular risk identification were not succeeded by investigations that aimed at systematic risk reduction. Hence, effective cardio protective treatment strategies remain undefined for substantial portions of the noncardiac surgery population. The development and implementation of such strategies for the entire surgical spectrum remains an important challenge for contemporary medicine. In that regard, it is noteworthy that the incidence of fatal perioperative cardiovascular complications at our center did not decline during the 10-year study period. Although information on large series of unselected surgical patients in comparable high-volume, tertiary referral centers is lacking, several observations in selected patients indicate that the Erasmus MC data are no exception.[26,27]

Conclusion

This single center study, which involved over 100000 subjects, demonstrated that perioperative cardiovascular mortality is a major burden in patients undergoing noncardiac surgery. Little progress has been achieved during the years behind. The Lee index had an admirable performance to predict cardiovascular mortality, but the simple classification of procedures as high / not high seems suboptimal. Caveats to our analysis include the fact that data are derived from an administrative database, the retrospective nature of the data, the ICD-9 coding of clinical characteristics, and the fact that we evaluated cardiovascular death rather than a broader range of clinical complications. Therefore, prospective studies are warranted to confirm our findings.

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CHAPTER TWO

Submitted for publication

PREDICTING PERIOPERATIVE MORTALITY IN NONCARDIAC SURGERY: DERIVATION AND VALIDATION OF A CUSTOMIZED RISK INDEX IN THE DUTCH POPULATION

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ABSTRACT

Background: Preoperative risk evaluation is used to assess the probability of perioperative mortality in patients scheduled for surgery. We aimed to develop a risk index that accurately estimates the probability of all-cause mortality in the general noncardiac surgical population. *Methods:* Data regarding Dutch surgical patients between 1991 and 2002 were obtained from Prismant, the institution responsible for national healthcare statistics. Our study population consisted of all patients with age > 40, scheduled for none day-case aabdominal; breast; ear, nose, throat; gynecology; endocrine, orthopedic; urologic; and vascular surgery (N=1,188,763). On admission, the treating physician classified surgical procedures according to a standardized national coding system. Each patient's medical history was classified according to the ninth International Classification of Diseases (ICD-9). In-hospital death was registered. A total of 594,132 procedures were selected for risk index development, in which the relation between patient characteristics, type of surgery and perioperative mortality was identified. Validation of our risk index occurred in 594,631 surgical procedures, by logistic regression analysis. *Results:* A total of 1,188,763 surgical procedures were performed in 102 hospitals. 23,613 (2.0%) patients died during hospital stay (median hospital stay: 8 days). The type of operation was the most important correlate with poor outcome. Age, gender, diabetes mellitus, angina pectoris, myocardial infarction, heart failure, cerebrovascular disease, renal disease, cardiac valve abnormality, cardiac arrhythmia, and pulmonary disease were independently associated with mortality, and provided additional information in mortality risk prediction of the study population. The risk index had excellent discriminative ability in the derivation cohort (c-statistic 0.89) and validation cohort (c-statistic 0.89). *Conclusion:* The type of surgical procedure predominantly determines mortality after noncardiac surgery. In addition, detailed data on patient characteristics further identifies patients at risk for perioperative mortality.

INTRODUCTION

Annually, approximately 4% of the Dutch population is scheduled for noncardiac surgery, with an estimated 1.9% mortality rate.[1] Major cardiac complications are important contributors to perioperative mortality. They are estimated to occur in 1 to 5% of the noncardiac surgical population, and contribute to 30% of deaths in the perioperative period.[1,2] As a result, more than 3,600 patients die each year, due to cardiac complications of noncardiac surgery, in The Netherlands alone.

Preoperative cardiac evaluation is used to assess the patient's medical status prior to surgery. It provides information on the functional capacity of the patient and the presence and extend of comorbidities, which put the patient at risk for perioperative complications.

Adequately identifying a patient's cardiac risk profile prior to surgery provides an important clinical tool, which a physician can use to make treatmentdecisions that possibly influence postoperative short-term and long-term outcome.[3,4]

Previous studies have identified several important clinical risk factors that are associated with an increased risk of perioperative adverse cardiac events in noncardiac surgical patients.[5-8] However, only estimating the risk of cardiac mortality, leads to an underestimation of the risk of perioperative mortality, as almost half the patients who experience perioperative cardiac morbidity develop other types of noncardiac complications and subsequent mortality.[9,10]

We aimed to develop a risk index that accurately estimates the probability of all-cause mortality in the noncardiac surgical population.

METHODS

Data source

Data regarding Dutch surgical patients between 1991 and 2002, age > 40, were obtained from Prismant, the institution responsible for national healthcare statistics.[11] Prismant obtains medical information from the National Medical Register (NMR). 102 hospitals are associated to the NMR. The database used for this study contained data on the type of surgical procedure, date of the procedure, age and gender of the patient, patient clinical characteristics, and in-hospital mortality.

Type of surgery

All surgical procedures were classified on admission by the treating physician according to a standardized national coding system (CVV code, classification of procedures[11]), developed by the National Health Service. This system is used by the NMR to record all surgical procedures in The Netherlands for national healthcare statistics. Our study population consisted of patients undergoing abdominal hepatic; abdominal pancreatic; abdominal billiary cholecystectomy; abdominal billiary duct; abdominal oesophago-gastric; abdominal intestinal; other abdominal; breast; ear, nose, throat; gynecology; endocrine, orthopedic; urologic; renal transplant; vascular aortic acute; vascular aortic elective; vascular carotid; vascular peripheral bypass; vascular thrombectomy, vascular arterio-venous shunt. Day case surgical procedures, were considered to be very low risk, and were not included.

Clinical risk factors

Each patient's medical history was classified by the treating physician according to the ninth International Classification of Diseases (ICD-9).[12] Based on prior research,[1,3,5-8] we analyzed the following medical conditions: diabetes mellitus (ICD-9 250), cardiac valve abnormality

(ICD-9 395, 396, 397 and 398), ischemic heart disease (ICD-9 410, 411, 412, 413 and 414), cardiac arrhythmia (ICD-9 426 and 427), heart failure (ICD-9 428), cerebrovascular accident (ICD-9 430), pulmonary disease (ICD-9 491, 492 and 493) and renal disease (ICD-9 580).

Endpoint

The vital status at hospital discharge was verified and documented for each patient. Events were counted until hospital discharge or 30 days after surgery, whichever day came first.

Risk index derivation and validation

A computer generated random number was used to divide the study cohort into 2 equally sized groups, with similar characteristics. The derivation cohort consisted of 594, 132 patients and was used to develop the risk index. The validation cohort, which existed of 594,631 patients, was used to validate the performance of our risk index. The determinants of perioperative mortality were then used to create a variable-weight index in which scores were assigned based on parameter estimates of the individual determinants. The performance of the multivariate risk index was studied with respect to discrimination and calibration. Discrimination refers to the ability to distinguish mortality from survival. It was quantified by a measure of concordance, the c-statistic. The c-statistic lies between 0.5 and 1, and is better if closer to one. Calibration refers to whether the predicted 30-day in-hospital mortality is in agreement with the observed mortality rates. Calibration was measured with the Hosmer-Lemeshow (H-L) goodness-of-fit-test.

Statistical analysis

Continuous data are described as median values and corresponding 25^{th} and 75^{th} percentiles, and dichotomous data are described as numbers and percentages. Multivariable logistic regression analyses were used to evaluate the relationship between patient characteristics, type of surgical procedure and the primary endpoint. Odds ratios and corresponding 95% confidence intervals are reported.

RESULTS

Characteristics of patients and procedures

Table 1 describes the major categories and subcategories of noncardiac surgery, as well as the total number of patients undergoing the procedure and their relation with perioperative mortality. Abdominal, orthopedic, gynecology and vascular surgery were the most frequent performed procedures. Ear, nose, throat (ENT) surgery was performed the least, the vast majority of all ENT procedures were laryngectomies (76%). Laparoscopic surgery was applied in 82,618 (0.7%) of patients. Important differences in mortality were observed in relation

Table 1. Type of surgery and incidence of in-hospital mortality

	All patients			Derivation cohort			Validation cohort			P value*	P value**
Type of surgery	N	Mortality (%)		N	Mortality (%)		N	Mortality (%)			
Abdominal	527,524	12,295	(2.3)	263,191	6,193	(2.4)	264,333	6,102	(2.3)	0.09	0.9
Hepatic	2,030	178	(8.8)	1,019	97	(9.5)	1,011	81	(8.0)	0.8	0.2
Pancreatic	3,034	257	(8.5)	1,477	131	(8.9)	1,557	126	(8.1)	0.2	0.4
Billiary	156,790	1,602	(1.0)	78,414	827	(1.1)	78,376	775	(1.0)	0.8	0.2
Cholecystectomy	146,092	1,213	(0.8)	72,941	619	(0.9)	73,151	594	(0.8)	0.7	0.4
Duct	10,698	389	(3.6)	5,473	208	(3.8)	5,225	181	(3.5)	0.01	0.4
Oesophago-gastric	17,331	1,705	(9.8)	8,623	857	(9.9)	8,708	848	(9.7)	0.6	0.7
Intestinal	96,846	7,243	(7.5)	48,302	3,621	(7.5)	48,544	3,622	(7.5)	0.5	0.8
Other	251,493	1,310	(0.5)	125,356	660	(0.5)	126,137	650	(0.5)	0.1	0.7
Breast	53,320	92	(0.2)	26,519	49	0.2)	26,801	43	(0.2)	0.3	0.5
Ear, Nose, Throat	1,302	46	(3.5)	666	23	(3.5)	636	23	(3.6)	0.4	0.9
Gynecology	168,032	256	(0.2)	84,157	133	(0.2)	83,875	123	(0.2)	0.4	0.5
Endocrine	10,425	14	(0.1)	5,195	10	(0.2)	5,230	4	(0.1)	0.8	0.1
Orthopedic	225,960	1,257	(0.6)	112,974	627	(0.6)	112,986	630	(0.6)	0.8	0.9
Urologic	42,691	891	(2.1)	21,271	448	(2.1)	21,420	443	(2.1)	0.5	0.8
Renal transplant	3,463	42	(1.2)	1,739	23	(1.3)	1,724	19	(1.1)	0.8	0.6
Vascular	156,046	8,720	(5.4)	78,420	4,191	(5.3)	77,626	4,078	(5.3)	0.02	0.4
Aortic	58,811	5,529	(9.8)	29,506	2,990	(10.1)	29,305	2,954	(10.1)	0.3	0.8
Carotid	15,445	162	(1.1)	7,708	87	(1.1)	7,737	86	(1.1)	0.9	0.9
Peripheral bypass	55,994	1,448	(2.6)	28,096	822	(2.9)	27,898	784	(2.8)	0.3	0.4
Trombectomie	4,241	108	(2.5)	2,175	61	(2.8)	2,066	47	(2.3)	0.09	0.3
A-V shunt	21,555	1,581	(4.3)	10,935	231	(2.1)	10,620	207	(2.0)	0.03	0.4
Any type	1,188,763	23,613	(2.0)	594,132	11,697	(2.0)	594,631	11,465	(1.9)	-	0.1

* P value for comparison of type of surgical procedures between the derivation cohort and the validation cohort

** P value for comparison of perioperative mortality per type of surgical procedures between the derivation cohort and the validation cohort

to type of surgery. Hepatic, pancreatic, oesophago-gastric, intestinal and aortic surgery had high mortality rates of > 5%. Mortality was < 0.5% in patients undergoing endocrine, gynecology and breast surgery. Laparoscopic surgery was associated with a mortality rate of 0.3% (not shown).

The baseline characteristics of the study population, together with the incidence of perioperative mortality, are described in table 2. The median age of the study population was 65 years (25th, 75th percentile: 53, 73 years), diabetes and renal insufficiency were the most frequent medical risk factors. A total of 23,613 patients (2.0%) had perioperative death, the incidence of perioperative mortality was greater in men compared to women (2.6% versus 1.5%, P < 0.001). Of all medical risk factors heart failure was associated with the highest death rate.

Table 2. Baseline characteristics and incidence of in-hospital mortality

		All patients			Derivation cohort			Validation cohort			P value*	P value**
Patient characteristic		N	Mortality (%)		N	Mortality (%)		N	Mortality (%)			
Gender											0.7	
Male		541,601	13,897	(2.6)	270,581	6,989	(2.6)	271,020	6,908	(2.6)		0.4
Female		647,162	9,265	(1.4)	323,551	4,708	(1.5)	323,611	4,557	(1.4)		0.1
Age - yr											0.9	
40 - 50		237,185	633	(0.3)	118,475	345	(0.3)	118,710	288	(0.2)		0.02
50 - 60		238,390	1,560	(0.7)	119,247	795	(0.7)	119,143	765	(0.6)		0.5
60 - 70		320,124	5,098	(1.6)	159,979	2,557	(1.6)	160,145	2,541	(1.6)		0.8
70 - 80		296,994	9,408	(3.2)	148,420	4,726	(3.2)	148,574	4,682	(3.2)		0.6
> 80		96,070	6,463	(6.7)	48,011	3,274	(6.8)	48,059	3,189	(6.6)		0.3
Medical history												
Diabetes	Yes	34,310	1,400	(4.1)	17,092	702	(4.1)	17,218	698	(4.1)	0.5	0.8
	No	1,154,453	21,762	(1.9)	577,040	10,995	(1.9)	577,413	10,767	(1.9)		0.1
Angina pectoris	Yes	4,821	302	(6.3)	2,419	139	(5.8)	2,402	163	(6.8)	0.8	0.1
	No	1,183,942	22,860	(1.9)	591,713	11,558	(2.0)	592,229	11,302	(1.9)		0.08
Myocardial infarction	Yes	14,114	897	(6.4)	7,018	447	(6.4)	7,096	450	(6.4)	0.5	0.9
	No	1,174,649	22,265	(1.9)	587,114	11,250	(1.9)	587,535	11,015	(1.9)		0.1
Heart failure	Yes	9,173	1,853	(20.2)	4,613	919	(20.0)	4,560	934	(20.5)	0.6	0.5
	No	1,179,590	21,309	(1.8)	589,519	10,778	(1.8)	590,071	10,531	(1.8)		0.08
Cardiac arrhythmia	Yes	15,957	1,736	(10.9)	7,795	885	(11.0)	7,982	851	(10.7)	1.0	0.4
	No	1,172,806	21,426	(1.8)	586,157	10,812	(1.8)	586,649	10,614	(1.8)		0.2
Cardiac valve abnormality	Yes	5,869	435	(7.4)	2,933	216	(7.4)	2,936	219	(7.5)	1.0	0.9
	No	1,182,894	22,727	(1.9)	591,199	11,481	(1.9)	591,695	11,246	(1.9)		0.1
Cerebrovascular disease	Yes	6,384	574	(9.0)	3,176	311	(9.8)	3,208	263	(8.2)	0.7	0.03
	No	1,182,379	22,588	(1.9)	590,956	11,386	(1.9)	591,423	11,202	(1.9)		0.2
Renal insufficiency	Yes	27,063	1,612	(6.0)	13,602	809	(6.0)	13,461	803	(6.0)	0.3	1.0
	No	1,161,700	21,550	(1.9)	580,530	10,888	(1.9)	581,170	10,662	(1.8)		0.1
Pulmonary disease	Yes	17,525	1,046	(6.0)	8,778	541	(6.2)	8,747	505	(5.8)	0.8	0.3
	No	1,171,238	22,116	(1.9)	585,354	11,156	(1.9)	585,884	10,960	(1.9)		0.2
Length of hospital stay												
Median		8			8			8			0.8	
Interquartile range		4-13			4-13			4-13				

* P value for comparison of baseline characteristics between the derivation cohort and the validation cohort
** P value for comparison of perioperative mortality between the derivation cohort and the validation cohort

Figure 1 shows the trends in age, mortality, average number of risk factors and length of hospital stay of the patients during the study period. Mortality rates remained between 1.9 and 2.0% between 1991-2002 (lower left panel), and the percentage of patients ≥ 80 years between 7-8% (upper right panel). On the contrary, the average length of hospital stay decreased gradually with 34% (lower right panel), and the average number of risk factors per patient showed a decrease after 1995 (upper left panel).

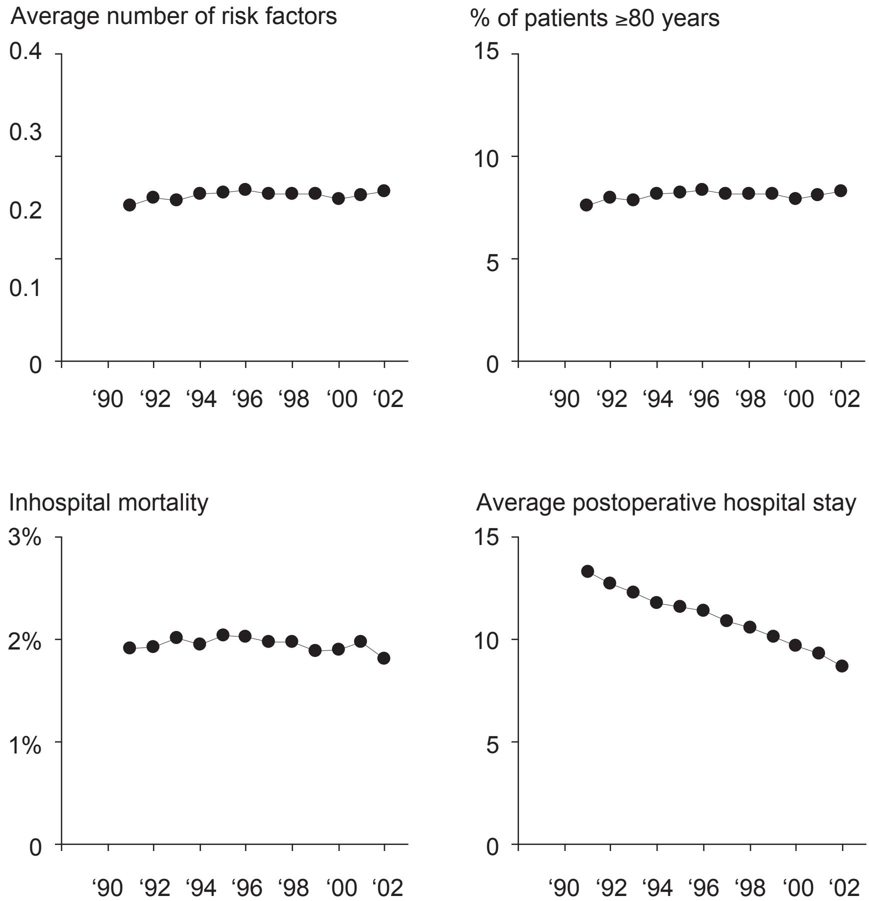

Figure 1. Trends in age, mortality, average number of risk factors and length of hospital stay of patients during the study period

Characteristics of the derivation and validation cohort

Table 1 presents detailed data on the number of surgical procedures performed, and the incidence of perioperative mortality, in the derivation (N=594,132) and validation cohort (N=594,631). Except for the vascular arterio-venous shunt procedure and billiary duct surgery, which were both more frequently performed in the derivation cohort (table 1, P=0.01 and P=0.03 respectively), no significant differences were observed between the two groups. The incidence of perioperative mortality, calculated for each type of surgical procedure, was not different in the validation cohort compared to the derivation cohort.

Table 2 presents information on baseline characteristics of both cohorts, in which no significant differences were present. Patients in the derivation cohort had the same age as patients in the validation cohort (median 65 years, and 25th, 75th percentile: 53, 73 years, P = 0.9). The incidence of perioperative death, calculated for each baseline characteristic, was similar except for a difference in mortality in patients with cerebrovascular disease (P=0.05).

Table 3. Relative risk for perioperative mortality risk factors in the derivation cohort (N=594,132)

	Adjusted odds ratios (95% CI)	
Patient characteristic	Derivation cohort	
Male gender	1.2	(1.2-1.3)
Age - yr		
≤ 50*	1	
50 - 60	1.4	(1.3-1.6)
60 - 70	2.7	(2.4-3.0)
70 - 80	5.3	(4.7-5.9)
> 80	12.8	(11.4-14.3)
Medical history		
Diabetes	1.1	(1.0-1.2)
Renal insufficiency	4.0	(3.7-4.5)
Angina pectoris	1.2	(1.1-1.3)
Myocardial infarction	1.2	(1.0-1.3)
Heart failure	4.4	(4.0-4.7)
Cardiac arrhythmia	2.1	(1.9-2.3)
Cerebrovascular disease	2.9	(2.6-3.4)
Pulmonary disease	1.4	(1.2-1.5)
Cardiac valve abnormality	1.4	(1.2-1.6)
Type of surgical procedure		
Abdominal		
Hepatic	65.1	(50.2-84.3)
Pancreatic	44.8	(35.4-56.6)
Billiary		
Cholecystectomy	6.0	(5.1-7.1)
Duct	12.5	(10.1-15.3)
Oesophago-Gastric	34.2	(29.1-40.2)
Intestinal	22.6	(19.4-26.2)
Other abdominal	2.0	(1.7-2.3)
Breast*	1	
Ear, Nose, Throat	14.5	(9.2-22.7)
Gynecology*	1	
Endocrine*	1	
Orthopedic	1.6	(1.4-1.9)
Urologic	7.6	(6.4-9.0)
Renal transplant	2.5	(1.6-3.9)
Vascular		
Aortic	33.8	(28.9-39.5)
Carotid endarterectomy	3.7	(2.8-4.9)
Peripheral bypass	8.0	(6.7-9.5)
Thrombectomy	6.7	(5.0-9.1)
AV shunt	2.3	(1.9-2.9)
Laparoscopic	0.3	(0.2-0.3)

* Reference group

Predictors of perioperative mortality in the derivation cohort

Table 3 identifies the multivariate predictors of perioperative mortality in the derivation cohort. Male gender, age, and all proposed cardiac risk factors were significant independent predictors of mortality. However, the strongest correlate with death was type of surgery. Compared with endocrine, gynecology and breast surgery, hepatic, pancreatic, oesophago-gastric, intestinal- and aortic procedures were most strongly associated with perioperative mortality. Laparoscopic surgery was associated with a reduction in risk of mortality.

Risk scores

The perioperative mortality risk factors identified by table 3 were used to create a variable-weight index in which scores were assigned based on parameter estimates of the individual predictors (table 4). The patient's probability estimate for perioperative mortality was estimated by adding the individual scores from the different parameters. A risk score was calculated for each patient by adding the points for each risk factor present. For example, a 72-year old (15 points) man (1 point) with a history of diabetes (1 point) and myocardial

Table 4. Perioperative mortality risk index*

Type of surgery	Score	Patient characteristics	Score
Abdominal		*Gender*	
Hepatic	+40	Male	+1
Pancreatic	+40		
Billiary		*Age - yr*	
Cholecystectomy	+20	50 - 60	+5
Duct	+25	60 - 70	+10
Oesophago-Gastric	+35	70 - 80	+15
Intestinal	+30	> 80	+25
Other	+5		
Ear, Nose, Throat	+25	*Medical history*	
Orthopedic	+5	Diabetes	+1
Urologic	+20	Angina pectoris	+1
Renal transplant	+10	Myocardial infarction	+1
Vascular		Heart failure	+15
Aortic	+35	Cardiac arrhythmia	+5
Carotid	+15	Cardiac valve abnormality	+5
Peripheral bypass	+20	Cerebrovascular disease	+10
Trombectomy	+20	Renal insufficiency	+15
A-V shunt	+10	Pulmonary disease	+5
Laparoscopic	-15		

* A patient's risk score is calculated by adding the points of each risk factor present. For example, a 72-year old (15 points) man (1 point) with a history of diabetes (1 point) and myocardial infarction (1 point), undergoing laparoscopic (-15) intestina l surgery (30 points) would have a total of 33 points.

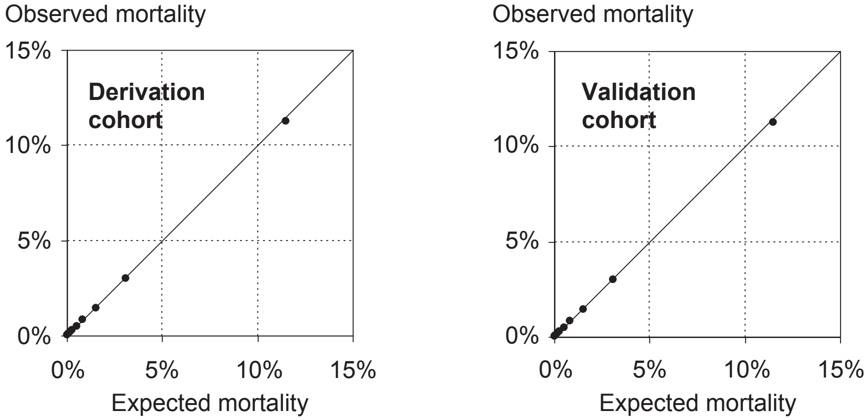

Figure 2. Calibration of the derivation and validation cohort, Hosmer-Lemeshow goodness-of-fit test 100.7 and 84.9 respectively (P <0.001)

Calibration refers to whether the predicted 30-day in-hospital mortality is in agreement with the observed mortality rates. Calibration was measured with the Hosmer-Lemeshow goodness-of-fit-test

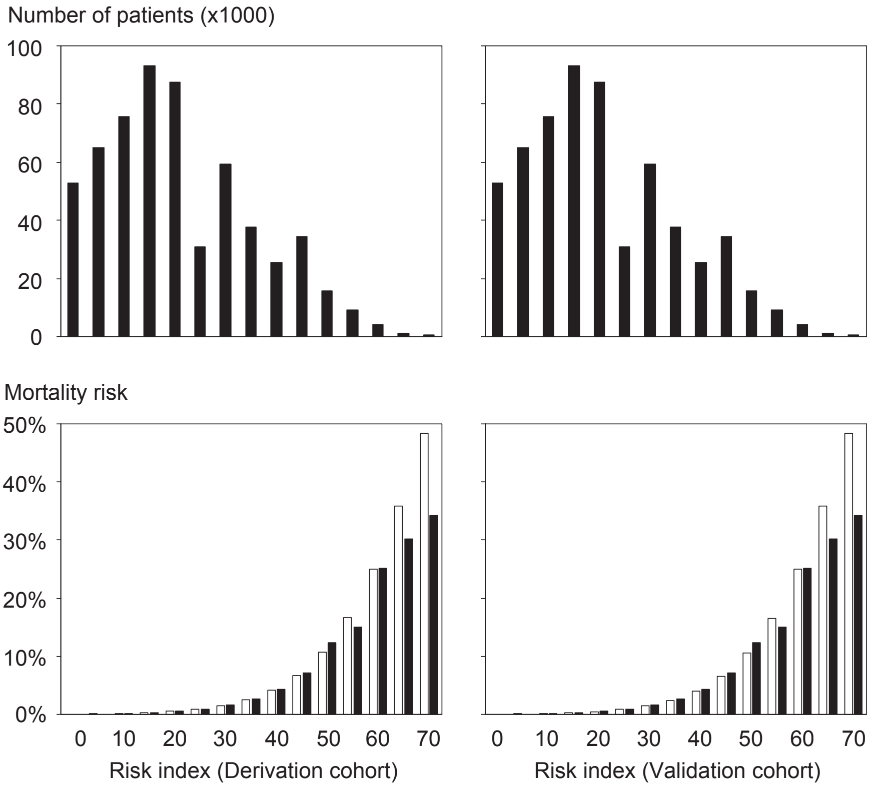

Figure 3. Upper panels: number of patients per risk index group. Lower panels: expected (white) and observed (black) mortality in derivation and validation cohort

infarction (1 point), undergoing laparoscopic (-15) intestinal surgery (30 points) would have a total of 33 points.

Risk index validation

In the derivation and validation cohort, the discriminative ability of the risk index for perioperative 30-day in-hospital mortality was excellent (c-statistic 0.89 and 0.89 respectively). Calibration in both cohorts was suboptimal (figure 2 left and right panel, H-L test 100.7 and 84.9 respectively, $P < 0.0001$). This discrepancy between expected and observed mortality in both cohorts can partly be explained by the overestimation of mortality risk in the very high-risk population (> 65 risk index points, figure 3 lower panels). Furthermore, it should be noted that relatively small differences between the estimated and observed percentages easily become statistically significant due to the large number of patients.

DISCUSSION

In this observational cohort study of more than one million noncardiac surgical procedures in the Dutch population, the type of surgical procedure predominantly determined perioperative mortality. Detailed information on type of operation and patient characteristics was used to construct a risk index that accurately predicts perioperative mortality.

Preoperative risk stratification is used to identify patients at increased risk for perioperative mortality. The possibility to accurately assess a patient's perioperative mortality risk, provides the physician with an important tool to make easier treatment decisions that may affect short and long term outcome of the surgical patient. Over the past two decades, several investigators have published clinical indices to estimate the risk of adverse events in patients undergoing noncardiac surgery.[3,5-8] Most of these studies were performed in a selected group of patients, and primarily focussed on patient comorbidities as contributors to perioperative mortality. Few studies have succeeded to accurately identify the degree of surgery-specific risk of perioperative mortality in the general population. The American Heart Association / American College of Cardiologists published a surgical risk classification in their 2002 guidelines on perioperative cardiovascular evaluation for noncardiac surgery.[13] Surgical procedures were classified into low, intermediate and high risk according to their risk of cardiac death and nonfatal myocardial infarction, based on a paper by Eagle and colleagues.[14] High risk procedures had a cardiac risk greater than 5%, and included emergency surgery, aortic and major vascular surgery, peripheral vascular surgery, and procedures with large fluid shifts and/or blood loss. Intraperitoneal and intrathoracic surgery, carotid endarterectomy, head and neck surgery, orthopedic surgery and prostate surgery were classified as intermediate risk (cardiac risk between 1-5%). In our study, overall mortality risk of abdominal procedures was 2.3% and could be considered intermediate risk, in agreement to the results of Eagle and colleagues. However, risk classification according to the actual scheduled procedure identified hepatic, pancreatic, oesophago-gastric, and intestinal surgery as high risk (>5% mortality), billiary duct surgery as intermediate (1-5% mortality risk), and other abdominal procedures as low risk (<1% mortality). Similar, in vascular surgery only aortic procedures were high risk, peripheral vascular surgery, A-V shunt, thrombectomy, and carotid endarterectomy had a mortality rate below 5%, and should be classified as intermediate risk surgery. Furthermore, in contrast to previous studies, the current study identified type of surgical procedure as the main determinant of perioperative mortality, compared to cardiac risk factors. As a result, detailed information on type of surgery will result in a more accurate mortality risk prediction.

The elderly are considered a high risk surgical population, although the relation between different age groups and perioperative death is poorly described. Goldman and colleagues were among the first to describe an association between increased age and risk of perioperative cardiac mortality. In their study of 1001 patients over 40 years of age undergoing noncardiac surgery, age over 70 was identified as an important risk factor.[6] The relation of age over 70 and an increased risk for perioperative mortality was confirmed by Lee and colleagues in their 4,315 patients undergoing major noncardiac surgery.[7] However, age was never added to the actual index itself. Since then, little has been published on this subject. Recently, Boersma and colleagues retrospectively validated the Lee cardiac risk index in a 10 year surgical cohort, showing that an addition of a more detailed classification of age resulted in a stronger prediction of perioperative mortality.[1] The results of our study confirm these findings. Age was a major predictor of perioperative mortality, the classification into 5 categories of increasing age resulted in further optimization of the performance of our risk index.

We realize that most of the previous surgical risk investigations were designed to predict perioperative cardiac complications (for example myocardial infarction, pulmonary edema, arrhythmia's, and cardiovascular death) instead of all cause mortality. However, recent findings showed that perioperative cardiac complications are strongly associated with noncardiac complications; almost half the patients who experience perioperative cardiac morbidity develop other types on noncardiac complications and subsequent mortality.[15,16] As a result, estimating the risk of perioperative cardiac mortality only, may lead to an underestimation of the risk of all cause mortality.

Limitations

Data are derived from an administrative database, which was not designed for research purposes. The ICD-9 coding of clinical characteristics, and the fact that we evaluated all-cause death rather than a broader range of clinical complications are important limitations. Therefore, prospective studies are warranted to confirm our findings.

Conclusion

This multi center study of more than one million noncardiac surgical procedures, in 102 Dutch hospitals during 1991-2002, identified type of surgery as the major determinant of mortality in noncardiac surgery. A risk index based on a surgery-specific risk classification and clinical risk factors, was derived and validated in our cohort, and accurately identified patients at risk for perioperative mortality.

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CHAPTER THREE

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PROGNOSTIC VALUE OF ROUTINE PREOPERATIVE ELECTROCARDIOGRAPHY IN PATIENTS UNDERGOING NONCARDIAC SURGERY

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ABSTRACT

Electrocardiography (ECG) is commonly performed as part of preoperative cardiovascular risk assessment in patients undergoing noncardiac surgery. However, the prognostic value of such ECGs is still not clear. We retrospectively studied 23,036 patients undergoing 28,457 surgical procedures at the Erasmus MC between 1991-2000. Patients were screened prior to surgery by type of surgery, cardiovascular risk factors (history of coronary heart disease, heart failure, diabetes mellitus, renal dysfunction and stroke) and preoperative ECG. An ECG with atrial fibrillation, left or right bundle branch block, left ventricular hypertrophy, premature ventricular complexes, a pacemaker rhythm, Q-wave or ST changes was classified as abnormal. Multivariable logistic regression was applied to evaluate the relation between ECG abnormalities and cardiovascular death. Inhospital cardiovascular death was observed in 199 / 28,457 (0.7%) cases. Patients with an abnormal ECG had higher cardiovascular death than those with a normal ECG (1.8% versus 0.3%; adjusted OR 4.5 and 95% CI 3.3 to 6.0). Adding ECG data to clinical risk factors and type of surgery resulted in an improved C-index for the prediction of cardiovascular death (0.79 versus 0.72). However, in patients undergoing low risk or low-intermediate risk surgery, the absolute difference in the incidence of cardiovascular death between those with and without ECG abnormalities was only 0.5%. We conclude that preoperative ECG provided prognostic information additional to clinical characteristics and type of surgery. However, the usefulness of its *routine* use in lower risk surgery can be questioned.

INTRODUCTION

Electrocardiography (ECG) is commonly performed in patients scheduled for noncardiac surgery as a marker of (a)symptomatic coronary artery disease. However, considering the improved accuracy of clinical cardiac risk factors to identify patients at increased risk for perioperative cardiovascular events the routine use of an ECG in all patients can be questioned. We hypothesized that a routinely performed ECG might be redundant in patients at suspected low risk according to clinical characteristics and type of surgical procedure.[1]

METHODS

During 1991-2000 a total of 108,593 noncardiac surgical procedures were performed in patients above the age of 15 years in the Erasmus MC.[2] According to hospital protocol, patients with established cardiovascular disease, and those at increased risk of coronary disease based on their age (>60) and clinical characteristics (including diabetes mellitus and hypertension), had a preoperative resting 12-lead ECG recorded. All ECGs were computer-interpreted.[3,4] The automated interpretation was evaluated by an experienced cardiology resident, changed if necessary, and recorded in the hospital information system. For the purpose of this study, the following abnormalities were considered: atrial fibrillation, left or right bundle branch block, left ventricular hypertrophy, premature ventricular complexes, pacemaker rhythm, Q-wave and ST-segment changes. An ECG within 90 days prior to surgery was available for 28,457 cases. The number of patients involved in this dataset amounts 23,036. We choose operation as unit of analysis.

Each patient's medical history was classified according to the ninth International Classification of Diseases (ICD-9).[5] We recorded medical conditions that are part of the Revised Cardiac Risk index, developed by Lee et al, including diabetes mellitus (ICD-9 250), myocardial infarction (ICD-9 410, 411, and 412), angina pectoris (ICD-9 413 and 414), heart failure (ICD-9 428), cerebrovascular accident (ICD-9 430), and renal disease (ICD-9 580).[1] Surgical techniques were classified by the treating physician according to a standardized national coding system. Based on prior research we modified type of surgery as a component of the Lee index, and grouped surgical procedures into 4 categories: low risk, low-intermediate risk, intermediate-high risk and high risk.[2,6]

The primary endpoint was 30-day cardiovascular death. Cardiovascular death was defined as any death with a cardiovascular complication as the principal or secondary cause, and included deaths following myocardial infarction, cardiac arrhythmia, resuscitation, heart failure, or stroke. Sudden death in a previously stable patient was considered cardiovascular. Investigators who classified cause of death (MDK, DP) were blinded to preoperative ECG results.

Univariable and multivariable logistic regression analyses were applied to determine crude and adjusted odds ratios (OR), and 95% confidence intervals (CI), for the relationship between ECG abnormalities and cardiovascular death. We adjusted for clinical cardiovascular risk factors according to the Lee index, type of surgery, and age (note that age is not part of the Lee index). The predictive performance of regression models was described by the C-statistic.

RESULTS

Perioperative cardiovascular death was observed in 199 (0.70%) of 28,457 patients with a preoperative ECG, which was significantly higher than the incidence observed in the patients without preoperative ECG (344 [0.34%] cardiovascular deaths in 80,136 patients; $P<0.0001$). The median age of patients with a preoperative ECG was 60.1 years (interquartile range 49.1 to 71.2). In total, 1,430 (5%) patients had a Lee risk index ≥1. The prognostic

Table 1. Univariable relation between the clinical components of the Lee Index, type of surgery and perioperative cardiovascular death

Characteristic		Procedures	Cardiovascular death		Crude, unadjusted odds ratio (95% CI)	
Lee index §	≥3	41	3	(7.3%)	13	(3.9, 42)
	2	160	4	(2.5%)	4.1	(1.5, 11)
	1	1229	25	(2.0%)	3.3	(2.2, 5.1)
	0	27027	167	(0.6%)	1	
Type of surgery†	High	335	21	(6.3%)	47	(22, 97)
	Intermediate-high	12016	124	(1.0%)	7.3	(3.9, 13)
	Low-intermediate	8435	43	(0.5%)	3.6	(1.8, 6.9)
	Low	7671	11	(0.1%)	1	
Coronary heart disease	Yes	775	18	(2.3%)	3.6	(2.2, 5.9)
	No	27682	181	(0.7%)	1	
Heart failure	Yes	172	8	(4.7%)	7.2	(3.5, 15)
	No	28285	191	(0.7%)	1	
Stroke	Yes	122	3	(2.5%)	3.6	(1.1, 12)
	No	28335	196	(0.7%)	1	
Renal insufficiency ‡	Yes	175	8	(4.6%)	7.0	(3.4, 15)
	No	28282	191	(0.7%)	1	
Diabetes mellitus	Yes	430	6	(1.4%)	2.0	(0.9, 4.6)
	No	28027	193	(0.7%)	1	

§ Index that assigns one point to each of the following clinical characteristics: history of ischemic heart disease, history of heart failure, history of cerebrovascular disease, renal insufficiency, and diabetes mellitus. Type of surgery as a cardiac risk factor according to Lee (high risk: intraperitoneal, intrathoracic, and suprainguinal vascular procedures vs low risk: other procedures) was excluded.

† Low risk (breast; carotid; dental; endocrine; eye; gynecology; reconstructive), low-intermediate risk (orthopedic; urologic), intermediate-high risk (abdominal; ear, nose, throat; neurologic; pulmonary; renal transplant; vascular, excluding aortic and carotid) and high risk (aortic).[2,6]

‡ Preoperative serum creatinine >2.0 mg/dL

value of the Lee index and type of surgery for cardiovascular death was confirmed in our data (table 1).

A total of 6,988 (25%) ECGs were classified as abnormal (table 2). Patients with an abnormal ECG had higher cardiovascular death than those with a normal ECG (1.8% versus 0.3%; crude OR 5.1 and 95% CI 3.9 to 6.9). Each separate ECG abnormality was associated with an increased risk of cardiovascular death. Information obtained from the preoperative ECG had independent value additional to clinical characteristics and type of surgery (adjusted OR 4.5 and 95% CI 3.3 to 6.0). The predictive value of an abnormal preoperative ECG remained strong once age was included in the regression model (adjusted OR 3.4 and 95% CI 2.5 to 4.5).

Table 2. Unadjusted and multivariable adjusted relation between the electrocardiogram abnormalities and perioperative cardiovascular death

Characteristic		Procedures	Cardiovascular death		Crude, unadjusted odds ratio (95% CI)		Multivariable adjusted odds ratio (95% CI)*	
Atrial fibrillation or flutter	Yes	748	28	(3.7%)	6.3	(4.2, 9.4)	4.0	(2.6, 6.2)
	No	27709	171	(0.6%)	1		1	
Left or right bundle branch block	Yes	1109	17	(1.5%)	2.3	(1.4, 3.8)	2.0	(1.2, 3.4)
	No	27348	182	(0.7%)	1		1	
Left ventricular hypertrophy	Yes	2836	38	(1.3%)	2.1	(1.5, 3.1)	1.8	(1.2, 2.6)
	No	25621	161	(0.6%)	1		1	
Premature ventricular complexes	Yes	980	19	(1.9%)	3.0	(1.9, 4.8)	2.3	(1.4, 3.7)
	No	27477	180	(0.7%)	1		1	
Pacemaker	Yes	151	4	(2.6%)	3.9	(1.4, 11)	4.4	(1.5, 12)
	No	28306	195	(0.7%)	1		1	
Q-wave	Yes	2772	56	(2.0%)	3.6	(2.7, 5.0)	2.4	(1.7, 3.3)
	No	25685	143	(0.6%)	1		1	
ST-segment depression	Yes	884	19	(2.1%)	3.3	(2.1, 5.4)	2.1	(1.3, 3.5)
	No	27573	180	(0.7%)	1		1	
Abnormal electrocardiogram	Yes	6988	124	(1.8%)	5.1	(3.9, 6.9)	4.5	(3.3, 6.0)
	No	21469	75	(0.3%)	1		1	

* Includes multivariable adjustment for the adapted Lee risk index and type of surgery

Adding ECG data to clinical characteristics and type of surgery resulted in an improvement of the C-index for the prediction of cardiovascular death from 0.72 to 0.79, which implies that 1,992 patients were more accurately classified according to their risk of perioperative cardiovascular death (table 3). We found no evidence of a differential predictive value of an abnormal ECG in subgroups of patients according to cardiac risk factors and type of surgery. However, the absolute difference in the incidence of cardiovascular death between patients with and without ECG abnormalities was most pronounced in those undergoing intermediate-high or high risk surgery (figure 1).

DISCUSSION

In patients undergoing noncardiac surgery, preoperative ECG testing improves cardiovascular risk stratification, regardless of clinical characteristics and type of surgery. Although, the added value of ECG findings seems limited in patients undergoing lower risk type of surgery, and it’s usefulness in these patients should be questioned. The large size of the

Table 3. Multivariable relation between the Lee index, type of surgery, ECG results, and perioperative cardiovascular death

Characteristic		Odds ratio (95% CI)		
		Lee index and type of surgery	Lee index, type of surgery and detailed ECG results	Lee index, type of surgery and summary ECG results
Model C-statistic		0.72	0.79	0.78
Lee index †	≥3	12 (3.5, 40)	5.0 (1.4, 18)	7.0 (2.0, 24)
	2	3.3 (1.2, 9.2)	2.2 (0.8, 6.4)	2.0 (0.7, 5.7)
	1	2.6 (1.7, 4.1)	1.8 (1.2, 2.9)	1.9 (1.3, 3.0)
	0	1	1	1
Type of surgery ‡	High risk	39 (19, 82)	32 (15, 68)	29 (14, 61)
	Intermediate-high risk	7.1 (3.8, 13)	7.4 (4.0, 14)	7.1 (3.8, 13)
	Low-intermediate risk	3.5 (1.8, 6.8)	3.5 (1.8, 6.9)	3.5 (1.8, 6.8)
	Low risk	1	1	1
Atrial fibrillation or flutter	Yes		4.0 (2.6, 6.2)	
	No		1	
Left or right bundle branch block	Yes		2.0 (1.2, 3.4)	
	No		1	
Left ventricular hypertrophy	Yes		1.8 (1.2, 2.6)	
	No		1	
Premature ventricular complexes	Yes		2.3 (1.4, 3.7)	
	No		1	
Pacemaker	Yes		4.4 (1.5, 12)	
	No		1	
Q-wave	Yes		2.4 (1.7, 3.3)	
	No		1	
ST-depression	Yes		2.1 (1.3, 3.5)	
	No		1	
Abnormal ECG	Yes			4.5 (3.3, 6.0)
	No			1

† Index that assigns one point to each of the following clinical characteristics: history of ischemic heart disease, history of heart failure, history of cerebrovascular disease, renal insufficiency, and diabetes mellitus. Type of surgery as a cardiac risk factor according to Lee (high risk: intraperitoneal, intrathoracic, and suprainguinal vascular procedures vs low risk: other procedures) was excluded.
‡ Low risk (breast; carotid; dental; endocrine; eye; gynecology; reconstructive), low-intermediate risk (orthopedic; urologic), intermediate-high risk (abdominal; ear, nose, throat; neurologic; pulmonary; renal transplant; vascular, excluding aortic and carotid) and high risk (aortic).[2,6]

lower risk surgical population is a keynote in this respect. Obviously, an important cost reduction can be obtained when preoperative ECGs can be omitted. Also, an abnormal ECG in patients who are a priori at low risk will most likely not influence pre- and perioperative management.

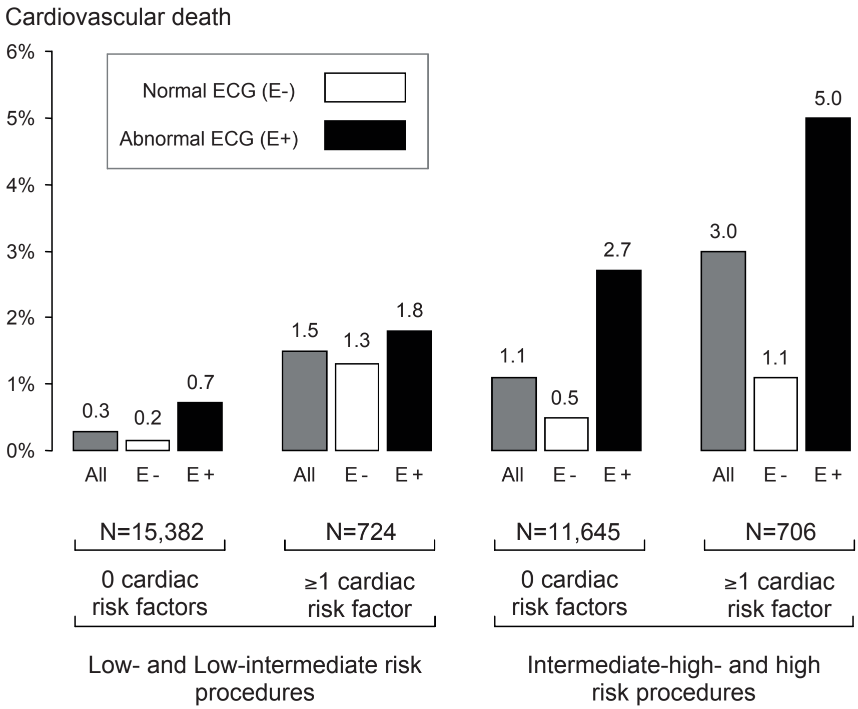

Figure 1. Incidence of perioperative cardiovascular death in subgroups of patients according to type of surgery, number of cardiac risk factors and preoperative electrocardiogram results

The amount of information used from a preoperative ECG for cardiac risk stratification has changed over the last 30 years. In the late 1970's ECG was commonly used as a preoperative cardiac risk marker. Not only the presence of a Q-wave but also several sorts of cardiac arrhythmias were part of the Goldman cardiac risk score.[7] These data were confirmed by the study of Detsky et al., showing an increased risk in the presence of supraventricular and ventricular arrhythmias.[8] In 1999 Lee et al, confirmed the prognostic value of the ECG. In their analysis, the presence of a Q-wave was associated with a 2.4-fold increased risk of perioperative events.[1] However, more recently these favourable results were questioned by Schein et al., who evaluated the use of routine ECG testing in 18,189 patients undergoing low risk cataract surgery. Preoperative testing, including ECG, did not result in improved risk stratification.[9] Our study confirmed the limited value of ECG testing in patients undergoing lower risk types of surgery. Liu et al. studied 513 patients over the age of 70 years undergoing intermediate and high risk procedures. In that study, preoperative ECG abnormalities were not associated with postoperative cardiac complications. However, this study is limited by the small number of patients and cardiac events.[10]

We acknowledge that our investigation has some limitations. First, patients were selected for preoperative electrocardiographic evaluation on the basis of a presumed increased risk of cardiovascular events. Second, our study endpoint was cardiovascular death, non-fatal cardiac events were not included in our analysis. Third, this is a retrospective analysis, and our data were derived from an administrative database, which was not designed for research purposes. Therefore, as all cases already underwent surgery at the time of our analysis, no data were available on how the preoperative ECG may have influenced the surgical decision. Fourth, the database contained written ECG results, quantitative values of ECG characteristics were not available. Finally, information on cardiovascular medication and interventions were not available.

Our data suggest that ECG testing should be performed in patients undergoing higher risk types of surgery. In our opinion, *routine* preoperative ECG testing should be abandoned in patients undergoing lower risk types of surgery. Still, baseline ECG testing might be useful in patients with established cardiovascular disease undergoing lower risk surgery for the management of possible postoperative cardiac complications.

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CHAPTER FOUR

Submitted for publication

THE PROGNOSTIC VALUE OF QTc INTERVAL IN PATIENTS UNDERGOING NONCARDIAC SURGERY

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ABSTRACT

Background: Prolonged QTc interval has been associated with increased mortality in high risk patients. However, its significance in a broader spectrum of patients has not been established. The aim of this study was to find whether QTc interval predicts mortality in patients undergoing noncardiac surgery. *Methods:* From 1994-2000, a total of 13,417 preoperative ECGs and their numerical characteristics were retrieved. All patients underwent noncardiac surgery at the Erasmus Medical Center, Rotterdam, The Netherlands. Surgical techniques were classified by the treating physician according to a standardized national coding system, and medical history in each patient was classified according to the ninth International Classification of Diseases (ICD-9). The following medical conditions were noted: diabetes mellitus, hyperlipidemia, hypertension, myocardial infarction, angina pectoris, heart failure, cerebrovascular accident, renal disease, and pulmonary disease. The endpoint was 30-day cardiovascular death. Multivariate logistic regression analysis of clinical and electrocardiographic data was used to identify the predictors of cardiovascular mortality. *Results:* Prolongation of the QTc interval was associated with increasing age, male gender, diabetes, hypertension, myocardial infarction, angina pectoris, heart failure, renal disease, and pulmonary disease. Perioperative all-cause mortality and cardiovascular death occurred in 341(2.5%) and 113 (0.5%) patients respectively. After adjustment for clinical and other ECG data, QTc prolongation was an independent predictor of cardiovascular mortality (adjusted odds ratio 1.16 and 95% confidence interval 1.11-1.21) *Conclusions:* QTc prolongation is an independent predictor of cardiac mortality in patients undergoing noncardiac surgery.

INTRODUCTION

Cardiac risk stratification is used to identify patients at increased risk for perioperative cardiac complications, which occur in up to one-third of patients undergoing noncardiac surgery.[1] In this respect, electrocardiography (ECG) is commonly performed as a marker of cardiac disease. Preoperative ECG results seem to provide additional prognostic information to clinical characteristics, particularly in the higher risk surgical population.[2,3]

Prolonged QTc interval on the 12-lead ECG has been associated with an increased cardiovascular mortality among high risk patients such as those with heart failure or diabetes mellitus.[4,5] However, the independent association of QTc prolongation with cardiac events has not been clearly demonstrated in a wider spectrum of patients. The aim of our study was to examine the association between QTc interval, and perioperative cardiac death in patients scheduled for noncardiac surgery.

METHODS

Study population

Between 1991-2000 a total of 108,593 noncardiac surgical procedures were performed in patients above the age of 17 years in the Erasmus Medical Center, Rotterdam, NL.[1] According to hospital protocol, patients with established cardiovascular disease, and those at increased risk of coronary disease based on their age (>60) and/or clinical characteristics (including diabetes mellitus and hypertension), had a preoperative resting 12-lead ECG recorded on paper. Numerical ECG characteristics were stored since 1994 in an ECG management system. ECGs within 90 days prior to surgery were considered preoperative, and were selected for study purposes. A total of 13,417 ECGs were retrieved.

Patient characteristics

Medical history in each patient was classified according to the ninth International Classification of Diseases (ICD-9).[6] The following medical conditions were noted: diabetes mellitus (ICD-9 250), hyperlipidemia (ICD-9 272), hypertension (ICD-9 401, 402, 403, 404), myocardial infarction (ICD-9 410, 411, and 412), angina pectoris (ICD-9 413 and 414), heart failure (ICD-9 428), cerebrovascular accident (ICD-9 430), renal disease (ICD-9 580), and pulmonary disease (ICD-9 491, 492 and 493). Surgical techniques were classified by the treating physician according to a standardized national coding system (classification of procedures: CVV code[7]). Based on prior research we grouped surgical procedures into low risk, low-intermediate risk, intermediate-high risk and high risk.[1] For the purpose of this study, we considered low-intermediate, intermediate-high, and high risk procedures.

ECG interpretation and measurements

A 12-lead resting ECG was recorded with an electrocardiograph (ELI-100, Mortara Instruments, Milwaukee, WI, USA), which calculated the heart rate, average RR-interval, QRS and QT interval. QT interval was corrected for heart rate using Bazett's formula: QTc=QT / (RR). All ECGs were computer-interpreted. The automated interpretation was evaluated by an experienced interpreter, and changed if necessary.

Endpoint

The primary endpoint was 30-day cardiovascular death. Cardiovascular death was defined when death was sudden, and when a cardiovascular complication was the principal or secondary cause of death, and included deaths following myocardial infarction, cardiac arrhythmia, resuscitation, heart failure, or stroke. Investigators who classified cause of death were blinded to preoperative ECG characteristics.

Statistical analysis

Univariable and multivariable logistic regression analyses were applied to determine crude and adjusted odds ratios (OR), and 95% confidence intervals (CI), for the relationship between the numerical ECG characteristics and cardiovascular death. Analysis was adjusted for all studied clinical cardiovascular risk factors, type of surgery, age, heart rate, QRS interval and the following ECG results: left ventricular hypertrophy, Q-wave, ST-segment depression, atrial fibrillation, pacemaker rhythm, premature ventricular complex, and bundle branch block.

RESULTS

Table 1 shows the baseline characteristics of the study population (N=13,417). A majority of the population was male. The median age of patients was 60 years (25th, 75th percentile: 50, 70 years). Mean QTc interval was 412 ms. The majority of patients underwent a low-intermediate risk surgical procedure.

Table 1. Baseline characteristics of the study population

Characteristics	N	(%)
Male gender	7,635	(56.9%)
Age		
<40	785	(5.9%)
40-50	2,474	(18.4%)
50-60	3,464	(25.8%)
60-70	3,397	(25.3%)
70-80	2,344	(17.5%)
≥80	953	(7.1%)
Diabetes mellitus	187	(1.4%)
Hyperlipidemia	44	(0.3%)
Hypertension	337	(2.5%)
Angina pectoris	358	(2.7%)
Myocardial infarction	235	(1.8%)
Heart failure	79	(0.6%)
Cerebrovascular accident	71	(0.5%)
COPD	113	(0.8%)
Renal failure	99	(0.7%)
Type of surgery		
High	2,463	(18.4)
Intermediate-high	5,242	(39.1)
Low-intermediate	5,712	(42.6%)
QTc interval (ms)	412	

Table 2. Patient characteristics in quartiles of QTc interval

Characteristics	Q1	Q2	Q3	Q4	P-value*
Male gender	31.4%	42.3%	48.6%	51.0%	<0.001
Age					<0.001
<40	7.3%	5.3%	5.1%	5.6%	
40-50	23.9%	19.9%	17.0%	12.5%	
50-60	29.8%	28.3%	25.8%	19.1%	
60-70	25.1%	25.7%	25.8%	24.7%	
70-80	11.0%	16.4%	19.4%	23.7%	
≥80	2.9%	4.4%	7.0%	14.4%	
Diabetes mellitus	0.7%	1.1%	1.6%	2.3%	<0.001
Hyperlipidemia	0.3%	0.2%	0.4%	0.5%	0.3
Hypertension	1.2%	2.0%	3.0%	3.9%	<0.001
Angina pectoris	1.7%	2.3%	2.9%	3.9%	<0.001
Myocardial infarction	1.1%	1.6%	1.8%	2.5%	<0.001
Heart failure	0.2%	0.3%	0.2%	1.6%	<0.001
Cerebrovascular accident	0.5%	0.5%	0.6%	0.6%	0.8
COPD	0.5%	0.8%	0.7%	1.5%	<0.001
Renal failure	0.5%	0.7%	0.7%	1.0%	0.1
Type of surgery					<0.001
High	16.7%	16.6%	18.9%	21.4%	
Intermediate-high	38.2%	40.7%	39.0%	38.3%	
Low-intermediate	45.1%	42.7%	42.1%	40.2%	
All-cause mortality	0.9%	1.4%	2.2%	5.7%	<0.001
Cardiovascular mortality	0.3%	0.5%	0.7%	2.0%	<0.001

* P values are presented for equality of values in quartiles of the QTc interval
Q1= lowest quartile of QTc interval (<392 ms)
Q2=second quartile of QTc interval (392-409 ms)
Q3=third quartile of QTc interval (409-427 ms)
Q4=highest quartile of QTc interval (>427 ms)

The relation between heart rate corrected QTc interval and baseline characteristics is shown in Table 2. Male gender was associated with increased QTc interval. The majority of patients aged > 70 had a QTc interval in the upper two quartiles. Prolonged QTc interval was observed in association with cardiac risk factors, except for hyperlipidemia, cerebrovascular accident and renal failure. Different types of surgical procedures were not evenly distributed over the quartiles of QTc interval.

Perioperative all-cause mortality and cardiovascular mortality occurred in 341 patients (2.5%), and 113 (0.8%) patients respectively, and were both associated with a prolonged QTc interval (figure 1, P<0.001). Figure 2 displays the crude and adjusted odds ratios for quartiles of QTc interval and (cardiovascular) mortality. In univariate analysis, the relation between heart rate corrected QT interval and all-cause mortality (figure 2, upper left panel)

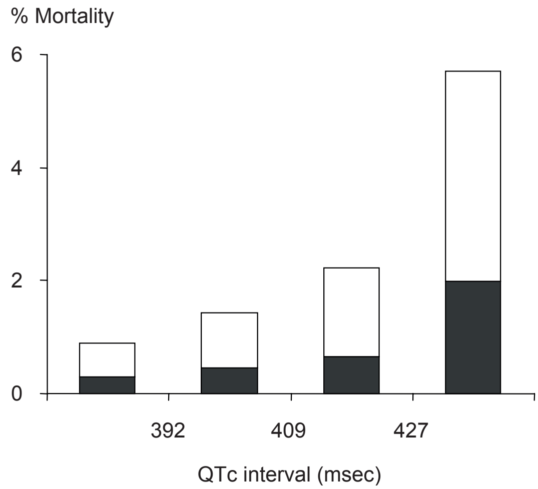

Figure 1. Peroperative all-cause mortality (white) and cardiovascular (black) mortality in QTc interval quartiles

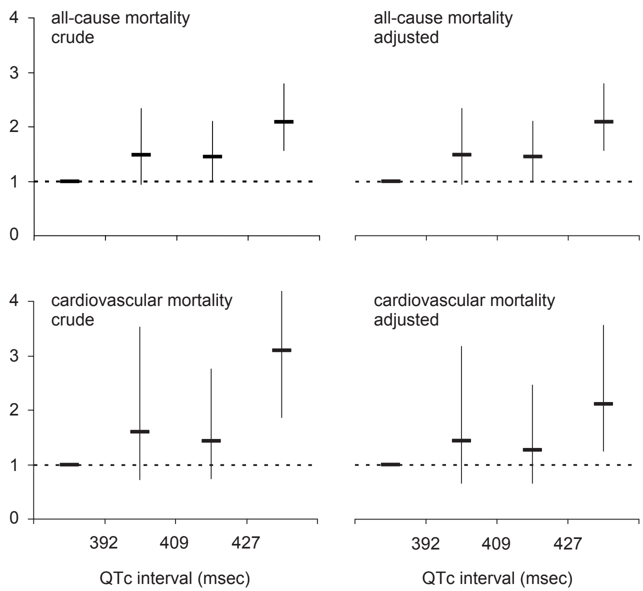

Figure 2. Crude and adjusted odds ratios and 95% confidence intervals for perioperative all-cause and cardiovascular mortality in QTc interval quartiles

the upper three quartiles of the QTc interval were associated with a significant increase in death rate (crude odds ratios 1.62, 1.57 and 2.67, and 95% confidence intervals 1.03, 2.54; 1.08, 2.26, and 2.02, 3.54 respectively). For cardiovascular death a similar trend was seen (figure 2, left lower panel), although only the highest quartile was significantly associated with cardiac mortality (crude odds ratios 1.60, 1.43 and 3.10, and 95% confidence intervals 0.73, 3.53; 0.74, 2.76, and 1.87, 5.11 respectively). After adjusting for multiple

Table 3. Relative risk of perioperative all-cause and cardiovascular mortality

Characteristic	All-cause mortality Adjusted OR (95% CI)		Cardiovascular mortality Adjusted OR (95% CI)	
QTc interval*	1.17	(1.14-1.20)	1.16	(1.11-1.21)
QTc interval > 400ms	2.26	(1.67-3.04)	1.81	(1.92-3.10)
QRS > 120 ms	0.78	(0.53-1.14)	1.13	(0.64-1.98)

* per 10 ms increase

In multivariate analysis, odds ratios are adjusted for all studied clinical cardiovascular risk factors, type of surgery, age, heart rate, QRS interval and the following ECG results: left ventricular hypertrophy, Q-wave, ST-segment depression, atrial fibrillation, pacemaker rhythm, premature ventricular complex, and bundle branch block.

confounders, the upper two quartiles of QTc interval remained independently associated with all-cause mortality (adjusted odds ratios 1.48, 1.45 and 2.09, and 95% confidence intervals 0.94, 2.34; 1.00, 2.10, and 1.56, 2.79 respectively. Figure 2, upper right panel). In cardiovascular analysis, the highest quartile of QTc interval remained independently associated with mortality (adjusted odds ratio 1.43, 1.27, and 2.11, and 95% confidence intervals 0.65, 3.17; 0.65, 2.47, and 1.25, 3.56 respectively).

When QTc interval was analyzed as a continuous variable, every 10 ms increase was related to a 17% increase for all-cause mortality and a 16% increase for cardiovascular death (table 3).

DISCUSSION

The results of our study demonstrated that prolongation of the heart rate corrected QT interval, is independently associated with perioperative all-cause and cardiovascular mortality after noncardiac surgery. Every 10 ms increase in QTc interval was related to a 17% increase for all-cause mortality and a 16% increase for cardiovascular death.

Electrocardiography testing is used as a marker for cardiac disease and increased perioperative risk in a large proportion of patients scheduled for noncardiac surgery.[3] However, the amount of information used from a preoperative electrocardiogram for cardiac risk stratification is limited. For example, only the presence of a Q-wave, or arrhythmias, are part of the risk indices of Goldman, Lee and Detsky.[8-10] A previous study of our group has shown that an abnormal ECG classified as left ventricular hypertrophy, Q-wave, ST-segment depression, atrial fibrillation, pacemaker rhythm, premature ventricular complex, and bundle branch block is of additional value in identifying patients at increased risk for perioperative cardiac death.[3] However, numerical ECG characteristics have not previously been a part of preoperative risk stratification.

The QTc interval on the surface ECG represents the time from onset of ventricular depolarization to completion of repolarization. Prolongation of the QTc interval has been associated with an increased risk of ventricular arrhythmias, which may trigger ventricular fibrillation and cardiac death. Cardiac arrhythmias are believed to be responsible for one third of all perioperative cardiac complications.[11] In our analysis, after adjustment for perioperative cardiac risk factors, ECG results and type of surgery, QTc interval remained associated with cardiac mortality. Consequently, it could be hypothesized that length of QTc interval marks the extend of subclinical cardiac disease, identifying the patient at risk for cardiac complications in the general surgical population.

Previous studies of QTc prolongation as a predictor of death in the general population have shown conflicting results. The Framingham study did not show an association of baseline QTc prolongation and all-cause mortality, cardiac mortality, and sudden cardiac death in healthy persons.[12] Whereas in The Strong Heart Study, Okin and colleagues showed that prolonged QTc interval was a predictor of cardiovascular death ($P<0.016$) and all-cause mortality ($P<0.0001$), and a QTc interval ≥ 460 ms was associated with a two-fold increased risk of cardiac and all-cause mortality in the general population.[13] In studies of clinical populations, prolongation of the QTc interval has been associated with an increased risk of cardiovascular and all-cause mortality. In a prospective 5-year follow-up study, Veglio and colleagues showed that in type 1 diabetic patients, QTc prolongation was predictive of increased mortality (adjusted odds ratio 24.6 and 95% confidence interval 6.51-92.85).[4] In patients with advanced heart failure, QTc prolongation was an independent predictor of all-cause mortality, cardiac mortality and sudden cardiac death (P values <0.001).[5]

The strength of our study lies in the fact that data were available on a large number of patients undergoing a wide spectrum of surgical procedures, QTc interval was measured automatically, and a specific heart rate–correction formula for the QT interval was used. However, our investigation has several limitations, common with studies based on retrospective acquired data. First, patients were selected for preoperative electrocardiographic evaluation on the basis of a presumed increased risk of cardiovascular events. Second, data in our analysis were derived from an administrative database, which was not designed for research purposes. Therefore, as all cases already underwent surgery at the time of our analysis, no data were available on how the preoperative ECG may have influenced the surgical decision. Third, information on cardiovascular medication and interventions were not available in our database and may have unintentionally influenced our results.

Conclusion

Our data suggest that preoperative prolongation of the QTc interval is an independent prognostic marker for perioperative cardiovascular mortality in patients undergoing noncardiac surgery.

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CHAPTER FIVE

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INCREASED PREOPERATIVE GLUCOSE LEVELS ARE ASSOCIATED WITH PERIOPERATIVE MORTALITY IN PATIENTS UNDERGOING NONCARDIAC, NONVASCULAR SURGERY

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ABSTRACT

Objective: To determine the relationship between preoperative glucose levels and perioperative mortality in noncardiac, nonvascular surgery. *Research design and methods:* We performed a case-control study in a cohort of 108,593 patients who underwent noncardiac surgery at the Erasmus MC during 1991 to 2001. Cases were 989 patients who underwent elective noncardiac, nonvascular surgery and died within 30 days during hospital stay. From the remaining patients, 1879 matched controls (age, sex, calendar year and type of surgery) were selected. Information was obtained regarding the presence of cardiac risk factors, medication and preoperative laboratory results. Preoperative random glucose levels <5.6 mmol/l (110 mg/dl) were normal. Impaired glucose levels in the range of 5.6-11.1 mmol/l were prediabetes. Glucose levels ≥11.1 mmol/l (200 mg/dl) were diabetes. *Results:* Preoperative glucose levels were available in 904 cases and 1247 controls. A cardiovascular complication was the primary cause of death in 207 (23%) cases. Prediabetes glucose levels were associated with a 1.7-fold increased mortality risk compared to normoglycemic levels (adjusted OR 1.7 and 95% CI 1.4-2.1; P-value <0.001). Diabetes glucose levels were associated with a 2.1-fold increased risk (adjusted OR 2.1 and 95% CI 1.3-3.5; P-value <0.001). In cases with cardiovascular death, prediabetes glucose levels had a 3.0-fold increased cardiovascular mortality risk (adjusted OR 3.0 and 95% CI 1.7-5.1) and diabetes glucose levels had a 4.0-fold increased cardiovascular mortality risk (OR 4.0 and 95% CI 1.3-12). *Conclusions:* Preoperative hyperglycemia is associated with increased (cardiovascular) mortality in patients undergoing noncardiac, nonvascular surgery.

INTRODUCTION

Annually, approximately 26 million patients are scheduled for noncardiac surgery in the United States.[1] Patients undergoing such surgery are at risk of perioperative cardiac events. In the study of Lee and colleagues, the incidence of major cardiac outcome in patients undergoing elective noncardiac surgery was 1.4%, of which perioperative myocardial infarction (MI) was the most frequent contributor.[2] The incidence of adverse cardiac events increases in patients at risk of cardiac disease prior to surgery.[3] In this respect, diabetes mellitus has been associated with adverse cardiac outcome in noncardiac surgery.[2,4-6]

The prevalence of diabetes continues to increase worldwide, and is predicted to increase to 300 million by 2025.[7] Type 2 diabetes is the most prevalent form and accounts for approximately 90% of patients. Before the onset of type 2 diabetes, prediabetes patients exhibit a long asymptomatic period of increased glucose dysregulation.[8] The relationship between diabetes and cardiovascular disease is thought to begin early in the progression from normal glucose tolerance to impaired glucose tolerance to diabetes.[9,10]

Impaired glucose metabolism is associated with adverse clinical outcome in the surgical and nonsurgical population.[11-14] However, the relationship between preoperative glucose levels and perioperative mortality in noncardiac surgical patients has not adequately been defined. We hypothesized that preoperative hyperglycemia was associated with increased perioperative mortality in noncardiac, nonvascular surgical patients.

METHODS

Study Design

We undertook a retrospective case-control study among 75,581 patients above the age of 15 years who underwent 108,593 noncardiac surgical procedures between January 1st, 1991 and January 1st, 2001 in the Erasmus MC, Rotterdam, The Netherlands. The computerized hospital information system was used to identify cases and controls. This system holds demographic and clinical data of all admitted patients, as well as information on the perioperative course.

Selection of cases and controls

The 2,816 patients undergoing vascular surgery and the 129 patients with an American Society of Anaesthesiologists (ASA) classification 5 (moribund, not expected to live 24 hours irrespective of operation) were excluded. Candidate case subjects were the 1040 patients from the remaining population who died of any cause during surgery or during the hospital stay after surgery within 30 days.

We intended to select 2 controls for each case from the remaining patients. Cases and controls were matched according to age (within an interval of plus or minus 5 years), gender, calendar year of surgery, and type of surgery. Surgical procedures were grouped according to a modified version of the American Heart Association / American College of Cardiology (AHA/ACC) classification.[4] For 890 cases, 2 matching controls could be selected. For 99 other cases only 1 matching control could be selected, whereas for 51 cases no matching controls could be selected. As a result, 989 cases were initially matched to1879 controls. Our study population consisted of 904 cases and 1247 controls, in which data on preoperative plasma glucose levels was available.

Data collection

The computerized hospital database, patient medical records, nursing reports, surgical reports, anesthetic reports and discharge letters were thoroughly analyzed by our investigators to obtain the following information on cases and controls; type of surgery, year of surgery, age, sex, diabetes, hypertension, family history of CAD, smoking, history of angina pectoris, myocardial infarction, heart failure, coronary artery bypass grafting, percutaneous coronary intervention, cerebrovascular disease, chronic obstructive pulmonary disease and renal insufficiency, as well as the ASA-classification and the perioperative use of aspirin, oral anti-coagulant therapy, beta-blockers, nitrates, angiotensin converting enzyme inhibitors, angiotensin 2 antagonists, statins, diuretics, prednisone, insulin and oral anti-diabetic medication.

Preoperative glucose and diabetes status

Patients were classified as having diabetes if their medical records showed documentation of a previous history of diabetes, or the use of oral anti-diabetes medication or insulin at the time of hospital admission before the planned surgical procedure. Preoperative random glucose levels <5.6 mmol/l (110 mg/dl) were classified as normal. Impaired glucose levels in the range of 5.6-11.1 mmol/l were classified as prediabetes.[15] Glucose levels ≥11.1 mmol/l (200 mg/dl) were considered diabetes.[16]

Endpoint definition

The hospital information system contains data regarding each patient's perioperative course. The vital status at hospital discharge was verified and documented for each patient. The occurrence of perioperative myocardial infarction and clinically apparent strokes were reported. To obtain the cause of death, two investigators (MDK, DP) independently reviewed all available peri-operative data, but were blind to preoperative characteristics. Cardiovascular death was defined as any death with a cardiovascular complication as the primary or secondary cause (according to the definitions of the World Health Organization), and included deaths following myocardial infarction, cardiac arrhythmia, resuscitation, heart failure, or stroke. Non-cardiovascular death was defined as any death with a principal non-cardiovascular cause, including surgery-related bleeding complications, cancer, trauma and infection. Sudden death in a previously stable patient was considered as cardiovascular. Events were counted until hospital discharge or 30 days after surgery, whichever day came first. We choose 30-day allcause mortality and 30-day cardiovascular mortality as the endpoints of our study.

Statistical analysis

Continuous baseline data are described as median values and corresponding interquartile range (IQR), and dichotomous data are described as numbers and percentages. Differences between cases and controls were analysed by Wilcoxon's tests for continuous variables, and chi-square tests for dichotomous variables.

Unconditional logistic regression analysis was applied to evaluate the relation between random preoperative glucose levels and perioperative mortality. We report crude and adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs). All statistical tests were two-sided. P-value <0.05 was considered significant.

RESULTS

Preoperative glucose levels in relation to mortality

Clinical baseline characteristics in cases and controls are presented in table 1. Overall preoperative glucose levels were higher in cases than in controls (median 6.7 mmol/l and IQR 5.3-8.8 versus median 5.7 mmol/l and IQR 4.8-7.2; P value <0.001, figure 1). In cases, prediabetes and diabetes glucose levels were more frequently seen compared to controls (57% and 13% versus 50% and 5%; P-value <0.001; Figure 2 left panel).

Table 1. Baseline Characteristics of Cases and Controls

	Cases	Controls	
No. of patients	904	1247	
Type of surgery §			
Low risk, %	7	8	
Low-intermediate risk, %	24	21	
Intermediate-high risk, %	69	71	
Age, years	64 (48, 74)	65 (51, 75)	
Male gender, %	61	63	
Medical risk factors			
Diabetes mellitus, %	27	12	‡
Hypertension, %	20	17	
Hypercholesterolemia, %	17	7	‡
Family history of coronary disease, %	2	2	
Current smoking, %	14	9	†
Angina pectoris, %	14	9	†
Myocardial infarction, %	26	10	‡
Heart failure, %	11	3	‡
Percutaneous coronary intervention, %	2	2	
Coronary artery bypass grafting, %	3	4	
Peripheral vessel disease	11	6	‡
Cerebro-vascular disease	7	6	
Chronic obstructive pulmonary disease	14	10	†
Renal insufficiency	35	16	‡
ASA classification			‡
I	11	35	
II	18	35	
III	42	28	
IV	29	2	

† P<0.01; ‡ P<0.001

§ According to a modified version of the Amercian Heart Association/American College of Cardiology classification: high risk = aortic; intermediate risk = abdominal; ear, nose, throat; neurologic; orthopedic; pulmonary; renal transplant; urologic; vascular, excluding aortic and carotid; low risk = breast; carotid; dental; endocrine; eye; gynecology; reconstructive.[4] Note that we excluded any vascular surgery, as a result we don't have patients in the high risk category.

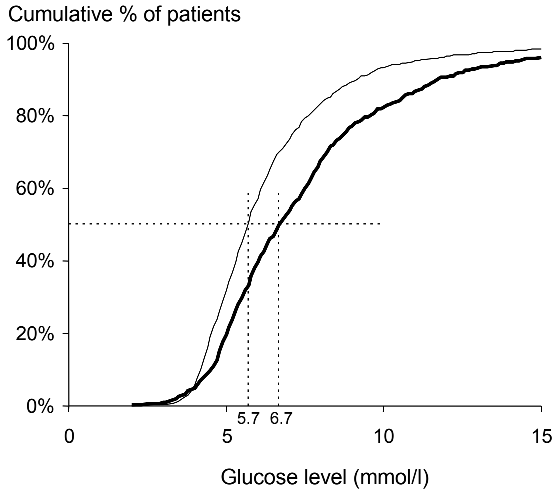

Figure 1. Cumulative distribution of glucose levels in cases (bold line) and controls

After adjustment for a broad range of potential confounders, prediabetes glucose levels were associated with a 1.7-fold increased mortality risk compared to normoglycemic levels (adjusted OR 1.7 and 95% CI 1.4-2.1; P-value <0.001; Table 2). Diabetes glucose levels were associated with a 2.1-fold increased risk (adjusted OR 2.1 and 95% CI 1.3-3.5; P-value <0.001).

In subjects with prediabetes glucose levels, a continuously increasing risk of perioperative mortality was observed along with increasing glucose concentration (Figure 3). Each 1 mmol/l increase was associated with a 19% risk increase for mortality (adjusted OR 1.19

Table 2 Relation between perioperative mortality, preoperative glucose levels and the use of anti-diabetic medication

	Cases	Controls	Adjusted odds ratio (95% CI) §
Glucose level			
Normal (<5.6 mmol/l)	268 (30%)	561(50%)	1
Prediabetic (5.6-11.1 mmol/l)	516 (57%)	626(50%)	1.7 (1.4-2.1)
Diabetic (≥11.1 mmol/l)	120 (13%)	60(5%)	2.1 (1.3-3.5)
Medication #			
Insulin	38 (15%)	51 (33%)	0.27 (0.14-0.53)
Oral anti-diabetic	16 (6%)	42 (27%)	0.11 (0.05-0.27)

§ Variables were adjusted for a history of diabetes, type of surgery, age, sex, hypertension, family history of CAD, smoking, angina pectoris, myocardial infarction, heart failure, coronary artery bypass grafting, percutaneous coronary intervention, cerebrovascular disease and renal insufficiency, as well as the ASA-classification and the perioperative use of aspirin, oral anti-coagulant therapy, beta-blockers, nitrates, angiotensin converting enzyme inhibitors, angiotensin 2 antagonists, statins, diuretics and corticosteroids.
# This analysis is based on 402 patients (247 cases and 155 controls) with a history of diabetes mellitus

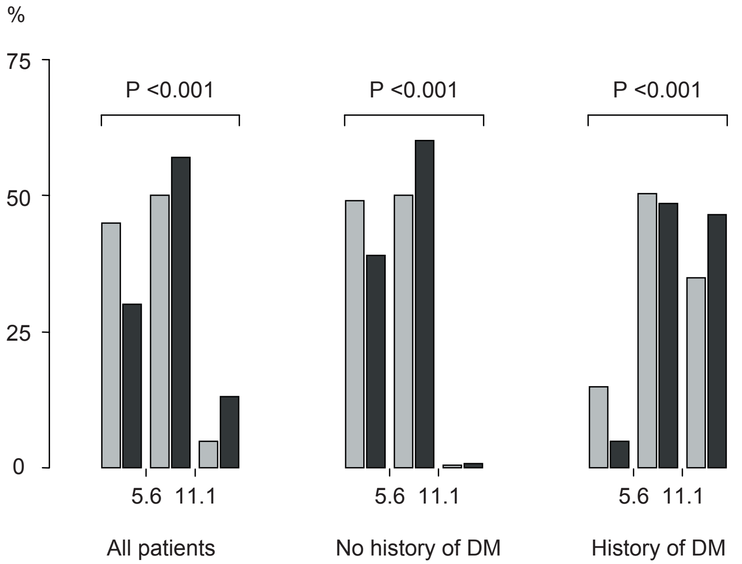

Figure 2. Incidence of normal, prediabetes and diabetes preoperative glucose levels in cases (black) and controls (grey)

Preoperative random glucose levels <5.6 mmol/l (110 mg/dl) were classified as normal. Impaired glucose levels in the range of 5.6-11.1 mmol/l were classified as prediabetes.[15] Glucose levels ≥11.1 mmol/l (200 mg/dl) were considered diabetes.[16]

and 95% CI 1.07-1.34; P-value 0.002). A similar relationship was not observed in subjects with diabetes glucose levels (adjusted OR 1.02 and 95% CI 0.91-1.15; P-value 0.71).

Preoperative glucose levels and cardiovascular mortality

A cardiovascular complication was the primary cause of death in 207 (23%) cases. The median glucose level of these cases was 7.1 mmol/l (IQR 5.3-9.0), significantly higher than the value in their matching controls (N=320; median 5.8 mmol/l and IQR 4.8-7.4; P-value <0.001). Prediabetes glucose levels were associated with a 3.0-fold increased cardiovascular mortality risk compared to normoglycemic levels (adjusted OR 3.0 and 95% CI 1.7-5.1). Diabetes glucose levels were associated with a 4.0-fold increased cardiovascular mortality risk (OR 4.0 and 95% CI 1.3-12). Again, in subjects with prediabetes glucose levels, a continuously increasing risk of perioperative cardiovascular mortality was observed along with increasing glucose levels, however, this relationship did not reach statistical significance (adjusted OR 1.24 per mmol/l and 95% CI 0.94-1.64; P-value 0.12).

History of diabetes mellitus and diabetes medication in cases and controls

A history of diabetes mellitus was present in 402 patients (247 cases and 155 controls). Patients with a history of diabetes had significantly higher glucose levels than those without such history (median 5.7 mmol/l and IQR 4.8-7.0 versus median 10.5 mmol/l and IQR 7.8-

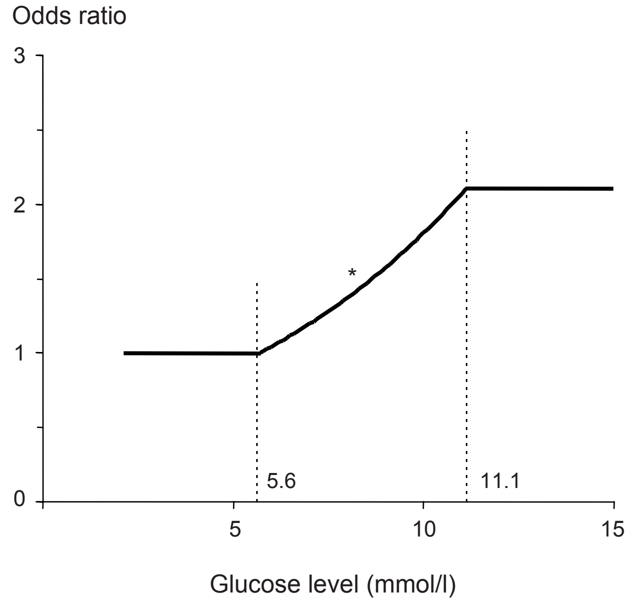

Figure 3. Relation between glucose level and relative risk for perioperative mortality
* Odds ratio for perioperative mortality 1.19 (95% confidence interval 1.1-1.3) per mmol/l increase of glucose level.
Odds ratios are adjusted for history of diabetes, type of surgery, age, sex, hypertension, family history of CAD, smoking, angina pectoris, myocardial infarction, heart failure, coronary artery bypass grafting, percutaneous coronary intervention, cerebrovascular disease and renal insufficiency, as well as the ASA-classification and the perioperative use of aspirin, oral anti-coagulant therapy, beta-blockers, nitrates, angiotensin converting enzyme inhibitors, angiotensin 2 antagonists, statins, diuretics and corticosteroids.

12.6; P <0.001). In patients without a history of diabetes, cases were more often classified with prediabetes glucose levels than controls (60% versus 50%; P-value <0.001; Figure 2 middle panel). In those with a history of diabetes, the percentage of cases and controls with prediabetes glucose levels were similar, but cases more often showed diabetes glucose levels compared to controls (47% versus 35%; P-value <0.001; Figure 2 right panel).

In patients with a history of diabetes, 20% used insulin, 12% used oral anti-diabetes medication and 2% used both therapies. The use of any anti-diabetes medication was associated with reduced glucose levels compared to patients without anti-diabetes medication (median 9.3 mmol/l and IQR 6.3-12.7 versus median 10.8 mmol/l and IQR 8.3-12.6; P-value 0.003). Insulin was used by 15% of cases versus 33% of controls (P-value <0.001), oral anti-diabetes medication was used by 6% of cases versus 27% controls (P-value <0.001). After adjustment for a broad range of potential confounders (table 2), insulin and oral anti-diabetes treatment were associated with reduced risk of perioperative mortality. When limited to the 207 cases with cardiovascular death and their matching controls, insulin therapy (adjusted OR 0.04 and 95% CI 0.01-0.22) as well as oral anti-diabetes medication (adjusted OR 0.04 and 95% CI 0.01-0.26) remained associated with lower perioperative risk.

DISCUSSION

In this case-control study of patients undergoing noncardiac, nonvascular surgery, elevated preoperative glucose levels were associated with increased perioperative mortality. Glucose levels in the diabetes range were associated with a more than 2-fold allcause mortality increase, and a 4-fold cardiovascular mortality increase, compared to normoglycemic levels. Importantly, glucose levels in the prediabetes range were also associated with increased risk for both endpoints. Anti-diabetes medication was associated with a reduction in all-cause mortality as well as cardiovascular mortality.

Prediabetes glucose levels in patients without a history of diabetes were associated with increased perioperative (cardiovascular) death. This can be explained by a number of possible mechanisms. First, the relationship between diabetes and cardiovascular disease is thought to start early in the progression from normal glucose tolerance to impaired glucose metabolism, and from impaired glucose tolerance to diabetes.[9,10] As a result of reduced insulin tolerance, and subsequent hyperglycemia, prediabetes patients may be at risk for cardiovascular disease. Second, patients with impaired glucose regulation are more frequently diagnosed with hypertension, obesity and dyslipidemia, compared to normoglycemic patients. This cluster of risk factors, also known as the metabolic syndrome, is associated with adverse cardiovascular outcome.[17]

Perioperative MI is the most frequent fatal cardiovascular complication during noncardiac surgery, however the pathophysiology underlying perioperative MI is not completely clear.[2,3] During surgery the patient is exposed to a stress response, which includes a catecholamine surge with associated hemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation and consequent hypercoagulability.[18] This stress state contributes to coronary plaque instability and rupture in patients with (asymptomatic) atherosclerotic coronary disease, which leads to thrombus formation and subsequent vessel occlusion.[18] Impaired glucose metabolism seems to be associated with increased inflammation of pre-existent atheromatous coronary plaques, resulting in intraplaque hemorrhage and possible plaque rupture leading to MI.[19,20]

Also, In patients with fixed stenotic coronary lesions, increased heart rate and contractility may induce an oxygen supply and demand mismatch leading to myocardial ischemia and eventually myocardial infarction.[18]

In patients with a known history of diabetes, preoperative hyperglycemia was associated with worse perioperative outcome. Previous studies in patients undergoing noncardiac surgery have identified a history of diabetes as a risk factor for perioperative cardiac events, without taking glucose levels into account.[2,4-6] Stratton and colleagues showed that in patients with known diabetes, the risk of atherosclerotic cardiovascular disease increased with increasing plasma glucose concentration, each 1% increase in HbA_{1c} level was associated with a 14% increase in the incidence of fatal and nonfatal myocardial infarction.[21] In patients with diabetes undergoing coronary artery bypass graft surgery, perioperative control of glucose levels was associated with a reduction in episodes of recurrent ischemia and an improved survival in the first 2 years after surgery.[24] Oral anti-diabetes medication as well as insulin therapy resulted in a significant reduction of perioperative mortality. In previous studies, glycemic control by insulin therapy has been shown to result in marked improvement in cardiac survival in hyperglycaemic nondiabetes patients and diabetes patients with acute coronary syndromes, myocardial infarction and those who have undergone recent cardiac surgery.[24-26] The switch from free fatty acid myocyte metabolism to glucose metabolism in ischemic myocardium may be an important therapeutic intervention during ischemia.[27] However, the protective effect is not entirely clear; is benefit derived from glycemic control or infused insulin or both? In our study population, the effect of oral anti-diabetes medication was similar to that of insulin treatment, and both therapies were associated with significantly lower preoperative glucose levels in controls compared to cases.

The results of our study suggest that screening for glucose dysregulation in surgical patients should be part of standard preoperative testing. The preoperative metabolic state, as measured by random blood glucose measurements, identifies patients at risk for perioperative cardiovascular events. Randomly determined glucose levels have been shown to be an efficient test to identify patients with prediabetes and undiagnosed diabetes.[15] As it seems to become increasingly clear that impaired glucose metabolism and the prediabetes state are associated with adverse clinical outcomes, we suggest that patients with preoperative glucose levels above 5.6mmol/l are further screened for associated cardiovascular risk factors. In this respect, the type of surgical procedure, patient clinical characteristics, further non-invasive test results and additional medical therapy may improve perioperative patient management.[4,28,29]

Our study has several limitations that are common with any case-control study relying on retrospective data collection. First, information on patient characteristics might have been missed because of observer bias prejudice. Second, multivariable adjustment for potential confounders is obviously limited to the available data elements. Unknown, unmeasured confounders might still be present. Third, the number of patients on oral anti-diabetes medication and insulin therapy were limited and data on perioperative glucose levels was not available. Therefore, we would like to emphasize that this early evidence needs confirmation by adequately powered randomized clinical trials.

Conclusion

This case control study provides evidence that preoperative hyperglycemia is associated with increased preoperative mortality.

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CHAPTER SIX

Submitted for publication

POOR GLYCEMIC CONTROL IN PATIENTS WITH DIABETES MELLITUS UNDERGOING MAJOR VASCULAR SURGERY IS ASSOCIATED WITH AN INCREASED INCIDENCE OF PERIOPERATIVE MORTALITY

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ABSTRACT

Background: Diabetic patients undergoing major vascular surgery are at increased risk of perioperative cardiac complications. However, the relation between preoperative glucose regulation and postoperative outcome is poorly defined in noncardiac surgery. *Methods:* Clinical cardiac risk factors and glycosylated hemoglobin (HbA_{1c}) levels were analysed in 304 consecutive patients with diabetes mellitus, scheduled for major noncardiac vascular surgery. Endpoints were all cause mortality, cardiac death and myocardial infarction. The study group was devided into tertiles based on HbA_{1c}. The highest tertile was compared to the two lower ones. Multivariate regression analysis was used to evaluate the prognostic value of HbA1c as a continuous variable. *Results:* The median preoperative HbA_{1c} was 6,8%. Preoperative HbA_{1c} values ≥7.6% were associated with increased 30-day all cause mortality and 30-day cardiac death or MI. Multivariate analysis showed an increased risk of 41% for every percent of HbA_{1c} increment. Although glucose management was equal for all patients, those with a higher (preoperative) HbA_{1c} had significantly higher perioperative glucose values. *Conclusion:* Elevated preoperative glycosylated haemoglobin is an important predictor of perioperative mortality, adverse cardiac events and perioperative hyperglycemia.

INTRODUCTION

Patients undergoing major vascular surgery are at increased risk of postoperative cardiac complications, due to underlying (a)symptomatic coronary artery disease. The incidence of cardiac death in patients undergoing vascular surgery varies between 3% and 6%[1]. Cardiac risk factors are used to identify high-risk patients prior to surgery. In this respect, diabetes mellitus (DM) has been associated with an increased risk of adverse cardiac outcome in patients undergoing vascular surgery[2,3] and is commonly presented as a dichotomous variable: the presence or absence of disease. The relation between preoperative glucose regulation and postoperative outcome is poorly defined in noncardiac surgery.

Diabetes mellitus is a major healthcare burden worldwide; currently at least 171 million people suffer from diabetes, a figure most likely doubled by 2030[4]. Diabetic patients have more extensive atherosclerosis with a high prevalence of multivessel coronary artery disease, (silent) myocardial ischemia and subsequent myocardial infarction and peripheral vascular disease compared to non-diabetics[5,6]. As a result, cardiovascular disease is listed as the cause of death in 65-70% of patients with diabetes[7].

Glycosylated haemoglobin (HbA_{1c}) is a marker of a patient's glycemic levels over the past 2 to 3 months and is considered a good marker of preoperative diabetic regulation. In patients with known diabetes, the level of hyperglycemia is correlated to the degree of coronary disease[8]. The present study evaluated the prognostic value of preoperative HbA_{1c}

levels by assessing the risk of 30-day postoperative mortality and adverse cardiac events in diabetic patients undergoing noncardiac vascular surgery.

METHODS

Patients

A total of 304 patients who underwent major vascular surgery between January 1st, 1992 and December 31st, 2005 at the Erasmus MC, Rotterdam, the Netherlands were retrospectively evaluated. The computerized hospital database, containing all cardiac risk factors, was used to identify all type II diabetic patients. HbA_{1c} was routinely measured two weeks prior to major vascular surgery. An independent anaesthesiology resident (FS) used the computerized hospital information system to review all available patient medical records and laboratory results to identify information on patient characteristics and medical therapy at time of surgery.

Perioperative glucose management

Perioperative glucose management was performed according to a standard hospital protocol. All patients received npo after midnight the day before surgery. Oral anti-diabetic medication was withheld on the night before surgery. Insulin dependent patients received continuous intravenous insulin infusion as of 06.00 AM prior to surgery. Patients on oral diabetic medication were treated with intravenous insulin when glucose levels were >8 mmol/l. Glucose levels were measured 6-10 times a day and patients were treated to obtain glucose values between 4 and 8 mmol/l. All glucose levels on the day before, the day of, and the day after surgery were retrieved.

Endpoints

The primary endpoints of our analysis were all cause mortality, cardiac death and myocardial infarction. Events were screened until hospital discharge or 30 days after surgery, whichever came first. Cardiac death was defined as any death with a cardiac complication as the principal or secondary cause, and included deaths following myocardial infarction, cardiac arrhythmia, resuscitation, heart failure and stroke. In addition, sudden death in a previously stable patient was considered cardiac. Noncardiac death was defined as any death with a principal noncardiac cause, including surgery-related bleeding complications, cancer, trauma and infection. Perioperative myocardial infarction was defined as elevated troponine levels and postoperative electrocardiogram abnormalities. Troponine levels and ECG recordings were taken on the first, third and seventh day after surgery and in case of clinical suspicion of myocardial ischemia.

Statistical Analysis

To our knowledge, a cutt-off point for HbA_{1c}, above which values predict perioperative morbidity or mortality has not been previously described. Therefore, the study group was divided into tertiles based on HbA_{1c} values and the highest tertile was compared to the two lower ones. Baseline clinical characteristics, medication, perioperative glucose levels and described endpoints were compared across both groups. Continuous variables were compared by Student's t-test and categorical variables by chi-square tests. Univariate and multivariate logistic regression analysis was applied to determine crude and adjusted odds ratios and 95% confidence intervals for the relationship between percentage of HbA1c and the previously described endpoints. The results were adjusted for age, gender, angina pectoris and heart failure.

RESULTS

A total of 304 patients were enrolled in the study with a median preoperative HbA_{1c} value of 6,8%. Patient characteristics and medical therapy are presented in table 1.

The patients were grouped in tertiles based on their HbA_{1c} values as described. Those placed in the highest tertile had HbA_{1c} values of 7,6% or higher. Patients in this tertile had a longer duration of diabetes and more often a history of known microvascular disease (retinopathy and renal failure) and coronary artery disease. In comparing medical therapy

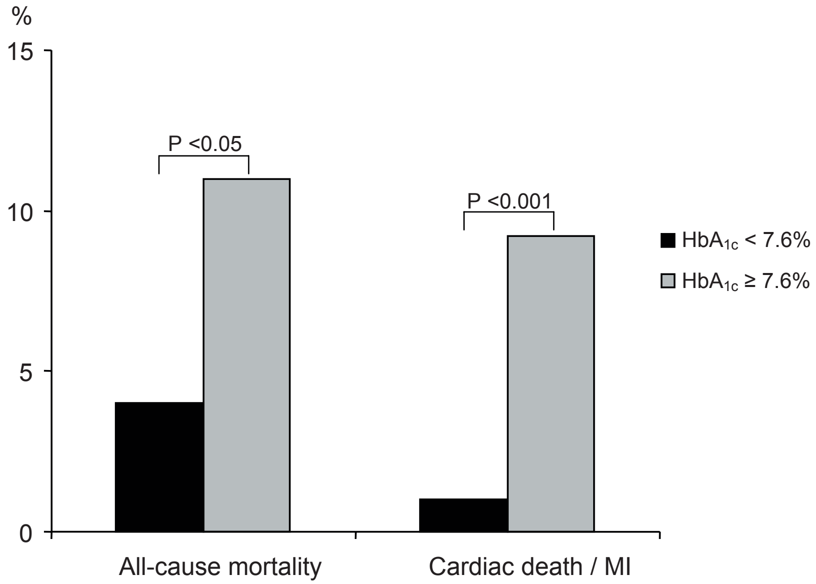

Figure 1. Perioperative mortality and cardiovascular death / nonfatal MI for subgroups of $HbA1_c$ levels

Table 1. Patient risk factors and medical therapy

Charateristics	All patients (N=304)	HbA1c < 7.6 (N=207)	HbA1c ≥ 7.6 (N=97)	P
Age (years)	63 ± 11	63 ± 11	62 ± 12	0.2
Male sex (%)	67	63	69	0.3
Duration of DM (years)	13 ± 11	9 ± 7	16 ± 12	<0.01
Renal failure (%)	26	19	42	0.001
Retinopathy (%)	17	5	46	<0.001
Prior myocardial infarction (%)	26	22	33	0.05
Angina Pectoris (%)	16	14	20	0.2
Heart failure (%)	5	4	7	0.3
CABG (%)	19	15	29	<0.01
PTCA (%)	4	5	3	0.5
COPD (%)	9	9	9	1.0
Elevated cholesterol (%)	28	29	27	0.8
Calcium channel blockers (%)	34	34	36	0.7
ACE-inhibitors (%)	33	28	45	<0.01
Statin (%)	31	32	30	0.7
β-blockers (%)	30	32	28	0.4
Diuretics (%)	15	12	24	<0.01
Nitrates (%)	14	11	22	<0.01
Coumarins (%)	134	12	18	0.2
Digoxine (%)	5	3	7	0.2

ACE: Angiotensin Converting Enzyme, CABG: Coronary Artery Bypass Graft, COPD: Chronic Obstructive Pulmonary Disease (FEV_1 <70% of predicted value), elevated cholesterol: >6.5 or medication, DM: Diabetes Mellitus, PTCA: Percutane Transluminal coronary angioplasty, renal failure: >160 mmol/l.

between both groups, no significant difference was observed in use of β-blockers or statins was observed.

Higher preoperative HbA_{1c} values were associated with increased all cause 30-day mortality and 30-day cardiac death or MI. HbA_{1c} levels ≥7.6 mmol/l were associated with a 2.9-fold all cause mortality increase, and a 9.2-fold cardiovascular mortality/MI increase, compared to HbA_{1c} levels < 7.6 mmol/l (figure 1).

Using univariate analysis, 30-day all cause mortality showed a non-significant trend of a 23% increase in mortality for every 1% increment in HbA_{1c} (table 2). After adjusting for the predetermined variables HbA1c was not found to be an independent predictor of all cause mortality.

Univariate analysis of 30-day cardiac death or MI showed a significant 43% higher risk of events for every 1% increment in HbA_{1c} (table 2). After adjusting for the predetermined risk factors a significant incremental risk was still observed for every percent added to the HbA_{1c} value (table 3).

Table 2. Univariate association of clinical data with 'all cause mortality' and 'cardiac death/MI'

	All cause mortality HR (95%-CI)	Cardiac death/MI HR (95%-CI)
HbA_{1c}	1.23 (0.97-1.57)	1.43 (1.08-1.89)
Age	1.02 (0.98-1.07)	1.01 (0.95-1.07)
Gender	0.36 (0.14-0.96)	0.33 (0.13-0.85)
Angina	3.30 (1.23-8.85)	3.00 (1.14-8.03)
Heart failure	3.90 (1.02-15.24)	3.70 (0.96-14.21)

HbA_{1c} was analysed as a continuous variable, HR per 1% increment in HbA_{1c}.

Table 3: multivariate* association of HbA_{1c} with 'all cause mortality' and 'cardiac death/MI'

	All cause mortality HR (95%-CI)	Cardiac death/MI HR (95%-CI)
HbA_{1c}	1.16 (0.87-1.55)	1.41 (1.01-1.96)

* preselected variables: Age, Gender, Previous Angina Pectoris and Previous Heart failure

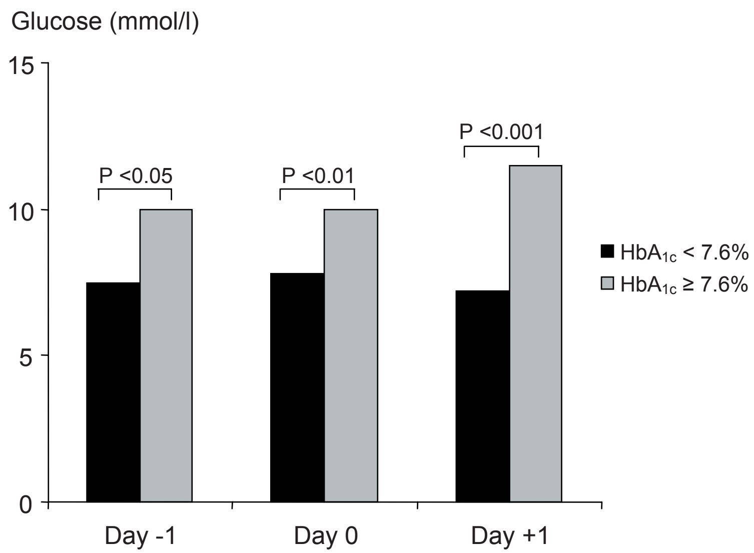

Figure 2. Preoperative (day –1), perioperative (day 0) and postoperative (day +1) glucose levels for subgroups of HbA1c levels

Perioperative glucose levels were associated with preoperative HbA_{1c} values. Patients in the highest tertile had significantly higher glucose levels on the day of admission. Despite a predetermined intensive glucose treatment regime, this difference increased on the day of surgery and was even more pronounced the day after surgery (figure 2).

DISCUSSION

This study showed that preoperative diabetes mellitus type II regulation, determined by HbA_{1c} values, was related to postoperative outcome, despite intensive perioperative glucose treatment regimens. With every 1% increment in HbA_{1c} postoperative cardiac death and adverse cardiac events increased with 43%. Using multivariate analysis HbA_{1c} was an independent predictor of cardiac death or MI.

Previous studies in patients undergoing vascular surgery have identified diabetes mellitus as a risk factor for perioperative cardiac events, without taking preoperative glucose regulation into account[2,3,9]. In our study, each 1% increase in preoperative HbA_{1c} level was associated with a 1.4-fold increase of cardiac death/MI. These results are consistent with the study of Stratton and colleagues[8]. They showed that in patients with known diabetes, the risk of atherosclerotic cardiovascular disease increased with increasing plasma glucose concentration, each 1% increase in HbA_{1c} level was associated with a 14% increase in the incidence of fatal and nonfatal myocardial infarction.

Perioperative MI is the most frequent fatal cardiovascular complication during vascular surgery, however the pathophysiology underlying perioperative MI is not completely clear. During surgery the patient is exposed to a stress response, which includes a catecholamine surge with associated hemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation and consequent hypercoagulability. This stress state contributes to coronary plaque instability and rupture in patients with (asymptomatic) atherosclerotic coronary disease, which leads to thrombus formation and subsequent vessel occlusion[10]. Impaired glucose metabolism seems to be associated with increased inflammation of pre-existent atheromatous coronary plaques, resulting in intraplaque hemorrhage and possible plaque rupture leading to MI[11]. Additionally, In patients with fixed stenotic coronary lesions, increased heart rate and contractility may induce an oxygen supply and demand mismatch leading to myocardial ischemia and eventually myocardial infarction[10].

Importantly, in our study diabetic patients with HbA_{1c} levels > 7.6 mmol/l had significantly higher perioperative glucose levels (fig2), although perioperative glucose management was equal for all patients. In previous studies, glycemic control has been shown to result in marked improvement in cardiac survival in hyperglycaemic diabetics with acute coronary syndromes, myocardial infarction and those who have undergone recent cardiac surgery[12-15]. The switch from free fatty acid myocyte metabolism to glucose metabolism in ischemic myocardium may be an important therapeutic intervention during ischemia[16]. In a recent study by Lazar and colleagues in patients with diabetes undergoing coronary artery bypass graft surgery, perioperative control of glucose levels was associated with a reduction in episodes of recurrent ischemia and an improved survival in the first 2 years after surgery[13].

The possible mechanisms trough which chronic and acute hyperglycemia lead to an increased risk of cardiac ischemic injury in diabetics have been described by Gu et al[17].

Endogenous protective signal transduction pathways are impaired, coronary bloodflow to ischemic myocardium is adversely affected, coronary collateral flow is decreased, nitric oxide availability is decreased, coronary flow reserve is diminished and an association exists between diabetes and abnormalities in myocardial contraction and relaxation.

Our study has several limitations that are common with any observational study relying on retrospective data collection. Firstly, information on patient characteristics may have been missed, because of observer bias prejudice. Secondly, multivariable adjustment for potential confounders is obviously limited to the available data elements, and unknown, unmeasured confounders might still be present. This early evidence needs to be confirmed by adequately powered randomized clinical trials.

In conclusion, this study provides evidence that elevated preoperative glycosylated hemoglobin is an independent risk factor for perioperative cardiac mortality and adverse cardiac events. The high perioperative glucose levels that were seen in patients with a high HbA_{1c} could be a partial explanation for increased morbidity and mortality. Further studies are needed to determine if tight preoperative and/or perioperative glycemic control are beneficial in diabetic patients undergoing noncardiac vascular surgery.

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CHAPTER SEVEN

Coronary Artery Disease: in press

BETA-BLOCKERS AND STATINS ARE INDIVIDUALLY ASSOCIATED WITH REDUCED MORTALITY IN PATIENTS UNDERGOING NONCARDIAC, NONVASCULAR SURGERY

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ABSTRACT

Background: Patients undergoing noncardiac, nonvascular surgery are at risk for perioperative mortality due to underlying (a)symptomatic coronary artery disease. We hypothesized that beta-blocker and statin use are associated with reduced perioperative mortality. *Methods:* We performed a case-control study in 75581 patients who underwent 108593 noncardiac, nonvascular surgery at the Erasmus MC between 1991 and 2001. Cases were the 989 patients who died during hospital stay after surgery. From the remaining patients, 1879 matched controls (age, sex, calendar year and type of surgery) were selected. Information was then obtained regarding the use of beta-blockers and statins and the presence of cardiac risk factors. *Results:* The median age of the study population was 63 years; 61% were men. Beta-blockers were less often used in cases than in controls (6.2% versus 8.2%; P=0.05), as were statins (2.4% versus 5.5%; P<0.001). After adjustment for the propensity of beta-blocker use and cardiovascular risk factors, beta-blockers were associated with a 59% mortality reduction (odds ratio [OR] 0.41; 95% confidence interval [CI] 0.28-0.59). Statins were associated with a 60% mortality reduction (adjusted OR 0.40; 95% CI 0.24-0.68). A significant interaction between beta-blockers and statins was observed (P<0.001). In the presence of each other drug, statins and beta-blockers were not associated with reduced mortality (adjusted OR 2.0 and 95% CI 0.74 to 5.7 and adjusted OR 1.3 and 95% CI 0.52 to 3.2). However, it should be noted that only 9 cases and 29 control patients used both agents simultaneously. *Conclusion:* This case-control study provides evidence that beta-blockers and statins are individually associated with a reduction of perioperative mortality in patients undergoing noncardiac, nonvascular surgery.

INTRODUCTION

Annually, approximately 4% of the Dutch population is scheduled for noncardiac surgery, with an estimated 1.9% mortality rate.[1] Major cardiac complications are important contributors to perioperative mortality. They are estimated to occur in 1 to 5% of the noncardiac surgical population, and contribute to 30% of deaths in the perioperative period.[1,2] Perioperative myocardial infarction is the most frequent fatal cardiovascular complication during noncardiac surgery.[3]

During surgery the patient is exposed to a broad spectrum of physiologic changes; an increased sympathetic tone by surgical and anesthesiological stress, hypercoagulability, hypothermia, anemia, and pain. This stress response contributes to coronary plaque instability and possible rupture, which is an important aspect of the pathophysiology of perioperative myocardial infarction.[4,5] Coronary plaque rupture may lead to thrombus formation and subsequent vessel occlusion, resulting in myocardial ischemia. In patients with fixed stenotic coronary lesions, increased heart rate and contractility induce an oxygen supply and demand mismatch, which results in myocardial ischemia and eventually myocardial infarction.[5]

Several factors are associated with an increased risk of perioperative myocardial infarction, including advanced age, cardiovascular risk factors and type of surgery.[1,6] Both beta-blockers and statins have previously been associated with improved outcome in high risk major noncardiac surgery.[7-12] However, the majority of patients are scheduled for low- to intermediate risk surgical procedures.[1] In this surgical population, data on the effect of perioperative beta-blocker and statin use are not available. Our study was designed to evaluate the possible protective effects of both agents in this large noncardiac, nonvascular surgical population.

METHODS

Study Design

We undertook a retrospective case-control study among the 75581 patients above the age of 15 years who underwent 108593 noncardiac surgical procedures between January 1st, 1991 and January 1st, 2001 in the Erasmus MC, Rotterdam, The Netherlands. The computerized hospital information system was used to identify cases and controls. This system holds demographic and clinical data of all admitted patients, as well as information on the perioperative course.

Selection of cases and controls

The 2816 patients undergoing vascular surgery and the 129 patients with an American Society of Anesthesiologists (ASA) classification 5 (moribund, not expected to live 24 hours irrespective of operation) were excluded. Candidate case subjects were the 1040 patients from the remaining population who died of any cause during surgery or during the hospital stay after surgery within 30 days. It is speculated that beta-blockers and statins mainly affect cardiac mortality. However, retrospective classification of cardiac death is often inaccurate due to a lack of autopsy reports in patients. Therefore, we chose all-cause mortality as the endpoint of our study.

We intended to select 2 controls for each case from the remaining patients. Cases and controls were matched according to age (within an interval of plus or minus 5 years), gender, calendar year of surgery, and type of surgery. Surgical procedures were grouped according to a modified version of the American Heart Association / American College of Cardiology (AHA/ACC) classification as follows: low risk, including breast, dental, endocrine, eye, gynecology, and reconstructive surgery; low-to-intermediate risk, including orthopedic and urologic surgery; intermediate-to-high risk, including abdominal, ear, nose, throat, neurologic, pulmonary, and renal transplant.[1] Note that we excluded all vascular procedures, therefore no patients were classified as high risk surgery. For 890 cases, 2 matching controls could be selected. For 99 other cases only 1 matching control could be selected, whereas for 51 cases no matching controls could be selected. The 51 cases without controls were excluded from the study population, as a result the study population consisted of 989 cases and 1879 matching controls.

Data collection

To study the relationship between beta-blocker use, statin therapy and perioperative mortality, the computerized hospital database, patient medical records, nursing reports, surgical reports, anesthetic reports and discharge letters were thoroughly analyzed by our investigators to obtain the following information on cases and controls; type of surgery, year of surgery, age, sex, diabetes, hypertension, family history of CAD, smoking, history of angina pectoris, myocardial infarction, heart failure, coronary artery bypass grafting, percutaneous coronary intervention, cerebrovascular disease, chronic obstructive pulmonary disease and renal insufficiency, as well as the ASA-classification and the perioperative use of aspirin, oral anti-coagulant therapy, beta-blockers, nitrates, angiotensin converting enzyme inhibitors, angiotensin 2 antagonists, statins, diuretics, prednisone, insulin and oral anti-diabetic medication.

Statistical analysis

Continuous data are presented as median value and corresponding 25th and 75th percentiles; dichotomous data are presented as numbers and percentages. Differences in baseline characteristics between cases and controls were studied by Mann-Whitney tests, Chi-square tests, or Fisher's exact tests, as appropriate.

To adjust for selection bias, we developed a propensity score for the likelihood of receiving perioperative beta-blocker (statin) therapy. Multivariable logistic regression analysis was applied to identify baseline factors that were associated with such early beta-blocker (statin) use. We considered a broad range of patient baseline characteristics, including age, sex, diabetes, hypertension, family history of CAD, smoking, history of angina pectoris, myocardial infarction, heart failure, coronary artery bypass grafting, percutaneous coronary intervention, cerebrovascular disease and renal insufficiency, as well as the ASA-classification and the perioperative use of aspirin, oral anti-coagulant therapy, beta-blockers (as appropriate), nitrates, angiotensin converting enzyme inhibitors, angiotensin 2 antagonists, statins (as appropriate), diuretics, prednisone, insulin and oral anti-diabetic medication. Potential interactions between these variables were not considered. All variables entered the multivariable stage. In general, for the development of a propensity score, it is recommended to use an extensive model, to ensure that any predictors (true and chance) are accounted for. For practical reasons, however, we decided to develop a somewhat reduced model, and excluded variables with a P-value >0.5 via a backward deletion procedure. We report adjusted odds ratios (OR) and 95% confidence intervals (CI) of the variables that compose the final propensity score. The performance of the propensity score model was studied with respect to discrimination and calibration. Discrimination refers to the ability to distinguish statin users from non-users; it was quantified by the c-statistic. Calibration refers to whether the predicted probability of statin use is in agreement with the observed probability; calibration was measured with the Hosmer-Lemeshow goodness-of-fit test.

Univariable and multivariable logistic regression analysis was applied to evaluate the relation between beta-blocker (statin) use, and perioperative mortality. We adjusted for the propensity of beta-blocker (statin) use, the matching factors age, sex, calendar year and type of surgery, as well as for a number of potential confounders, including cardiovascular risk factors, history of cardiovascular or cerebrovascular disease, renal disease, and ASA classification. The multivariable models were constructed by backward deletion of the least significant characteristics, while applying the Akaike information criterion [that is, the applied threshold of significance depended on the degrees of freedom (DF) associated with the variable at hand; if DF = 1, then $P \approx 0.157$]. We report crude and adjusted ORs and corresponding 95% CIs.

Stratified analyses were performed according to statin (beta-blocker) use, and the factors that compose the Lee risk index for perioperative cardiovascular events: type of surgery, age, angina pectoris, myocardial infarction, heart failure, CVA/TIA and renal insufficiency.[6] To reveal a possible heterogeneity in ORs between subgroups of patients, interaction terms between the stratification characteristic and beta-blocker (statin) use were included in the models.

All statistical tests were two-sided, including tests for interaction. P-value <0.05 was considered significant.

RESULTS

Characteristics of cases and controls

There were important differences in clinical baseline characteristics between cases and controls (Table 1). In total, 237 patients (24%) died of a definite cardiac cause according to available autopsy reports. The prevalence of cardiovascular risk factors, including diabetes, hypertension, hypercholesterolemia, and current smoking was higher in cases than in controls. A history of circulatory disease, pulmonal disease, and renal disease, was also more often seen in cases than in controls. Finally, the general condition of cases prior to surgery, as reflected by the ASA classification, was worse compared to controls.

Table 1. Baseline characteristics of cases and controls

	Cases	Controls	
No. of patients	989	1879	
Type of surgery §			
Low risk, %	8	6	
Low-intermediate risk, %	20	22	
Intermediate-high risk, %	72	72	
Age, years	63.5 (48, 74)	63.3 (47, 74)	
Male gender, %	61	62	
Medical risk factors			
Diabetes mellitus, %	25	9	‡
Hypertension, %	19	14	‡
Hypercholesterolemia, %	16	6	‡
Family history of coronary disease, %	2	1	
Current smoking, %	14	8	‡
Angina pectoris, %	13	7	‡
Myocardial infarction, %	26	8	‡
Heart failure, %	11	2	‡
Percutaneous coronary intervention, %	2	1	
Coronary artery bypass grafting, %	3	3	
Peripheral vessel disease, %	11	5	‡
Cerebro-vascular disease, %	7	5	*
Chronic obstructive pulmonary disease, %	13	8	‡
Renal insufficiency, %	34	14	‡
ASA classification, %			‡
I	13	47	
II	18	31	
III	41	21	
IV	28	1	

* P<0.05; † P<0.01; ‡ P<0.001

§ According to the Amercian Heart Association/American College of Cardiology classification: high risk = aortic; intermediate risk = abdominal; ear, nose, throat; neurologic; orthopedic; pulmonary; renal transplant; urologic; vascular, excluding aortic and carotid; low risk = breast; carotid; dental; endocrine; eye; gynecology; reconstructive. We have demonstrated,[1] that within the intermediate risk group, patients undergoing orthopedic or urologic surgery had significantly lower risk than patients undergoing other types of surgery. Therefore, we labeled orthopedic and urologic procedures as low-intermediate risk, and the remaining procedures as intermediate-high risk. Note that we excluded any vascular surgery, therefore we don't have any patients in the high risk category.

Propensity of beta-blocker or statin use

The most relevant characteristics that were associated with beta-blocker use included hypertension (adjusted OR 4.8; χ^2-value 76), a history of angina pectoris (OR 4.5; χ^2-value 58), ASA-classification III or IV (OR 2.9; χ^2-value 22), the use of oral anticoagulant medication (OR 2.5; χ^2-value 15), and a history of heart failure (OR 0.34; χ^2-value 11). The most relevant characteristics that were associated with statin use included a history of CABG (adjusted OR 5.0; χ^2-value 21), the use of oral anticoagulant medication (OR 3.3; χ^2-value 18), the

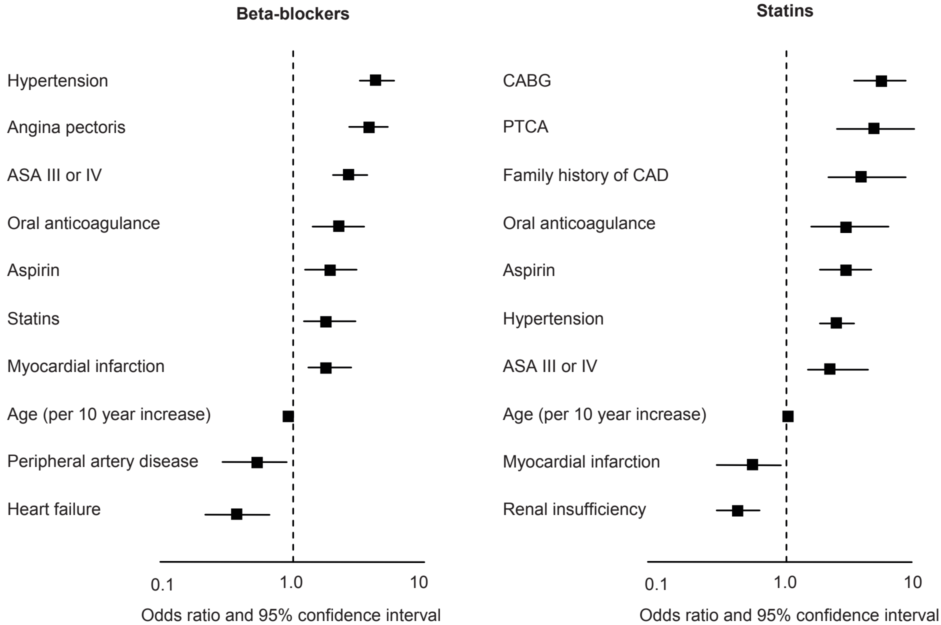

Figure 1. Propensity scores of the likelihood of beta-blocker and statin use in the study population

use of aspirin (OR 3.2; χ^2-value 17), hypertension (OR 2.5; χ^2-value 15), and renal insufficiency (OR 0.37; χ^2-value 13). The propensity scores (figure 1) were highly predictive of the likelihood of beta-blocker (C-statistic 0.90) or statin use (C-statistic 0.85). However, the Hosmer-Lemeshow test showed a significant value for the beta-blocker propensity model (P-value 0.001), indicating that its calibration was not optimal.

Relation between beta-blocker and statin use and perioperative mortality

Data on perioperative beta-blocker use was lacking in 1 case and in 4 controls. Beta-blocker use was less common in cases than in controls (61 cases [6.2%] and 153 controls [8.2%]; P-value 0.05). After adjustment for multiple confounders and the propensity of their use, beta-blockers were associated with a significant 59% relative reduction in perioperative mortality (adjusted OR 0.41 and 95% CI 0.28 to 0.59). Data on perioperative statin use was missing in 2 cases and in 4 control patients. Statins were significantly less commonly used by cases than controls (24 cases [2.4%] and 103 controls [5.5%]; P-value <0.001). After adjustment for multiple confounders and the propensity of their use, statins appeared associated with 60% reduced mortality (adjusted OR 0.40 and 95% CI 0.24 to 0.68).

The observed relations between beta-blocker and statin use and perioperative mortality were significantly modified by each other drug (P-value for interaction <0.001). In the absence of statins, beta-blockers were associated with 66% reduced mortality (adjusted OR 0.34 and 95% CI 0.23-0.50), whereas in the presence of statins, beta-blockers were not associated with reduced mortality (adjusted OR 2.0 and 95% CI 0.74 to 5.7). Similarly, in

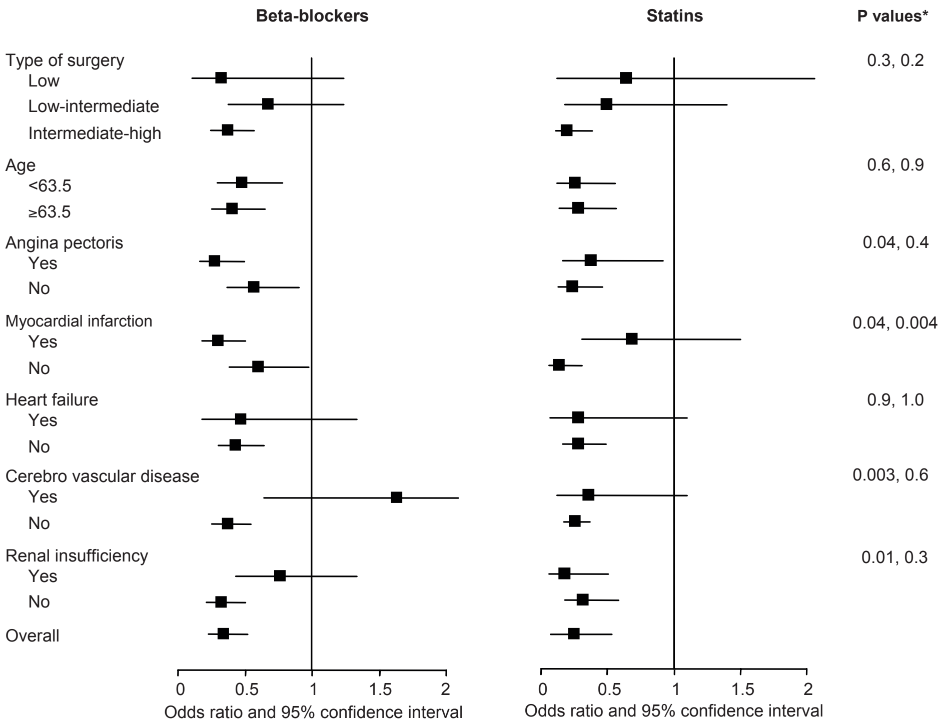

Figure 2. Odds Ratios for perioperative mortality in relation to beta-blocker and statin use in selected subgroups of patients

Odds ratios are adjusted for the propensity of beta-blocker (statin) use and the following variables that appeared related (P-value <0.157; see method section) with perioperative mortality: age, gender, diabetes, family history of coronary disease, current smoking, history of angina pectoris, myocardial infarction, heart failure, peripheral vessel disease, cerebro-vascular disease, chronic obstructive pulmonary disease, renal insufficiency, and ASA classification.

* P values for homogeneity of odds ratios in subgroups of patients using beta-blockers and statins respectively.

the absence of beta-blockers, statins were associated with 73% reduced mortality (adjusted OR 0.27 and 95% CI 0.14 to 0.51), whereas in the presence of beta-blockers, statins were not associated with reduced mortality (adjusted OR 1.3 and 95% CI 0.52 to 3.2). It should be noted, however, that there were only 9 cases and 29 control patients who used both agents simultaneously.

Although there was evidence of heterogeneity in treatment effect in relation to specific patient characteristics, beta-blockers and statins were consistently associated with reduced mortality in the specified strata (figure 2). Patients with a history of cerebro-vascular disease formed the single exception. The mortality reduction associated with beta-blocker use was particularly profound in patients with a history of angina pectoris or myocardial infarction, and in patients with normal renal function. Statin use was associated with a larger mortality reduction in patients without than in those with prior myocardial infarction.

DISCUSSION

In this case-control study of patients undergoing noncardiac, nonvascular surgery, beta-blockers and statins were individually associated with reduced perioperative mortality. As compared with nonusers, beta-blocker users as well as statin users had a 2.5 fold lower risk of mortality. These results are consistent with case-control studies and randomized clinical trials in patients undergoing major noncardiac, vascular surgery.[7-12]

Patients scheduled for low- or intermediate risk surgery represent the majority of the surgical population. The results of our study showed a beneficial effect on perioperative mortality of beta-blockers in the entire strata of surgical procedures. In a recently published paper, Lindenauer et al. reported the results of a large retrospective cohort study on perioperative beta-blocker therapy and perioperative mortality reduction in patients undergoing major noncardiac surgery.[11] Perioperative beta blockade was associated with significantly reduced in-hospital mortality rates in higher risk subgroups of the total cohort. In contrast, perioperative beta blockade was associated with significantly increased in-hospital mortality rates among the lowest risk patients. The protective effect of perioperative beta-blockade in our patient population was consistent in all types of surgical procedures, including low-risk and low-intermediate risk surgery. The possible harmful effect of beta blocker therapy in low-risk patients undergoing major surgical procedures, found by Lindenauer and colleagues, could be contributed to the design of that study. Patients who were treated with a beta-blocker on the first or second hospital day were assumed to be on prophylaxis. However, this seems unlikely in lower risk patients. In these patients beta-blocker therapy might have been a response to a cardiovascular complication, rather than the prevention of one.[13]

The protective effect of beta-blocker therapy is caused by perioperative heart rate control and reduced myocardial contractility, resulting in a prolonged coronary diastolic filling time and a subsequent correction of the myocardial oxygen demand and supply mismatch in patients with fixed coronary artery lesions. Our results support this cardioprotective mechanism. In the subgroup of patients with an established diagnosis of coronary artery disease (previous myocardial infarction, history of angina pectoris) a stronger effect in perioperative mortality reduction on beta-blocker therapy was present, compared to those without symptomatic disease (figure 2).

A considerable proportion of the surgical population has undiagnosed, asymptomatic coronary artery disease, characterized by non-blood flow limiting, vulnerable atherosclerotic plaques.[14] Acute coronary plaque rupture, due to an increased stress response to surgery, may be the first expression of cardiac disease. In our study, the estimate of treatment effect favored statin therapy in all prognostically relevant subgroups. However, our data suggested a larger perioperative mortality reduction in patients without previously diagnosed coronary artery disease (figure 2). These patients could have silent cardiac disease, characterized by non-bloodflow limiting vulnerable plaques. The beneficial effect from statin therapy can be ascribed to stabilization of these plaques, a result of the anti-inflammatory action and reversal of endothelial dysfunction.

There was an interaction between beta-blocker use and statin therapy. In the presence of each other drug, both beta-blockers and statins failed to show a statistically significant effect. However, a protective effect in simultaneous beta-blocker and statin use could not be excluded on the basis of our results. A part of the interaction between both drugs can be explained by a similar treatment effect between statins and beta-blockers. Anti-inflammatory effects after prolonged beta-blocker therapy have previously been described in long time users.[15] Nevertheless, the amount of patients who used both drugs simultaneously (9 cases and 29 controls) was small and data on therapy duration and dose were not available.

Physicians should continue beta-blocker and / or statin therapy in their patients undergoing low- and intermediate risk surgery. The results of our study confirm the individual protective effects of both therapies. Also, withholding therapy in chronic beta-blocker users results in a rebound effect, causing tachycardia and hypertension, with possible myocardial ischemia.[16] Future studies are needed to provide Information on duration, dose and effect of prophylactic beta-blocker and statin use in patients undergoing low- and intermediate risk types of surgery.

Our study has several limitations that are common with any case-control study relying on retrospective data collection. Firstly, we should mention that cases and controls might have been misclassified because of inappropriate information on vital status at discharge, although we consider this highly unlikely. Secondly, and this is a more realistic scenario, information on beta-blocker and statin use might have been missed, probably differently so in cases and controls because of observer bias prejudice. Thirdly, multivariable adjustment for potential confounders is obviously limited to the available data elements, and unknown, unmeasured confounders might still be present. Consequently, our estimates of the beneficial effects of beta-blockers and statins might be overestimated. Therefore, we would like to emphasize that this early evidence needs confirmation by adequately powered randomized clinical trials.

Conclusion

This case-control study provides evidence that beta-blockers and statins are individually associated with a reduction of perioperative mortality in patients undergoing noncardiac, nonvascular surgery.

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SUMMARY AND CONCLUSIONS

In this thesis, the value of preoperative testing in cardiac risk stratification of patients scheduled for noncardiac surgery, is described.

In chapter one, the predictive performance of Lee et al's cardiac risk index for cardiovascular mortality in patients undergoing noncardiac surgery is validated in the surgical population of the Erasmus Medical Center between 1991-2000. In total, 108,613 noncardiac surgical procedures were analyzed to evaluate trends in the incidence of fatal perioperative cardiovascular complications over time, study the relationship between patient characteristics, type of surgery and perioperative adverse cardiac events, and determine the value of a well established cardiac risk index in predicting cardiovascular death in this population. There were no significant changes in cardiovascular mortality during the study period in either men or women. A total of 1,877 patients (1.7%) had perioperative death, and 543 (0.5%) had cardiovascular death. The Lee index yielded cardiovascular death rates of 0.3%, [255/75352], 0.7% [196/28892], 1.7% [57/3380] and 3.6% [35/969] for scores of 0, 1, 2 and ≥3. Corresponding odds ratios were 1 (reference), 2.0, 5.1 and 11.0, with no overlap for the 95% confidence interval of each score. The Lee index had an admirable performance to predict cardiovascular mortality (C-statistic 0.63). However, the simple classification of surgical related risk as high/not high, and the absence of age as a cardiac risk factor was suboptimal. If more detailed information regarding the type of surgery, and age, was added, then the C-statistic improved to 0.85. In conclusion, predicting cardiovascular risk in noncardiac surgery is most accurately done by an index based on detailed information on the type of surgery, in addition to patient characteristics.

Based on the results of the first chapter, a newly derived perioperative mortality risk index for patients scheduled for noncardiac surgery, is presented in chapter two. In an observational cohort study of more than one million noncardiac surgical procedures in the Dutch population, perioperative mortality and its relation with patient characteristics and type of surgery was examined. Age, gender, diabetes mellitus, angina pectoris, myocardial infarction, heart failure, cerebrovascular disease, renal disease, cardiac valve abnormality, cardiac arrhythmia, and pulmonary disease were independently associated with mortality. Type of surgery was the major determinant of mortality in noncardiac surgery. In a derivation cohort of 594,132 procedures, a risk index based on a detailed surgery-specific risk classification, in addition to clinical risk factors, was derived. In the validation cohort of 594,631 procedures, our risk index had excellent discriminative ability to identify patients at risk for perioperative mortality (C-index 0.89).

In addition to surgery-specific risk and patient characteristics, preoperative electrocardiography is commonly performed in cardiac risk assessment to further determine the risk level of patients undergoing noncardiac surgery. Chapter three describes the additional prognostic value of routine electrocardiography in preoperative testing in 23,036 patients undergoing 28,457 surgical procedures at the Erasmus MC between 1991-2000. In-hospital cardiovascular death was observed in 199 / 28,457 (0.7%) cases. An ECG with atrial fibrillation, left or right bundle branch block, left ventricular hypertrophy, premature ventricular complexes, a pacemaker rhythm, Q-wave or ST changes was classified as abnormal. Information obtained from the preoperative ECG was an independent predictor of perioperative cardiovascular mortality (adjusted odds ratio 4.5 and 95% confidence interval 3.3 to 6.0). In addition to clinical characteristics and type of surgery, preoperative electrocardiography results provided prognostic information for the prediction of perioperative cardiovascular mortality. However, in patients undergoing low risk or low-intermediate risk surgery, the absolute difference in the incidence of cardiovascular death between those with and without electrocardiography abnormalities was minimal (0.5%). As a result, the usefulness of its routine use in lower risk surgery can be questioned.

In chapter four, the analysis of preoperative electrocardiogram characteristics is continued. In the non-surgical cardiac population, prolonged QTc interval on the 12-lead electrocardiogram has previously been associated with an increased cardiovascular risk of mortality in patients with (a)symptomatic cardiac disease. To examine the association between QTc interval, and perioperative cardiac death in patients scheduled for noncardiac surgery, we retrieved information on the numerical electrocardiogram characteristics, patient characteristics and type of surgery of 13,417 patients. Perioperative cardiovascular death occurred in 113 (0.5%) patients. After adjustment for clinical and other ECG data, QTc prolongation was an independent predictor of cardiovascular mortality (adjusted odds ratio 1.16 and 95% confidence interval 1.11-1.21). This specific electrocardiogram characteristic can be used as a prognostic factor for perioperative cardiovascular mortality in noncardiac surgical patients.

Diabetes mellitus is strongly related to cardiac disease and is a well-known cardiac risk factor in noncardiac surgery. The relationship between diabetes and cardiovascular disease is thought to begin early in the progression from normal glucose tolerance to impaired glucose tolerance to diabetes. In a case control study of patients undergoing non-vascular, noncardiac surgery, chapter five evaluates the value of routine preoperative glucose testing to identify (a)symptomatic hyperglycaemic patients at risk for adverse perioperative outcome. In this study of 904 cases and 1,247 controls, a cardiovascular complication was the primary cause of death in 207 (23%) cases. In cases, prediabetic and diabetic glucose levels were more frequently seen compared to controls (57% and 13% versus 50% and 5%; P-value <0.001). After adjustment for a broad range of potential confounders, prediabetic glucose levels were associated with a 3.0-fold increased cardiovascular mortality risk compared to normoglycemic levels (adjusted odds ratio 3.0 and 95% confidence interval 1.7-5.1). Diabetic glucose levels were associated with a 4.0-fold increased cardiovascular mortality risk (adjusted odds ratio 4.0 and 95% confidence interval 1.3-12). Patients on anti-diabetic medication showed a reduction in perioperative all-cause mortality as well as cardiovascular mortality.

In chapter six, the relation between preoperative glucose levels and adverse cardiac events is further clarified. In type II diabetic patients undergoing major vascular surgery, preoperative HbA_{1c} levels were used to assess the relation between preoperative hyperglycemia and perioperative (non)fatal cardiac events. Preoperative HbA_{1c} values ≥7.6% were associated with increased 30-day all cause mortality and 30-day cardiac death or MI. Multivariate analysis showed an increased risk of 41% for every percent of HbA_{1c} increment. Although glucose management was equal for all patients, those with a higher (preoperative) HbA_{1c} had significantly higher perioperative glucose values.

The final chapter of this thesis, chapter seven, discusses the use of pharmacological therapy to possibly reduce perioperative cardiac risk. Both beta-blockers and statins have previously been associated with improved outcome in high risk major noncardiac surgery. In the lower risk surgical population, data on this matter is lacking. In a case control study of 989 cases and 1,879 matching controls undergoing non-vascular, noncardiac surgery, beta-blockers were less often used in cases than in controls (6.2% versus 8.2%; P=0.05), as were statins (2.4% versus 5.5%; P<0.001). After adjustment for the propensity of beta-blocker use / statin use and cardiovascular risk factors, beta-blocker use was associated with a 59% mortality reduction and statin therapy was associated with a 60% mortality reduction. However, in a small group of patients in the presence of each other drug no mortality reduction was seen.

SAMENVATTING EN CONCLUSIES

Dit proefschrift beschrijft de voordelen van preoperatief testen bij het inschatten van het cardiale risico van patiënten die niet-cardiale chirurgie ondergaan.

In het eerste hoofdstuk wordt in een chirurgische populatie uit het Erasmus Medisch Centrum tussen 1991-2000 de voorspellende waarde gevalideerd van Lee's cardiale risico-index voor perioperatieve cardiovasculaire mortaliteit. In totaal werden er 108.613 chirurgische procedures geanalyseerd om de trends in de incidentie van fatale cardiale complicaties, de relaties tussen patiëntenkarakteristieken, het type chirurgie en cardiale complicaties en de voorspellende waarde van deze gerenommeerde risico-index voor cardiovasculaire dood te bepalen. Tijdens de studieperiode werden geen significante veranderingen waargenomen in de incidentie van cardiovasculaire dood bij mannen en vrouwen. In totaal overleden 1.877 (1,7%) patiënten tijdens de operatieve fase en hadden 543 (0,5%) patiënten een cardiovasculair incident als doodsoorzaak. De Lee scores 0, 1, 2 en ≥3 kwamen overeen met respectievelijk een cardiovasculaire mortaliteitsincidentie van 0,3%, [255/75352], 0,7% [196/28892], 1,7% [57/3380] en 3,6% [35/969]. De overeenkomstige relatieve risico's waren 1 (referentiewaarde), 2,0, 5,1 en 11,0 zonder overlapping tussen de 95% betrouwbaarheidsintervallen van de verschillende scores. De Lee index had een goede voorspellende waarde voor cardiovasculaire mortaliteit (C-statistiek 0,63). De eenvoudige classificatie van het chirurgisch gerelateerd risico in hoog en niet hoog en de afwezigheid van de cardiale risicofactor "leeftijd" waren echter suboptimaal. Na het toevoegen van gedetailleerde informatie betreffende het type chirurgie en de leeftijd van de patiënt verbeterde de C-statistiek naar 0,85. Geconcludeerd kan worden dat het voorspellen van cardiovasculair risico in niet-cardiale chirurgie het meest nauwkeurig gebeurt door middel van een index die gebaseerd is op gedetailleerde informatie omtrent het type chirurgie en de karakteristieken van de patiënt.

Op basis van de resultaten van het eerste hoofdstuk wordt in hoofdstuk twee een nieuw ontwikkelde risico-index voor het voorspellen van perioperatieve mortaliteit bij chirurgische patiënten gepresenteerd. In een observationele cohortstudie van meer dan één miljoen chirurgische ingrepen uit de Nederlandse populatie werd de relatie tussen perioperatieve mortaliteit, de karakteristieken van de patiënt en het type chirurgie onderzocht. Leeftijd, geslacht, diabetes mellitus, angina pectoris, myocard infarct, hartfalen, cerebrovasculaire ziekte, nierziekte, cardiale klepafwijkingen, cardiale ritmestoornissen en longziekte waren alle onafhankelijk geassocieerd met perioperatieve mortaliteit. Het type chirurgie bleek de belangrijkste voorspeller van mortaliteit tijdens de operatieve fase. Uit een cohort van 594.132 procedures werd een risico-index ontwikkeld gebaseerd op een gedetailleerde chirurgische classificatie en de klinische risicofactoren van de patiënt. De risico-index werd gevalideerd in een cohort van 594.631 procedures en had een uitstekend onderscheidend vermogen om patiënten met een verhoogd mortaliteitsrisico tijdens de operatieve fase te identificeren (C-statistiek 0,89).

Naast het chirurgisch gerelateerd risico en risicofactoren van de patiënt wordt een pre-operatief electrocardiogram (ECG) regelmatig vervaardigd als onderdeel van de inschatting van het cardiaal risico van de chirurgische patiënt. Hoofdstuk drie beschrijft de toegevoegde waarde van het routinematig vervaardigen van een ECG als onderdeel van preoperatief testen bij 23.036 patiënten die tussen 1991-2000 28.457 procedures ondergingen in het Erasmus Medisch Centrum. In 199 van de 28.457 gevallen werd een cardiovasculaire doodsoorzaak tijdens de ziekenhuisopname aangetroffen. Een ECG met atrium fibrillatie, linker- of rechter bundeltakblok, links ventriculaire hypertrofie, premature ventriculaire complexen, pacemaker ritme, Q-golf of ST veranderingen werd geclassificeerd als afwijkend. Informatie betreffende het preoperatieve ECG was een onafhankelijke voorspeller voor cardiovasculaire dood tijdens de operatieve fase (gecorrigeerd relatief risico 4,5 en 95% betrouwbaarheidsinterval 3,3 tot 6,0). Naast de klinische karakteristieken van de patiënt en het type chirurgie had het preoperatieve ECG aanvullende voorspellende waarde voor cardiovasculaire dood tijdens de operatieve fase. Bij patiënten die laag- of laaggemiddelde risico-ingrepen ondergingen was het absolute verschil in cardiovasculaire mortaliteit tussen patiënten met en zonder ECG afwijkingen echter minimaal (0,5%). De toegevoegde waarde van het routinematig vervaardigen van een preoperatief ECG in deze populatie kan dus in twijfel getrokken worden.

In hoofdstuk vier wordt de analyse van de waarde van het preoperatieve electrocardiogram gecontinueerd. In de niet-chirurgische populatie is een verlengd QTc interval op het 12-afleidingen ECG geassocieerd met een verhoogd cardiovasculair mortaliteitsrisico in patiënten met (a)symptomatisch cardiaal lijden. Om de relatie tussen QTc interval en perioperatieve cardiale dood in chirurgische patiënten te bepalen werden de ECG karakteristieken, de risicofactoren en het type chirurgie van 13.417 patiënten achterhaald. Een cardiovasculaire doodsoorzaak vond plaats in 113 (0,5%) patiënten. Na correctie voor risicofactoren van de patiënt en overige ECG karakteristieken lieten de resultaten zien dat QTc duur gecorreleerd was met cardiovasculaire dood tijdens de ingreep. Deze specifieke ECG afwijking kan gebruikt worden om fatale cardiovasculaire complicaties bij patiënten tijdens de chirurgische fase te voorspellen.

Diabetes mellitus is sterk gerelateerd aan hart -en vaatziekten en is een bekende perioperatieve risicofactor. Het ontstaan van hart- en vaatziekten in patiënten met diabetes mellitus begint hoogstwaarschijnlijk vroeg in de asymptomatische fase van beginnende glucose intolerantie, tot de daadwerkelijk ziekte gediagnosticeerd wordt. Hoofdstuk vijf evalueert de waarde van preoperatieve screening door middel van routinematige glucosebepalingen op asymptomatische hyperglycemie bij chirurgische patiënten met een verhoogd cardiaal risico. In deze studie van 904 cases en 1.247 controle patiënten, die een niet-cardiale, niet-vasculaire ingreep ondergingen, was een cardiovasculaire complicatie de belangrijkste doodsoorzaak in 207 (23%) gevallen. Cases werden op basis van hun preoperatieve glucosewaarde vaker gediagnosticeerd als zijnde prediabetes en diabetes in vergelijking met controle patiënten (57% en 13% versus 50% en 5%; P-waarden <0,001). Na correctie voor een groot aantal factoren die mogelijk van invloed was op de resultaten hadden patiënten met prediabetes een 3,0 maal verhoogde kans op cardiovasculaire mortaliteit tijdens de operatie in vergelijking met patiënten met normale glucosewaarden (gecorrigeerd relatief risico 3,0 en 95% betrouwbaarheidsinterval 1,7-5,1). Patiënten met diabetes waren geassocieerd met een 4,0 maal verhoogd cardiovasculair mortaliteitsrisico (gecorrigeerd relatief risico 4,0 en 95% betrouwbaarheidsinterval 1,3-12). Bij patiënten die medicatie voor diabetes mellitus gebruikten werd een duidelijk verminderd perioperatief cardiovasculair mortaliteitsrisico waargenomen.

In hoofdstuk zes wordt de relatie tussen preoperatieve glucosewaarden en cardiale complicaties verder opgehelderd. Bij 304 patiënten met type II diabetes mellitus die een grote vaatingreep ondergingen werden HbA_{1c} spiegels gebruikt om de relatie tussen preoperatieve hyperglycemie en perioperatieve cardiale complicaties te bepalen. De gemiddeld HbA_{1c} waarde was 6,8%. HbA_{1c} spiegels ≥7,6% waren geassocieerd met een verhoogd risico op perioperatieve dood of myocard infarct. In de multivariaat analyse leidde elke één procentstijging van het HbA_{1c} tot een stijging van het cardiaal risico met 41%. Ondanks een vergelijkbaar perioperatief glucosebeleid bij alle patiënten hadden patiënten met een preoperatieve hogere HbA_{1c} waarde hogere glucosewaarden tijdens de operatie.

In het laatste hoofdstuk van dit proefschrift wordt het gebruik van farmacologische therapie tijdens de operatie om het aantal cardiale complicaties te verlagen bediscussieerd. Eerder verrichte studies hebben aangetoond dat zowel statines als bètablokkers geassocieerd zijn met een vermindering van het aantal cardiale complicaties bij patiënten die hoogrisico chirurgie ondergaan. In de populatie met een lager risico is omtrent dit onderwerp onvoldoende data beschikbaar. In een casecontrol studie van 989 cases en 1.879 controle patiënten die chirurgie met een lager risico ondergingen in het Erasmus Medisch

Centrum tussen 1991-2000 werden bètablokkers en statines minder gebruikt in cases dan bij controlepatiënten (6,2% versus 8,2%; P-waarde 0,05 en 2,4% versus 5,5%; P-waarde <0,001). Na correctie voor de patiëntenkarakteristieken geassocieerd met betablokker- en statinegebruik en cardiale risicofactoren konden beide medicamenten geassocieerd worden met een verlaging van de perioperatieve mortaliteit (respectievelijk 59% en 60%). In een kleine groep patiënten die beide medicamenten echter tegelijkertijd gebruikten werd geen afname van de mortaliteit gezien.

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CURRICULUM VITAE

Peter Noordzij werd op 11 maart 1975 geboren in Rotterdam en woonde gedurende zijn jeugd in Klaaswaal, een dorpje gelegen in de Hoekse Waard. Het middelbaar onderwijs volgde hij aan de Rijksscholengemeenschap in Oud-Beijerland, waar hij in 1993 zijn VWO diploma behaalde.

Nadat hij uitgeloot werd voor de studie Geneeskunde, woonde hij het daaropvolgende jaar als uitwisselingsstudent in de Verenigde Staten. In 1994 behaalde hij daar zijn diploma aan Washita Heights Highschool in Colony, Oklahoma.

In de zomer van 1994 begon Peter met de studie Geneeskunde aan de Erasmus Universiteit in Rotterdam. Van 1998-1999 werd deze studie tijdelijk onderbroken voor een voorzittersfunctie van het dagelijks bestuur van studentenvereniging S.S.R.-Rotterdam. Om zijn doctoraalfase af te sluiten, werkte hij in 2000 gedurende zes maanden aan een afstudeeronderzoek onder begeleiding van Dr. W. Ang op de afdeling Immunologie aan de Erasmus Universiteit. Voor deze scriptie ontving hij de Gerrit Jan Mulder Prijs. Na een afsluitend co-schap Tropengeneeskunde in Sesheke, Zambia, behaalde hij in juni 2002 het artsexamen cum laude.

Peter deed zijn eerste werkervaring op in 2003 bij Prof.dr. G.J. Scheffer op de afdeling Intensive Care in het Amphia ziekenhuis te Breda, waarna hij op 1 januari 2004 bij Prof.dr. J. Klein begon met de opleiding Anesthesiologie in het Erasmus Medisch Centrum. In dezelfde periode startte hij zijn promotie onderzoek onder begeleiding van prof.dr. D. Poldermans.

Op 1 januari 2009 zal hij de opleiding tot anesthesioloog afronden, waarna hij als fellow Intensive Care werkzaam zal zijn bij Prof.dr. D. Zandstra in het Onze Lieve Vrouwe Gasthuis te Amsterdam. Naast zijn opleidingswerkzaamheden is Peter betrokken als instructeur bij de stichting ATLS Nederland.