Thromboembolic Events in the Perioperative Period

Felix van Lier

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Thromboembolic Events in the Perioperative Period

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Promotiecommissie:

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

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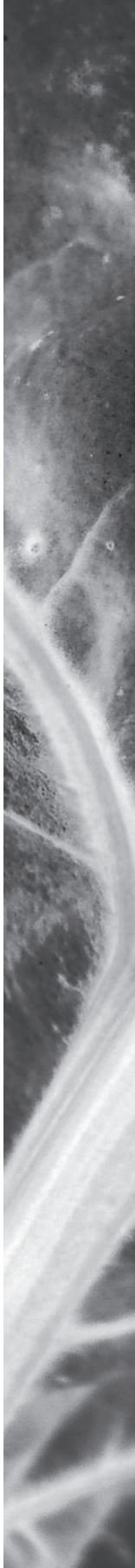
Preface



Annually more than 1.5 million people are scheduled for some form of noncardiac surgery in the Netherlands. Perioperative adverse cardiovascular events such as myocardial infarction, arrhythmias, stroke or pulmonary embolism are a major cause of perioperative morbidity and mortality. It is estimated that around 3% of the patients undergoing major noncardiac surgery experience a major adverse cardiac event and approximately 1% of these patients die because of a cardiovascular cause.

The risk of postoperative complications is influenced by preoperative factors, intraoperative events and postoperative aspects of care. Depending on the condition of the patient prior to surgery and the degree of invasiveness of the procedure, a risk-benefit analysis should be made before patients are presented for surgery. If the risks exceed the benefits, the indication for the operation should be reevaluated; otherwise the condition of the patient should be optimized using various pharmacologic and nonpharmacologic methods.

Cardiovascular risk assessment and risk reduction

The first step in optimizing care is identifying those patients with an increased risk for adverse cardiovascular events in the perioperative period. Based on the condition of the patient prior to surgery, i.e. the presence and severity of co-morbidities, various risk identification models can be used to identify the patient at risk. The second step is that once an increased risk has been established, risk reduction strategies should be initiated. Beta-blocker therapy, aspirin and HMG-CoA reductase inhibitors (statins) have shown to decrease perioperative morbidity and mortality in various subgroups of surgical patients. The final step is optimizing care during the postoperative period. Risk reduction therapy should not be limited to the perioperative period but should be extended well into the postoperative period. High risk patients remain at risk for their entire life and pose a thread for short and long-term adverse cardiovascular complications.

Thromboembolic events in the perioperative period

Thromboembolic events are a group of diseases which consist of arterial or venous thromboembolic diseases. Venous thromboembolic events which include deep vein thrombosis and pulmonary embolism are common in the postoperative period. Perioperative immobilization, coagulation abnormalities, and venous injury all contribute to the development of postoperative venous thrombosis. Arterial thromboembolic events are mainly related to chronic inflammation of the vascular wall (atherosclerosis) and include angina pectoris, arterial thrombosis, cerebral infarct, cerebral ischemia, cerebrovascular accident, myocardial infarction, and myocardial ischemia.

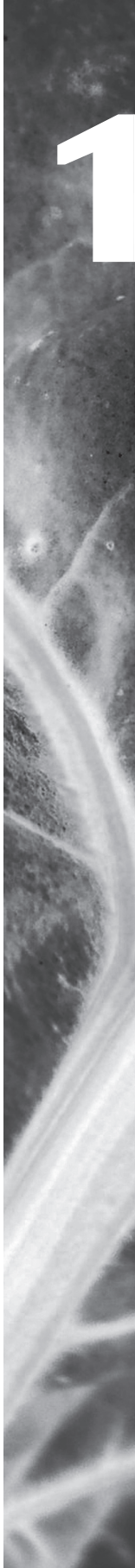
Pathophysiology of thromboembolic events

Venous thromboembolic events occur because of abnormalities of blood flow, blood vessel wall, and blood clotting components, known collectively as Virchow's triad. Abnormalities of blood flow or venous stasis normally occur after prolonged immobility

or confinement to bed. Venous obstruction can arise from external compression by enlarged lymph nodes, bulky tumors, or intravascular compression by previous thromboses. Cancers, particularly adenocarcinomas and metastatic cancers, are also associated with increased venous thromboembolism.
Arterial thromboembolic events are linked to endothelium dysfunction and inflammation of the endothelium wall, the pathophysiology behind atherosclerosis. The pathogenesis of atherosclerosis involves a complex series of events, similar to a chronic inflammatory process, with the formation of atherosclerotic plaque as the end result. Arterial thrombi consist mainly of platelets and are induced by arterial plaque ruptures which tend to occur at sites where shear rates are high such as in coronary, extracranial cerebral and lower extremity arteries.

Outline of the thesis

The first chapter provides an overview of cardiovascular risk identification and modification in the perioperative period. In this chapter the identification of patients at risk using various risk models and biomarkers is described. Noninvasive and invasive preoperative (stress) testing as well as preoperative coronary revascularization is discussed. Finally short- and long-term risk reduction strategies such as beta-blocker therapy, statins and aspirins are evaluated.
Chapter 2 summarizes the findings on perioperative stroke in noncardiac surgery. This chapter describes the pathophysiology of perioperative stroke and focuses on important issues regarding the initiation of beta-blocker therapy preoperative.
Chapter 3 and 4 evaluate the risk for perioperative stroke in patients on beta-blocker therapy. Risk factors for perioperative stroke are discussed. Perioperative stroke is evaluated in patients on chronic beta-blocker use as well as in patients where beta-blockers are initiated prior to surgery.
Intraoperative cardiac arrests are discussed in chapter 5. In a case-control study of surgical patients at the Erasmus Medical Center, the relationship between preoperative cardiovascular risk factors and intraoperative cardiac events is analyzed.
In chapter 6 a risk model for postoperative pulmonary embolism after noncardiac surgery is developed. This chapter highlights the importance of on time thromboprophylaxis in relation to adverse postoperative venous thromboembolic processes.
Chapter 7 describes the value of statins in the (postoperative) intensive care period. Proper use of statins in the postoperative period after both cardiac and noncardiac surgery is discussed. The second part of the chapter focuses on potential indications for statin therapy in the near future. The indication of statins has expanded to other patient categories often admitted to an intensive care unit. Therefore statin therapy may be the next logical step in the search for adjuvant therapy in common intensive cares diseases.
The final chapter, chapter 8, discusses the value of epidural analgesia in addition to general anesthesia in COPD patients undergoing major abdominal surgery. Epidural analgesia is associated with improved outcome in surgical patients. However, since epidural analgesia might worsen postoperative respiratory function, it is unclear whether COPD patients benefit from epidural analgesia. This study aimed to examine the effects of epidural analgesia in addition to general anesthesia in COPD patients scheduled for major abdominal surgery.



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Perioperative Cardiovascular Risk Identification and Modification

Felix van Lier MD, Louis van de Ven MD PhD, Don Poldermans MD PhD

Textbook:

Myocardial Ischemia: Causes, Symptoms and Treatment

Nova Publishers

Introduction

Cardiac complications are a major cause of perioperative morbidity and mortality in patients undergoing noncardiac surgery. It is estimated that the incidence of such complications varies between 0.5% and 1.0%. Worldwide, about 100 million adults undergo some form of noncardiac surgery each year, and so between 500,000 and 1,000,000 people will suffer from perioperative cardiac complications; one of four of them will die from this cause. In particular patients undergoing vascular surgery are prone to develop perioperative cardiovascular complications as they have a high-generalised atherosclerotic burden. In order to prevent the devastating effects of perioperative cardiovascular complications, it is of critical importance to identify those at increased risk and treat them accordingly. The first part of this chapter covers current knowledge on preoperative risk assessment. Current risk indices, the value of additional testing as well as new preoperative cardiac risk makers are discussed. In the second part of this chapter risk reduction strategies are discussed, including beta-blocker therapy, statins, aspirins and preoperative prophylactic coronary revascularization in noncardiac surgery. The final part of this chapter will focus on long-term cardiovascular risk reduction.

Defining cardiac complications

Several cardiac events have been considered as endpoints in clinical studies on perioperative cardiovascular complications including: unstable angina pectoris, congestive heart failure, arrhythmias, detection of serum biomarkers, myocardial ischemia, nonfatal myocardial infraction and cardiac death. Considering this broad definition of cardiac complications, studies on perioperative cardiac complications might be difficult to assess in a uniform way, though 'hard' endpoints (myocardial infarction and cardiac death) make comparison much easier. The incidence of cardiac complications might therefore rather be a crude estimation of the true incidence, depending on the definition used.

Incidence of cardiac complications

Given the high incidence of Coronary Artery Disease (CAD) in vascular surgery patients (i.e. 92%), knowledge about perioperative cardiac complications has mostly been gained from patients undergoing vascular surgery. In a study by Landesberg et al. [1] 447 patients, scheduled for different types of vascular surgery, were monitored on the first three postoperative days using continuous 12-lead ECG recording, cardiac troponin T and I and CK/CK-MB measurement. Up to 23.9% of the patients experienced cardiac troponin T or I release, while perioperative ST-segment changes were detected in 14.8% of the patients. In the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation) II study by Poldermans et al. [2] 1476 patients scheduled for elective open abdominal aortic or infragenuial arterial reconstruction were monitored for cardiac events during hospital stay after surgery. Twelve-lead electrocardiography and serum troponin-T levels were routinely assessed in the postoperative period. Cardiovascular death, defined as death caused by acute myocardial infarction, significant cardiac arrhythmias, congestive heart failure or as a death occurring suddenly without another

explanation, occurred in 27 (1.8%) patients. Myocardial infarction was diagnosed in 39 (2.6%) of the patients while elevated serum troponin-T levels were present in 354 (24%) of the patients. The magnitude of these adverse cardiac events can be viewed as an iceberg; only a small part of cardiovascular complications are directly visible, while most lie hidden below the water surface (figure 1).

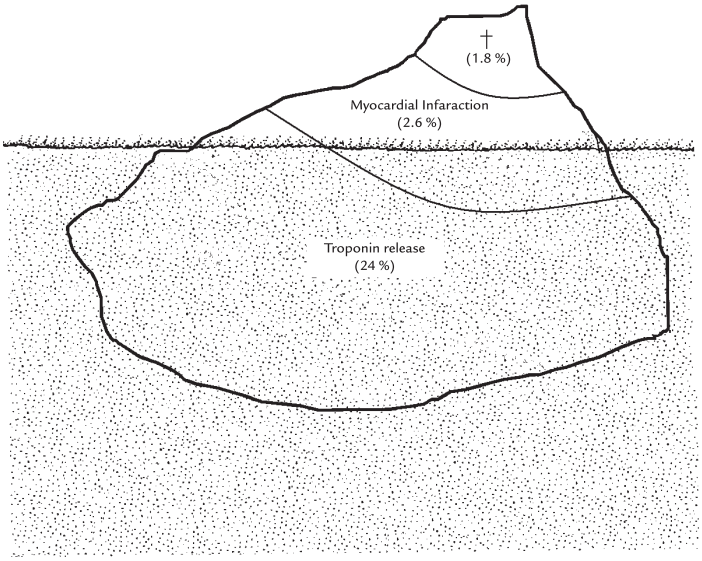

Figure 1: Incidence of cardiac complications among 1476 patients scheduled for elective open abdominal aortic or infragenuial arterial reconstruction.

Pathophysiology of perioperative myocardial complications

Although the pathophysiology of Perioperative Myocardial Infarction (PMI) is not entirely clear, it is now well accepted that coronary plaque rupture, leading to thrombus formation and subsequent vessel occlusion, is an important cause of acute perioperative coronary syndromes. This is similar to the nonoperative setting. 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 [3]. The perioperative surgical stress response includes a catecholamine surge with associated hemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation, and consequent hypercoagulability [4].

In patients with significant CAD, perioperative myocardial infarction may also be caused by a sustained myocardial supply/demand imbalance due to tachycardia and increased myocardial contractility. 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 2).

As demonstrated in the autopsy study by Dawood et al. [5], 55% of the fatal PMIs have direct evidence of plaque disruption defined as fissure or rupture of plaque and hemorrhage into the plaque cavity. Similar autopsy results were found in the study by Cohen and Aretz [6]; a plaque rupture was found in 46% of patients with PMI. Time-to-death interval in patients with plaque rupture was significantly longer than in patients without plaque rupture.

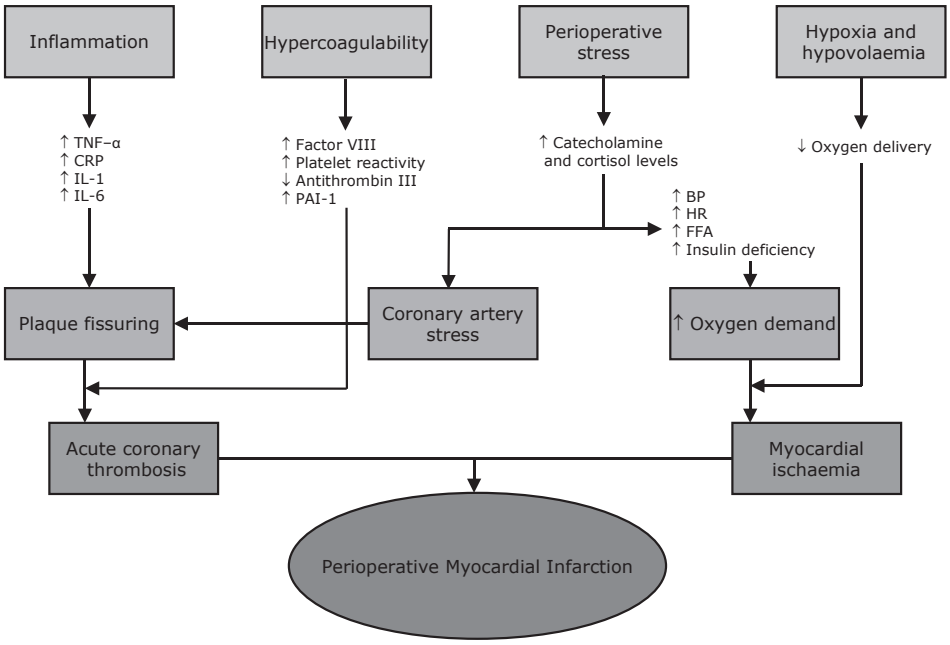

Figure 2: Pathophysiology of perioperative myocardial infarction.

Episodes of perioperative ST-segment depression, indicating subendocardial myocardial ischemia, have been described in up to 41% of vascular surgery patients, mostly occurring within the first 2 days after surgery [7]. The association of PMI with myocardial ischemia and nontransmural or circumferential subendocardial infarction supports this mechanism. Landesberg et al. [8] demonstrated that 85% of postoperative cardiac complications were preceded by prolonged ST-segment depression. Fleisher et al. [9] found that 78% of patients with cardiac complications had at least 1 episode of prolonged myocardial ischemia (i.e., >30 min), either before or at the same time as the cardiac event. In the majority of cases, it presents without Q waves. The hypothesis that ST-segment depression can lead to PMI is further supported by increased troponin T levels during or shortly after prolonged ST-segment depression ischemia [10]. In a study by London et al. among 105 patients with known or suspected CAD, intraoperative ST-segment elevation type ischemia was found to be relatively uncommon, confirmed by the incidence (12%) compared to episodes involving ST-segment depression (88%) [11].

Preoperative Cardiac Evaluation

Preoperative cardiac risk assessment is essential for identifying high risk patients for perioperative cardiac events. 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. Several risk indices have been developed for stratification of surgical patients based on clinical cardiac risk factors.

Functional capacity

Determination of functional capacity is considered to be a pivotal step in preoperative cardiac risk assessment. Functional capacity is measured in metabolic equivalents (METs). One MET equals the basal metabolic rate. Exercise testing provides an objective assessment of functional capacity. Without testing, functional capacity can be estimated by the ability to perform the activities of daily living. Given that 1 MET represents metabolic demand at rest, climbing two flights of stairs demands 4 METs, and strenuous sports like swimming >10 METS. The inability to climb two flights of stairs or run a short distance (< 4 METs) indicates poor functional capacity and is associated with an increased incidence of postoperative cardiac events. In a study among 5939 patients scheduled for noncardiac surgery Wiklund et al. showed the predicitive value of preoperative functional capacity in relation to perioperative complications [12]. Using receiver-operator characteristic (ROC) curve analysis, the association of functional capacity with postoperative cardiac events or death showed an area under the ROC curve of just 0.664, compared with 0.814 for age. Considering the relatively weak association between functional capacity and postoperative cardiac outcome, what importance should we attach to functional capacity assessment in the preoperative evaluation of the risk of noncardiac surgery? When functional capacity is high, the prognosis is excellent, even in the presence of stable CAD or risk factors [13]. In this case, perioperative management will rarely be changed as a result of further cardiac testing and the planned surgical procedure can proceed. Using functional capacity evaluation prior to surgery, the ability to climb two flights of stairs or run for a short distance indicated a good functional capacity. On the other hand, when functional capacity is poor or unknown, the presence and number of risk factors in relation to the risk of surgery will determine preoperative risk stratification and perioperative management.

Clinical risk factor indices

Over the past decades, several investigators have published clinical indices to estimate the risk of a major perioperative cardiac event in patients undergoing noncardiac surgery. The cardiac risk index of Goldman et al. [14] was the first multifactorial model specifically for perioperative cardiac complications to be widely used. This risk index was developed among 1001 patients over 40 years of age undergoing noncardiac surgery. By multivariate discriminant analysis, the authors identified nine independent significant correlates of life-threatening and fatal cardiac complications: (1) preoperative third

heart sound or jugular venous distention; (2) myocardial infarction in the preceding six months; (3) more than five premature ventricular contractions per minute documented at any time before operation; (4) rhythm other than sinus or presence of premature atrial contractions on preoperative electrocardiogram; (5) age over 70 years; (6) intraperitoneal, intrathoracic or aortic operation; (7) emergency operation; (8) important valvular aortic stenosis; and (9) poor general medical condition. This index was modified by Detsky et al. [15], who added the presence of angina and a remote history of MI to the original model of Goldman et al.

The Revised Cardiac Risk Index by Lee et al. [16], which is in fact a modification of the multifactorial risk index by Goldman and colleagues, is the largest en currently most widely used model of risk assessment. This index identifies six predictors of major cardiac complications: (1) high-risk type of surgery; (2) history of ischemic heart disease; (3) history of congestive heart failure; (4) history of cerebrovascular disease; (5) preoperative treatment with insulin; and (6) preoperative serum creatinine > 2.0 mg/dl. Based on the presence of none, 1, 2, or ≥ 3 predictors, the rate of major cardiac complications in the validation cohort (n = 1422) was estimated to be 0.4%, 0.9%, 6.6% and 11% respectively (figure 3). Boersma et al. [17] introduced a modification of the Revised Cardiac Risk Index by Lee. They showed that if more detailed information regarding the type of surgery was added to the model, the accuracy of model would improve significantly. The optimal model for predicting postoperative adverse cardiac events would be a model consisting of several clinical risk factors combined including continuous variables. However, in search of the perfect model, one would probably create a model that is not user-friendly and not suitable in daily practice. The Revised Cardiac Risk Index by Lee still is an easy and practical model and remains the most cited model in literature.

High-risk type of surgery†
History of ischemic heart disease
History of congestive heart failure
History of cerebrovascular disease
Preoperative treatment with insulin
Preoperative serum creatinine > 2.0 mg/dl

† High-risk type of surgery is defined as intraperitoneal, intrathoracic or suprainguinal vascular procedures

* Major cardiac complications includes myocardial infarction,pulmonary edema, ventricular fibrillation or primary cardiac arrest and complete heart block.

Major Cardiac Complications*

No. of risk factors	Incidence of Complications (%)
0	0.4
1	0.9
2	6.6
≥3	11.0

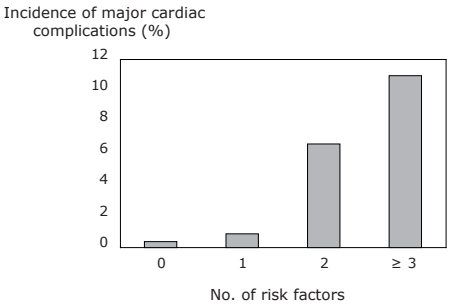

Figure 3: The revised cardiac risk index by Lee.

Laboratory

Diabetes mellitus is a common risk factor in patients scheduled for vascular surgery with a prevalence of approximately 50% if all patients are thoroughly screened [18]. Diabetes mellitus is known to be a strong predictor for perioperative events. Therefore fasting glucose values should be obtained in all patients scheduled for vascular surgery and glucose loading should be considered in all. Recently it was shown that the level of preoperative glycosated haemoglobin in diabetic patients is strongly related to perioperative cardiac outcome [19]. In a large case-control study by Noordzij et al. [20] in noncardiac nonvascular surgery surgical patients it was also shown that random preoperative glucose levels were associated with postoperative outcome. Those with a random glucose level ≥ 11.1 mmol/L had a 4-fold increased risk for perioperative cardiovascular death. Importantly, glucose levels of 5.6-11.1 mmol/L were independently associated with a 3-fold increased risk for perioperative cardiovascular events.

Metabolic syndrome

The metabolic syndrome is characterized by a group of metabolic risk factors. These risk factors include: abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance or glucose intolerance, prothrombotic and proinflammatory state (e.g., high fibrinogen or plasminogen activator inhibitor–1 and elevated C-reactive protein in the blood). The metabolic syndrome is rapidly increasing in prevalence and is an emerging risk factor for cardiovascular morbidity and mortality [21,22]. In a recent study by Protack et al. among 921 patient who underwent carotid revascularization the metabolic syndrome was present in 31% of the patients [23]. More importantly, a major part of these patients (48%) were asymptomatic. Patients with asymptomatic atherosclerosis do not experience organ failure and where therefore classified as asymptomatic patients. After adjustment for age, gender, history of MI, congestive heart failure, atrial fibrillation, and COPD patients with the metabolic syndrome had an increased risk for major adverse events Hazard Ratio (HR) 1.5 (95% Confidence Interval (CI): 1.2 to 2.1) and postoperative myocardial infarction HR 4.6 (95% CI: 2.7 to 7.8).

Future biomarkers

Apart from those measurements indicating clinical risk factors (for example, serum creatinine for renal failure, fasting glucose for diabetes mellitus, etc) currently no routine laboratory measurements are related to perioperative cardiac complications.
There has been recent interest in brain natriuretic peptide (BNP) and N-terminal pro-brain natriureticpeptide (NT-proBNP) as prognostic biomarkers of death and major cardiovascular events, even after correction for other cardiovascular risk factors [24]. NT-proBNP is increased in patients with left ventricular dilatation caused by fluid overload (e.g. heart failure and renal dysfunction), pressure overload (e.g. aortic valve stenosis) and myocardial ischemia, which might explain the excellent relation with adverse postoperative outcome. In a recent review article Rodseth et al. [25] concluded that a elevated BNP or NT-proBNP was associated with a significantly increased risk of early (< 30 day) cardiac mortality, nonfatal MI and Major Adverse Cardiac Events (MACE); defined as a composite of cardiac death and nonfatal myocardial infarction. It was also

associated with a significantly increased risk of intermediate-term (< 180 day) all-cause mortality, nonfatal MI and MACE. Short-term all-cause mortality and intermediate-term cardiac death were only associated with a trend towards an adverse outcome with an elevated BNP. Gibson et al. [26] confirmed the predictive value of BNP in 149 major vascular surgical patients; using receiver-operator curve analysis a BNP concentration of 108.5 pg/ml best predicted the likelihood of cardiac events, with a sensitivity and specificity of 87%. Although renal dysfunction (serum creatinine > 2.0 mg/dl) is an important predictor of major adverse cardiac events in noncardiac surgery, decreasing renal function is associated with a lower specificity of NT-proBNP for adverse cardiac events [27]. The utility of NT-pro-BNP as a predictive marker is highly dependant on the severity of the renal dysfunction, with the best performance in patients with a Glomerular Filtration Rate (GFR) 90 ml/min. With a GFR < 30 ml/min the prognostic ability of NT-proBNP is questionable in vascular surgical patients.

Uric acid is the major product of purine metabolism and is formed from xantine, a reaction catalyzed by dehydrogynase/oxidase. The association between serum uric acid levels and the risk of cardiovascular disease has been confirmed by numerous epidemiological studies [28,29]. Dunkelgrun et al. [30] assessed the contribution of elevated preoperative serum uric acid levels to the risk of 30-day and late mortality and MACE in patients scheduled for open vascular surgery. In total, 936 patients were enrolled. After adjustment for all clinical risk factors, the presence of hyperuricemia was not significantly associated with an increased risk of 30-day mortality or MACE, Odds Ratios (OR) of 1.5 (95 % CI: 0.8 to 2.8) and 1.7 (95% CI: 0.9 to 3.0), respectively. However, the presence of hyperuricemia was associated with an increased risk of late mortality and MACE, with hazard ratios of 1.4 (95% CI: 1.1 to 1.7) and 1.7 (95% CI: 1.3 to 2.3), respectively.

Laboratory evidence and findings from clinical and population studies suggest more and more that inflammation is an important factor in atherosclerosis. C-reactive protein (CRP) is one of the acute phase proteins that increase during systemic inflammation. It has been suggested that testing CRP and highly sensitive C - reactive protein (hs-CRP), in the blood may be an additional way to assess patients at risk for postoperative cardiovascular complications. In a recent study Goei et al. [31] evaluated 592 patients, scheduled for elective noncardiac vascular surgery. Patients were routinely screened for cardiac risk factors, hs-CRP, and NT-proBNP. After adjustment for cardiac risk factors, site of surgery and type of procedure, preoperative hs-CRP was strongly associated (OR: 2.5; 95% CI: 1.5 to 4.3) with study endpoints (composite of cardiovascular death, Q-wave myocardial infarction, and cardiac troponin T release).

In conclusion, biochemical markers seem to be of important additional value in assessing preoperative risk. However, its role in identifying surgical patients at risk for perioperative plaque rupture and hemorrhage has yet to be studied. Future studies are needed to evaluate the perioperative potential of this and other biochemical markers.

Noninvasive testing

Once the assessment of risk factors indicates an increased cardiac perioperative risk, or if there is a suspicion of CAD upon examination, further cardiac testing might be warranted. According to the current guidelines of the American College of Cardiology/ American Heart Association, preoperative noninvasive tests should be considered [32].

Assessment of LV Function

Resting left ventricular (LV) function has been evaluated before noncardiac surgery by radionuclide angiography, echocardiography, and contrast ventriculography. In a study of 570 patients having transthoracic echocardiography before major noncardiac surgery, Rohde and colleagues found that any degree of LV systolic dysfunction was marginally associated with postoperative MI or cardiogenic pulmonary edema (OR 2.1; 95% CI: 1.0 to 4.5) [33]. The finding of any degree of LV dysfunction had a poor sensitivity (43%) and positive predictive value (13%) in predicting perioperative nonfatal MI or cardiac death, with a specificity of 76% and negative predictive value of 94%. This finding is concordant with a subsequent meta-analysis of 8 studies of preoperative resting LV function as assessed by radionuclide angiography [34]. In this study, Kertai et al. found that the Left Ventricular Ejection Fraction (LVEF) less than 35% had a sensitivity of 50% and a specificity of 91% in the prediction of perioperative nonfatal MI or cardiac death. The greatest risk of complications was observed in patients with an LVEF at rest of less than 35%. In the perioperative phase, poor LV systolic or diastolic function is mainly predictive of postoperative heart failure and, in critically ill patients, death. It is noteworthy, however, that resting LV function was not found to be a consistent predictor of perioperative ischemic events.

The 12-Lead electrocardiography (ECG)

Different studies have shown an association between abnormal ECG findings and perioperative cardiac complications [14,15]. In a large prospective study by Lee et al. [16] involving 4315 patients undergoing major noncardiac surgery, a history of ischemic heart disease was one of the six independent predictors of major cardiac complications. Pathological Q-waves, as an electrocardiographic sign of MI in the past, were found in 17% of patients, with a 2.4-fold increased risk for adverse perioperative events. A recent retrospective study confirmed the prognostic value of routine preoperative electrocardiography in 22,457 noncardiac operations [35]. Patients with abnormal ECG findings had a higher incidence of 30-day cardiovascular death compared with patients with a normal ECG (1.8% versus 0.3%; adjusted OR, 3.4; 95% CI: 2.4 to 4.5). In addition, it was demonstrated that a preoperative ECG is also predictive of long-term outcome, independent of clinical findings and perioperative ischemia, in CAD patients undergoing major noncardiac surgery [36]. The resting 12-lead ECG did not identify increased perioperative risk in patients undergoing low-risk surgery [37]. In a study of 18,189 patients at 9 centers undergoing elective cataract surgery, half of the patients underwent basic testing that included a 12-lead ECG, complete blood count, and electrolyte measurement. There was no difference in outcome between the group that had routine testing versus the group that did not.

ST-segment Holter recording

The use of ambulant 24-hour ST-segment registration for evaluation of perioperative cardiac risk was described by Raby et al. [38]. They reported a sensitivity of 75% and a specificity of 83% for the prediction of a combined endpoint of cardiac death and nonfatal MI. A large meta-analysis showed lower values, comprising eight studies with

a total of 893 patients, with a weighted sensitivity of 52% (95% CI: 21% to 84%) and a specificity of 70% (95% CI: 57% to 83%) [34]. The advantages of ST-segment Holter include its low cost and wide availability.

Noninvasive stress testing

The aim of additional preoperative stress testing is to provide an objective measure of functional capacity, to identify the presence of important preoperative myocardial ischemia or cardiac arrhythmias and to estimate perioperative cardiac risk and long-term prognosis. Poor functional capacity in patients with chronic CAD or those convalescing after an acute cardiac event is associated with an increased risk of subsequent cardiac morbidity and mortality. Decreased functional capacity may be caused by several factors, including inadequate cardiac reserve, advanced age, transient myocardial dysfunction from myocardial ischemia, deconditioning, and poor pulmonary reserve. According to the guidelines by the American College of Cardiology/American Heart Association, stress testing is reserved for patients scheduled for intermediate risk or vascular surgery and with 1 or more clinical risk factors. Additional testing is only recommended if outcome will change management. Several tests are available for additional stress tests.

Exercise Electrocardiogram

The most commonly used physiologic stress test for detecting myocardial ischemia uses a treadmill test or cycle ergometer. Among its advantages, this test provides an estimate of functional capacity, and hemodynamic response, and detects myocardial ischemia through ST-segment changes. The accuracy of an exercise ECG varies widely among studies. A meta-analysis by Kertai et al. [34] for the detection of myocardial ischemia with treadmill testing in vascular surgery showed a rather low sensitivity of 74% (95% CI: 60% to 88%) and specificity of 69% (95% CI: 60% to 78%). However, important limitations in patients with peripheral vascular disease as well as patients scheduled for major orthopedic surgery involve their frequently limited exercise capacity.

Stress Echocardiography

Since only a limited number of patients at risk are able to perform an exercise electrocardiogram, stress echocardiography with pharmacologic stressors (such as dobutamine) is a good alternative. Although vasodilatators (e.g. dipyridamole or adenosine) may have advantages for the assessment of myocardial perfusion, dobutamine is the preferred pharmalogical stressor when the test is based on an assessment of regional wall-motion abnormalities [39]. Dobutamine is a synthetic catecholamine with predominantly beta-1 adrenoceptor-stimulating properties, resulting in a strong positive inotropic effect and modest chronotropic effect on the heart. During the stress test, dobutamine is intravenously administered. A graded dobutamine infusion starting at 5 μg/kg/min, and increasing at 3-minute intervals to 10, 20, 30 and 40 μg/kg/min, is the standard for Dobutamine Stress Echocardiography (DSE). During dobutamine infusion, contractility and heart rate increase, leading to increased myocardial oxygen demand. Myocardial ischemia leading to systolic contractile dysfunction, detectable

by echocardiography, occurs in regions by hemodynamically significant stenotic coronary arteries. Tissue harmonic imaging is advised for stress echocardiography. This special imaging setting reduces near-field artefacts, improves resolution, enhances myocardial signals, and is superior to fundamental imaging for endocardial border visualization. The improvement in endocardial visualization is further enhanced by the use of contrast agents for left ventricular opacification. Contrast agents increase the number of interpretable left ventricular wall segments. These recent developments exhibit decreased interobserver variability and have improved the sensitivity of stress echocardiography [40]. Several studies have shown that DSE can be performed safely and with acceptable patient tolerance [41-44]. The predictive value of a positive test ranged from 0% to 33% for hard events (nonfatal MI or death). The negative predictive value ranges from 93% to 100%. In the series by Poldermans et al. [45], the presence of a new wall-motion abnormality was a powerful determinant of an increased risk for perioperative events after multivariable adjustment for different clinical and echocardiographic variables.

Myocardial perfusion Scintigraphy

Myocardial Perfusion Scintigraphy (MPS) is a widely used technique in the preoperative risk assessment of patients undergoing vascular surgery. The technique involves intravenous administration of a small quantity of a radioactive tracer. The detection of CAD is based on a difference in blood-flow distribution through the LV myocardium. These differences in perfusion can be explained by insufficient coronary blood flow based on coronary stenosis. Nowadays, technetium-99m-labeled radiopharmaceutical is the most widely used tracer. Myocardial perfusion scintigraphy is used in combination with exercise or pharmacologic stress testing to diagnose the presence of CAD. If there is a decrease or loss in regional perfusion after maximal vasodilatation with, for example, adenosine, as seen in hemodynamically significant CAD or in transmural MI, a reduced radiopharmaceutical signal is observed. Shaw et al. [46] conducted a meta-analysis of dipyridamole myocardial perfusion imaging for risk stratification before elective vascular surgery that demonstrated significant prognostic utility for this scintigraphic technique. In addition, they noted that the positive predictive value of perfusion imaging was correlated with the pretest cardiac risk of the patients. Overall, a reversible myocardial perfusion defect predicted perioperative events, and a fixed thallium defect predicted long-term cardiac events. Semiquantitative analysis of myocardial perfusion imaging improved the clinical risk stratification by defining a relationship of increasing risk for cardiac events as defect size increased. A second meta-analysis was performed by Etchells et al. [47] in 2002. In 9 studies comprising 1179 patients, they found that reversible defects in fewer than 20% of myocardial segments were associated with a small, nonsignificant increased risk for perioperative death or MI. Reversible defects that involved more than 20% of myocardial segments were associated with a significantly higher risk of perioperative cardiac death or MI that increased progressively as the extent of reversible defects increased. As reported by Kertai and colleagues [34], the overall sensitivity of myocardial perfusion scintigraphy is 83% (95% CI: 77% to 89%) with a low specificity of 47% (95% CI: 41% to 57%). In summary, stress nuclear myocardial perfusion imaging has a high sensitivity for detecting patients at risk for perioperative cardiac events. Perioperative cardiac risk

appears to be directly proportional to the amount of myocardium at risk as reflected in the extent of reversible defects found on imaging. Because of the overall low positive predictive value of stress nuclear imaging, it is best used selectively in patients with a high clinical risk of perioperative cardiac events.

Invasive testing

To understand the value of preoperative evaluation, it is important to understand the pathophysiology of perioperative cardiac morbidity. Ellis et al. [48] analyzed the coronary angiograms of 63 patients undergoing major vascular surgery in a case-control study that indirectly supported benefit from preoperative coronary bypass surgery and found that a coronary occlusion proximal to viable myocardium was associated with a higher rate of perioperative MI and death, which raises the question of whether revascularizing coronary occlusions might not reduce the frequency of these adverse events. However, in that study, the number of mild, "nonobstructive" lesions was also associated with MI and death. This is consistent with studies that show that the most severe stenoses may not always be responsible for MI and that coronary thrombosis frequently occurs at the site of milder stenoses. Thus, preoperative revascularization of severe stenosis may not reduce perioperative ischemic complications. Recent studies indicate that only a selected patient population may benefit from revascularization [49,50]. The randomized Coronary Artery Revascularization Prophylaxis (CARP) trial was the first study that addressed the strategy of prophylactic revascularization, the ultimate consequence of invasive testing, compared to optical medical therapy in patients with clinically stable coronary artery disease who were scheduled for major noncardiac vascular surgery [50]. This trial showed that prophylactic revascularization was safe but did not improve perioperative or long-term outcome. The long-term (median follow-up 2.7 years) mortality was 22% in patients allocated to prophylactic coronary revascularization, compared to 23% in the medical only strategy, p=0.92. Also, the incidence of perioperative nonfatal myocardial infarction was similar, respectively 12% and 14%, p=0.37. However it must be noted that the majority of patients in the CARP trial had only 1 or 2 vessel disease. In the nonrandomized cohort of the CARP trial 48 patients (4.6%) had left main stenosis. In this cohort, patients who had undergone preoperative revascularization did seem to have an improved 2.5 year survival (84% versus 52%). In a post-hoc analysis coronary artery bypass grafting was associated with fewer myocardial infarctions and a shorter hospital stay compared to percutaneous coronary interventions in patients receiving multivessel coronary artery revascularization as prophylaxis [51]. For the DECREASE V study, a total of 1880 patients scheduled for major noncardiac vascular surgery were screened [52]. Those with 3 or more clinical risk factors (age > 70 yrs, myocardial infarction, angina pectoris, congestive heart failure, diabetes mellitus, renal failure and cerebrovascular disease) all underwent preoperative cardiac stress testing. Those with extensive stress-induced ischemia (≥ 5 segments or ≥ 3 walls) were randomly assigned for additional revascularization. All received beta-blockers aiming at a heart rate of 60-65 bpm and antiplatelet therapy was continued during surgery. Of 430 high-risk patients, 101 (23%) showed extensive ischemia and were randomly assigned to revascularization (n=49) or no-revascularization (n=52). Coronary angiography showed 2-vessel disease in 12 (24%), 3-vessel disease in 33 (67%), and left main in 4 (8%). This study population reflects the patients at the highest cardiac risk in the perioperative

period. Compared to the CARP trial, the perioperative cardiac risk in the DECREASE V population was even higher; all patients had extensive stress induced myocardial ischemia and 75% had 3-vessel disease or left main disease. If a beneficial effect on postoperative outcome could have been expected of prophylactic coronary revascularization, then it would be seen at least in this group of patients. However, the results of the trial were disappointing. Two patients died after revascularization, prior to operation because of ruptured aneurysm. Revascularization did not improve perioperative outcome, the incidence of cardiac death and myocardial infarction was 43 versus 33%, (OR: 1.4; 95% CI: 0.7 to 2.8). Also no benefit during 1-year follow-up was observed after coronary revascularization, 49 versus 44% (OR: 1.2; 95% CI: 0.7 to 2.3) (figure 4).

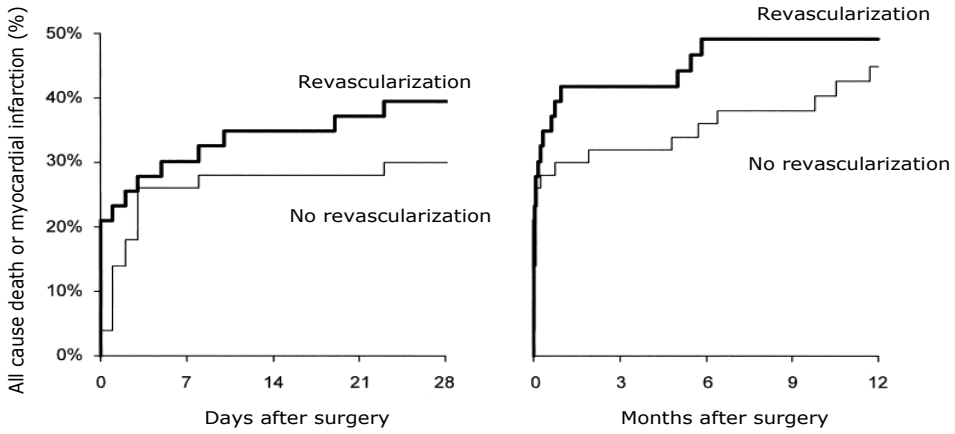

Figure 4: Incidence of all-cause death or myocardial infarction during 1-year follow up in DECREASE V.

The recommendations of the American College of Cardiology/American Heart Association 2007 guidelines on preoperative prophylactic coronary revascularization are as follows. Coronary revascularization is considered useful in patients with stable angina who have significant left main coronary artery disease, three-vessel disease, and two-vessel disease with a significant stenosis of the proximal left anterior descending coronary artery and either an ejection fraction less than 50% or demonstrable ischemia on noninvasive testing (class I, (Level Of Evidence (LOE): A). It is also recommended in patients with unstable angina, non-ST-segment elevation myocardial infarction, and those with acute ST-segment elevation myocardial infarction (class I, LOE: A). The usefulness of preoperative coronary revascularization is not well established in high-risk ischemic patients (such as in the presence of an abnormal stress echocardiograph with ≥ 5 segments of regional wall motion abnormalities; class IIb, LOE: C) and in low-risk ischemic patients with an abnormal dobutamine stress echocardiography (≤ 4 segments ; class IIb, LOE: B). Finally, prophylactic coronary revascularization is not recommended in patients with stable coronary artery disease (class III,LOE: B).

Coronary Artery Bypass Grafting (CABG) versus Percutaneous Coronary Intervention (PCI)

Once the decision for preoperative coronary revascularization has been taken, a choice should be made between Coronary Artery Bypass Grafting (CABG) and a percutaneous coronary intervention (PCI). A recent study by Garcia et al. [49] on patients receiving multivessel coronary artery revascularization as prophylaxis for elective vascular surgery indicated that patients having coronary surgery had fewer myocardial infarctions after the vascular surgery than those who had a PCI. Garcia et al. analysed the patients who were randomized in the CARP study, as well as the 4414 patients in the nonrandomized registry. In the nonrandomized registry 124 patients had revascularization before elective vascular surgery. The main finding of their study was that in patients with multivessel CAD who underwent vascular surgery, the only subset of patients who benefited from a strategy of preoperative coronary artery revascularization before elective vascular surgery was those with unprotected left main coronary artery stenoses. This subset of patients constituted 4.6% of the total cohort who underwent preoperative coronary angiography and, with revascularization before vascular surgery, was associated with improved survival.

PCI and antiplatelet therapy

Percutaneous coronary revascularization with the use of stents represents another issue. Stents have been introduced to reduce the incidence of restenosis. To prevent early in-stent thrombosis, all patients receiving a coronary stent are prescribed dual antiplatelet therapy, the duration of which depends on the type of stent used. Recently, data have indicated that especially in Drug Eluting Stents (DES), late in-stent thrombosis may occur related to the interruption of antiplatelet therapy [53]. Approximately 5% of patients who had coronary stenting require some form of noncardiac surgery within 1 year after stenting [54]. As antiplatelet therapy may increase the risk of perioperative bleeding, these drugs are usually discontinued at the time of surgery. It has been recognized for some time that such action may have disastrous consequences for the surgical patient and therefore specific guidelines have been developed for the management of such patients [55,56]. With respect to potential preoperative revascularization by percutaneous coronary angioplasty, a strategy of balloon angioplasty or bare-metal stent placement followed by 4–6 weeks of dual-antiplatelet therapy is recommended (class IIa, LOE: B). In patients who have received drug-eluting coronary stents and who need an urgent surgical procedure, necessitating the discontinuation of thienopyridine therapy, it is suggested to continue aspirin therapy and restart the thienopyridine as soon as possible (class IIa, LOE: C). Elective noncardiac surgery is not recommended within 4–6 weeks of bare-metal coronary stent implantation or within 12 months of drug-eluting coronary stent implantation in patients in whom thienopyridine therapy, or the dual therapy, aspirin–thienopyridine, will need to be discontinued perioperatively (class III, LOE: B). Finally, elective noncardiac surgery is also not recommended within 4 weeks of balloon angioplasty (class III, LOE: B) (figure5).

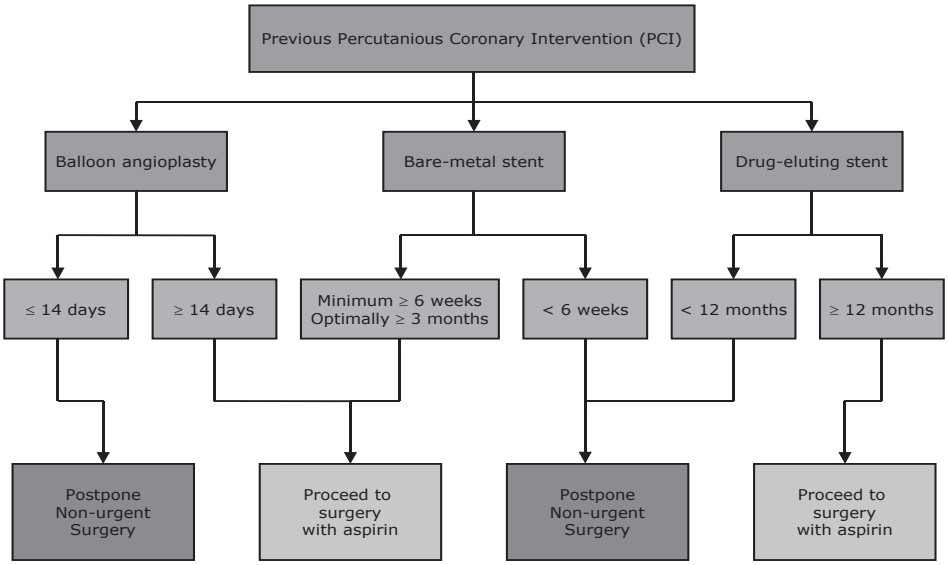

Figure 5: Recommendations for timing of non-cardiac surgery in patients with previous PCI

Medical treatment

Beta-blockers

The hypothesis that beta-blockers actually improve cardiovascular outcomes during surgery was tested in a 1973 trial, the results of which showed a decrease in myocardial
ischemia, ventricular arrhythmia, and blunting of the hypertensive response on intubation associated with this therapy [57]. As clinical data accumulated, beta-blockers quickly became first-line therapy in acute myocardial infarction, stable coronary artery disease, and systolic heart failure. Their use also grew in the perioperative treatment of patients undergoing vascular surgery with coronary ischemia, ultimately leading to a Class I recommendation in the 2002 American Heart Association/American College of Cardiology Joint Guidelines [58]. In 1996, Mangano et al. [59] performed the first randomised controlled trial on perioperative beta-blockade, comparing atenolol to placebo in 200 patients with known coronary artery disease undergoing noncardiac surgery. Analyses at study completion showed that overall mortality was 55% lower in the atenolol group than the placebo group. Although no difference in immediate perioperative cardiac events was observed, the benefit of beta-blockade was evident at 6-month follow-up, where the rate of cardiac events was 0 in the study group versus 12 in the placebo group ($p<0.001$). Poldermans et al. [60] followed the Mangano study with the DECREASE I trial, which involved 112 high-risk patients (clinical markers of risk and inducible myocardial ischemia on dobutamine echocardiography) randomized to either bisoprolol or placebo before major vascular surgery. Importantly, the study protocol called for the initiation of bisoprolol at least 1 week before surgery with titration of the drug to achieve a heart rate of 60 bpm. The study was stopped prematurely when interim analyses revealed a 10-fold reduction in the incidence of perioperative cardiac

death and myocardial infarction versus placebo (3.4% versus 34%; p <0.001). The study thus reaffirmed the value of perioperative beta-blockers in a high-risk cohort. Recent clinical trials have reported adverse effects from the use of perioperative beta-blockers, particularly in patients at low to moderate risk of cardiac events. In the POBBLE (PeriOperative Beta BlockadE) trial, only low-risk patients (history of ischemic heart disease was an exclusion) scheduled for vascular surgery were studied [61]. This low risk population was randomized to receive either metoprolol 25 mg or 50 mg or placebo, starting the day before surgery and continued during the first 7 days of surgery. There was no difference in the incidence of perioperative cardiovascular events between the placebo and metoprolol groups (34% versus 32%). The duration of hospitalization though was shorter for those patients receiving metoprolol versus placebo (10 days versus 12 days). The Metoprolol after Vascular Surgery (MaVS) study investigated whether perioperative administration of metoprolol was associated with a reduction in cardiac events in patients undergoing vascular surgery [62]. The trial randomized 496 patients without known ischemic heart disease in a double-blinded manner to placebo (n=250) or perioperative metoprolol (n=246) dosed according to patient body weight (>75 kg: 100 mg; 40-75 kg: 50 mg; <40 kg: 25 mg). Metoprolol was given 2 hours preoperatively and was continued for 5 days or until hospital discharge. Mean follow-up was 6 months, with analysis for the composite endpoint of cardiac death, nonfatal myocardial infarction, unstable angina, congestive heart failure, or arrhythmia requiring treatment, performed at 30 days. The study reported that while the postoperative heart rate was lower in the metoprolol group (69.4 versus 79.1 bpm, p <0.001), the rate of intraoperative complications, including hypotension requiring treatment (46.3% versus 33.6%, p <0.001) and bradycardia requiring treatment (21.5% versus 7.6%, p <0.001), was significantly higher. Importantly, MaVS showed no difference in cardiac events in patients receiving perioperative beta-blockers versus those receiving placebo (10.2% versus 12%, p=0.57), thus demonstrating no benefit, but potential harm from this practice. In a review, Lindenauer et al. [63] performed a retrospective cohort study analyzing the effects of beta-blockers according to preexisting cardiac risk defined by Lee's Revised Cardiac Risk Index. The study reviewed 782,969 patients, of whom 122,338 (16%) received beta-blockade during the first 2 days of hospitalization. Within this study cohort, 14% had a Revised Cardiac Risk Index score of 0, portending low cardiovascular risk, whereas 44% had a score of 3 or higher, suggestive of high risk. Analysis of results revealed that the relationship between perioperative beta-blockade and the risk of death varied directly with cardiac risk; thus, individuals at high risk showed the greatest benefit from beta-blockade, whereas those in the low to moderate risk categories showed a trend toward harm from this practice owing to bradycardia and hypotension. Due to inconclusive results from previous studies on perioperative beta-blocker use, investigators started a major randomised controlled trail in 2002: The Perioperative Ischemic Evaluation (POISE) study [64]. This study remains the largest randomized controlled trial examining the role of beta-blockers in the perioperative setting. The study prospectively randomized 8351 patients with or at risk for coronary artery disease scheduled to undergo noncardiac surgery into 2 arms receiving either oral extended-release metoprolol succinate (n=4174) or placebo (n=4177). The trial protocol called for administration of 100 mg of the study drug 2-4 hours before surgery, with a second dose 6 hours after surgery if prespecified hemodynamic parameters remained acceptable. Patients were then given 200 mg

extended-release metoprolol 12 hours after their postoperative dose, with this regimen continued for 30 days. Results from POISE showed cardiac benefit. Fewer patients in the metoprolol group reached the primary endpoint of death, nonfatal myocardial infarction, or nonfatal cardiac arrest (244 (5.8%) versus 290 (6.9%)) than in the placebo group (HR 0.84; 95% CI: 0.7 to 0.99). Additionally, fewer patients in the metoprolol treated group had a myocardial infarction (176 (4.2%) versus 239 (5.7%), HR 0.73; CI 95%: 0.60 to 0.89). However, there were more deaths in the metoprolol group (129 versus 97) than placebo. Subgroup analyses indicated that the major contributor to mortality in the beta-blocker group were noncardiac deaths. In addition, significantly more patients in the metoprolol group developed ischemic stroke (41 versus 19) compared with placebo. Predictably, clinically significant hypotension and bradycardia was noted in the metoprolol group (15% and 6.6%, respectively). POISE thus demonstrated that there is significant risk in the assumption that a perioperative beta-blocker regimen has benefit without harm, illustrating that for every 1200 patients treated, metoprolol would prevent 15 myocardial infarctions at a cost of 8 excess deaths and 5 disabling strokes. There are several explanations for the divergent findings from randomized trials of perioperative beta-blockers, including the use of a fixed versus individualized dose titrated to the patients heart rate. In a study of 150 patients, Raby et al. [65] assessed the heart rate threshold for myocardial ischemia before surgery using Holter monitoring. Patients with myocardial ischemia (n=26) were then randomized to receive IV esmolol titrated to aiming at tight heart rate 20% less then the ischemic threshold but > 60 bpm or placebo. Of the 15 patients receiving esmolol, 9 had mean heart rates below the ischemic threshold and none experienced postoperative ischemia. Four of 11 patients receiving placebo had a mean heart rate below the ischemic threshold, and 3 of the 4 had no postoperative ischemia. Together, of the 13 patients with heart rates below the ischemic threshold, 1 (7.7%) had postoperative myocardial ischemia versus 12 of 13 (92%) patients with heart rates exceeding the ischemic threshold. Feringa et al. [66] found similar results in a study of 272 patients receiving beta-blocker therapy and undergoing vascular surgery. In this study it was shown that higher doses of beta-blockers and lower heart rate were associated with reduced holter monitoring-detected perioperative myocardial ischemia (HR 0.40; 95% CI: 0.21 to 0.56) and troponin-T release (HR 0.65; 95% CI 0.49 to 0.86). These data suggest that monitoring of the heart rate and consequent beta-blocker dose adjustment is of critical importance. The conflicting results of perioperative beta-blocker trials might be further explained by varying durations of therapy. As mentioned, although the sympathico-inhibitory effects of beta-blockers occur almost instantly, the anti-inflammatory effects may be observed only after prolonged treatment. As mentioned, in the Mangano et al. study, the major benefits of atenolol were observed in the months after surgery [59]. Further, withdrawal of beta-blocker therapy shortly before surgery, or in the immediate postoperative period, might contribute to adverse myocardial effects resulting from a 'rebound' effect resulting in increased arterial blood pressure, heart rate and plasma noradrenalin concentrations [67]. More importantly, patients on chronic beta-blocker therapy should continue their therapy in the perioperative period as sudden beta-blocker withdrawal increases the risk of adverse cardiac events [68,69]. Hoeks et al. [68] demonstrated this in a prospective survey among 711 patients scheduled for peripheral vascular surgery. In the group of patients who continued beta-blocker therapy in the postoperative period 1-year mortality rate was 6%, while in the group of

patients who discontinued their beta-blocker therapy the 1-year mortality rate rose to 38%. After adjustment beta-blocker withdrawal was associated with an increased risk for 1-year mortality compared to nonusers (HR 2.7; 95% CI: 1.2 to 5.9). Perioperative beta-blocker use remains an issue of debate in recent literature. Further studies will be required to determine the optimal dose and timing to initiate the drug before surgery.

Statins

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme involved in the synthesis of cholesterol. This inhibition lowers low-density lipoprotein cholesterol (LDL-C) levels by slowing down the hepatic synthesis of cholesterol. It also increases the ability of the liver to remove the LDL-C already in the blood. Over the past few years, it has become clear that over and above their effects on lipids, statins have other effects, usually described under the term pleiotropic. These include anti-inflammatory properties which may play an important role in the prevention of cardiovascular events. The role of unstable plaques in the development of acute coronary syndromes has been recognised and it is clear that plaque instability is a frequent cause of perioperative coronary events. As mentioned before it is estimated that half the perioperative myocardial infarctions are caused by major plaque disruption, while critical coronary stenoses are responsible for the other half [5,6]. Inflammatory mediators play an important role in making plaques unstable and prone to disruption [70]. Ischemia-reperfusion is a feature of major vascular surgery. While very brief periods of ischemia-reperfusion at a distance from the heart are associated with myocardial preconditioning and therefore can be protective, in the case of major vascular surgery ischemia is likely to be prolonged and, therefore, damaging. Ischemia-reperfusion can be associated with the systemic inflammatory response syndrome (SIRS) and multiple organ failure (MOF) resulting from the release of IL-1, IL-6, and TNF-α [71,72]. Ischemia-reperfusion is most pronounced after rupture of abdominal aortic aneurysms as several episodes of hypoperfusion are likely to have occurred. Ischemia-reperfusion triggers a very large inflammatory response and explains the poor outcome compared to elective repairs.
Statin therapy may attenuate the effect of inflammation on risk of cardiovascular events. While elevated levels of inflammatory markers such as CRP, IL-6, ICAM-1, and serum amyloid A (SAA) have been shown to be associated with an increased risk for vascular events, statins have been shown to reduce the risk of postinfarction complications to a larger extent in patients with high levels of CRP and SAA than in those with normal levels of these mediators, and more than in those given a placebo (CARE trial) [73-75]. These effects might also be present in the postoperative period.
Poldermans et al. was one of the first who observed that the perioperative mortality rate among the vascular surgery patient population treated with statins was reduced 4.5-fold (OR 0.22; 95% CI: 0.10 to 0.47) when compared with those patients without statin therapy [76]. Similarly, in a retrospective cohort study of 780,591 patients who underwent noncardiac surgery, Lindenauer et al. observed that statin therapy was associated with a reduced risk of postoperative death [77]. The first blinded, placebo-controlled, randomized that investigated the influence of statin use on perioperative cardiovascular complications has been reported by Durazzo et al. [78]. This research group randomly assigned 100 patients to treatment with either 20 mg of atorvastatin or

placebo. Patients received treatment for 45 days and at least 2 weeks before surgery. One month after surgery, patients with elevated cholesterol levels were advised to continue or start statin therapy. The outcome of this trial was the endpoint of cardiovascular events, defined as cardiac death, nonfatal myocardial infarction, stroke or unstable angina pectoris. Patients were monitored up to 6 months after the surgical procedure. Of 100 patients, 44 statin users and 46 nonusers underwent elective vascular surgery. The 6-months incidence of cardiovascular events was reduced 3.1-fold in statin users compared with nonusers (p=0.022). A major concern of perioperative statin therapy is the risk of statin-induced elevated serum transaminases, myopathy and rhabdomyolysis. An important potential risk factor in the perioperative setting is the use of concomitant medications. The risk for myopathy might increase with concomitant drugs that are myotoxic or increase serum statin levels. Besides concomitant medication use, numerous other factors in the perioperative might increase the risk of statin-induced myopathy, including impairment of renal function after major surgery, the use of analgesic agents and postoperative pain that might mask signs of myopathy. Failure to detect statin-induced myopathy may then lead to continuous statin use and the subsequent development of rhabdomyolysis and acute renal failure. In a retrospective study of 885 consecutive patients undergoing major vascular surgery, no case of rhabdomyolysis or a significant higher creatine kinase level in the 211 statin users was observed [79]. Considering that the risk for cardiovascular complications is far greater then the risk for statin-induced myopathy and rhabdomyolysis, the potential benefits of perioperative statin use seem to outweigh the potential hazards. The safety of statins should be confirmed in blinded, randomized trials, however.

Antiplatelet therapy

Studies on the effectiveness of antiplatelet therapy to prevent cardiac complications in patients undergoing vascular surgery are non-existent. However, a large proportion of patients with peripheral arterial disease are on antiplatelet therapy as a mean of secondary prevention. Numerous publications on major morbidity and mortality have shown the efficacy of antiplatelet therapy in secondary prevention of cardiovascular events [80,81]. The perioperative risk for hemorrhage varies with the type of antiplatelet therapy and the surgical procedure. As a general rule, bleeding increases when the patient receives two or more antiplatelet drugs or when antiplatelet therapy is associated with heparin. It is widely thought (and plausible), although unproven, that bleeding is more important with thienopyridines than with non steroid anti-inflammatory drugs (NSAIDS). Finally, the sensitivity to antiplatelet drugs varies from one individual to another; even if the risk of bleeding is acceptable or slightly elevated in a majority of surgical patients, in a small number of patients the risk is severe, for reasons that remain unclear [82,83]. In their extensive review on the impact of antiplatelet therapy in the perioperative bleeding complications, Harder et al. [84] concluded that monotherapy with aspirin or thienopyridines alone usually does not have to be discontinued in the perioperative period. This conclusion was confirmed in the meta-analysis of Burger et al. [85]. In 41 studies, including a total of 49.590 patients undergoing a variety of noncardiac surgical procedures, aspirin continuation led to a 1.5 times increased risk of bleeding complication, but not to a higher level of the severity of bleeding complications. Based on this meta-analysis aspirin should only

be discontinued perioperatively if bleeding risks with increased mortality or sequels are comparable to the observed cardiovascular risks after aspirin withdrawal. One of the problems with aspirin withdrawal is the risk of a rebound phenomenon. Abrupt cessation of aspirin results in an increase in thromboxane A2 activity and a decrease in fibrinolysis, resulting in increased platelet adhesion and aggregation [86,87]. This issue is of particular relevance to patients with (recent) coronary stent placement. Surgery increases the in-stent thrombosis risk in these patients due to a perioperative stress response including sympathetic activation promoting sheer stress on arterial plaques, enhanced vascular reactivity conductive to vasospasm, reduced fibrinolytic activity, platelet activation and hypercoagulability. In addition, while the surgical patient is in a hypercoagulable state, dual platelet therapy is often interrupted because of the fear of excessive bleeding complications during surgery. This double-edged sword of dual antiplatelet therapy, prevention of cardiac complications on one hand, and an excess bleeding risk on the other, remains a controversial issue in perioperative management. It has recently been suggested that noncardiac surgery after PCI with stenting should be delayed at least 6 weeks and dual antiplatelet therapy is associated with improved outcome [88]. It is advisable to continue at least single antiplatelet therapy in patients with a history of coronary stent placement.

Long-term risk reduction and prognosis

The preoperative evaluation offers a unique opportunity to identify patients at increased perioperative risk and initiate appropriate lifestyle changes and risk reduction therapy, as these will also improve long-term outcome. Importantly, patients should live long enough to enjoy the benefits of surgery. In a recent article Hoeks et al. showed that the prognostic value of the Lee Cardiac Risk extends from major complications in the perioperative period to long-term mortality and health status [89]. 701 patients who underwent undergoing peripheral vascular repair were followed up during a 3-year period. During this 3-year follow-up the Lee Risk Index proved to be an independent prognostic factor for late mortality; 1 risk factor HR 2.1; 95% CI: 1.2 to 3.6, 2 risk factors HR 2.4; 95% CI: 1.4 to 4.1 and ≥3 risk factors HR 3.3; 95% CI: 1.7 to 6.3).
Several authors demonstrated the prognostic value of preoperative dobutamine stress echocardiography, relative to clinical risk assessment, in predicting late cardiac events [90-92]. Poldermans et al. demonstrated the long-term value of dobutamine stress echocardiography in 323 consecutive patients scheduled for vascular surgery [92]. During a mean follow-up of 19 months patients with a history of myocardial infarction combined with ≥ 3 ischemic segments during dobutamine stress echocardiography were at the highest risk for late cardiac events (HR 31; 95% CI: 11.4 to 87.3), compared to those with a history of myocardial infarction, but who had no ischemic segments on dobutamine stress echocardiography (HR 3.1; 95% CI: 1.4 to 6.6). The DECREASE V study as well as the CARP study showed that prophylactic coronary revascularization in vascular surgery patients was not associated with improved perioperative cardiac outcome [50,52]. Recently, long-term follow-up results from the DECREASE V study were published by Schouten et al. [93]. During a median follow-up of 2.8 years 42 of 101 patients died. After 2.8 years, the overall survival rate was 64% for patients randomly assigned to no preoperative coronary revascularization versus 61% for patients assigned to preoperative coronary revascularization (HR 1.18; 95% CI: 0.6 to 2.2). The incidence

of all-cause death, nonfatal myocardial infarction, and coronary revascularization was similar in both groups. Event-free survival rates after 2.8 years were 49% and 42% for patients allocated to medical treatment or coronary revascularization, respectively (HR 1.51; 95% CI: 0.89 to 2.6). There was no difference in long-term event-free survival between patients who underwent preoperative PCI or coronary artery bypass grafting (HR 0.91; 95% CI: 0.44 to 1.9). After a median of 2.8 years, event-free survival rates were 41% versus 44% for PCI and CABG, respectively. In addition, for the end point of all-cause death, no significant difference was observed (HR 0.81; 95% CI: 0.33 to 2.0) (figure 6)

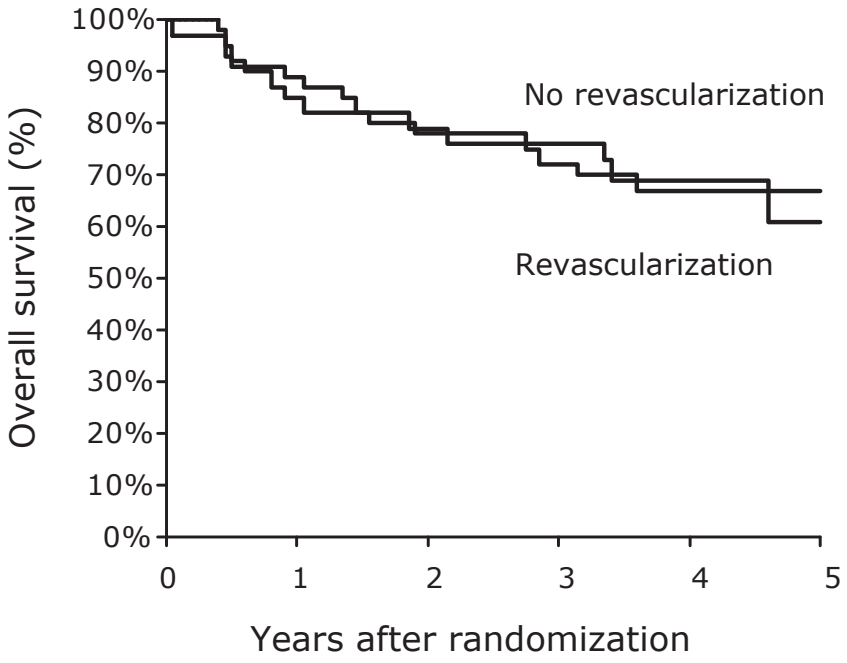

Figure 6: Long-term follow up in DECREASE V.

The role of statins and beta-blockers in preventing late cardiac events has been proven in multiple studies in the nonoperative setting. Feringa et al. [66] emphasised the importance of tight heart rate control in study among 273 patients undergoing elective major vascular surgery. During a median follow-up of 2.6 years, mortality, cardiac death and nonfatal myocardial infarction occurred in 66 (24.2%), 48 (17.6%), and 6 (2.2%) patients, respectively. In multivariate analysis, higher doses of beta-blockers were significantly associated with a reduced incidence of mortality and cardiac events. Higher heart rates and higher absolute heart rate changes were associated with an increased incidence of long-term mortality and cardiac events; a 10 bpm increase in heart rate was asscociated with increased risk for long-term mortality (HR 1.42; 95% CI: 1.1 to 1.8) as well as with an increased with for long-term cardiac events (HR 1.56; 95% CI: 1.2 to 2.0). Finally it should therefore be emphasized that patients undergoing noncardiac vascular surgery are at higher risk for long-term cardiac events, even those without perioperative cardiac complications. In fact, patients who undergo vascular

surgery have a worse prognosis compared to patients who experienced an acute coronary event [94]. Optical medical treatment of these patients is of critical importance and recent guidelines such as the American College of Cardiology/American Heart Association guidelines and the TASC2 guidelines should be adhered to so that the patient lives long enough to enjoy the benefits of vascular surgery [95,96].

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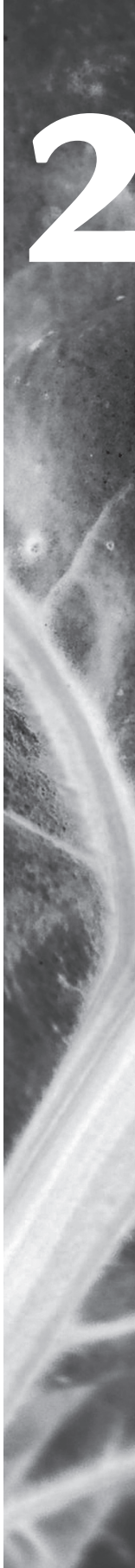

2

Perioperative Strokes and Beta-Blockade

Don Poldermans MD PhD, Olaf Schouten MD PhD, Felix van Lier MD,
Sanne E. Hoeks PhD, Louis van de Ven MD PhD,
Robert Jan Stolker MD PhD, Lee A. Fleisher MD PhD

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Recently the results of the PeriOperative Ischemic Evaluation (POISE) study have caused concern regarding beta-blocker use in the perioperative setting [1]. Though beta-blocker therapy was associated with an improved cardiac outcome, overall mortality was increased in the metoprolol treated group. This was partially related to the increased incidence of postoperative stroke occurring early after surgery. These findings might have important implications on perioperative beta-blocker use, not only for initiation of therapy prior to surgery in beta-blocker naïve patients but also whether or not to continue therapy throughout surgery. This commentary reviews the incidence and pathophysiology of perioperative stroke and the relation of beta-blockers and perioperative stroke, focusing on noncardiac surgery. The risk of clinically apparent perioperative brain injury such as stroke varies widely among different types of surgery. Whereas patients undergoing general surgery appear to be at low risk (0.08 - 0.7%), those undergoing heart valve surgery and aortic arch repair have a high incidence of perioperative stroke (8-10%) [2]. In Europe annually 40 million general surgical procedures are performed. Therefore it is estimated that 32,000 – 280,000 patients suffer from postoperative stroke. However, the true incidence of cerebral complications is probably underestimated as subtle forms of brain injury are commonly classified as delirium that may only be detected by rigorous neuropsychological testing. The knowledge of the pathophysiology of postoperative cerebral complications is predominantly based on cardiothoracic surgery patients. It is estimated that 62% of strokes in this population have an embolic origin, 10% are related to hypoperfusion, and 10% have multiple causes [2]. Importantly, only 1% of strokes are caused by intracerebral hemorrhage. However, it should be acknowledged that the true pathophysiological basis of perioperative stroke is not as straightforward as it might seem. Embolic and hypoperfusion cerebral infarction most likely do not occur in isolation [3]. Impaired clearance of emboli (washout) seems to be the link between hypoperfusion, embolism, and ischemic stroke [4]. Intraoperative microemboli and low middle cerebral artery blood flow velocity are additive in predicting development of cerebral ischemic events after carotid endarterectomy [5]. Second, newer data where sensitive diffusion weighted MRI (Magnetic Resonance Imaging) was performed suggest that as many as 2/3 of post-cardiac surgery strokes have watershed or hypoperfusion pattern [6]. Finally, what appears to be occurring in cardiac surgery patients is that there is a rising prevalence of mostly unrecognized cerebral vascular disease concurrent with the rising age of our population. In fact, one study (that interestingly excluded patients with known cerebral vascular disease) found that as many as 75% of patients had evidence of impaired cerebral perfusion based on SPECT (Single Photon Emission Computed Tomography) imaging before CABG (Coronary Artery Bypass Grafting) surgery [7]. Approximately 45% of perioperative strokes are identified within the first day after surgery. The remaining 55% occur after uneventful recovery from anesthesia, from the second postoperative day onward. Early embolism results especially from manipulations of the heart and aorta or release of particulate matter from the cardiopulmonary-bypass pump. Delayed embolism is often attributed to postoperative atrial fibrillation, myocardial infarction resulting from an imbalance between myocardial oxygen supply and demand, and coagulopathy. Compared to stroke after cardiac surgery, the pathophysiology of stroke after noncardiac surgery is ill defined. Perioperative hemodynamic instability and cardiac events, such as myocardial infarction and arrhythmias likely play a major role. Recently, the POISE study identified a new risk factor for perioperative ischemic

strokes: high-dose metoprolol succinate initiated for cardiac protection in patients undergoing noncardiac surgery.

Perioperative beta-blockade

Beta-blockers in the non-surgical setting are used widely and proven effective in patients with documented CAD (Coronary Artery Disease) to restore the balance of myocardial oxygen demand and supply [8]. Although initially contraindicated in patients with heart failure and peripheral atherosclerotic disease, beta-blockers are now recommended therapy for these patients [9,10]. Similar to the non-surgical setting, beta-blockers are advocated for patients with documented CAD undergoing vascular surgery [11]. However, there is still controversy regarding perioperative beta-blocker use in the general surgical population. Several randomized studies have shown a beneficial cardiac effect of perioperative beta-blocker use. In a placebo-controlled trial involving 200 high-risk patients, Mangano et al. found that atenolol (50 or 100 mg), administered intravenously beginning 30 minutes prior to surgery and then orally throughout hospitalization was discharged from the hospital (up to a maximum of seven days), did not lower the risk of death from cardiac causes or myocardial infarction during hospitalization [12]. However, it did result in a 50 percent reduction in myocardial ischemia as assessed by continuous 48-hour Holter monitoring. The authors observed a non-significant increase in incidence of stroke (i.e. 4% vs. 1%, p=0.21). The DECREASE study (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography) confirmed the benefits of beta-blockers in noncardiac surgery. In a high-risk population of 112 patients with a positive dobutamine echocardiography for CAD undergoing vascular surgery, the rate of perioperative cardiac death and myocardial infarction among patients who were randomly assigned to bisoprolol therapy (5 or 10 mg) started at least 30 days before surgery was 90 percent lower than that among patients assigned to standard care (3.4 percent vs. 34 percent) [13]. More recent studies have shown mixed results of beta-blocker therapy (figure 1) [14-17]. The MaVS (Metoprolol After Vascular Surgery) trial randomized 496 patients to metoprolol or placebo starting 2 h before surgery until hospital discharge or a maximum of 5 days after surgery [16]. No significant differences in outcome were observed at 30 days after 6 months after surgery. The incidence of stroke in MaVs was 1.6% in controls and 2.0% in beta-blocker users. In the POBBLE (Perioperative Beta-Blockade) trial, 103 patients undergoing vascular surgery were randomized to metoprolol or placebo, starting less than 24 h before surgery until 7 days after, and showed no difference in 30-day cardiovascular outcome [14]. Within 30 days, cardiovascular events occurred in 32% and 34% patients in the metoprolol and placebo groups, respectively (adjusted RR (Relative Risk) 0.87, 95% CI (Confidence Interval) 0.48 to 1.55) while stroke occurred in 2/53 vs. 0/46 respectively. The DIPOM (Diabetic Postoperative Mortality and Morbidity) trial, which started therapy at the earliest in the evening before major noncardiac surgery, again showed no difference in 30-day cardiac outcome and a non-significant increase in strokes (0.4% vs. 0%) [15]. The mixed results of early beta-blocker trials necessitated a large randomized trial. In the landmark study of the POISE investigators, 8351 patients were randomly assigned to either metoprolol succinate controlled release or placebo. The primary endpoint of cardiac death, non-fatal myocardial infarction, or non-fatal cardiac arrest was reduced in the metoprolol CR (controlled release) group compared with placebo (5.8% vs.

6.9%, hazard ratio 0.84, 95% CI 0.70–0.99, p=0.04). However, this beneficial cardiac effect was at the cost of an increased incidence of all-cause mortality and stroke. The incidence of stroke was increased from 0.5% to 1.0% (p=0.005) in patients randomized to metoprolol treatment. Stroke was associated with perioperative hypotension, bleeding, atrial fibrillation, and a history of stroke or transient ischemic attack. The recently concluded DECREASE IV trial, including 1066 patients randomized in a 2x2 factorial design to receive perioperative beta-blocker, i.e. bisoprolol 2.5 mg started a median 34 days prior to surgery, and/or statins vs. no additional medical therapy, showed that beta-blocker use was associated with 67% relative risk reduction in the endpoint of non-fatal myocardial infarction and cardiac death (p=0.002) [18]. Patients on beta-blocker therapy had a stroke incidence of 0.8% vs. 0.6% in patients not on beta-blockade.

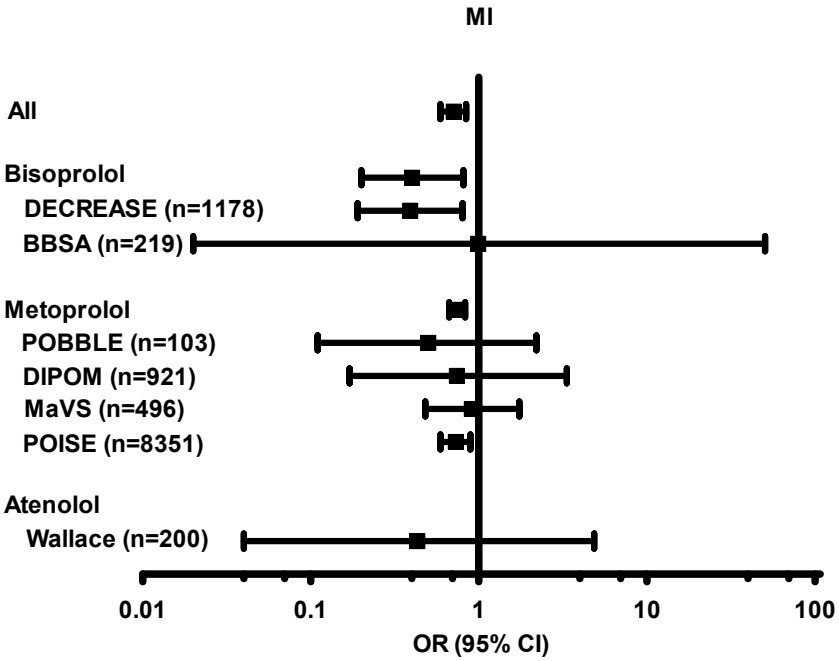

Figure 1: Odds ratios (OR) of randomized beta-blocker trials for perioperative myocardial infarction (MI). BBSA = beta blocker in spinal anaesthesia; CI = confidence interval; DECREASE = Dutch Echographic Cardiac Risk Evaluating Applying Stress Echo; DIPOM = Diabetes Postoperative Mortality and Morbidity; MaVS = metoprolol after surgery; POBBLE = perioperative beta-blockade; POISE = PeriOperative ISchaemic Evaluation trial.

Perioperative beta-blocker therapy and stroke

The increased risk for perioperative stroke in the POISE trial has caused serious concerns on the safety profile of perioperative beta-blocker therapy. In patients with a diseased cerebrovascular tree, perioperative hypotension, and bleeding an increased incidence of ischemic strokes was observed in those randomized to metoprolol. This has been augmented by the meta-analysis published in the same Lancet article [1]. The meta-analysis demonstrated that overall perioperative beta-blocker therapy was associated with a 2.19-fold (95% CI 1.06-4.50) increased risk for nonfatal perioperative stroke;

however, the DECREASE I, II and IV studies were not included. Recently, Bangalore et al. published a meta-analysis on the effect of perioperative beta-blocker therapy including 12,306 patients [19]. The results of this meta-analysis seem to confirm the findings of the POISE trial: a decrease (OR 0.65, 95% CI 0.54-0.79) in non-fatal myocardial infarction (number needed to treat 63) at the expense of an increase (OR 2.01, 1.27-3.68) in non-fatal strokes (number needed to harm 293). The authors concluded that current evidence does not support the use of beta-blocker therapy for the prevention of perioperative clinical outcomes in patients having non-cardiac surgery. Importantly, the impact of different dosing regimens, timing of initiation and type of beta-blocker therapy were not fully appreciated in these analyses. If the results of DECREASE I and IV are added to the meta-analysis, beta-blockers are still associated with an increased risk for perioperative stroke. However, as is shown in figure 2, the overall result in the randomized low-dose bisoprolol studies show no association with perioperative stroke at all (OR 1.06, 95% CI 0.32 – 3.56) in contrast to studies using metoprolol (OR 2.07, 95% CI 1.27 – 3.39). It should be noted that the cardioprotective effect was clear for both beta-blocker types; OR for bisoprolol 0.40 (95% CI 0.20 – 0.81) and OR for metoprolol 0.74 (95% CI 0.61 – 0.89, figure 1). The key question is whether it is the type of beta-blockers that makes the difference or that other factors play a significant role in these results. Considering this, there are several potential pitfalls in the perioperative administration of beta-blockers that should be considered including: timing of initiation of therapy, dosage of beta-blockers, the impact of beta-blocker withdrawal, and treatment targets.

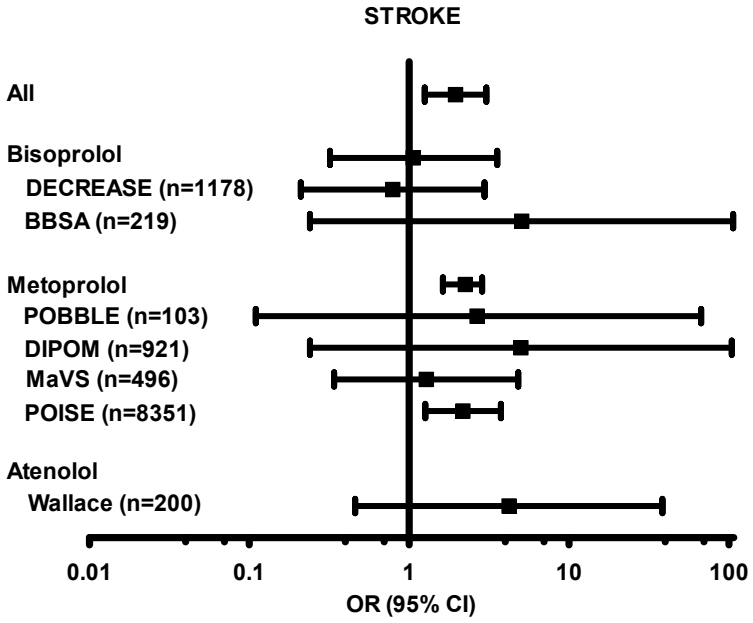

Figure 2: Odds ratios (OR) of randomized beta-blocker trials for perioperative stroke. BBSA = beta blocker in spinal anaesthesia; CI = confidence interval; DECREASE = Dutch Echographic Cardiac Risk Evaluating Applying Stress Echo; DIPOM = Diabetes Postoperative Mortality and Morbidity; MaVS = metoprolol after surgery; POBBLE = perioperative beta-blockade; POISE = PeriOperative ISchemic Evaluation trial.

Timing

Timing of initiation of perioperative beta-blocker therapy seems to play a pivotal role in the risk of stroke, as shown in figure 3. In patients undergoing surgery in which beta-blocker therapy is initiated within hours before surgery, there might be an increased risk of hypotension and bradycardia if beta-blockers are administered too aggressively. The response to beta-blocker therapy cannot be adequately monitored during this short period of time leading to a danger of overdosing. Although the sympathico-inhibitory effects of beta-blockers occur almost instantly, the anti-inflammatory effects may be observed only after prolonged treatment. As mentioned, in the Mangano et al study, the major benefits of atenolol were observed in the months after surgery [12]. In studies starting beta-blocker therapy hours before surgery, the incidence of postoperative stroke was higher compared to those who were on beta-blockers for at least a week prior to surgery. It should be noted that the same study group performed the two trials that started beta-blockade weeks in advance of surgery, using bisoprolol. Although bisoprolol is not commonly used in the US for patients with proven CAD, it would be interesting to determine whether other centers achieve similar results with this low-dose bisoprolol regimen. In most non-surgical studies, in particular in heart failure, there is a similar up titration of beta-blockers. In other words, beta-blocker therapy is started at a relative low dose and is subsequently up titrated according to blood pressure and heart rate. This approach has been shown to be effective and safe in heart failure patients [9]. Importantly, patients on chronic beta-blocker therapy should continue their therapy in the perioperative period as sudden beta-blocker withdrawal increases the risk of adverse cardiac events.[20]

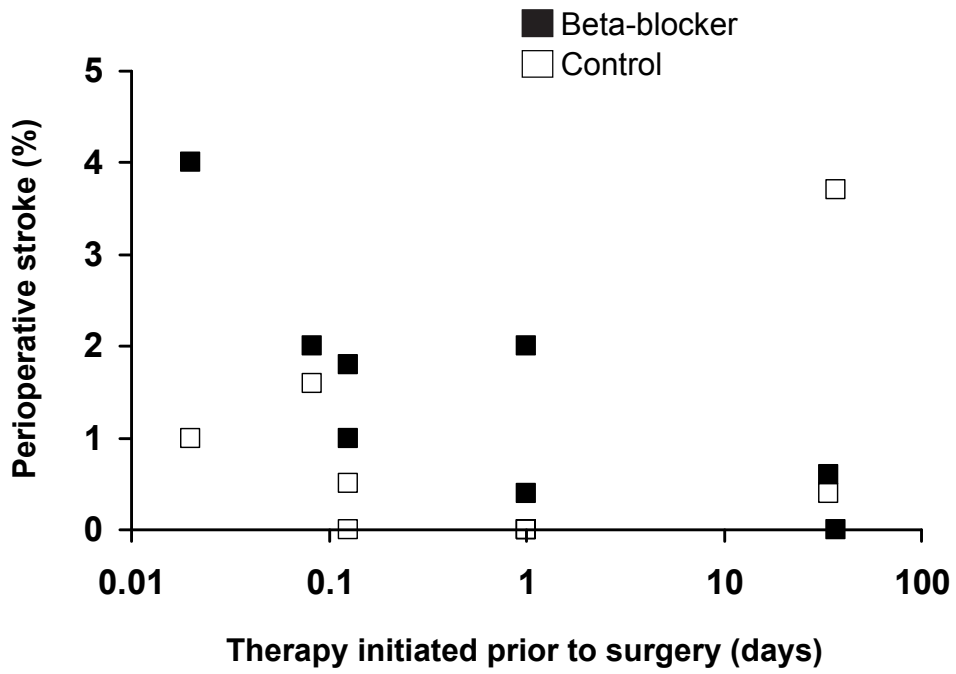

Figure 3: Relation between timing of initiation of beta-blocker therapy and the risk for perioperative stroke.

Dosing

Closely related to the issue of timing in perioperative beta-blocker therapy is the question regarding what dosing scheme should be used. In contrast to other beta-blocker studies, patients randomized in the POISE trial could receive up to 400 mg metoprolol succinate controlled release the day of surgery; 100 mg 2-4 hours prior to surgery, another 100 mg within 6 hours after surgery and 200 mg within 12-18 hours after the first postoperative dose. The use of high dose beta-blocker therapy may block the heart rate response to cope with hypotension e.g., due to bleeding. In the non-surgical setting, lower starting doses and slower up titration are commonly recommended. For instance, in patients with heart failure, 12.5–25 mg a day is started for 2 weeks and for hypertension the initial dose is 25–100 mg, usually increased at weekly intervals. This is important since a large proportion of high-risk elderly patients undergoing surgery may have some form of (asymptomatic) left ventricular dysfunction. The DECREASE IV treatment regimes start 2.5 mg bisoprolol, which is approximately the same strength as 50 mg of metoprolol. The starting dose of metoprolol succinate in the POISE trial was 2–8 times the commonly prescribed dose for perioperative beta-blocker therapy; other trials using metoprolol start usually at ranges from 50 to 100 mg per day[14-16]. It is noteworthy that in the DECREASE II trial, starting with 2.5 mg bisoprolol once daily, in approximately 75% of patients the target heart rate of 60-65 beats per minute was achieved without dose adjustment [21]. For safety reasons beta-blocker therapy is withheld in case of a systolic blood pressure lower than 100 mmHg or a resting heart rate less than 50 beats per minute. These criteria are nearly the same as used in the POISE study (100 mm Hg or a heart rate below 45 beats per minute).

Chronic Beta-Blocker use and stroke

Considering the results found in the POISE study, one should question what the effect of chronic beta-blocker use on (postoperative) stroke is. In recent literature questions are raised whether beta-blocker therapy should still be used as first-line therapy for hypertension [22-24] . The use of beta-blocker therapy as first-line treatment for hypertension was systematically evaluated in a Cochrane review by Wiysonge et al [25]. In this review the effectiveness and safety of beta-blockers on morbidity and mortality endpoints in adults with hypertension were evaluated. Compared to placebo, beta-blocker therapy was associated with a significant decrease in stroke (RR 0.80, 95%CI 0.66 to 0.96). However, there was an increased risk for stroke compared to other blood lowering medications; calcium-channel blockers (RR 1.24, 95% CI 1.11 to 1.40) and renin-angiotensin system inhibitors (RR 1.30, 95% CI 1.11 to 1.53). Considering these results beta-blockers should not be the drug of choice for the first-line treatment of hypertension. These results, however, cannot be extrapolated to beta-blocker use in the perioperative period. The initiation of beta-blocker therapy in patients at risk for cardiovascular complications in the perioperative period focuses on lowering on heart rate rather than blood pressure. It would be interesting to see if patients undergoing noncardiac surgery, who are on chronic beta-blocker use, would also be at risk for postoperative stroke. In a study by van Lier et al. 186,779 patients who underwent noncardiac surgery were evaluated for postoperative stroke [26]. Patients with intracerebral surgery, carotid surgery or head and / or carotid trauma were excluded.

In total 34 patients (0.02%) experienced a stroke within 30 days after surgery. Chronic beta-blocker use was as common in cases as in controls (29% vs 29%; P=1.0). The adjusted odds ratio for perioperative stroke among beta-blocker users compared to nonusers was 0.4 (95% confidence interval 0.1 to 1.5). Similar results were obtained in subgroups of patients according to the use of cardiovascular therapy and the presence of cardiac risk factors. These results show no increased risk for postoperative stroke after noncardiac surgery in patients on chronic beta-blocker use. This favours the dosing regime used in the DECREASE studies where beta-blocker therapy is initiated well in advance and is up carefully up titrated to a desired effect.

Other effects related to Beta-Blocker use and stroke

Lemaitre et al. [27] investigated the interaction of variations in beta adrenegeric receptor genes with beta-blocker use on the risk of MI and ischemic stroke. Several genetic variations in the beta-1 adrenergic receptor gene interacted with beta-blocker use in both risks for MI and ischemic stroke. Beta-blocker use was associated with higher risk of combined MI and ischemic stroke in carriers of rs#2429511 (OR: 1.24, 95% CI: 1.03–1.50) compared to carriers of common allele (OR: 0.70, 95% CI: 0.51–0.94). Two other major single nucleotide polymorphisms in beta adrenergic receptors genes (Ser49Gly and Arg389Gly) have been identified in several studies which might affect drug responses [28-30]. The role of these polymorphisms in the perioperative setting is still unclear. A number of clinical studies have associated acute anemia with cerebral injury in perioperative patients. Two recent large observational studies have demonstrated that the incidence of adverse composite cardiovascular outcomes, including stroke, increases in anemic cardiac surgical patients when the preoperative Hb level decreases below 12 g/dL [31,32]. In a study by Weiskopf et al. [33] healthy human volunteers demonstrated impairment in central neuronal processing and cognitive function after acute isovolemic anemia. Concurrent exposure to additional risk factors such as surgical stress, drugs which limit cardiovascular compensatory responses (e.g. beta-blockers), hemodynamic instability, cardiovascular co-morbidities, and advanced age could increase the risk of brain injury in perioperative patients. The combination of patients at risk of adverse cardiovascular complications, where the initiation of preoperative beta-blocker therapy might be indicated, and acute perioperative isovolemic hemodilution deserves thorough investigation. Finally beta-blockers have been implicated in altering glucose homeostasis, primarily through inhibition of pancreatic insulin secretion and promoting insulin resistance [34-36]. Insulin resistance is one of the main underlying physiological processes which may lead to the metabolic syndrome. In a meta-analysis by Galassi et al, it was indicated that individuals with the metabolic syndrome have a 61% increased risk of cardiovascular disease compared to individuals without the metabolic syndrome [37]. Beta-receptor selectivity appears to play a role in the degree of downstream metabolic effects, which include not only glucose increases but also weight gain and dyslipidemia. Nonselective and higher-dose selective agents result in the largest adverse metabolic changes. The mechanisms by which beta-blocker treatment modifies insulin sensitivity are not yet fully understood, but several possibilities exist. Insulin clearance is reduced in hypertensive patients and beta-blocker treatment appears to attenuate it further. As plasma insulin increases, the resulting hyperinsulinemia could down regulate the insulin receptors and consequently lower insulin sensitivity.

In conclusion, initiating prophylactic high-dose beta-blocker therapy in patients undergoing noncardiac surgery is associated with fewer cardiac events but with an increase in strokes and mortality. However, if prophylactic beta-blocker therapy is initiated at a low dose and up titrated in the preoperative period, the risk of stroke seems to be similar to that of patients not on beta-blockers while the cardioprotective effect is maintained. In these patients, strict hemodynamic control during surgery is mandatory. Preferably these results should be confirmed in a large-scale trial, starting beta-blocker weeks before surgery at a low dose, as well as determining the optimal approach in patients at high risk of perioperative cardiac morbidity and present the morning of surgery without having been placed on a beta-blocker. Patients on chronic beta-blocker therapy should continue medication. In patients with proven coronary artery disease beta-blocker therapy should be started sufficiently long prior to surgery to evaluate the hemodynamic impact. Importantly, hypotension and bradycardia should be avoided. Therefore a low-dose highly beta-1 selective drug is recommended.

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Effect of Chronic Beta-Blocker Use on Stroke After Noncardiac Surgery

Felix van Lier MD, Olaf Schouten MD, Ron T. van Domburg PhD,
Patrick J. van der Geest MD, Eric Boersma PhD,
Lee A. Fleisher MD, Don Poldermans MD PhD

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Abstract

Introduction:
The incidence of postoperative stroke ranges from 0.08 to 0.7% in noncardiac surgery. Recently the PeriOperative ISchemic Evaluation (POISE) study results reported an incidence of postoperative stroke of 1% in patients scheduled for noncardiac surgery when beta-blockers were initiated immediately prior to surgery.

Methods:
To assess the association between chronic beta-blocker use and postoperative stroke in noncardiac surgery we undertook a case-control study among 186,779 patients who underwent noncardiac surgery from 2000 to 2008 at the Erasmus Medical Center. Patients with intracerebral surgery, carotid surgery or head and/or carotid trauma were excluded. Case subjects were all 34 (0.02%) patients who experienced a stroke within 30 days after surgery. From the remaining patients, 2 controls were selected for each case and were stratified according to calendar year, type of surgery, and age. For cases and controls, information was obtained regarding beta-blocker use before surgery, the presence of cardiac risk factors, and the use of other cardiovascular medication.

Results:
Beta-blockers were as common in cases as in controls (29% vs 29%; P=1.0). The adjusted odds ratio for postoperative stroke among beta-blocker users compared to nonusers was 0.4 (95% confidence interval 0.1 to 1.5). Similar results were obtained in subgroups of patients according to the use of cardiovascular therapy and the presence of cardiac risk factors.

Conclusion:
This case-control study shows no increased risk for postoperative stroke in patients on chronic beta-blocker therapy.

Introduction

Recently, the results of the PeriOperative ISchemic Evaluation (POISE) study [1] and a meta-analysis by Bangalore et al [2] have pointed towards perioperative beta-blocker use as a potential cause of postoperative stroke. Beta-blockers in the non-surgical setting are widely used and have proven to be effective in patients with cardiovascular disease to restore the balance of myocardial oxygen demand and supply. In surgical patients several randomised studies have shown a beneficial cardiac effect of perioperative beta-blocker use in non-cardiac surgery. It is unclear whether this increased incidence of stroke is due to the sudden initiation of beta-blocker therapy or due to beta-blocker therapy itself. In the POISE study patients in the treatment group started taking high-dose beta-blockers 2-4 hours before surgery. Little is known about chronic beta-blocker use and the risk of postoperative stroke. The current study aimed to examine the possible association between chronic beta-blocker use and postoperative stroke in patients undergoing noncardiac surgery.

Methods

We undertook a case control study among the 186,779 patients, above the age of 18 years who underwent noncardiac surgical procedures between January 1 2000, and January 1 2008 at the Erasmus Medical Centre, 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. The discharge letters of all 186,779 patients were automatically scanned for the words 'stroke', 'transient ischemic attack (TIA)' or 'cerebrovascular accident (CVA)'. Positive matches were checked for the timing of the stroke, i.e. whether it concerned a history of cerebrovascular disease or whether it was a "new" stroke within 30 days after surgery. Patients presenting with stroke beyond 30 days after surgery as well as strokes after intracerebral surgery, carotid surgery or head and/or carotid trauma were excluded from the current study. Cases were included in the study if the presence of stroke was confirmed by CT-scan according to the criteria stated in the guidelines from the Stroke Council, American Heart Association [3]. As per hospital protocol all patients suspected to have an in-hospital stroke underwent a CT scan. We retrieved 3342 patients with a potentially postoperative stroke between January 2000 and January 2008 from the hospital information system after our initial search. From these 3342 patients, we identified 87 (0.05%) patients with a recorded stroke during or after non-cardiac surgery within 30 days after the operation. We excluded 39 patients who experienced a stroke after intracerebral surgery or carotid trauma; another 14 patients were excluded because stroke occurred after carotid surgery. After exclusion, 34 patients with a postoperative stroke remained for initial analysis. (Figure 1).

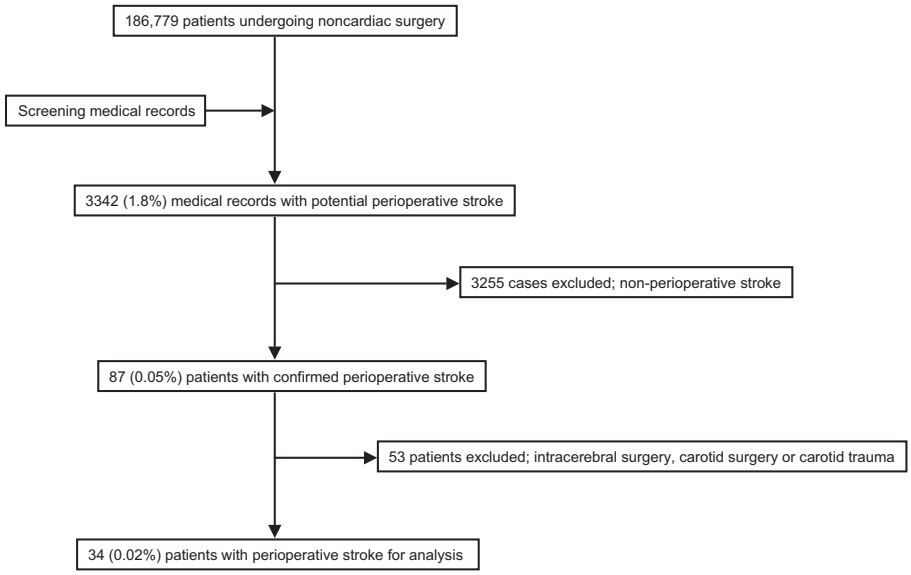

Figure 1: Study profile

From these 34 patients 6 patients (18%) had no evidence of stroke on the CT scan and where therefore classified as TIA. The other 28 patients (82%) were classified as ischemic stroke. For each case two controls were selected from the total surgical population of 186,779 patients. Cases and controls were matched according to age, sex, calendar year of surgery and type of surgery. Type of surgery was classified, according to the classification recommended by the American Heart Association/American College of Cardiology [4].

To study the relation between postoperative stroke and possible risk factors, including medication use, the computerized hospital database, patient medical records, nursing reports, surgical reports, anaesthetic reports and discharge letters were analyzed to obtain the following information on cases and controls: type of surgery, year of surgery, age, sex, presence of coronary heart disease, hypertension, heart failure, peripheral arterial disease, cerebrovascular disease, chronic obstructive pulmonary disease, diabetes, renal insufficiency, electrocardiographic abnormalities and smoking. Coronary heart disease was defined as a history of angina pectoris, myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention. Perioperative medication use was noted and included beta-blockers, statins, angiotensin-converting enzyme inhibitors, calcium channel blockers, angiotensin-II antagonists, nitrates, aspirin, dipyridamole and clopidogrel. Beta-blocker therapy was scored as chronic when medication was prescribed for more than one month prior to surgery. Beta-blocker dose was converted to a percentage of maximum recommended therapeutic dose (MRTD) according to the Food and Drug Administration's Center for Drug Evaluation and Research database [5]. The MRTD for atenolol was 3.330 mg/kg (body weight) per day, for bisoprolol 0.330 mg/kg (body weight) per day, for metoprolol 6.670 mg/kg (body weight) per day, for carvedilol 0.417 mg/kg (body weight) per day, for propranolol 10.700 mg/kg (body weight) per day, and for labetalol 40.700 mg/kg (body weight) per day. Unconditional logistic regression analyses were applied to

evaluate the relation between beta-blocker use and postoperative stroke. Stratified analyses were performed according to a number of clinically important baseline characteristics. To reveal a possible heterogeneity in odds ratios between subgroups of patients, interaction terms between the stratification characteristic and statin use were included in the models. Interaction was considered statistically significant at the classic 0.05 probability level. We adjusted for the stratification factors calendar year and type of surgery, and for a number of potential confounding factors, including age, gender, history of cardiovascular or cerebrovascular disease, and cardiovascular therapy. Individual factors were omitted from the regression models when stratification made adjustment inappropriate. We only report the adjusted odds ratios and corresponding 95% confidence intervals.

Results

Baseline clinical characteristics of cases and controls are presented in Table 1.

Table 1. Baseline patient characteristics of cases with perioperative stroke and matched controls undergoing non cardiac surgery*

Variable	Cases (N=34)	Controls (N=68)	p-value
Age (years)	72.4	71.4	0.63
Men	19 (56%)	38 (56%)	0.63
Coronary heart disease ‡	12 (35%)	14 (21%)	0.15
Hypertension	19 (56%)	24 (35%)	0.06
Heart failure	1 (3%)	5 (7%)	0.66
Peripheral arterial disease	3 (9%)	1 (2%)	0.11
Chronic obstructive pulmonary disease	2 (6%)	5 (7%)	1.0
Cerebrovascular disease	13 (38%)	4 (6%)	< 0.001
Diabetes mellitus	5 (15%)	1 (2%)	0.02
Renal dysfunction	8 (24%)	11 (16)	0.42
Current smoking	8 (24%)	9 (13%)	0.26
Atrial fibrillation	7 (21%)	5 (7%)	0.1
Medication use			
Statins	11 (32%)	11 (16%)	0.08
Beta-blockers	10 (29%)	20 (29%)	1.0
Angiotensin converting enzyme- inhibitors	5 (15%)	13 (19%)	0.78
Calcium channel blockers	11 (32%)	10 (15%)	0.07
Angiotenstin-II receptor blockers	2 (6%)	2 (3%)	0.6
Nitrates	0 (0%)	4 (6%)	0.03
Aspirin	18 (53%)	14 (21%)	0.01
Persantin	3 (9%)	0 (0%)	0.04
Type of surgery			
Hepatico/pancreatico/billary	3 (9%)	6 (9%)	
Esophagogastric	6 (18%)	12 (18%)	
Other abdominal	4 (12%)	8 (12%)	
Ear/nose/throat	3 (9%)	6 (9%)	
Reconstructive	1 (3%)	2 (3%)	
Urologic	2 (6%)	4 (6%)	
Renal transplant	1 (3%)	2 (3%)	
Orthopedic	11 (32%)	22 (32%)	
Vascular	3 (9%)	6 (9%)	

* Patients presenting with stroke beyond 30 days after surgery as well as strokes after intracerebral surgery, carotid surgery or head and/or carotid trauma were excluded

‡ Coronary heart disease was defined as a history of angina pectoris, myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention

The median day on which strokes occurred was the second postoperative day, interquartile range (IQR) 1-5. A history of hypertension, previous cerebrovascular disease and diabetes mellitus were significantly more common in cases than in controls. Chronic beta-blocker use was similar in cases and in controls (10 cases [29%] and 20 controls [29%]). In the 53 excluded patients beta-blocker use was similar as in the cases (16 out of 53 [30%]). In none of the cases beta-blockers were prescribed within one month of surgery. After adjustment for clinical risk factors, the risk of postoperative stroke among chronic beta-blocker users was not increased compared with nonusers (adjusted OR 0.4; 95% confidence interval 0.1 - 1.5) (Table 2).

Table 2. Adjusted odds ratios for perioperative stroke in relation to risk factors and medication using multivariable analysis. Data are adjusted for coronary heart disease, hypertension, cerebrovascular disease, diabetes mellitus, peripheral arterial disease and atrial fibrillation

	Adjusted odds ratio	95% confidence interval
Medical risk factors		
Coronary heart disease	3.7	1.1 - 12
Hypertension	1.4	0.5 - 4.0
Cerebrovascular disease	10.3	2.7 - 40
Diabetes mellitus	12.1	1.1 - 138
Peripheral vessel disease	8.0	0.6 - 98
Atrial fibrillation	5.2	1.1 - 24
Medication use		
Statins	1.4	0.3 - 5.6
Beta blockers	0.4	0.1 - 1.5
Angiotensin converting enzyme-inhibitors	0.4	0.1 - 1.2
Calcium channel blockers	0.7	0.2 - 2.1
Angiotensin-II receptor blockers	0.9	0.1 - 7.1
Aspirin	1.6	0.6 - 4.4

The percentage of maximum recommended therapeutic dose was also similar in cases and controls of beta-blocker users (median 25% vs 25%, p=0.239). There was no evidence of heterogeneity in incidence of stroke among beta-blocker users compared to nonusers between subgroups of patients according to clinically important baseline characteristics or type of surgery (Figure 2).

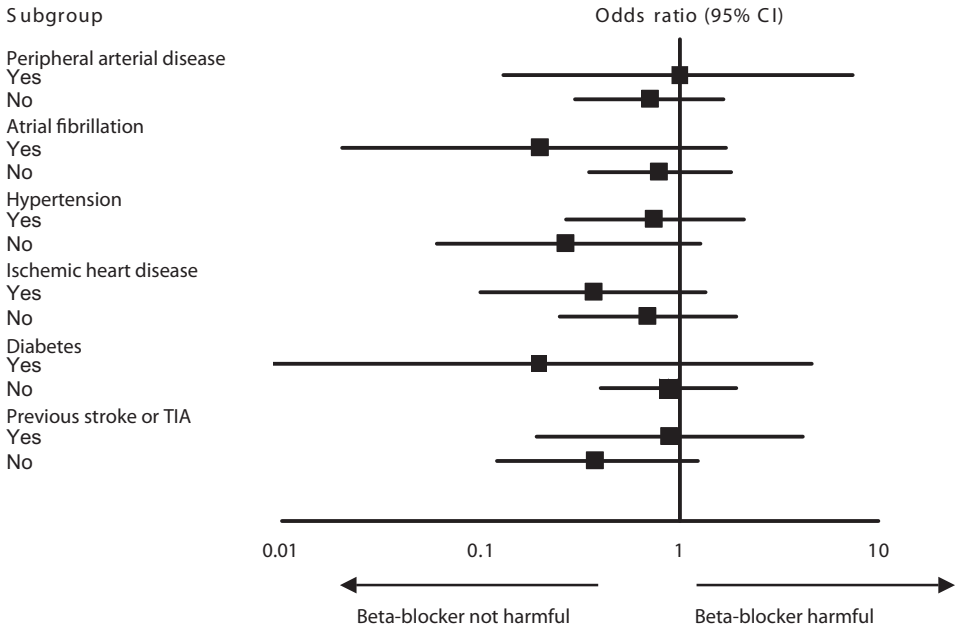

Figure 2: Odds ratios for perioperative stroke in relation to beta-blocker use in selected subgroups of patients.

Aspirin was more frequently used in cases than in controls (18 cases [53%] and 14 controls [21%]; P=0.01). Aspirin use was associated with a high prevalence of cardiovascular disease, including myocardial infarction and stroke. After adjustment for these differences, aspirin use was no longer associated with an increased risk of postoperative stroke (adjusted OR 1.6; 95% confidence interval 0.6 - 4.4) (Figure 3).

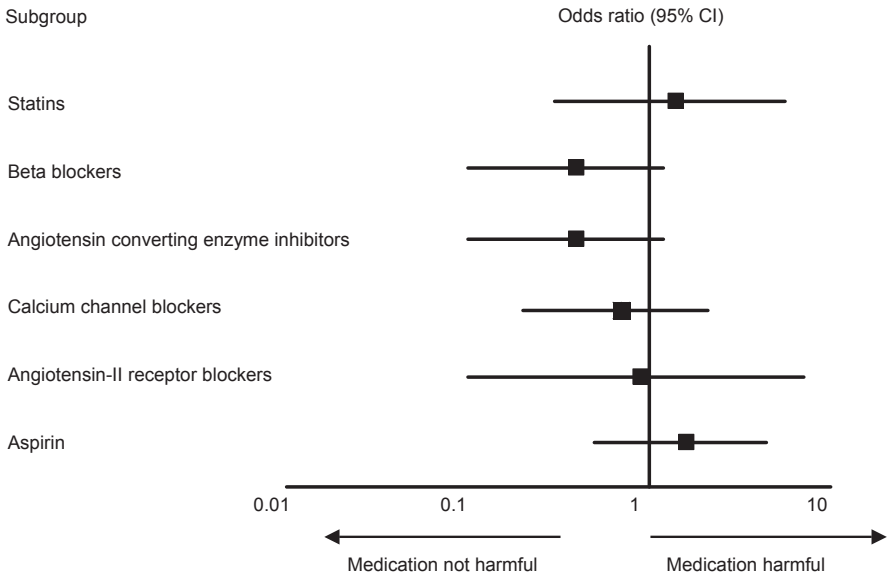

Figure 3: Odds ratios for postoperative stroke in relation to medication use

Statin therapy was more common in cases than in controls (11 cases [32%] and 11 controls [16%]; P=0.08). This higher incidence, though not significant, might be related to the higher prevalence of cardiovascular disease in the cases. After adjustment for these differences, statin therapy was no longer associated with an increased risk of postoperative stroke (adjusted OR 1.4; 95% confidence interval 0.3 to 5.6).

Discussion

This case-control study among 186,779 patients undergoing noncardiac surgery demonstrates that chronic beta-blocker use, started at least one month prior to surgery, is not associated with postoperative stroke. Overall the incidence of postoperative stroke in our study (0.05%) is low compared to previous studies [6,7]. No association was observed between the dose or type of beta-blockers and stroke. This result is consistent in subgroups of patients according to various risk factors. A history of a previous cerebrovascular accident is the greatest risk factor for a new stroke in the postoperative period (adjusted OR 10.3). Limburg et al [8] found that patients with previous cerebrovascular disease even had more than a 12-fold increased risk for postoperative stroke. The presence of atrial fibrillation has been found to be a second important risk factor for stroke in patients undergoing non-cardiac surgery. Further evidence that perioperative atrial fibrillation is a major risk factor is provided by the studies by Larsen et al [7] and Parikh et al [9]. Other risk factors for postoperative stroke in our study, a history of coronary heart disease and diabetes mellitus, are similar as found in previous studies [6,7,10-12]. The POISE study[1] was a landmark trial which investigated the use of perioperative beta-blockers. At 30 days, the incidence of the primary composite endpoint (cardiovascular death, nonfatal myocardial infarction, or nonfatal cardiac arrest) was lower with metoprolol than with placebo (5.8% vs. 6.9%; P=0.04). This difference was driven by a significantly lower incidence of nonfatal MI in the metoprolol group (3.6% vs. 5.1%; P=0.001). However, overall mortality was higher in the metoprolol group than in the placebo group (3.1% vs. 2.3%, P=0.03), as was stroke incidence (1.0% vs. 0.5%; P=0.005). These findings were confirmed in a recent meta-analysis by Bangalore et al [2] of 33 randomised trials on perioperative beta-blocker treatment. They also found a protective effect of perioperative beta-blockade on non-fatal myocardial infarction, but at the expense of more non-fatal strokes. However, Bangalore et al acknowledged the influence of the POISE study in their analyses, especially since other studies failed to show a significant relation between beta-blocker use and postoperative stroke. The mechanism how beta-blockers would contribute to an increased risk for postoperative stroke in noncardiac surgery is not fully understood. The authors from the POISE study found that stroke was associated with perioperative hypotension (Population Attributable Risk (PAR)=14.6%), bleeding (PAR=10.1%), atrial fibrillation (PAR=6.9%), and a history of stroke or transient ischemic attack (PAR=30.5%). Overall preoperative, intraoperative and postoperative predictors could explain only 51.8% of the strokes. With the lack of evidence for any direct correlation between the initiation of beta-blocker therapy and postoperative stroke, the exact mechanism of postoperative stroke remains unclear. Comments by Boersma and Poldermans have been made regarding the timing prior to surgery and the high dose metoprolol succinate used in the POISE trial [13,14]. In patients undergoing surgery in which beta-blocker therapy was initiated within hours before surgery, there might be an increased risk of hypotension

and bradycardia if beta-blockers were administered without titration. The response to beta-blocker therapy cannot be adequately monitored during this short period of time leading to a danger of overdosing on a patient group who are already at risk for cardiovascular complications. The increased incidence of stroke found in the POISE study might therefore be due to the sudden initiation of a high dose rather than beta-blocker therapy itself. Beta-blockers still form a cornerstone of chronic cardiovascular medication for patients with coronary heart disease and congestive heart failure. Slowly up titrating beta-blocker therapy, starting at a relative low dose and subsequently up titrating according to blood pressure and heart rate, is considered standard care in the non-surgical setting for patients with heart failure. This approach has been shown to be effective and safe in heart failure patients and is advocated in the ESC guidelines[15]. More importantly, patients on chronic beta-blocker therapy should continue their therapy in the perioperative period as sudden beta-blocker withdrawal increases the risk of adverse cardiac events [16,17]. Hoeks et al [16] demonstrated this in a prospective survey among 711 patients scheduled for peripheral vascular surgery. In the group of patients who continued beta-blocker therapy in the postoperative period 1-year mortality rate was 6%, while in the group of patients who discontinued their beta-blocker therapy the 1-year mortality rate rose to 38%. After adjustment beta-blocker withdrawal was associated with an increased risk of 1-year mortality compared to non-users (HR=2.7; 95% CI=1.2-5.9). This study adds to safety for the use of chronic beta-blocker in the perioperative period.

Our study has several limitations that are common with any study relying on retrospective data collection. Multivariable adjustments for potential confounders is obviously limited to the available data, and unknown unmeasured confounders, might still be present. Perioperative hemodynamic data, clarifying how beta-blockers would change patients hemodynamic state, are also hard to distillate in retrospective studies. Therefore, we emphasize that this evidence needs conformation by adequately randomised clinical trials. Given the low incidence rate of postoperative stroke in noncardiac surgery, we repeat our call to colleagues who are working on similar trials to release data about clinical conditions and hemodynamic changes. This will be the key to further research.

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4

Impact of Prophylactic Beta-Blocker Therapy to Prevent Stroke After Noncardiac Surgery

Felix van Lier MD, Olaf Schouten MD PhD, Sanne E. Hoeks PhD, Louis van de Ven MD PhD, Robert Jan Stolker MD PhD, Jeroen J. Bax MD PhD, Don Poldermans MD PhD

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Abstract

Introduction:
Beta-blockers are widely used to improve postoperative cardiac outcome in patients with coronary artery disease scheduled for noncardiac surgery. However, recently serious concerns regarding the safety of perioperative beta-blockers have emerged.

Methods:
In order to assess the incidence, risk factors and beta-blocker use associated with postoperative stroke in the DECREASE trials, we evaluated all 3884 patients of the DECREASE trials for postoperative stroke. All cardiac risk factors and medication use were assessed. The incidence of stroke within 30 days after surgery is reported.

Results:
The incidence of postoperative stroke in the DECREASE trials was 18/3884 (0.46%). Among beta-blocker users, the incidence was 0.5%. All of the strokes had an ischemic origin. A history of stroke was associated with higher incidence of postperative stroke: OR 3.79, 95% CI 1.2-11.6. Statins and anti-coagulants were not associated with postoperative stroke; OR 0.85; 95% CI 0.3-2.4 and OR 1.27, 95% CI 0.4-4.6. No association with bisoprolol therapy was found, OR 1.16, 95% CI 0.4-3.4.

Conclusion:
With a low dose bisoprolol regimen started at least 30 days prior to surgery no association can be observed between beta-blocker use and postoperative stroke.

Introduction

Beta-blockers are prescribed in the perioperative period to reduce myocardial oxygen consumption by decreasing sympathetic tone and myocardial contractility. Several randomised clinical trials have shown beneficial effects of initiating beta-blockers to patients at risk for cardiovascular complications [1,2], while other trials failed to show any significant improvement in outcome [3,4]. In order to resolve these inconsistencies a large multinational randomised controlled trial was started in 2002: the PeriOperative ISchemic Evaluation (POISE) trial [5].

POISE randomly assigned 8351 patients with, or at risk of atherosclerotic disease who were undergoing noncardiac surgery to receive extended-release metoprolol succinate (n=4174) or placebo (n=4177). In the POISE trial high doses of metoprolol, up to 400 mg was administered in four doses starting 2 to 4 hours prior to surgery and was continued for 30 days. The 30 day results showed a significant reduction in cardiac events. However, this came at the cost of a significant increase in total mortality and stroke. The high incidence of stroke found in the POISE trial makes one question the liberal use of beta-blockers during the perioperative period.

In the DECREASE trials (Dutch Echographic Cardiac Risk Evaluation Applying Stress Echo), a low-dose beta-blocker regimen was used. No relation was found between stroke and beta-blocker use. However, this experience was based on individual DECREASE studies with associated weak statistical power. Therefore we combined the results of the DECREASE I, II, and IV studies to evaluate the effect of low-dose beta-blocker use in the perioperative period on postoperative stroke and identify risk factors for postoperative stroke.

Methods

We performed a pooled analysis of all 3884 patients, who were enrolled in the DECREASE I (1996-1999), DECREASE II (2000-2005), and DECREASE IV (2004-2008) trials [2,6,7]. We did not include the DECREASE III trial because this was a randomised controlled trial in wich vascular surgery patients were randomised for satins or placebo. The DECREASE I was a randomised controlled trial that clearly demonstrated a cardioprotective effect of bisoprolol, in high-risk patients undergoing major vascular surgery. The aim of the DECREASE-II study was to assess the value of cardiac testing according to the ACC/AHA (American College of Cardiology/American Heart Association) guidelines in intermediate-risk patients receiving beta-blocker therapy with tight heart rate control scheduled for major vascular surgery. DECREASE IV was a large prospective, randomised trial aiming to assess the effect of different pharmaceutical strategies (Beta-blockers, statins or both) to prevent perioperative cardiac complications in intermediate-risk patients. The results and study protocols have previously been published in detail [2,6,7] . The following potential risk factors for postoperative stroke were recorded from all trials and included in the current analysis: age over 70 years, angina pectoris, prior myocardial infarction (MI) on the basis of history or a finding of pathologic Q waves on electrocardiography, compensated congestive heart failure or a history of congestive heart failure, drug therapy for diabetes mellitus, renal dysfunction (serum creatinine >160 μmol/l), and prior stroke or transient ischemic attack. Throughout the DECREASE I, II and IV studies the definition of the several risk factors were not changed.

Also, the type and dosage of perioperative beta-blocker use were noted. Beta-blocker dose was converted to a percentage of maximum recommended therapeutic dose (MRTD) according to the Food and Drug Administration's Center for Drug Evaluation and Research database [8]. The MRTD for atenolol is 3.330 mg/kg (body weight) per day, for bisoprolol 0.330 mg/kg (body weight) per day, for metoprolol 6.670 mg/kg (body weight) per day, for carvedilol 0.417 mg/kg (body weight) per day, for propranolol 10.700 mg/kg (body weight) per day, and for labetalol 40.700 mg/kg (body weight) per day. The endpoint for the current study was stroke, either a transient ischemic attack or cerebrovascular accident within 30 days after surgery. Stroke was confirmed by CT-scan according to the criteria stated in the guidelines from the Stroke Council, American Heart Association [9]. As per protocol all patients suspected to have an in-hospital stroke were evaluated by CT scan. Since the results of the POISE trial urged us to perform this analysis, we also compared the rate of strokes of POISE trial reported in the recently published paper. We also compared both studies concerning possible risk factors for postoperative stroke.

Continuous data are described as mean values and standard deviation (±SD) or median values and interquartile range. Dichotomous data are described as numbers and percentages. Logistic regression analysis was used to identify clinical characteristics and medical therapy (statins, beta-blockers, antiplatelet agents, oral anticoagulants) associated with postoperative stroke. Interaction terms were included if statistically significant. Odds ratios (OR) are reported with corresponding 95% confidence interval (CI). For all tests, a P-value < 0.05 (two-sided) was considered significant. All statistical analyses were performed using SPSS 15.0 for Windows.

Results

The baseline clinical characteristics of patients included in DECREASE I, II, and IV are shown in table 1

Table 1. Baseline characteristics of patients in the DECREASE and POISE trial

Variable	DECREASE I (N=1351)	DECREASE II (N=1467)	DECREASE IV (N=1066)	OVERALL DECREASE (N=3884)	POISE (N=8351)
Age (years)	67,5	67.0	66.8	67.1	69.0
Male gender	1050 (77%)	1075 (73%)	639 (60%)	2764 (71%)	5293 (63%)
Ischemic heart disease				1596 (41%)	3589 (43%)
Myocardial infarction	562 (42%)	396 (27%)	54 (5%)	1012 (26%)	
Angina pectoris	229 (17%)	808 (55%)	55 (5%)	1092 (28%)	
Heart failure	96 (7%)	168 (11%)	8 (1%)	272 (7%)	220 (3%)
Diabetes mellitus	187 (13%)	320 (21%)	115 (11%)	622 (16%)	2427 (29%)
Cerebrovascular disease	104 (8%)	280 (19%)	46 (4%)	428 (11%)	1263 (15%)
Renal dysfuction	59 (4%)	124 (8%)	11 (1%)	194 (5%)	401 (5%)
Medication use					
Statins	285 (21%)	617 (42%)	533 (50%)	1435 (37%)	2677 (32%)
Angiotensin converting enzyme inhibitors	394 (29%)	478 (32%)	96 (9%)	968 (25%)	3717 (44%)
Aspirin	406 (30%)	664 (45%)	102 (9%)	1174 (30%)	3011 (36%)

The key characteristics were as follows: mean age 67 years; 71% male; 16% diabetes mellitus; 28% angina pectoris; 26% prior myocardial infarction; 11% history of cerebrovascular disease. Overall 37% of the patients were on statin therapy; patients in the DECREASE IV study were randomised for statin therapy. The majority of patients (73%) underwent vascular surgery. The incidence of postoperative stroke in the DECREASE trials was 18/3884 (0.46%). Three strokes occurred in DECREASE I, eight strokes in DECREASE II and seven in DECREASE IV.

Table 2. Baseline patient characteristics of patients with postperative stroke

Variable	N= 18
Age (years)	71.6
Male gender	13 (72%)
Myocardial Infraction	5 (27%)
Angina Pectoris	1 (5%)
Heart failure	0 (0%)
Diabetes mellitus	3 (16%)
Cerebrovascular disease	6 (33%)
Renal dysfunction	1 (5%)
Medication use	
Beta-blocker	12 (67%)
Statins	11 (32%)
ACE inhibitors	4 (22%)
Aspirin	8 (44%)
Type of surgery	
Colorectal	1 (5%)
Esophagogastric	3 (16%)
Ear/nose/throat	1 (5%)
Urologic	1 (5%)
Orthopedic	1 (5%)
Vascular	11 (61%)

Baseline characteristics of stroke patients are shown in table 2.
Perioperative beta-blocker use was present in 12/18 (67%) patients who suffered an postoperative stroke. The average dose of bisoprolol used among stroke patients was 15% of the MRTD. Among beta-blocker users, the incidence was 12/2366 (0.5%). All strokes had an ischemic origin. The median day on which strokes occurred was the second postoperative day, interquartile range (IQR) 1-4. A history of stroke was associated with postoperative stroke: OR 3.79, 95% CI 1.2-11.6. Statins and anti-coagulants were not associated with postoperative stroke; OR 0.85; 95% CI 0.3-2.4 and OR 1.27, 95% CI 0.4-4.6. No association with bisoprolol therapy was found, OR 1.16, 95% CI 0.4-3.4 (table 3).

Discussion

This study shows that low dose bisoprolol started at least 30 days prior to surgery is not associated with an increased risk for postoperative stroke. Compared to the increased risk for postoperative stroke found in the POISE study (OR 2.2, 95% CI 1.3-3.8), we did not find a significant increased risk for postoperative stroke (OR 1.16, 95% CI 0.4-3.4). The key question is how this difference could be explained. To explain the difference in odds ratios found, several aspects should be considered including: indication for perioperative beta-blocker therapy, timing of initiation of therapy, type of beta-blockers, dosage and treatment targets.

Table 3. Adjusted odds ratios for perioperative stroke in relation to risk factors and medication using multivariable analysis.

	Odds Ratio	95% Confidence Interval
Medical risk factors		
Age (per year increase)	1.04	0.99 - 1.10
Male gender	1.41	0.45 - 4.42
Ischaemic heart disease	0.40	0.13 - 1.21
Cerebrovascular disease	3.79	1.24 - 11.6
Diabetes mellitus	0.88	0.31 - 3.93
Medication use		
Beta blockers	1.16	0.40 - 3.35
Statins	0.85	0.30 - 2.40
Antiplatelet therapy	1.75	0.60 - 5.15
Oral anticoagulants	1.27	0.35 - 4.64

The 2007 update on perioperative beta-blocker therapy in the American College of Cardiology and American Heart Association (ACC/AHA) guidelines for perioperative cardiovascular assessment for noncardiac surgery recommends beta-blockers for patients already on therapy or those who are having vascular surgery and have ischemia on preoperative testing (class I). Beta-blocker therapy is also recommended for patients undergoing vascular surgery or intermediate or high-risk non-vascular surgery and have a high risk for coronary disease or those with established disease (class II) [10]. Some randomised trials, including POISE, do not support the recommendations in the guidelines and have shown no beneficial effect of perioperative beta-blockade [3-5,11]. In a review Lindenauer et al. attempted to identify risk categories that may benefit or be harmed by beta-blockers [12]. They found that individuals with the highest risk, stratified according to the revised cardiac risk index by Lee [13], showed the greatest benefit from beta-blockade. However, those in the low to moderate risk categories showed a trend towards harm from beta-blockade due to bradycardia and hypotension. Therefore patient evaluation and selection is the first and most import element before beta-blocker therapy should be initiated. The DECREASE I trial included patients within the highest risk category: inducible ischemia on dobutamine stress echocardiography. The POISE study as well as the DECREASE II and IV trials included patients who were low to moderate risk patients. Although the inclusion criteria of both studies were roughly the same, the results were different. Therefore other aspects of beta-blocker initiation should be evaluated. The timing of initiation plays is a second key element. By starting beta-blockers hours before surgery, adverse effects from beta-blockers, might be overlooked. The response to beta-blocker therapy in these patients cannot be adequately assessed in this short period of time and the danger of overdosing these patients seems obvious. In studies starting beta-blocker therapy hours before surgery, the incidence of postoperative stroke was higher compared to those who were on beta-blockers for at least a week prior to surgery [2-5,7,11,14]. Evidence also suggest that acute effects of beta-blockade (decreased heart rate, systolic pressure, and reduced myocardial ischemia) may not fully explain the benefit of perioperative therapy, since anti-inflammatory and plaque-stabilizing properties take days to develop [15]. In heart failure patients it has been shown safe and effective to start beta-blocker therapy at a relative low dose and subsequently slowly uptitrate to blood pressure and heart rate

[16]. Thirdly, the type of beta-blocker used may have led to different study outcomes. Although both POISE and DECREASE trials clearly demonstrated cardioprotective effects from beta-blockers, some evidence suggests that beta-blockers which are highly beta-1 selective show better results than those which are moderately beta-1 selective. This may explain why bisoprolol (highly beta-1 selective) has been associated with better results, whereas metoprolol and atenolol (moderately beta-1 selective) are associated with mixed results in clinical trials. In a study by Redelmeier et al, among 37151 patients receiving perioperative beta-blockers, longer-acting agents (atenolol) show greater cardioprotection than short-acting agents (metoprolol) [17]. Fourthly, genetic en cultural differences may play an import role. Lemaitre et al. [18] investigated the interaction of variations in beta adrenegeric receptor genes with beta-blocker use on the risk of myocardial infarction (MI) and ischemic stroke. Several genetic variations in the beta-1 adrenergic receptor gene interacted with beta-blocker use in both risks for MI and ischemic stroke. Beta-blocker use was associated with higher risk of combined MI and ischemic stroke in carriers of rs#2429511 (OR: 1.24, 95% CI: 1.03–1.50) compared to carriers of common allele (OR: 0.70, 95% CI: 0.51–0.94). Two other major single nucleotide polymorphisms in beta adrenergic receptors genes (Ser49Gly and Arg389Gly) have been identified in several studies which might affect drug responses [19,20]. The role of these polymorphisms in the perioperative setting is still unclear. Similarly, interethnic difference in the response to beta-blocker therapy has been reported. African American patients are shown to respond poorly and Chinese patients respond well to beta-blockers [21]. These intercultural differences might easily lead to overdosing or underdosing and therefore does not favour a fixed dose regime. Since more than 40% of the patients included in the POISE trial were from Asian and South-American origin, a subanalysis in these patient groups would be justified. Finally the balance between beta-blockers dose to achieve target heart rates in relation to drug side effects should be optimised. The bisoprolol dose used in the DECREASE studies is 10-20% of the maximum recommended therapeutic dose (MRTD), while POISE used 50-100% of the MRTD of metoprolol. Both POISE and DECREASE withheld the administration of beta-blockers if the heart rate dropped below 50 bpm or if the systolic blood pressure dropped below 100 mmHg. The importance of heart rate control has been shown in several studies: the trials that achieve the most effective control of heart rate are associated with a reduced incidence of postoperative MI suggesting that effective control of heart rate is a key item for achieving cardioprotection [22-24]. Both the DECREASE and POISE study show that, although they have different treatment protocols, beta-blockers are effective in reducing perioperative cardiac complications. POISE prescribes a high dose immediately prior to surgery, while DECREASE favours a dose titration approach over a prolonged period. However, the cardioprotective effect of high dose regimen comes at the cost of an increased incidence of side effects, such as stroke. In a recent review article by Bangalore et al 112 randomised controlled trials on perioperative beta-blocker use were analysed [25]. They concluded that for the overall cohort treatment of 1000 patients with beta-blockers results in 16 fewer non-fatal myocardial infarctions in survivors but at the expense of three disabling strokes, 45 patients with clinically significant perioperative bradycardia, 59 with hypotension, and potentially increased mortality. The overall odds ratio for perioperative non-fatal stroke was 2.16 (95% CI 1.27 – 3.68). This was mainly driven by the results from the POISE study, especially since other randomised controlled trials failed to show

a significant correlation between perioperative beta-blocker use and postoperative stroke. Unfortunately, the results from the DECREASE studies were not taken into account in the analysis. We believe that the protocol utilized in the DECREASE studies (low dose long-acting agents titrated to effect at least 30 days in advance) is associated with overall benefit compared to risk, while high dose therapy started the morning of surgery is associated with increased risk than benefit.

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5

Intraoperative cardiac arrest during noncardiac surgery:

a single center case-control study

Felix van Lier MD, Yvette R.B.M. van Gestel PhD, Jaap W. Hol MD,
Sanne E. Hoeks PhD, Frank Grüne MD, Robert Jan Stolker MD PhD,
Lee A. Fleisher MD, Don Poldermans MD PhD

Submitted

Abstract

Introduction:
The authors determined the incidence and risk factors for intraoperative cardiac arrest in large population of elective surgical patients at a tertiary referral center in the Netherlands.

Methods:
We undertook a case-control study among 309,639 patients who underwent noncardiac surgery from 1991 to 2008 at the Erasmus Medical Center. Patients presenting for emergency surgery as well as intensive care patients were excluded. Case subjects were all 42 patients who experienced an intraoperative cardiac arrest. From the remaining patients, 2 controls were selected for each case and were stratified according to calendar year, type of surgery, type of anesthesia, sex, and age.

Results:
Cardiac arrest occurred in 42 of 309,639 anesthetics (1.4 per 10,000) during the study period. A history of coronary heart disease was more common in cases then in controls (26% vs 8%; $P < 0.05$). Cases had a significant lower level of hemoglobin preoperative (Males: 12.0 vs 13.7 g/dl, Females: 12.0 vs 12.9 g/dl; $P=0.003$). The adjusted odds ratio for intraoperative cardiac arrest among patients with a history of coronary heart disease was 4.0 (95% confidence interval 1.3 to 12). A lower hemoglobin level preoperative was associated with an increased risk for intraoperative cardiac arrest (OR 0.66; 95% CI 0.50 - 0.87).

Conclusion:
A history of coronary heart disease as well as a preoperative anemia are known risk factors for adverse cardiac events postoperatively and are also associated with an increased risk for intraoperative cardiac arrest.

Introduction

Intraoperative cardiac arrest is a devastating complication. Over the past several decades the rate of intraoperative cardiac arrest is declining, although comparisons between studies are difficult due to different populations and definitions used. The widespread implementation of medical guidelines and improvement in patient care has led to an increase in patient safety and a decrease in anesthesia related deaths. The incidence of intraoperative cardiac arrests, associated with anesthesia, varies between 0.5 to 23 per 10,000 anesthetics [1-5]. This incidence is low compared to the incidence of major adverse cardiac events postoperatively. Several risk indices have been developed for predicting postoperative adverse cardiac events in patients undergoing noncardiac surgery, while it remains difficult to predict patients at risk for intraoperative adverse cardiac events. In this single center, case-control study we aimed to examine risk factors for intraoperative cardiac arrest in patients undergoing noncardiac surgery.

Methods

The study was approved by the Medical Ethics Committee of the Erasmus Medical Center. Since the data were recorded retrospectively and without any specific intervention, the Medical Ethics Committee agreed to waive informed consent. We undertook a case control study among all patients, above the age of 18 years who underwent noncardiac surgical procedures between January 1 1990, and January 1 2008 at the Erasmus Medical Center, 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. The surgical and anesthetic reports of all 309,639 patients were automatically scanned for the words 'cardiac arrest', 'cardiopulmonary resuscitation (CPR)', 'chest compressions' or 'cardiac massage'. Positive matches were checked for type of surgery and time of perioperative cardiac arrest. Cardiac arrest was defined as an intraoperative event that required resuscitation with either closed-chest compressions or open cardiac massage. Cardiac arrests that occurred during cardiac surgery, cardiac catheterisations as well as cardiac arrests in the recovery room or in the intensive care unit were not included. Due to selection bias we excluded all patients presenting for emergency surgery as well intensive care patients. Emergency surgery was defined as surgery in hemodynamic instable patients (e.g. ruptured abdominal aorta, blunt and penetrating trauma with prehospital blood loss). We retrieved 380 patients with an intraoperative cardiac arrest between January 1990 and January 2008 from the hospital information system after our initial search. From these 380 patients, we excluded 270 patients because patients underwent cardiac surgery; another 68 patients who underwent emergency surgery or were preoperatively admitted to the intensive care unit were excluded. After exclusion, 42 patients with an intraoperative cardiac arrest remained for initial analysis (Figure 1).

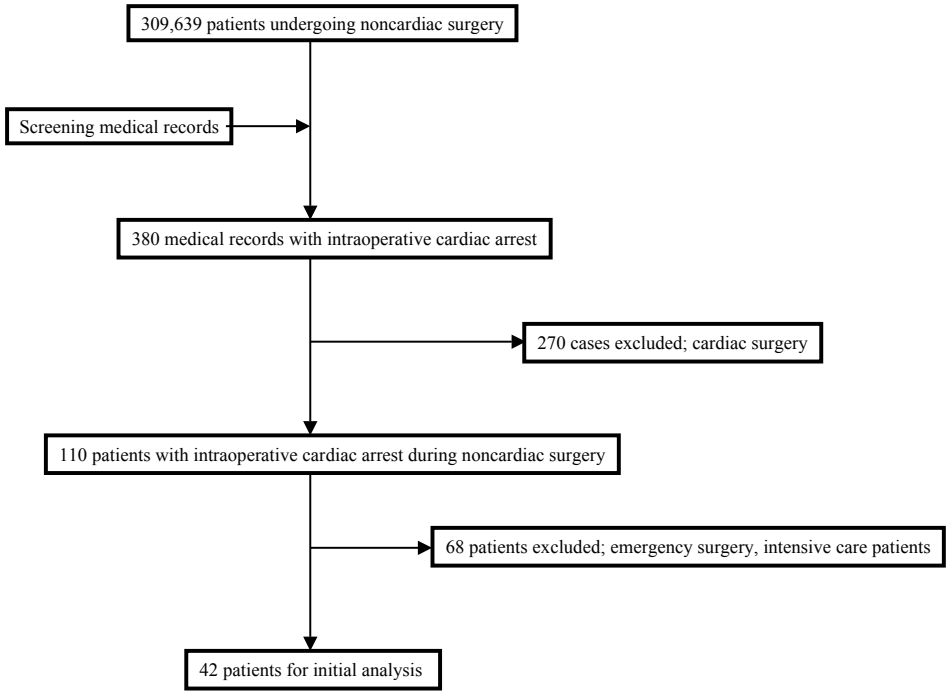

Figure 1: Study profile

All 42 patients were screened by an attending anesthesiologist at the outpatient clinic preoperatively and were found to be fit for surgery. For each case two controls were selected from the total surgical population of 309,639 patients. Cases and controls were matched according to age, sex, calendar year of surgery, type of anesthesia and type of surgery. Type of surgery was classified, according to the classification recommended by the American Heart Association/American College of Cardiology [6]. The computerized hospital database, patient medical records, nursing reports, surgical reports, anesthetic reports and discharge letters were analyzed to obtain the following information on cases and controls: type of surgery, year of surgery, age, sex, presence of coronary heart disease, heart failure, peripheral arterial disease, cerebrovascular disease, diabetes mellitus, renal insufficiency and electrocardiographic abnormalities. We also noted the estimated blood loss at the time the arrest took place. Coronary heart disease was defined as a history of angina pectoris, myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention. Perioperative medication use was noted and included beta-blockers, statins, and aspirin. We also noted the preoperative hemoglobin level (g/dl). Unconditional logistic regression analyses were applied to evaluate the relation between risk factors and intraoperative cardiac arrest. Stratified analyses were performed according to a number of clinically important baseline characteristics. To reveal a possible heterogeneity in odds ratios between subgroups of patients, interaction terms between the stratification characteristic and hemoglobin level use were included in the models. Interaction was considered statistically significant at the classic 0.05 probability level. Since the interaction terms were not significant for the prediction of intraoperative cardiac arrest, it was not

included in the final logistic regression model. We adjusted for the stratification factors calendar year and type of surgery, and for a number of potential confounding factors, including age, gender, history of cardiovascular disease, and cardiovascular therapy. Individual factors were omitted from the regression models when stratification made adjustment inappropriate. We only report the adjusted odds ratios and corresponding 95% confidence intervals.

Results

The overall incidence of cardiac arrest was 1.4 per 10,000 anesthetics. Over the 18-year study period the incidence of cardiac arrest remained the same over time, with around 2 per year. The majority, 41 patients (98%), received general anesthesia. One patient received spinal anesthesia. One patient with laryngeal cancer suffered cardiac arrest due to the loss of airway patency. Baseline clinical characteristics of cases and controls are presented in Table 1. A history of coronary heart disease was significantly more common in cases than in controls. Patients who suffered cardiac arrest had a lower preoperative hemoglobin level (Males: 12.0 vs 13.7 g/dl, Females: 12.0 vs 12.9 g/dl; P=0.003). Beta- blocker, statin and aspirin use was as common in cases as in controls. The overall intraoperative survival rate among patient with cardiac arrest was 27 out of 42 patients (64%). The primary electrocardiographic rhythm recorded was pulseless electrical activity in 15 (36%) patients, bradycardia in 8 (19%) patients, ventricular fibrillation in 4 (9%) patients and asystole in 15 (36%) patients (table 2). There was no major difference in blood loss at the time the arrest occurred. Estimated blood loss in cases: median 450 (IQR 0 - 750); estimated blood loss in controls: Median 350 (IQR 0 - 500); P=0.6. After adjustment for risk factors a history of coronary heart disease proved to be a significant risk factor for intraoperative cardiac arrest (OR 4.0; 95% Confidence interval (CI) 1.3 – 12). Preoperative atrial fibrillation was found not to be a significant risk factor (OR 3.8; 95% CI 0.8 – 18). A higher hemoglobin level preoperative was associated with decreased risk for intraoperative cardiac arrest (OR 0.66; 95% CI 0.50 – 0.87). There was no evidence of heterogeneity in incidence of cardiac arrest among patients with a history of coronary heart disease between subgroups of patients according to type of surgery. Beta-blockers (OR 0.56; 95% CI 0.2 -1.8), statins (OR 0.84; 95% CI 0.2 -3.8) and aspirin (OR 0.50; 95% CI 0.1 -2.6) use were not significantly related to a decreased risk for intraoperative cardiac arrest (table 3).

Table 1. Baseline patient characteristics of cases with cardiac arrest and matched controls undergoing noncardiac surgery*

	Cases N(%)	Controls N (%)	p-value
No. of patients	42	84	
Age (years)	60.9	60.7	0.97
Male gender	23 (55)	46 (55)	1.00
Risk factors			
Coronary heart disease	11 (26)	7 (8)	0.007
Congestive heart failure	3 (7)	8 (9)	0.65
Cerebrovascular disease	4 (10)	11 (13)	0.56
Diabetes mellitus	3 (7)	3 (4)	0.40
Renal dysfunction	4 (10)	7 (8)	0.82
Atrial fibrillation	5 (12)	3 (4)	0.07
Preoperative hemoglobin level (g/dl)			0.003
Males	12.0	13.7	
Females	12.0	12.9	
Lee Risk Index			0.11
0	15 (35)	29 (35)	
1	12 (29)	39 (46)	
2	12 (29)	11 (13)	
≥3	3 (7)	5 (6)	
Medication use			
Statins	7 (17)	14 (17)	1.0
Beta blockers	8 (19)	18 (21)	0.76
Aspirin	7 (17)	16 (19)	0.74
Type of surgery			1.0
Hepatico/pancreatico/billary	10 (24)	20 (24)	
Esophagogastric	2 (5)	4 (5)	
Other abdominal	3 (7)	6 (7)	
Dental	1 (2)	2 (2)	
Ear/nose/throat	4 (10)	8 (10)	
Endocrine	1 (2)	2 (2)	
Gynecology	2 (5)	4 (5)	
Reconstructive	2 (5)	4 (5)	
Neuro	4 (10)	8 (10)	
Pulmonal	1 (2)	1 (2)	
Urologic	2 (5)	4 (5)	
Orthopedic	4 (10)	8 (10)	
Aorta elective	1 (2)	2 (2)	
Carotid endarterectomy	2 (5)	4 (5)	
Peripheral bypass	3 (7)	6 (7)	

* Intraoperative cardiac arrest in patients undergoing emergency surgery, as well as intensive care patients were excluded

Table 2. Primary electrographic rhythm recorded and intraoperative survival ratesamong 42 patients with intraoperative cardiac arrest

	N (%)	Survival (%)
Pulsless electrical activity	15 (36)	8 (53)
Bradycardia	8 (19)	7 (84)
Ventricular fibrillation	4 (9)	1 (33)
Asystole	15 (36)	11 (73)

Table 3. Adjusted odds ratios for intraoperative cardiac arrest in relation to risk factors and medication using multivariable analysis. Data are corrected for coronary heart disease, preoperative hemoglobin level and the of presence of atrial fibrillation

	Adjusted odds ratio	(95% CI)
Risk factors		
Coronary heart disease	4.0	1.3 - 12
Atrial fibrillation	3.8	0.8 - 18
Preoperative hemoglobin level (g/dl)	0.66	0.5 - 0.9
Medication use		
Statins	0.84	0.2 - 3.8
Beta blockers	0.56	0.2 - 1.8
Aspirin	0.50	0.1 - 2.6

Discussion

In this case-controlled study, among 309,639 patients, we found that a history of coronary heart disease was associated with a 4-fold increased risk for intraoperative cardiac arrest in patients undergoing noncardiac surgery. This result was consistent in subgroups of patients according to the type of surgery, preoperative hemoglobin level, and cardiovascular therapy, including aspirin, statins and beta-blockers. The revised cardiac risk index by Lee is a widely accepted risk model for predicting adverse postoperative cardiac events, including cardiac arrest [7]. It consists of 6 equally weighted risk factors including: high risk type of surgery, history of coronary heart disease, history of congestive heart failure, history of cerebrovascular disease, preoperative treatment with insulin and preoperative renal failure. Our study could not detect a relation between 4 risk factors and intraoperative cardiac arrest. Due to the nature of our study we had to exclude emergency surgery patients, as well as intensive care patients. However, from all patients (n=110) who underwent intraoperative cardiac arrest during the study period, the majority of the procedures (80/110; 73%) would have been classified as emergency surgery. Therefore emergency procedures should be classified as major risk factor as well. Previous studies have shown that emergency surgery is a major risk factor for intraoperative cardiac arrest and is associated with a poor outcome [5,8]. A study by Braz et al. showed that the incidence of intraoperative cardiac arrest in emergency surgery was more than 14-times higher compared to elective surgery [8].

Secondly, we found that lower preoperative hemoglobin levels were associated with a higher incidence of cardiac arrests. In the case of major blood loss, patients who are already anemic would be more susceptible for cardiac ischemia. However, there was no difference in blood loss at the time of the arrest between cases and controls in our study. A preoperative anemia has been shown to be an independent risk marker for adverse postoperative events and has been studied extensively [9-11]. Dunkelgrun et al. showed that, among a group of 1211 patients scheduled for elective noncardiac open vascular surgery, a preoperative moderate anemia (hemoglobin levels 11.0 -12.1 g/dl) was independently associated with an increased risk for 30-day major adverse cardiac events (OR 2.3; 95% CI 1.1 – 5.4). Although anemia is often seen in patients with major risk factors like congestive heart failure and renal failure, anemia proved to be an independent risk marker. Therefore a preoperative anemia can be seen as a risk marker for unrecognised comorbidity. The pathway by which a preoperative anemia leads to an increased risk for perioperative mortality is not fully understood. One explanation would be that, through intraoperative blood loss, anemic patients require RBC transfusions more often than nonanemic patients. Although much has improved in safety, perioperative RBC transfusions are associated with an increased risk for short term and long-term morbidity and mortality [12-14]. Secondly, (subclinical) ischemic artery disease may decrease the tolerance for anemia because coronary vasodilatation is not possible in the presence of significant stenosis. Several pre- and intraoperative therapeutic options are available to prevent intraoperative anemia [15-17]. Blood conservation strategies and preoperative optimalisation of hemoglobin levels are ongoing items of discussion and will be the key to further research.

Several limitations should be considered when interpreting our study. First, inherent to a retrospective analysis, causality could not be determined. Second, the effects of unknown or unmeasured confounders on the observed association cannot be ruled out. Especially in the event of cardiac arrest, several other intraoperative variables which can not be measured or retrieved retrospectively may have led to the final event of cardiac arrest. Computer-assisted data registration will be of major value in the future so that more precise data about intraoperative variables will be available. Thirdly, selection bias may be present because of our search method. Cases could have been missed in the case of missing or incomplete data. Given the low incidence of intraoperative cardiac arrest, retrospective studies are the preferred method of research. Therefore, the findings of our study should be verified across institutions worldwide.

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6

Pulmonary Embolism After Noncardiac Surgery: Derivation of a Risk Model

Felix van Lier MD, Patrick J. van der Geest MD, Sanne E. Hoeks PhD,
Jaap W. Hol MD, Don D. Sin MD FCCP, Don Poldermans MD PhD

Submitted

Abstract

Introduction:
Surgical patients are at increased risk of developing postoperative pulmonary embolism. The purpose of this case control study was to develop a risk index for the risk of postoperative pulmonary embolism.

Methods:
We undertook a case control study among 210,269 patients who underwent noncardiac surgery from 2000 to 2009 at the Erasmus Medical Center. Case subjects were all 199 (0.09%) patients who experienced a pulmonary embolism within 30 days after surgery. From the remaining patients, 1 control was selected for each case and was stratified according to calendar year. For cases and controls, information was obtained regarding risk factors and the type and dose of thromboprophylaxis as well as the time of initiation postoperative.

Results:
Overweight, surgery for malignancy, a history of cerebrovascular disease and a history of thromboemblic diseases, intraoperative blood transfusions and delayed use of thromboprophylaxis were more common in cases than in controls. A simple prognostic risk score derived from these 6 variables predicts postoperative pulmonary embolism.

Conclusion:
This case control study identified 6 independent risk factors for predicting postoperative pulmonary embolism. In patients undergoing noncardiac surgery, this index can be used as a tool to predict which patients are likely to benefit most from prophylaxis.

Introduction

Surgical patients are at increased risk of developing postoperative venous thromboembolic complications (VTE) which include deep vein thrombosis (DVT) and pulmonary embolism (PE). In the absence of prophylactic treatment, the incidence of postoperative VTE varies between 10% to nearly 80% [1,2]. Pulmonary embolism is a devastating complication with mortality rates between 0.2% and 7.5% [1,3]. A variety of prophylactic strategies via physical and pharmalogical means have shown to be effective in preventing postoperative VTE in different surgical populations. The efficacy of thromboprophylaxis with low-molecular weight heparin (LMWH) administered during the in-hospital period is well documented, but the optimal dose, timing of initiation and duration of thromboprophylaxis after surgery still remains controversial. Concern among surgeons about the risks of bleeding may result in delayed and suboptimal use of thromboprophylaxis. The current study aimed to examine the association between risk factors and postoperative pulmonary embolism in a large cohort of patients undergoing noncardiac surgery. In addition, our goal was to develop a simple prognostic risk model for the prediction of postoperative pulmonary embolism following noncardiac surgery.

Methods

The study was approved by the Medical Ethics Committee of the Erasmus Medical Center. Since the data were recorded retrospectively and without any specific intervention, the Medical Ethics Committee agreed to waive informed consent. We performed a case control study using a cohort of 210,269 adult patients, 19 years of age and older, who underwent a noncardiac surgical procedure between January 1 2000, and January 1 2009 at the Erasmus Medical Center, Rotterdam, the Netherlands.

Patient selection

Both cases and controls were identified using a computerized hospital information system which contained data on demographic and clinical characteristics, as well as the clinical course in hospital of all patients, who were admitted for noncardiac surgery (n=210,269). Using key words 'pulmonary embolism', 'PE' or 'pulmonary infarct', all cases of perioperative pulmonary embolism were ascertained from discharge abstracts. The case definition included only incident cases and those confirmed by computed tomography (CT) or a high probability on ventilation and perfusion lung scanning or by autopsy. Patients readmitted to our hospital, as well as in hospital patients with a pulmonary embolism occurring more than 30 days following surgery were excluded from the current study. Using this approach, we identified 343 (0.16%) patients with postoperative pulmonary embolism. We excluded 144 patients because the embolic event occurred following cardiac surgery (n=2) or because the event did not occur postoperatively (n=142). This left 199 patients for initial analysis. In 183 patients (92%) pulmonary embolism was confirmed by CT scan, in 12 patients (6%) by high probability on ventilation and perfusion lung scanning and in 4 patients (2%) by autopsy. For each case one control patient was selected from the total surgical population of 210,269 patients. Cases and controls were matched according to calendar year of surgery

using the computerized hospital information system. Type of surgery was classified, according to the classification recommended by the American Heart Association/ American College of Cardiology [4].

Definitions

To study the relationship of postoperative pulmonary embolism and various risk factors medication use, patient medical records, nursing reports, surgical reports, anaesthetic reports and discharge letters were analyzed to obtain the following information on cases and controls: type of surgery, intraoperative- and postoperative blood transfusions, year of surgery, age, sex, BMI, presence of coronary heart disease, previous DVT or PE, heart failure, peripheral arterial disease, cerebrovascular disease, chronic obstructive pulmonary disease, diabetes, renal insufficiency, electrocardiographic abnormalities and smoking. Coronary heart disease was defined as a history of angina pectoris, myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention. Preoperative medication use was noted and included statins, beta-blockers, steroids, oral anticoagulants, heparin/LMWH and aspirin. The type and dose of thromboprophylaxis was noted as well as the time of initiation postoperatively. The timing of postoperative thromboprophylaxis was at the discretion of the surgeon. Delayed use of thromboprophylaxis was defined as thromboprophylaxis starting more than 24 hours after surgery. As per hospital protocol nadroparin 2850 IE or dalteparin 2500 IE subcutaneous once daily is the standard for postoperative thromboprophylaxis in low risk patients. Patients with an increased risk of VTE are prescribed 5700 IE of nadroparin or 5000 IE of dalteparin once daily. Ambulatory surgery patients did not receive thromboprophylaxis, unless indicated by the surgeon.

Statistical Analysis

The baseline characteristics between cases and controls were compared using a chi-square test for categorical variables and t-test for continuous variables. Logistic regression analyses were applied to evaluate the relation between clinically important characteristics (age > 70, bmi ≥ 25, gender, surgery for malignancy, history of VTE, history of cardiovascular or cerebrovascular disease, chronic obstructive pulmonary disease, renal dysfunction, intraoperative blood transfusion and delayed use of thrombophylaxis) and postoperative pulmonary embolism. The final regression model for the risk score included all risk factors with a p-value < 0.10 for PE. To develop a parsimonious risk score for postoperative pulmonary embolism, the coefficient of each risk factor was divided by 0.71 (the smallest beta coefficient in the model which was overweight) and rounded to the nearest integer. The weighted scores were then assigned to each categorical predictor variable and the scores were summed together to produce a total score. The total scores were then used to generate postoperative pulmonary embolism probabilities. Model discrimination between patients with PE and patients without PE was quantified by a c-statistic and its calibration was determined by Hosmer-Lemeshow goodness-of-fit-test. We only report the adjusted odds ratios and corresponding 95% confidence intervals. For all tests, a 2 sided p-value of <0.05 was considered significant. All statistical analyses were performed using SPSS 15.0 for Windows.

Validation

To validate our model we applied our risk model to a group of 125 randomly selected patients who underwent noncardiac surgery where a clinical suspicion of pulmonary embolism existed, but pulmonary embolism could not be confirmed by contrast CT scanning.

Results

Baseline clinical characteristics of cases and controls are presented in Table 1. Increased age, increased BMI, history of cerebrovascular disease, history of VTE, surgery for malignancy and blood transfusions intraoperatively were more common in cases than in controls. The median day on which pulmonary embolisms occurred was the seventh postoperative day, interquartile range (IQR) 4-15. Pulmonary embolism was most often diagnosed after abdominal surgery (33%), neurosurgery (16%), orthopedic surgery (9%) and gynecologic surgery (8%). Nine patients (5%) with postoperative pulmonary embolism died, while no deaths were reported in control patients. Massive pulmonary embolism was the cause of death in 6 patients, 2 patients died because of cardiovascular failure and 1 patient suffered postoperative stroke. Intraoperative bloodtransfusions were needed in 29% of the cases versus 15% of the control patients ($p = 0.001$).

Thromboprophylaxis

Dalteparin was used most often as thromboprophylaxis (50 % of the cases and 46% of the control patients). The dose of thromboprophylaxis used was not different between cases and controls, except for nadroparin. The median dose of nadroparin used in cases was 5700 IE while the median dose in control patients was 2850 IE of nadroparin ($p = 0.02$). Delayed use (more than 24 hours after surgery) of thromboprophylaxis was more common in cases than in controls (57 cases [29%] and 20 controls [10%]; $p < 0.001$). Delayed use was most often seen after abdominal surgery (31%) and neurosurgical procedures (18%). In patients who received thromboprophylaxis > 24 hours after surgery, thromboprophylaxis was given on the fourth postoperative day (IQR 2-6). There was no relation between intraoperative bloodtransfusions and delayed use of thromboprophylaxis (Table 2). Also no relationship was observed between the initiation of thromboprophylaxis less than 24 hours after surgery and the need for bloodtransfusions postoperatively.

Risk model

In multivariable analyses several risk factors were identified for postoperative pulmonary embolism (Table 3 and Figure 1): BMI ≥ 25 (OR 2.0; 95% CI: 1.3 - 3.3); Surgery for malignancy (OR 5.6; 95% CI: 3.4 - 9.3); Blood transfusions intraoperatively (OR 2.4; 95% CI 1.3 – 4.3); History of VTE (OR 3.0; 95% CI 1.0 – 10.2) and delayed use of thromboprophylaxis (OR 3.5; 95% CI: 1.8 – 6.7). No significant correlation was found for medication use, type of surgery and dose and type of thromboprophylaxis. A risk model for postoperative pulmonary embolism was developed which included 6 factors

(BMI ≥ 25, surgery for malignancy, history of cerebrovascular disease, history of VTE, blood transfusions intraoperatively and delayed use of thromboprophylaxis (table 3). By summing the individual scores from the given predictors and using the total score, the probability for postoperative embolism could be estimated.

Table 1. Baseline patient characteristics of cases with pulmonary embolism and controls undergoing noncardiac surgery*

Variable	Cases (N=199)	Controls (N=193)	p-value
Age (years)	59.4	49.9	< 0.001
Age ≥ 70	56 (28%)	35 (18%)	0.02
BMI (kg/m²)	26.9	24.9	< 0.001
BMI ≥ 25	127 (54%)	79 (41%)	< 0.001
Male gender	105 (53%)	118 (61%)	0.10
Surgery for malignancy	124 (62%)	43 (22%)	< 0.001
History of VTE	17 (9%)	5 (2%)	0.01
Coronary heart disease†	20 (10%)	10 (5%)	0.07
Congestive heart failure	12 (6%)	5 (2%)	0.10
Chronic obstructive pulmonary disease	17 (9%)	14 (7%)	0.64
Cerebrovascular disease	16 (8%)	6 (3%)	0.03
Renal dysfunction	7 (4%)	10 (5%)	0.42
Current smoking	33 (17%)	42 (22%)	0.23
Medication use			
Statins	21 (11%)	9 (5%)	0.03
Beta-blockers	53 (27%)	20 (10%)	< 0.001
Steroids	38 (19%)	12 (6%)	< 0.001
Aspirin	20 (10%)	12 (6%)	0.16
Oral anticoagulants/LMWH	39 (20%)	27 (14%)	0.13
Type of surgery‡			0.01
Low	72 (36%)	73 (38%)	
Low-intermediate	10 (5%)	27 (14%)	
Intermediate-high	114 (57%)	92 (48%)	
High	3 (2%)	1 (1%)	
Thrombophylaxis			0.18
No prophylaxis used	8 (4%)	36 (18%)	
Dalteparin	99 (50%)	88 (46%)	
Nadroparin	76 (39%)	63 (33%)	
Heparin	16 (8%)	6 (3%)	
Delayed thrombophylaxis	57 (74%)	20 (26%)	<0.001
Intraoperative blood transfusion	57 (29%)	29 (15%)	0.001

* Patients presenting with pulmonary embolism beyond 30 days after surgery were excluded
† Coronary heart disease was defined as a history of angina pectoris, myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention
‡ Type of surgery classified to AHA/ACC guidelines

Table 2. Timing of thrombophylaxis postoperatively in relation to intra- and postoperative blood transfusions

	< 24 hours	> 24 hours	
Variable	(N=314)	(N=77)	p-value
Intraoperative bloodtransfusions			0.35
Transfusion	66 (21%)	20 (26%)	
No transfusion	248 (79%)	57 (74%)	
Postoperative bloodtransfusions			0.49
Transfusion	51 (16%)	15 (20%)	
No transfusion	263 (84%)	62 (80%)	

Table 3. Adjusted odds ratios for postoperative pulmonary embolism using multivariable analysis*

Variable	Adjusted odds ratio	(95% CI)	β coefficient	Score
Age ≥ 70	1.1	0.6 - 2.0		
BMI ≥ 25	2.0	1.3 - 3.3	0.74	1
Male gender	0.8	0.5 - 1.2		
Surgery for malignancy	5.6	3.4 - 9.3	1.76	2
History of VTE	3.3	1.0 - 10.2	1.14	2
Coronary heart disease	1.2	0.4 - 3.1		
Congestive heart failure	1.8	0.5 - 6.2		
Chronic obstructive pulmonary disea	0.9	0.4 - 2.1		
Cerebrovascular disease	2.7	0.9 - 8.4	1.04	1
Renal dysfunction	0.4	0.1 - 1.3		
Smoking	0.8	0.4 - 1.4		
Intraoperative blood transfusion	2.4	1.3 - 4.3	0.85	1
Delayed use thrombophylaxis	3.5	1.8 - 6.7	1.18	2

* Data are corrected for age, BMI, coronary heart disease, history of VTE, congestive heart failure, chronic obstructive pulmonary disease, cerebrovascular disease, renal dysfunction and timing of thromboprophylaxis

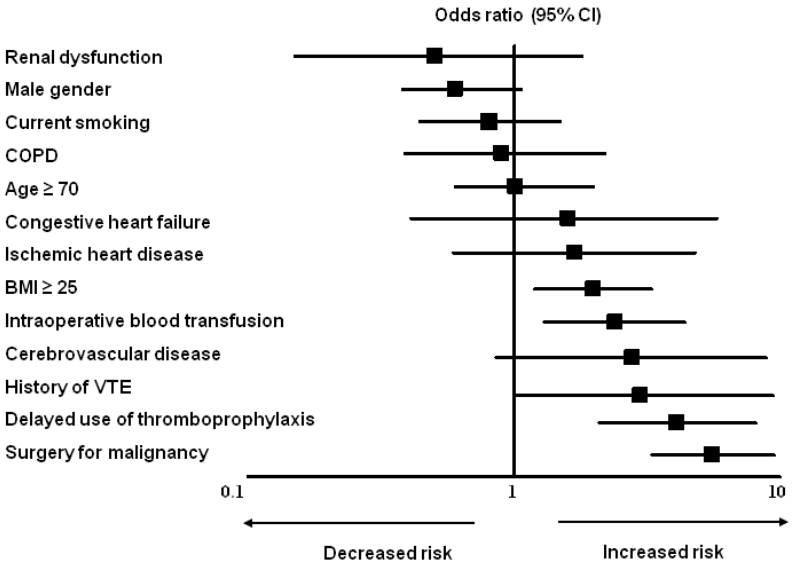

Figure 1: Odds ratios for pulmonary embolism

The c-statistic of the prognostic risk model was 0.79 (95% CI; 0.75 – 0.84). Calibration assessment with the use of the Hosmer-Lemeshow goodness-of-fit test produced a non-significant outcome (p=0.61).

Validation

We validated our risk model to a group of 125 randomly selected patients who underwent noncardiac surgery where there was a clinical suspicion of pulmonary embolism, but where pulmonary embolism could not be confirmed by contrast CT scanning. Figure 2 confirms that these patients had a low risk score compared to the cases.

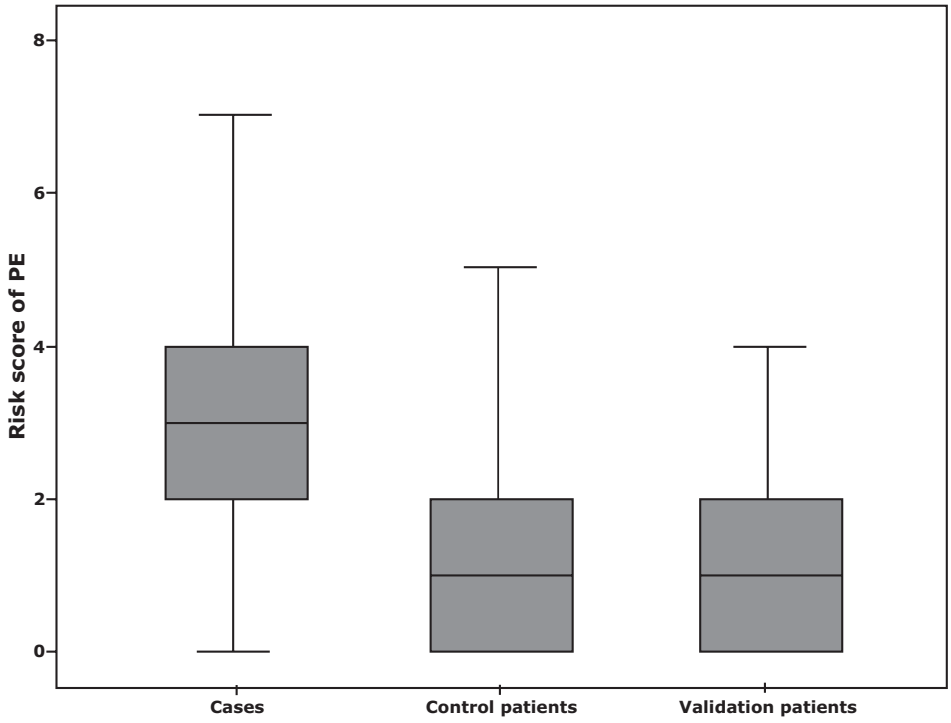

Figure 2: Prognostic risk model for pulmonary embolism

Discussion

In this case control study we evaluated risk factors for postoperative pulmonary embolism and developed a risk model for the prediction of postoperative pulmonary embolism. Several risk factors are patient related and can not be influenced, however, timing of thromboprophylaxis is a risk factor that can be influenced by the treating physician. Compared with patients who received thromboprophylaxis within 24 hours after surgery, delayed use patients had a more than 3-fold increased risk. Risk factors for VTE have been studied extensively and are well defined. Previous studies have identified major risk factors for VTE. Operations for cancer surgery are associated with a higher risk compared to general surgery procedures and orthopedic surgery puts patients

at the highest risk of developing postoperative VTE [5,6]. Our study confirms these risk factors. Insufficient use of thromboprophylaxis despite the existence of guidelines has been reported in several previous studies [7,8]. The recently published ENDORSE survey showed that among a group of 17,084 patients who were at risk for VTE, only 62.3% of the patients received prophylaxis [6]. The rate of prophylaxis use varied across the participating countries according to surgery type and the presence of comorbidities including active malignancy. The highest rates of prophylaxis were seen in orthopedic patients, while patients undergoing abdominal and neurosurgical procedures were least likely to receive prophylaxis. Concern about the risk of postoperative bleeding is an important reason why anticoagulants remain underutilized. The most feared complication after intracranial surgery is intracranial hemorrhage. The use of LMWH in neurosurgical patients is associated with an increased risk of intracranial hemorrhage, but on the other hand LMWH are more effective than non pharmacologic prophylaxis in the prevention of DVT [9]. As demonstrated in a meta-analysis by Eikelboom et al., the risk of major postoperative bleeding is increased with the use of thromboprophylaxis (OR 1.56; 95% CI 1.24 – 1.96) [10]. The same study showed that at 30 days the risk of death was 7-times higher among patients with a major bleeding event (HR 6.96; 95% CI 4.60 – 10.51). Therefore, the use of thromboprophylaxis is more or less a double-edged sword. It is intended to prevent adverse thromboembolic complications, while minimizing the risk of excessive blood loss in postoperative patients. However, patients who received thromboprophylaxis regardless of major bleeding showed a consistent pattern of reduced mortality compared to patients who did not receive thromboprophylaxis (1.6% vs 2.1%; p=0.06). Therefore timing of thromboprophylaxis is a key factor. Considering this, there are several potential pitfalls in the perioperative administration of thromboprophylaxis that should be considered. Historically, prophylaxis in North America is started postoperative, usually delayed for at least 12 h after surgery to allow for hemostasis of the surgical wound. In contrast, European orthopedic surgeons often commence anticoagulant prophylaxis 12 h preoperatively. The North American Fragmin Trial investigated this issue of starting pre- or postoperative [11,12]. No differences were found in postoperative total and proximal DVT between preoperative or postoperative administration of LMWH. If started postoperative, the timing of the first postoperative dose of prophylaxis in relation to bleeding complications is a key issue. Previous studies have shown that early initiation (< 6 hours postoperatively) of thromboprophylaxis increased the risk of major bleeding, without improved efficacy. On the other hand, it has been found that initiation 12 to 24 hours postoperatively may be less effective than initiation at 6 hours [13,14]. Therefore, it appears that that the optimum timing of thromboprophylaxis should be between 6 to 12 hours postoperatively. In our study renal failure was associated with a nonsignificant decreased risk of pulmonary embolism. Since renal clearance is the primary mode of elimination of several anticoagulants, including LMWH, reduced renal function results in the accumulation of anticoagulant drugs and may increase the risk of bleeding, while preventing adverse thromboemblic events. Preoperative no adjustments in LMWH dose were made for decreased renal function in our hospital.

Our study has several limitations that are common with any study relying on retrospective data collection. Most importantly, information about thromboprophylaxis use might have been missed, and probably differently so in cases and controls because of observer bias. However, our results are in line with other studies evaluating side

effects of thromboprophylaxis in relation to timing. Surprisingly, we found that a history of cerebrovascular disease was associated with a significant increased risk of pulmonary embolism, while a history of coronary heart disease was not. The number of patients in our study is relatively small and this might explain this difference. In this study, we show that thromboprophylaxis should not be delayed for more than 24 hours postoperatively due to an increased risk of postoperative pulmonary embolism. Given after 6 hours of the operation, the risk of bleeding related complications can be minimized. Our developed risk model identified 6 independent risk factors for predicting postoperative pulmonary embolism. We would like to encourage validation of this score in representative patient populations. In patients undergoing noncardiac surgery, this index can identify patients at a higher risk for postoperative pulmonary embolism. This index may be useful as a tool to predict which patients are likely to benefit most from prophylaxis.

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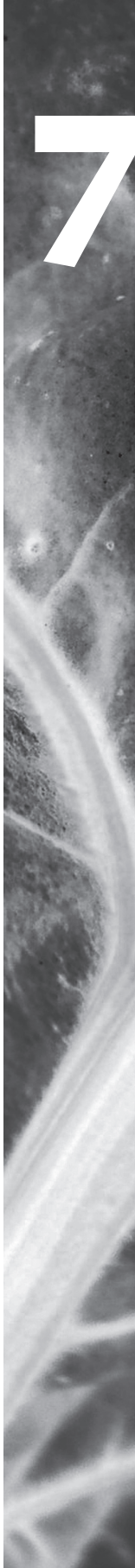

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Statins in Intensive Care Medicine: still too early to tell.

Review

Felix van Lier MD, Olaf Schouten MD PhD, Don Poldermans MD PhD

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Introduction

HMG-CoA reductase inhibitors (statins) are effective lipid lowering drugs often used for primary and secondary prevention of cardiovascular disease. However, the overall benefits observed with statins appear to be greater than what might be expected from changes in lipid levels alone, suggesting effects beyond cholesterol lowering. Indeed, recent studies indicate that some of the cholesterol-independent or 'pleiotropic' effects of statins involve improving endothelial function, enhancing the stability of atherosclerotic plaques, decreasing oxidative stress and inflammation, and inhibiting the thrombogenic response [1,2]. Therefore the indications for the prescription of statins have broadened over the years. The last decade has seen an extraordinary proliferation of evidence that statins decrease mortality in patients who have, or are at risk for developing, cardiovascular disease. The benefits extend to high-risk patients with normal cholesterol levels and have led some to suggest that all individuals older than 55 years of age should receive statins as part of a "polypill". Therefore more and more frequently patients admitted to intensive care units (ICUs) are on statin treatment for primary or secondary cardiovascular prevention and posses a new challenge to treating physicians. In this review we will first focus on the evidence for statin treatment of critically ill cardiovascular patients. Secondly, we will discuss the role of statins in other patients categories often admitted to the ICU.

Methods

We performed a search of the PubMed databases up to December 2009. Review articles, meta-analyses, original papers of clinical trials on the effects of statin therapy were searched combining the following MESH terms: 'Hydroxymethylglutaryl-CoA Reductase Inhibitors', 'Intensive Care, 'Perioperative Care', 'Sepsis', 'Systemic Inflammatory Response Syndrome' and 'Critical illness'. Case reports were not included. Language restrictions were not applied. References were searched for other potentially useful articles.

Statins and noncardiac surgery

Patients after major (vascular) surgery are often admitted to an ICU for postoperative care. Vascular surgery patients are at the highest risk for postoperative adverse cardiac events, due to their underlying systemic atherosclerotic disease and high incidence of coronary artery disease. In a study by Landesberg et al. [3] 447 patients, scheduled for different types of vascular surgery, were monitored on the first three postoperative days using continuous 12-lead ECG recording, cardiac troponin T and I and CK/CK-MB measurement. Up to 23.9% of the patients experienced cardiac troponin T or I release, while perioperative ST-segment changes were detected in 14.8% of the patients. In the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation) II study by Poldermans et al. [4] 1476 patients scheduled for elective open abdominal aortic or infragenuial arterial reconstruction were monitored for cardiac events during hospital stay after surgery. Twelve-lead electrocardiography and serum troponin-T levels were routinely assessed in the postoperative period. Cardiovascular death, defined as death caused by acute myocardial infarction, significant cardiac arrhythmias, congestive heart failure or as a

death occurring suddenly without another explanation, occurred in 27 (1.8%) patients. Myocardial infarction (MI) was diagnosed in 39 (2.6%) of the patients while elevated serum troponin-T levels were present in 354 (24%) of the patients. Fatal perioperative MI has two potential origins [5,6]. One is a culprit coronary plaque that fissures and ruptures, causing a cascade of thrombogenic events (hemorrhage and thrombosis) inside the vessel wall, culminating in an MI. Less often, fatal perioperative MI results from long-lasting myocardial ischemia (a demand/supply mismatch of oxygen), typically as a consequence of a fixed coronary stenosis. In nearly half of patients with fatal MI, coronary inflammation is a key contributor. In the perioperative setting, surgical stress induces the release of inflammatory cytokines that disrupt smooth muscle cells in the endothelium and contribute to disruption of a nonobstructing coronary plaque, predisposing to acute thrombus formation.
Retrospective cohort data and data from randomized clinical trials have demonstrated reductions in perioperative cardiac complications with statin use in patients undergoing various types of noncardiac vascular surgery [7-9]. Recently, the evidence for a beneficial effect of statins has been augmented by DECREASE III [10], a large randomized controlled trial. DECREASE III included nearly 500 statin-naive patients randomized to receive either placebo (n = 247) or fluvastatin (n = 253)-extended release at a dose of 80 mg once daily. One month after surgery, 27 patients in the fluvastatin group (10.9%) had experienced myocardial ischemia, compared with 47 (18.9%) in the placebo group (OR 0.55; 95% CI: 0.34 – 0.88). The number needed to treat to prevent one patient experiencing myocardial ischemia was 12.5. Similarly, the combined secondary endpoint of cardiac death or non-fatal MI occurred in 12 (4.8%) patients of those taking fluvastatin, compared with 25 (10.0%) of those on placebo (OR 0.47; 95% CI: 0.24–0.94).

Timing of statin therapy preoperative

A major point of discussion is how many days preoperative statin therapy should be started. In the non-operative setting trials have shown that it takes about 30 days after statin initiation for inflammation levels to minimize, and at least that long for halting of plaque progression to be detected by intravascular ultrasonography [11,12]. On the other hand several studies have demonstrated that high-dose statin loading before percutaneous coronary intervention may improve microvascular coronary perfusion and blood flow within hours [13-15]. There are no data available regarding the timing preoperative, but we prefer to start 30 days before surgery or to postpone surgery of this is possible.

Safety issues

A major concern of administering statins in the ICU is that patients who undergo major vascular surgery frequently are not able to take oral medications shortly after surgery, for example because of postoperative paralytic ileus. Since there is no intravenous formula for statins, the interruption of statin therapy in the immediate postoperative period is a serious concern, especially because it is known that these vascular surgical patients are at the highest risk for adverse cardiac events in the first 3 days after surgery. A study by Schouten et al. [16] showed that acute statin withdrawal in

the perioperative period is associated with an increased risk for perioperative cardiac events compared with statin continuation in long-term users. Patients unable to take statins postoperatively had more than a 7-fold increased risk of nonfatal myocardial infarction and cardiac death. More importantly, the study showed that the extended-release formula of fluvastatin was superior compared to other statins used by patients who discontinued statin therapy. There are several possible explanations for these observations. Fluvastatin is the only statin with an extended-release formula. Because most patients with statin withdrawal restarted statin therapy < 3 to 4 days after surgery, it might be hypothesized that the extended-release fluvastatin formula is capable of extending the duration of the pleiotropic effects of statins. Furthermore, the pharmacokinetics of statins might be influenced by concomitant drug use in the perioperative period. Of special interest in this respect is the cytochrome P450 (CYP) isoenzyme system. Most drugs are metabolized in the liver by the CYP 3A4 isoenzyme. As a consequence, this might cause interaction with simvastatin and atorvastatin, which are also metabolized by this pathway [17]. Fluvastatin, in contrast, has only limited interactions with the CYP 3A4 pathway, because it is mainly metabolized by the CYP 2C9 isoenzyme. As shown in a review by Bellosta et al, other differences between statins include half-life, systemic exposure, maximum plasma concentration, bioavailability, protein binding, lipophilicity, the presence of active metabolites, and excretion routes [18]. Fluvastatin is the only statin that is a racemic compound, half of the molecule being presumably inactive at reducing plasma cholesterol. It is not excluded that some of the beneficial pleiotropic effects may be shared by the "nonactive" half, therefore potentially increasing that capacity. Side effects of statins include elevations in creatine kinase, myopathy, back pain, and arthropathy. Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with fluvastatin and other HMG-CoA reductase inhibitors as well.

Cardiothoracic surgery

Over 20 years of experience has accrued with the use of statins in patients undergoing Coronary Artery Bypass Graft Surgery (CABG). The long-term results after CABG are compromised by the progression of atherosclerosis in native coronary arteries and saphenous vein bypass grafts, a process influenced by hyperlipidemia. Therefore the role of statins in CABG surgery has been studied intensively. To summarize the data regarding preoperative statin use, Liakopoulos et al. [19] recently performed a meta-analysis of 19 cardiac surgery studies that reported the outcomes of 31,725 patients who were treated with (N = 17,201) or without (N = 14,524) statins before surgery. The authors demonstrated that preoperative statin therapy resulted in a 1.5% absolute risk reduction (2.2 versus 3.7%, statins versus no statins, $p < 0.01$) and 43% odds reduction for all-cause mortality after surgery (OR: 0.57; 95% CI: 0.49 - 0.67), but not for MI (OR: 1.11; 95% CI: 0.93 - 1.33). Secondly, it is increasingly recognized that the inflammatory response triggered by on-pump CABG surgery is of clinical importance as it may contribute to the genesis of common postoperative complications and may even exert adverse vascular biological effects on native or grafted coronary vessels. Statins may influence the on-pump inflammatory response, through their pleiotropic effects. Several studies have evaluated the role of statins as anti-inflammatory medications. Dereli et al. [20] showed that pre-operative atorvastatin therapy is effective in reducing

the systemic inflammatory reaction associated with CABG and cardiopulmonary bypass by lowering serum high sensitive CRP and IL-6 concentrations. Chello et al.[21-23] showed that statins reduce neutrophil endothelial-adhesion and increase neutrophil apoptosis, reduce circulating adhesion molecules such as ICAM-1 and ELAM-1, improve endothelial function and reduce cytokine release, all by mechanisms that seem unrelated and independent of cholesterol level reduction.

Thirdly, several studies have evaluated the role of statins in the prevention of neurological events after on-pump surgery. After on-pump surgery the incidence of postoperative stroke is high, ranging from 1.3% to 9.7% [24]. In their meta-analysis, Liakopoulos et al. [19] reported that preoperative statin therapy significantly reduced the risk of stroke after cardiac surgery, with a 0.8% absolute risk reduction (2.1 versus 2.9%, statins versus no statins, $p < 0.01$) and a 26% odds reduction (OR 0.74; 95% CI: 0.60 - 0.91) compared to the non-use of statins before surgery. Similarly, statin users show a decreased incidence of postoperative delirium after cardiac surgery as observed in a recent study by Katznelson et al. [25]. Statin use was associated with a decreased incidence of postoperative delirium (OR 0.61; 95% CI 0.39 - 0.95).

Renal dysfunction

Acute renal failure (ARF) is a major problem among ICU patients with mortality rates around 60% [26]. Despite advances in management strategies, in particular renal replacement therapy, the mortality of ARF in critically ill patients remains high because of coexistent nonrenal organ dysfunction. Although some observational studies have suggested that statin therapy is also associated with improved survival among patients undergoing hemodialysis, an overall benefit of statin therapy in these patients has not been proved [27,28]. Other studies have shown that statin therapy is related to an improvement in renal function. A post hoc analysis of the 'Treating to New Targets (TNT)' trial data suggests that statin treatment may slow or reverse the decline in renal function normally seen over time in patients with stable coronary disease [29]. In the TNT trial over 10.000 patients with coronary heart disease and LDL cholesterol levels of <130 mg/dl were randomly assigned to double-blind therapy with 10 or 80 mg/d atorvastatin. Mean change from baseline estimated GFR showed a progressive increase during the course of the study in both treatment groups. At the end of a 5-year follow-up, mean change from baseline estimated GFR showed an increase of 3.5 ml/min per 1.73 m^2 in the 10-mg group and 5.2 ml/min per 1.73 m^2 in the 80-mg group, which represented increases of 5.6 and 8.3%, respectively. The mechanisms that are involved in this observed nephroprotective effect of atorvastatin have yet to be determined. The observed effect could be linked to the cardiovascular benefits of LDL cholesterol reduction, because on-treatment LDL cholesterol proved to be a significant predictor of change in estimated GFR. However, the pathophysiology of ARF in ICU patients differs from ARF in patients with chronic cardiovascular disease. In the ICU, 35% to 50% of ARF can be attributed to sepsis [30,31]. Postsurgery acute tubular necrosis (ATN) accounts for approximately 20% to 25% of all hospital acquired ARF [32]. Finally, acute radiocontrast nephropathy is the third leading cause of ATN in patients admitted into a hospital and up to 7% require transient dialysis or progress to end-stage renal disease [33]. The preventive effects of statins in these patients has recently been demonstrated in a study by Xinwei et al. [34]. They showed that patients taking a higher dose of

simvastatin (80 mg vs 20 mg) show a lower incidence of contrast induced nephropathy after they underwent a percutaneous coronary intervention (5% versus 14%; $p < 0.05$). In a retrospective cohort study among 2760 patients who underwent cardiac surgery Huffmyer et al. showed that preoperative statin therapy was associated with a reduction in the need for postoperative renal replacement therapy (OR 0.54; 95% CI 0.38 - 0.77) [35]. Similarly Welten et al. [36] studied the relation between preoperative statin use and postoperative kidney injury in a group of 2170 vascular surgery patients. The incidence of kidney injury, defined as > 10% decrease in creatinine clearance, was similar among statin users and non-users (29 versus 25%, OR 1.15; 95% CI 0.9 – 1.5). However, if kidney function deteriorated, statin use was associated with increased odds of complete kidney function recovery (OR 2.0; 95% CI 1.0 – 3.8). To our knowledge no other human studies have shown preventive effects of statins in patients with ARF. All of these effects can be explained by the reversal of (atherosclerotic) kidney injury. The question still remains if statins are also protective in non-atherosclerotic kidney injury. Cholesterol-independent tissue-protective effects of statins are thought to be mediated by their immunomodulatory and anti-inflammatory effects that relate to statin's ability to block the synthesis of important intermediate products, including the isoprenoids in the mevalonate pathway [37]. The mevalonate pathway mediates the sequential biochemical reactions leading to the synthesis of cholesterol and might be responsible for kidney protection in healthy subjects. In an experimental ischemia-reperfusion model using healthy mice, Sharyo and collegues demonstrated that pravastatin protected normal mice from renal ischemia-reperfusion injury without any reduction in plasma cholesterol levels [38]. Other studies have shown that in a model of sepsis induced AKI (i.e. cecal ligation and puncture), pre-treatment with simvastatin improved kidney function, as measured by serum creatinine and blood urea nitrogen [39]. In this study simvastatin was observed to improve tubular vacuolar degeneration and reverse the increase vascular permeability, renal microperfusion and hypoxia seen in this model. Similarly, Sabbatini and colleagues examined whether treatment with atorvastatin could improve the course of ARF after ischemia-reperfusion injury in ageing rats compared with untreated age-matched rats [40]. These investigators were able to show that pre-administration of atorvastatin mitigated renal vasoconstriction and restored glomerular filtration values to the baseline by increasing nitric oxide availability and, therefore, improving renal hemodynamics. It therefore can be concluded that statins show protective effects on renal function, regardless of the presence of atherosclerosis.

Sepsis

The hallmark of sepsis syndrome is an intense inflammatory response, which reflects a delicate interaction between the extensive activation of host defence mechanisms and direct and indirect effects of the invading microorganisms and their toxins. As a result, a number of important abnormalities occur during sepsis, including endothelial dysfunction and apoptosis, activation and increased production of cytokines and other pro-inflammatory mediators, activation and extravascular transmigration of leukocytes, and activation of platelets and coagulation and complement systems. To date, activated protein C and low-dose hydrocortisone have emerged as the only inflammation-modulating substances which have been confirmed to be of benefit in patients with severe sepsis [41,42]. Consequently, several investigators have evaluated the role of statins

in the prevention and treatment of sepsis. Clinical studies that have described effects of statins in sepsis have either addressed the effects of statins in reducing sepsis incidence and severity or retrospectively looked at mortality in those taking statins who developed sepsis. Although the exact mechanisms behind the observed beneficial effects of statins in septic patients are still unknown, it could be attributed to several factors, including the immunomodulatory and anti-inflammatory effect of statins and their impact on endothelial function. Several clinical studies have shown the beneficial effect of statins on clinical outcome [43-45]. In a small prospective observational study Almog et al. have shown that patients who were treated with statins before the occurrence of a bacterial infection had a recued rate of severe sepsis (rate ratio 0.07 (95% CI 0.01 – 0.51) and ICU admission [43]. More recently Christensen et al. have shown that preadmission use of statins was associated with reduced risk of death within 30 days and one year in general ICU patients [46]. In a recent meta analysis by Tleyjeh et al., an improvement in the chance of 30 day survival in favour of patients on statin therapy (treatment cohorts) was found compared to those patients not on statins (OR 0.55; 95% CI 0.36 - 0.83). A same beneficial effect was found in the prevention cohorts (OR 0.57; 95% CI 0.43 - 0.75)[47]. The overall conclusion is that there is circumstantial evidence from retrospective database enquiries and observational studies that statins may be helpful in sepsis. However, properly conducted, randomized, placebo-controlled trials in the context of sepsis and septic shock are still lacking. Currently several such trials are under way or will soon be ready to include patients [48].

Neurovascular diseases

Traumatic brain injury (TBI) and subarachnoid haemorrhage (SAH) remain one of the leading causes of mortality and morbidity worldwide in individuals under the age of 50 years, and, despite extensive efforts to develop neuroprotective therapies, there has been little successful outcome in any trial of neuroprotection to date. So far, nimodipine is the only drug that decreases the incidence of vasospasm and poor outcome after SAH [49]. One suggested therapeutic option is treatment with statins. Several earlier conducted randomised controlled studies have shown that acute initiation of statin treatment directly after aneurysmal SAH decreased the incidence of radiological vasospasm and clinical signs of delayed cerebral ischemia [50,51]. However, a recent meta-analysis by Vergouwen et al. could not detect a statistically significant reduction in delayed cerebral ischemia (pooled risk ratio 0.57; 95% CI 0.29 - 1.13), vasospasm (pooled risk ratio 0.99; 95% CI 0.66 - 1.48), poor outcome (pooled risk ratio 0.92; 95% CI 0.68 - 1.24) and mortality (pooled risk ratio 0.37; 95% CI 0.13 -1.10) [52]. Unfortunately, all studies so far are conducted only with small sample sizes. A large-scale Phase III study is presently being conducted to investigate the effect of statins in aneurysmal SAH (www.stashtrial.com), but the results are not expected soon. Several animal studies have evaluated the role of statins in TBI [53,54]. In a study by Chen et al. pre-administration of lovastatin to rats subjected to TBI improves functional outcomes and reduces the extent of brain damage, with a concomitant decrease in tissue levels of TNF-α and IL-1β mRNA and protein [53]. So far, there are no data available about the role of statins in TBI in humans. Results from recently started clinical phase II trials can be expected in the next few years.

Safety of statins in the ICU setting

As mentioned before rhabdomyolysis and myopathy can be devastating side effects in combination with statin use. In the intensive care setting of prolonged sedation clinical monitoring may not be possible and important and dangerous side effects or drug interactions can stay unnoted. There are several known interactions between statins and other drugs that are metabolized by, or are of influence on CYP3A4. Drugs that inhibit this isoenzyme are antifungals, erythromycin and other macrolides, histamine-2 blockers, cyclosporine, calcium channel blockers and grapefruit juice. All these agents lead to an increase in plasma concentration of statins and the use of pravastatin or fluvastatin may be preferable since these are not primarily metabolized by CYP3A4 [55-57]. Rifampicin, phenobarbital, carbamazepine and phenytoin are examples of drugs that induce both CYP3A4 and CYP2C9 and therefore lead to increased metabolism of hepatically metabolized statins. The lipid-lowering effect of statins can be reduced by concomitant use of these drugs. Warfarin is metabolized by CYP3A4 and CYP2C9, and there have been few reports indicating that patients on statins and warfarin are potentially at risk for bleeding complications. Careful monitoring of the International Normalized Ratio (INR) is advised in patients on warfarin, following the start of or any change in statin use (except pravastatin)[58,59]. Commonly used agents for sedation may have interactions with statin therapy as well. Midazolam, commonly used for sedation in an ICU, is metabolized in part by the same CYP isoenzyme as most statins, CYP3A4. In theory this could lead to interactions and alterations on the efficacy of either drug or both. However, a recent report showed that statins had no influence on midazolam pharmacokinetics in healthy subjects, thus dismissing this theory [60]. The incidence of side effects therefore depends on the type of statin used. For lovastatin, simvastatin, and atorvastatin, which are metabolized by CYP3A4, an incidence of 0.73 cases/million prescriptions has been reported. For pravastatin and fluvastatin which are not oxidized by the cytochrome P 450 system, the rate is 0.15/million prescriptions [55].

Discussion

Statins have become a cornerstone in the treatment of patients with atherosclerotic disease, since their use has resulted in improvements in outcome. Current evidence also shows that statins decrease perioperative morbidity and mortality in patients undergoing (noncardiac) vascular and cardiothoracic surgery. However, a sudden discontinuation of statin therapy postoperatively appears to lead to a rapid loss of its vascular protective effects, and, in some instances, vascular deleterious and prothrombotic activity may increase above baseline levels leading to adverse effects. Beyond their lipid lowering properties statins have pleiotropic properties that may modulate the inflammatory cascade and potentially could be useful in the management of inflammatory conditions such as acute renal failure, neurovascular diseases and sepsis. Several studies have demonstrated beneficial effects of prior use of statins in the development and the progression these diseases and there is evidence supporting that the use of statins may be associated with a decreased hospital mortality caused by the above disorders. It should be underlined that these data come mainly from observational retrospective investigations and randomized prospective studies are warranted to confirm these encouraging results. Finally it should be noted that

statins are infrequently associated with adverse events and are generally safe and well tolerated. However, in the ICU setting, the critically ill patients treated on intensive care units certainly represent a population at increased risk and should thus be monitored closely for signs of adverse effects. Future trials will give us more insight in known and possible unexpected side effects.

Conclusion

Perioperative statin therapy reduces postoperative myocardial infarction and mortality after (cardio) vascular surgery. The available evidence suggests that patients on statin therapy should not discontinue their statin intake in the postoperative (intensive care) period. Indications where statin therapy might be indicated in the near future are expanding, but the evidence at this point in time is still not strong enough to justify a generalised use of statins in the intensive care setting. At this point in time the risk of potential side effects and drug interactions outweigh the possible benefits. We therefore do not recommend the liberal use of statins in the ICU setting. If there is an indication for statin therapy pravastatin and fluvastatin seem to have the highest safety profile and should be first choice in the ICU.

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Epidural analgesia is associated with improved health outcomes of surgical patients with chronic obstructive pulmonary disease

Felix van Lier MD, Patrick J. van der Geest MD, Sanne E. Hoeks PhD, Yvette R.B.M. van Gestel PhD, Jaap W. Hol MD, Don D. Sin MD FCCP, Robert Jan Stolker MD PhD, Don Poldermans MD PhD

Submitted

Abstract

Introduction:
Chronic Obstructive Pulmonary Disease (COPD) patients have increased postoperative morbidity and mortality. Epidural analgesia (EDA) improves postoperative outcome, but may worsen postoperative lung function. It is unknown whether COPD patients benefit from EDA. The objective of this study was to determine whether COPD patients undergoing major abdominal surgery benefit from EDA in addition to general anesthesia.

Methods:
This cohort study included 541 consecutive patients with COPD who underwent major abdominal surgery between 1995 and 2007 at a university medical center. Propensity scores estimating the probability of receiving EDA were used in multivariate correction. The primary outcome was postoperative pneumonia, 30-day and 1-year mortality.

Results:
There were 324 (60%) patients who received EDA in addition to general anesthesia. The incidence of postoperative pneumonia (16% vs 11%), 30-day (9% vs 5%) and 1-year mortality (34% vs 28%) was lower in patients who received EDA. After correction EDA was associated with improved outcome for postoperative pneumonia (OR 0.5; 95% CI: 0.3–0.9) and 1-year mortality (HR 0.7; 95% CI: 0.5-0.9). The strongest preventive effect was seen in patients with the most severe type of COPD.

Conclusion:
This study provides evidence that in COPD patients who are scheduled for major abdominal surgery, epidural analgesia might improve postoperative and 1-year health outcome.

Introduction

Perioperative pulmonary complications are common especially in elderly patients with co-morbidities. Nearly 5% of all patients undergoing noncardiac surgery experience significant pulmonary complications [1,2]. Postoperative pulmonary complications include respiratory failure, pneumonia, and atelectasis. Patients with Chronic Obstructive Pulmonary Disease (COPD) are particularly vulnerable to postoperative pulmonary complications with risk that is on average 300 to 700% higher than those without COPD [3]. Major abdominal surgery, especially operations near the diaphragm, further increases this risk by causing respiratory muscle weakness and abdominal pain, which together lead to reduced lung volumes, a blunted cough reflex and atelectasis [4]. One anesthetic method of mitigating abdominal pain is by using epidural analgesia (EDA). Studies have shown that EDA offers superior postoperative pain control with less adverse effects compared to intravenous opioids [5,6]. A recent study suggests that the use of EDA is associated with small improvement in survival following elective intermediate to high risk noncardiac surgical procedures [7]. EDA might also be associated with improved respiratory outcome after surgery [8-10]. However, some studies suggest that EDA can cause a transient impairment in lung function [11]. There are no studies available regarding the effect on patients that are at a high risk for postoperative pulmonary complications. The impact of EDA on COPD patients is thus unknown. The aim of the present study was to determine the relationship between the use of postoperative EDA and health outcomes in a large cohort of COPD patients presenting for major abdominal surgery.

Materials and Methods

Study population

The patient population for this study has been described previously [12]. This observational retrospective study included 556 consecutive COPD patients who underwent elective major abdominal surgery between 1995 and 2007 at the Erasmus Medical Center, Rotterdam, The Netherlands. Major abdominal surgery was defined as any procedure under general anaesthesia involving a midline laparotomic incision that was expected to take more than 60 minutes and required at least 6 days hospitalization for acute recovery. Patients who had surgery for a ruptured abdominal aortic aneurysm or emergent abdominal surgery for other indications including trauma were excluded from the present study. These patients were excluded, since no pulmonary function testing was available in these patients. In the second place, patients presenting for emergent operations often do not receive EDA preoperative due to hemodynamic and/or respiratory instability or due to pain. Patients who underwent liver transplantation surgery were also excluded because EDA is generally not used in these patients. In the remaining patients, we abstracted the following information from their medical records: demographics (age and sex) and salient risk factors for post-operative pulmonary complications including: obesity (body mass index, BMI $\geq$ 30 kg/m^2), a history of coronary heart disease, congestive heart failure, diabetes mellitus, renal dysfunction (serum creatinine >160 µmol/l), stroke or transient ischemic attack. Coronary heart disease was defined as angina pectoris or prior myocardial infarction

(MI) on the basis of history or a finding of pathologic Q waves on electrocardiography. The revised cardiac risk index (LRI) by Lee was calculated for all patients [13]. The use of cardiovascular medication was also noted. These included beta-blockers, statins, clopidogrel, and aspirin. Information on the type, duration and indications for surgery was retrieved from the anesthesia reports.

Pulmonary Function Testing

A diagnosis of COPD was based on post-bronchodilator spirometric values in conjunction with a history of cough, sputum production, and/or dyspnoea. COPD was defined according to the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (FEV1 to FVC ratio less than 70%) [14]. Disease severity was classified into three groups: I = mild COPD (FEV1/FVC < 0.70 and FEV1 ≥ 80% of the predicted FEV1), II = moderate COPD (FEV1/FVC < 0.70 and FEV1 50% ≤ FEV1 < 80% of the predicted FEV1), and III = severe COPD (FEV1/FVC < 0.70 and FEV1 30% ≤ FEV1 < 50% of the predicted FEV1) [14]. We used the equation of Quanjer and colleagues, adjusted for age, sex, and height, to calculate the predicted FEV1 value, which has been demonstrated to make an accurate prediction [15]. The equation for males is 4.30 x height (m) – age x 0.029 – 2.49 and for women is 3.95 x height (m) – age x 0.025 – 2.60 [16]. Patients who did not perform spirometry were excluded from the study population. As per hospital protocol, all patients with mild COPD continued their own medication in the perioperative period. Patients with moderate and severe COPD continued their own medication and received a perioperative stress dose of steroids (20 mg of prednisone the day before surgery, 20 mg on the day of surgery and 20 mg on the first postoperative day).

Perioperative pain management

All operations were performed under general anaesthesia with neuromuscular block and inhalation agents as per hospital protocol. Epidural analgesia was offered to all patients at the outpatient clinic if no contraindications existed. There were no documented cases where there were any contraindications for epidural analgesia present. As per hospital protocol, all anticoagulant drugs are stopped 10 days before surgery. LMWH heparins are not started preoperatively. The evening before surgery plasmatic coagulation tests were performed if the patient was taking coumarin derivatives. In case of an INR > 1.6, vitamin K is provided to the patient. Overall no coagulation abnormalities were present that limited the choice between EDA and non-EDA. Before induction of anaesthesia, an epidural catheter was placed at the level T7–10 using a midline or paramedian approach for those who received EDA. The quality of the EDA was tested before the start of the surgery using cold and warm discrimination. There was one documented case where no block was obtainable after initial placement. A second attempt led to successful placement. Epidural infusions were standardized using a combination of bupivacaine 0.1% with sufentanil 0.5 mcg/ml to achieve an epidural infusion rate of 5–10 ml/h. During surgery continuous infusion is started at the discretion of the anesthesiologist. If epidural placement was not possible or if patients refused, patients were given patient-controlled i.v. analgesia (PCA). PCA consisted of morphine 1 mg/ml with a 6 min lock-out and was left in place as long as necessary. From the total

population of 541 patients, 5 patients were placed in the PCA group because of patients refusal to EDA. Another 10 patients were placed in the PCA group after EDA placement was considered unsuccessful. To make sure that those patients placed in the EDA group had a working EDA, patients were placed in the EDA or PCA group based on the fact how they were discharged from the recovery ward. In the postoperative phase all patients were visited once daily by a nurse who is experienced in treating postoperative pain. Numeric analog scale (NAS) scores were obtained and the pain management was adjusted if needed (NAS >6). All patients received 1000 mg of acetaminophen four times daily. The epidural catheter was removed on the fourth postoperative day and patients were instructed to take tramadol if needed. Information about how long epidural were actually left in place was only found in 25% of the patients. In all of these patients the EDA was removed on the 4th postoperative day.

Follow-up and endpoints

Follow-up was completed in 541 (97%) of the study patients, with a median follow-up of 5 years. Ten patients were excluded because anesthesia reports were missing, and 5 patients were lost to follow-up. Survival status was obtained from the municipal civil registries and the postoperative clinical characteristics were retrieved from the hospital medical records. The primary endpoints of the study were postoperative pneumonia within 10-days and death within 30-days of surgery as well as one year mortality regardless of the cause. Postoperative pneumonia was defined as clinical symptoms of pneumonia (e.g. cough, shortness of breath, fever, hypoxemia, or phlegm production) plus a new or progressive infiltrates or consolidations on a chest radiograph.

Statistical analysis

Continuous data are presented as means ± SD and were compared using a Student's t test. Categorical variables are expressed as percentages and were compared using a chi-square test. Univariate and multivariate logistic regression analyses were used to determine the relationship of EDA use to postoperative morbidity and mortality. Cox proportional hazards models were used to analyze the impact on one year mortality. Regression analyses were adjusted for relevant covariates, including age, sex, obesity, LRI, surgery for malignancy and severity of COPD. In addition, using a multivariate logistic regression model, we developed a propensity score to adjust for the likelihood of receiving EDA. The variables in this model included age, sex, obesity, severity of COPD, length of surgery, diabetes mellitus, renal dysfunction, surgery for malignancy, year of surgery, all variables on cardiovascular history, and cardiovascular medications. The model fit and predictive power of the propensity score model were validated with the Hosmer-Lemeshow goodness-of-fit test (P=0.797) and c-statistic (0.69), respectively. The EDA propensity score was included as an additional covariate in our regression models to adjust the effect of treatment method in evaluating outcome endpoints. Odds ratios (ORs) and hazard ratios (HRs) were calculated from these models together with their 95% confidence intervals (CIs). For all tests, a two-sided P value of less than 0.05 was considered significant. All statistical analyses were performed using SPSS 17.0 (SPSS Inc.,Chicago, IL).

Results

Baseline characteristics

The baseline characteristics of the study patients are presented in table 1. Overall the majority of the patients were men (74%). Of the 541 patients, 231 (43%) of the patients were classified with mild COPD, 195 (36%) with moderate COPD and 115 (21%) with severe COPD. An epidural procedure was performed in 60% of the patients and was performed more frequently in patients with mild or moderate COPD than in those with severe disease. No procedural-related complications were noted in the EDA group, except for one patient who described a paresthesia sensation in the legs for several hours after surgery. After EDA removal the patient left the hospital a week later without complaints.

Association between epidural analgesia and postoperative pneumonia

Postoperative pneumonia was diagnosed in 68 (13%) patients. The incidence of pneumonia was slightly higher in patients without than in those with EDA (16% vs 11%; p=0.08). Severity of COPD did not significantly modify the risk of pneumonia (mild COPD, 10%; moderate COPD, 17%; and severe COPD, 13%; p= 0.07). Multivariate analysis was performed using a propensity score to adjust for various factors including severity of disease. The results of this analysis are presented in table 2. In this analysis, the use of EDA was associated with reduced risk of postoperative pneumonia (OR 0.5; 95% CI: 0.3–0.9). This effect was observed in all severity groups (Mild: OR 0.6; 95% CI: 0.2-1.5, Moderate: OR 0.6; 95% CI: 0.3-1.5, Severe: OR 0.2; 95% CI 0.04-1.3). The c-index of the model predicting pneumonia was 0.67.

Epidural analgesia and 30-day mortality

Within 30 days after surgery, 35 (6.5%) patients died. The risk of mortality also increased along the Lee Risk Index gradient (2% with LRI of 1, 7.0% with LRI of 2 and 21% with LRI of 3 or more; p<0.001). Death was more common in patients without than in those with EDA (9% vs 5%; p=0.03). However, with inclusion of potential confounders into a multivariate model, the use of EDA was no longer significantly with 30-day mortality (OR 0.6; 95% CI: 0.3-1.2).

Epidural Analgesia and 1 year mortality

163 (30%) of the patients died within 1 year of surgery. In the crude analysis, the risk of death was not significantly different in patients with and without EDA (28% versus 34%; p=0.15). However, with multivariate adjustment, the use of EDA became significantly related to reduced risk of 1 year mortality (HR 0.7; 95% CI: 0.5-0.9). The strongest effect was seen in patients with severe COPD (figure 1). Postoperative pneumonia was also associated with higher 1-year mortality rates (28% vs 42%; p< 0.001). After multivariate adjustment, postoperative pneumonia was still associated with an increased risk of 1-year mortality (HR 1.7; 95% CI: 1.1-2.6). Expectedly, there was a higher incidence of mortality in patients who had surgery for malignancy (39% vs 18%; p< 0.001).

Table 1. Baseline patient characteristics of COPD patients with and without epidural analgesia undergoing major abdominal surgery

	Epidural N(%)	No epidural N (%)	p-value
No. of patients	324	217	
Age (years)	66.2	65.3	0.38
Male gender	252 (77)	149 (69)	0.02
BMI > 30	28 (9)	25 (12)	0.27
COPD classification			< 0.001
Mild	152 (47)	79 (36)	
Moderate	129 (40)	66 (30)	
Severe	43 (13)	72 (33)	
Risk factors			
Coronary heart disease	44 (14)	34 (16)	0.50
Congestive heart failure	7 (2)	17 (8)	0.002
Cerebrovascular disease	22 (7)	18 (8)	0.51
Diabetes mellitus	157 (48)	88 (41)	0.07
Renal dysfunction	6 (2)	10 (5)	0.07
Lee Risk Index			0.35
1	142 (44)	98 (45)	
2	143 (44)	85 (39)	
≥3	39 (12)	34 (16)	
Medication use			
Statins	41 (13)	20 (9)	0.22
Beta blockers	99 (31)	53 (24)	0.12
Aspirin	59 (18)	25 (12)	0.04
Clopidogrel	2 (1)	2 (1)	1.0
Surgical procedure			1.0
Length of procedure (minutes)	279	238	< 0.001
Surgery for malignancy	212 (68)	106 (49)	< 0.001
Types of surgery			0.008
Colon	174 (54)	139 (64)	
Hepatico/pancreatico/billary	8 (3)	10 (5)	
Esophagogastric	15 (5)	7 (3)	
Other abdominal	17 (5)	5 (2)	
Endocrine	1 (0)	0 (0)	
Gynecology	7 (2)	11 (5)	
Urologic	33 (10)	22 (10)	
Aorta elective	63 (19)	20 (9)	
Other	6 (2)	3 (1)	

Table 2. Adjusted odds ratios for outcome parameters using multivariable analysis§ and additional propensity score adjustment *

	Pneumonia		30-day mortality		1-year mortality	
	Multivariate	Propensity adjusted	Multivariate	Propensity adjusted	Multivariate	Propensity adjusted
	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]	HR [95% CI]	HR [95% CI]
Age (per year increase)	1.02 (0.997-1.05)	1.02 (0.99-1.05)	1.06 (1.02-1.11)	1.06 (1.02-1.11)	1.03 (1.01-1.05)	1.03 (1.01-1.05)
Male gender	1.7 (0.9-3.3)	1.6 (0.8-3.3)	1.0 (0.4-2.3)	1.0 (0.4-2.4)	1.0 (0.7-1.5)	1.0 (0.7-1.5)
BMI ≥ 30	0.9 (0.3-2.2)	0.9 (0.4-2.3)	0.8 (0.2-3.0)	0.8 (0.2-3,0)	0.6 (0.3-1.1)	0.6 (0.3-1.1)
COPD classification						
Mild	1	1	1	1	1	1
Moderate	2.0 (1.1-3.6)	2.0 (1.1-3.6)	1.0 (0.4-2.8)	1.1 (0.4-2.8)	1.2 (0.8-1.7)	1.2 (0.8-1.7)
Severe	1.0 (0.4-2.1)	1.1 (0.4-3.1)	3.0 (1.3-7.4)	3.0 (1.2-7.4)	1.1 (0.7-1.7)	1.4 (0.6-2.0)
Lee Risk Index						
1	1	1	1	1	1	1
2	1.3 (0.7-2.3)	1.2 (0.7-2.3)	4.4 (1.4-13)	4.4 (1.4-14)	1.1 (0.8-1.5)	1.1 (0.7-1.5)
≥3	1.8 (0.9-3.9)	1.9 (0.9-3.9)	15 (4.6-49)	15 (4.6-49)	1.4 (0.9-2.3)	1.4 (0.9-2.3)
Surgery for malignancy	0.8 (0.5-1.4)	0.7 (0.4-1.4)	1.4 (0.6-3.0)	1.4 (0.6-3.0)	2.6 (1.8-3.8)	2.6 (1.7-3.9)
Epidural analgesia	**0.6 (0.3-0.9)**	**0.5 (0.3-0.9)**	**0.6 (0.3-1.2)**	**0.6 (0.3-1.2)**	**0.7 (0.5-0.9)**	**0.7 (0.5-0.9)**

§ Variables included in multivariate analysis included: EDA, age, sex, obesity, LRI, surgery for malignancy and severity of COPD.
* The following variables were used for constructing the a propensity score for the prediction of receiving epidural analgesia: age, sex, obesity, severity of COPD, length of surgery, diabetes mellitus, renal dysfunction, surgery for malignancy, all variables on cardiovascular history, and cardiovascular medications.

Discussion

In a large group of patients with COPD who underwent abdominal surgery, we showed that the use of EDA, in concert with general anesthesia, was associated with reduced incidence of postoperative pneumonia and improved 1 year mortality. COPD is a well known risk factor for postoperative pulmonary complications (PPC) [1,10,17]. A recent study by Canet et al identified seven independent risk factors for PPC: low preoperative arterial oxygen saturation, acute respiratory infection during the previous month, age, preoperative anemia, upper abdominal or intrathoracic surgery, surgery duration of at least 2 h and emergency surgery [2]. Although the number patients with PPC in COPD patients were nearly 5 times higher compared to non COPD patients (16.4% vs 3.5%; p<0.001), COPD was not identified as an independent risk factor in this study. Potential interventions to reduce PPC include: smoking cessation, preoperative exercise training, early mobilisation, postoperative total parenteral nutrition and optimal treatment of postoperative pain [4]. Although postoperative pain management is enhanced by the use of EDA, its use in patients with COPD has been controversial owing to ongoing fears that it may acutely reduce lung function. For example, the use of high thoracic epidurals has been associated with decreased spirometric values by possibly blocking intercostal muscle innervation [18]. However, other studies have failed to show any deleterious respiratory effects from EDA [19]. Whether EDAs cause any material changes in lung function in patients with COPD is uncertain. EDA appears to provide superior pain control over systemic opioids in patients undergoing major abdominal surgery [6,20]. EDA may also reduce postoperative pulmonary complications [8-10]. In a meta-analysis by Ballantyne et al. there was a non-significant trend towards lower incidence of pulmonary infections postoperatively in favour of epidural opioids over the use of systemic opioids (RR 0.53; 95% CI: 0.18-1.53) [21]. The same study also showed that the use of epidural local anesthetics significantly decreased the incidence of pulmonary infections (RR 0.36; 95% CI: 021-0.65). In a more recent review, which included more heterogeneous surgical procedures, neuroaxial blockade was associated

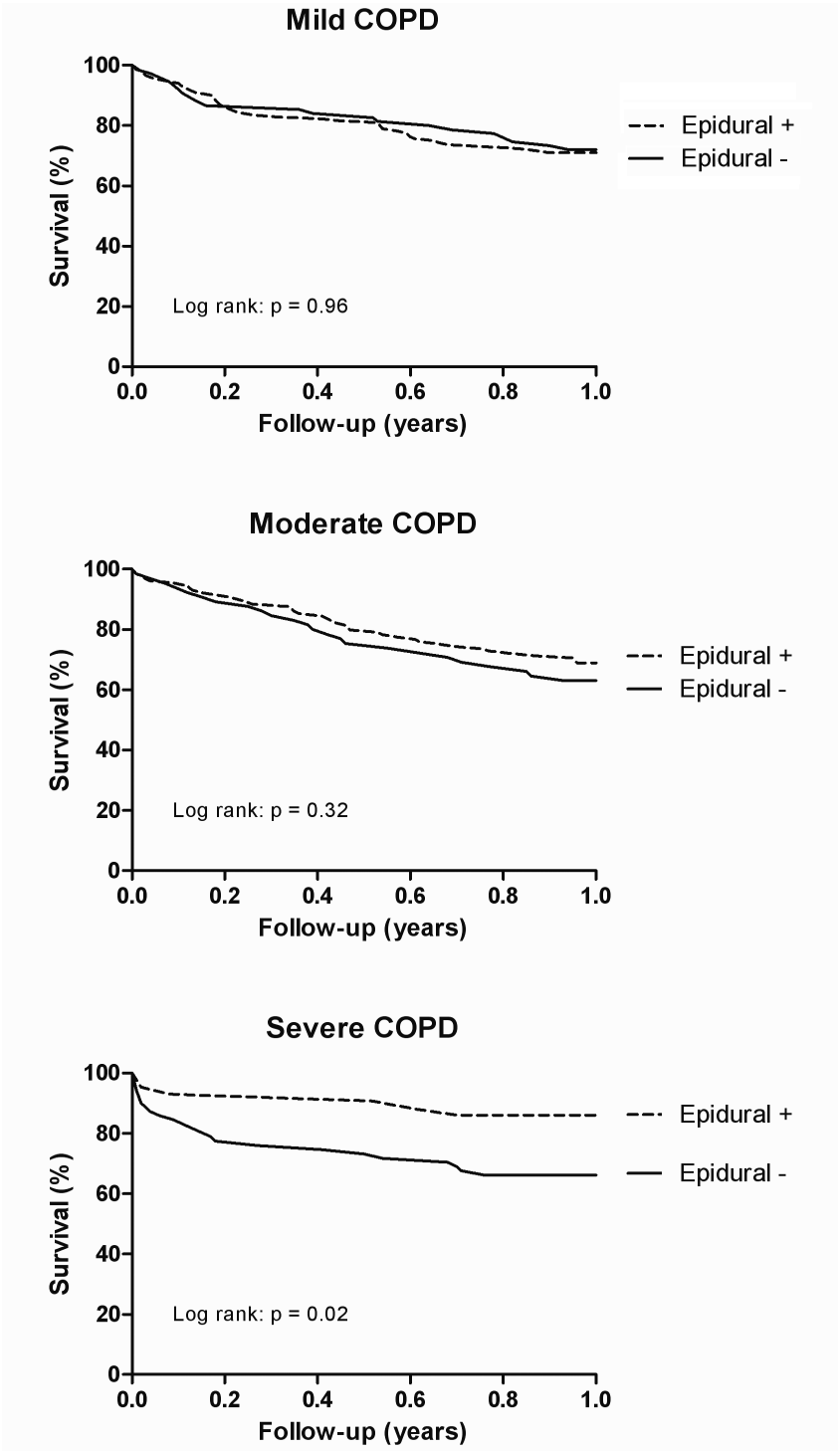

Figure 1. Kaplan-Meier survival curves for 1-year mortality, stratified according to the severity of COPD

with decreased incidence of postoperative pneumonia (OR 0.61; 95% CI: 0.48-0.76) [22]. However, other studies have failed to demonstrate a beneficial effect of EDA on postoperative pneumonia [23,24]. In a randomised controlled trial by Norris et al, 168 patients undergoing surgery of the abdominal aorta were randomly assigned to receive either thoracic epidural analgesia combined with a light general anesthesia or general anesthesia alone intraoperatively or either intravenous or epidural patient-controlled analgesia postoperatively [25]. Although length of stay was considered as the primary outcome variable, postoperative outcomes were similar among the four treatment groups with respect to death, myocardial infarction, myocardial ischemia, reoperation, pneumonia and renal failure. It should be noted that the treatment groups were relatively small and only 2 patients with a postoperative pneumonia were identified. By studying a large group of patients and by focusing on the highest risk group (i.e. those with COPD) for postoperative pneumonia, our study does affirm the benefits of EDA in mitigating the risk of postoperative pneumonia and most importantly enhancing survival of patients who undergo abdominal surgery. As with postoperative pneumonia, the effects of EDA on postoperative mortality have also shown conflicting results [7, 9, 22, 26]. A recent retrospective cohort study of 259,037 patients showed a small improvement in 30-day postoperative survival (RR 0.89; 95% CI 0.81-0.98) with a number needed to treat of 477 [7]. In their systematic review, Rodgers et al. report that overall mortality was reduced by a third in patients who were allocated to neuraxial blockade (OR 0.7; 95% CI: 0.54-0.90) [22]. Our study results are in general agreement with these findings and extend them by showing that the survival benefits of EDA in COPD patients may extend to 12 months and longer following surgery and that EDA may be most effective in patients with severe disease.

Several limitations should be taken into account when interpreting our results. First, this was an observational study. Causality can therefore not be assumed. To minimize the possibility of confounding we carefully collected salient clinical and demographic information and performed adjustments for these covariates in the regression analysis. In addition, EDA was not randomly assigned and therefore subject to confounding by indication. To address this limitation, propensity score analysis was used as a post hoc statistical method that estimates treatment impact when subjects are not randomly assigned to a specific treatment group [27]. Three propensity score-based methods are commonly used in medical literature: matching, covariate adjustment, and stratification. Recognizing that there is no universally accepted "gold standard" technique, the fact of our restrictive pool of controls and our relative small sample size, we decided to use covariate adjustment. However, the most important limitation of propensity methods is, like other adjustment methods, that it can only adjust for observed and known confounders and does not protect against bias from unknown or imperfectly measured confounders [28]. Residual bias can therefore not be excluded. Second, we could not fully rule out the possibility that some individuals with COPD also had asthma. However, although bronchial hyperresponsiveness is more common (and more severe) in asthma than in COPD, over 70% of patients with COPD (who smoke) also demonstrate bronchial hyperresponsiveness. Third, since we did not have lung function or biochemical measurements following surgery, the mechanism by which EDA reduces postoperative pneumonia and mortality remains unknown. Fourth, as per hospital protocol patients with moderate and severe COPD all received a perioperative stress dose of steroids. A stress dose of steroids remains a point of discussion since some

hospitals only treat COPD patients with their own dose of steroids in the perioperative phase. Studies and COPD guidelines still advocate the use of systemic glucocorticosteroid treatment in the perioperative phase to prevent exacerbations [10, 29-31]. However, the use of steroids is also associated with increased wound infections in the postoperative period. Finally, it should be emphasised that performing EDA is not a procedure free of risk. Although only one complication was noted in our population, epidural abscess and bleedings are rare but serious complications which should be brought to the attention of all surgeons and anesthesiologists since it has major impact for the patient. A risk-benefit analysis should be made for each individual patient.

In summary, the results of the present study suggest that epidural analgesia reduces postoperative morbidity and mortality in COPD patients undergoing major abdominal surgery. Although the exact mechanisms by which this occurs are unknown, our data suggest that the use of epidural analgesia should be encouraged in patients with COPD undergoing major abdominal surgery.

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Summary and Conclusions
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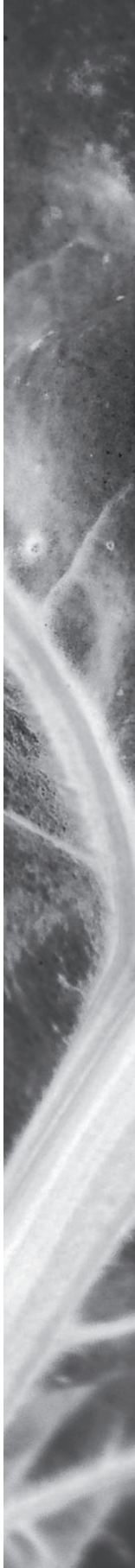
Samenvatting en Conclusies



Summary and Conclusions

This thesis describes risk factors and risk reduction strategies for major adverse thromboembolic events in the perioperative period.

Chapter one describes the importance of preoperative screening for patients at risk in the perioperative period. The pathophysiology of perioperative cardiac ischemia and myocardial infarction is discussed. Approximately 50% of the perioperative myocardial infarctions have their origin in plaque disruption and can therefore be seen as a thromboembolic event. The other half of the perioperative myocardial infarctions are related to sustained myocardial oxygen supply mismatch. Perioperative stress and hypoxia may lead to an increased demand for oxygen by the myocardium. In the case of advanced atherosclerosis insufficient coronary blood flow may cause myocardial oxygen debt eventually leading to ischemia and infarction. As demonstrated in the second part of the chapter, only a small proportion of the patients at risk benefit from preoperative coronary revascularization. The majority of the patients will not benefit from preoperative revascularization. Pharmacological treatment, using beta-blockers, statins and aspirins has proven to reduce perioperative risk in different subsets of patients and is therefore the preferred form of prevention preoperative.

Perioperative stroke is discussed in chapters two to four. The incidence of perioperative stroke in noncardiac surgery is relatively low (0.08 - 0.7%) compared to cardiac surgery (8 – 10%). Therefore perioperative stroke after noncardiac surgery can be seen as a rare complication; however stroke has major impact for the individual patient and should therefore be seen as a major adverse event. Recently several studies have related beta- blockers to an increased risk of perioperative stroke. Beta-blockers have shown to reduce perioperative myocardial infarction, but are associated with an increased risk for postoperative stroke. Chapter two summarizes the findings on perioperative stroke in relation to beta-blockers. Several important issues such as type of beta-blocker, timing of initiation as well as dosing are discussed in detail.

In chapter three patients on chronic beta-blocker use were evaluated for postoperative stroke after noncardiac surgery. In this case-control study among 186,779 patients risk factors for postoperative stroke were identified. This study showed that patients who were on chronic beta-blocker use, did not have an increased risk of postoperative stroke. This study demonstrates that beta-blockers can be used safely in the perioperative period as long as important safety precautions are respected.

Chapter four focuses on the initiation of beta-blockers in the perioperative period. Current guidelines recommend that beta-blocker therapy should be initiated in high risk patients undergoing noncardiac surgery to prevent patients for cardiovascular complications. In this cohort study, 3884 patients were evaluated for postoperative stroke who recently were started on beta-blocker before surgery. Unlike the landmark POISE trial no relationship was found between beta-blocker use and postoperative stroke in the DECREASE trials. This chapter discusses how this difference can be explained. Before starting beta-blockers several aspects should be considered including: indication for perioperative beta-blocker therapy, timing of initiation of therapy, type of beta-blockers, dosage and treatment targets.

Intraoperative cardiac arrest is discussed in chapter five. The last 40 years many improvements have been seen in patient safety during anesthesia. Therefore the incidence of anesthesia related cardiac arrest and its mortality have declined over recent decades. Patients presenting for emergency surgery (e.g. trauma and patients with sepsis) are at the highest risk of adverse cardiovascular events due to reduced cardiovascular reserve capacity. In this case-control study 42 patients scheduled for elective noncardiac surgery, who suffered intraoperative cardiac arrest, were selected as cases. A preoperative anemia and a history of ischemic heart diseases were identified as independent risk factors for intraoperative cardiac arrest.

In chapter six a risk prediction model for postoperative pulmonary embolism is constructed. Pulmonary embolism is a well known venous embolic life threatening event common in the postoperative period. This study reveals several risk factors for pulmonary embolism. Most of these risk factors can not be modified by the treating physician, except for the thromboprophylaxis used in the perioperative period. Thromboprophylaxis with low molecular weight heparin has shown to prevent patients for venous thromboembolic events. However, surgeons often delay thromboprophylaxis if they 'feel' hemostasis is compromised. As shown in this study, delaying thromboprophylaxis for more than 24 hours after surgery is a major risk factor for pulmonary embolism in the postoperative period. Finally, this study shows that a simple risk model can be used to identify patients at risk for pulmonary embolism.

Chapter seven summarizes the use of statins in the intensive care unit. Statins have shown to reduce cardiovascular events in the perioperative period in patients undergoing both cardiac and noncardiac surgery. More importantly, statins should not be withheld in the postoperative period. Since there is no intravenous formula for statins, discontinuation in the intensive care is often seen because of impaired gastrointestinal function. Patients unable to take statins postoperatively have an increased risk of (nonfatal) myocardial infarction and cardiac death. The second part of this chapter describes other potential roles for statin use in the intensive care unit. In the near future there may be an indication for statins in other diseases often seen in the intensive care unit (e.g. renal failure, neurovascular diseases and sepsis).

Chapter eight provides evidence that epidural analgesia in addition to general anesthesia in COPD patients undergoing major abdominal surgery improves postoperative outcome. The results of this study show that COPD patients with epidural analgesia have an decreased chance of developing a postoperative pneumona. The use of epidural analgesa is not only associated with improved short term outcome, but may also be related to improved outcome up to one year after surgery.

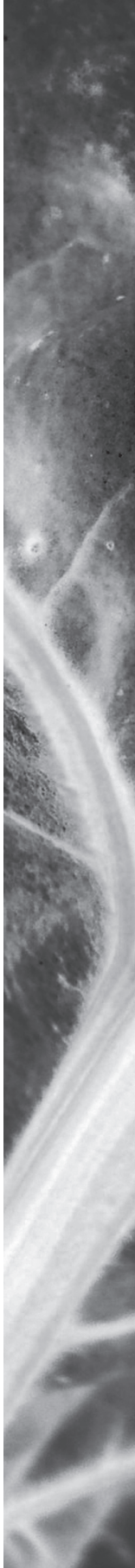
Samenvatting en Conclusies

Dit proefschrift beschrijft risicofactoren en preventiestrategieën voor ernstige thromboembolische complicaties in de perioperatieve periode.
Hoofdstuk één beschrijft de waarde van het preoperatief screenen van patiënten met een verhoogd risico op cardiovasculaire complicaties in de perioperatieve periode. De pathofysiologie van cardiale ischemie (onvoldoende doorbloeding van de hartspier) en van het hartinfarct wordt in detail besproken. Bij ongeveer 50% van de hartinfarcten, die ontstaan in de perioperatieve periode, ligt de oorsprong in het loslaten van een atherosclerotische plaque in de kransslagaders van het hart. Het hartinfarct kan daarom gezien worden als een vorm van een thromboembolische complicatie. De andere helft van de hartinfarcten kan verklaard worden door een langdurige disbalans tussen zuurstofaanbod en zuurstofvraag. Perioperatieve stress en hypoxie (een laag zuurstof gehalte in het bloed) kunnen leiden tot een verhoogde zuurstofvraag van de hartspier. Als gevolg van atherosclerose van de kransslagaders bereikt onvoldoende zuurstof de hartspier, met als gevolg ischemie en infarcering. Het tweede gedeelte van dit hoofdstuk toont aan dat slechts een kleine groep patiënten baat heeft bij het preoperatief revasculariseren ('dotteren') van de kransslagaders. Preoperatief 'dotteren' verlaagt slechts bij een subgroep van de patiënten het risico op cardiovasculaire complicaties na algemene chirurgie. Het is aangetoond dat medicamenteuze behandeling, met behulp van bèta-blockers, statines en aspirines het perioperatieve complicatierisico vermindert in verschillende subgroepen van patiënten. De medicamenteuze vorm is daarom ook de primaire vorm van preventie preoperatief.
Perioperatieve beroertes worden besproken in de hoofdstukken twee tot en met vier. De incidentie (het voorkomen) van een perioperatieve beroerte bij algemene chirurgie is relatief laag (0.08 – 0.7%) vergeleken met hartchirurgie (8 – 10%). Een beroerte na algemene chirurgie kan daarom een zeldzame complicatie genoemd worden. Echter, een beroerte is een dusdanig ernstige complicatie, met dramatische gevolgen voor de korte en lange termijn, dat deze complicatie als zeer ernstig beschouwt dient te worden. Verschillende studies hebben recentelijk de relatie gelegd tussen het gebruik van bèta-blockers en een verhoogde kans op het krijgen van een perioperatieve beroerte. Bèta-blockers zijn bewezen effectief bij het voorkomen van een hartinfarct in de perioperatieve periode, maar geven wel een verhoogde kans op een beroerte.
Hoofdstuk twee geeft een samenvatting over de relatie tussen bèta-blockers en beroerte. In dit hoofdstuk wordt gedetailleerd ingegaan op de verschillende soorten bèta-blockers, de dosering en het moment van starten voor de operatie.
In hoofdstuk drie wordt de relatie tussen een beroerte na algemene chirurgie en patiënten die chronisch bèta-blockers gebruiken onderzocht. In een case-control studie met 186,779 patiënten worden risicofactoren voor het krijgen van een beroerte gedefinieerd. Deze studie laat zien dat patiënten die chronisch bèta-blockers gebruiken, geen verhoogde kans hebben op het krijgen van een beroerte na algemene chirurgie. In deze studie wordt aangetoond dat bèta-blockers veilig gebruikt kunnen worden, bij een selectieve groep patiënten in de perioperatieve periode, mits hiermee op tijd gestart wordt voor de operatie.

Hoofdstuk vier richt zich op het starten van bèta-blockers in de perioperatieve periode. De huidige richtlijnen adviseren dat bij hoog risico patiënten, die gepland staan voor algemene chirurgie, bèta-blockers gestart dienen te worden ter preventie van cardiovasculaire complicaties. In deze cohort studie werden 3884 patiënten, bij wie bèta- blockers gestart waren voor de operatie, geëvalueerd voor een postoperatieve beroerte. In tegenstelling tot de relatie gevonden in de POISE studie, kon er in de DECREASE studies geen relatie aangetoond worden tussen het starten van bèta-blockers preoperatief en een verhoogde kans op een beroerte. Er wordt nader ingegaan op hoe dit verschil verklaard kan worden. Voordat bèta-blockers preoperatief gestart worden, dient aandacht geschonken te worden aan belangrijke voorwaarden.
Hartstilstand tijdens een operatie wordt besproken in hoofdstuk vijf. Ten gevolge van modernere medicatie en monitoring is in de laatste decennia de patiëntveiligheid tijdens anesthesie enorm verbeterd. De incidentie van de anesthesie gerelateerde hartstilstanden en sterfte is afgenomen. Patiënten die aangemeld worden voor spoedeisende operaties (bijv. traumaslachtoffers en intensive care patiënten) hebben de grootste kans op het krijgen van intraoperatieve cardiale complicaties ten gevolge van een verminderde cardiale reserve. In deze case-control studie zijn 42 patiënten, welke tijdens geplande algemene chirurgie een hartstilstand kregen, nader geanalyseerd. Een preoperatieve bloedarmoede en een voorgeschiedenis van ischemische hartziektes bleken onafhankelijke voorspellers te zijn voor een hartstilstand tijdens een operatie.
In hoofdstuk zes wordt een predictiemodel voor het krijgen van een postoperatieve longembolie geconstrueerd. Longembolieën zijn een beruchte, levensgevaarlijke, veneuze complicatie in de postoperatieve periode. In deze studie worden zes risicofactoren geïdentificeerd voor het krijgen van een longembolie na algemene chirurgie. Op de tromboseprofylaxe na, zijn de meeste risicofactoren patiënt gerelateerd en kunnen daarom niet beïnvloed worden door de behandelend arts. Tromboseprofylaxe middels laag moleculair gewicht heparines is bewezen effectief voor de preventie van veneuze thromboembolische complicaties. Vanwege een verhoogde kans op postoperatief bloedverlies worden laag moleculair gewicht heparines regelmatig niet gebruikt in de eerste 24 uur na een operatie, als de chirurg het 'gevoel' heeft dat de stolling tijdens de operatie reeds suboptimaal is. Deze studie laat zien dat het uitstellen van tromboseprofylaxe, tot meer dan 24 uur na een operatie, een grote risicofactor is voor het krijgen van een postoperatieve longembolie. Tenslotte wordt aangetoond dat een simpel predictiemodel gebruikt kan worden voor de identificatie van patiënten met een verhoogd risico op longembolieën.
Hoofdstuk zeven is een samenvatting betreffende het gebruik van statines op de intensive care afdeling. Het is bewezen dat statines een beschermend effect hebben op cardiovasculaire complicaties bij patiënten die gepland staan voor zowel algemeen chirurgische als ook hartchirurgische operaties. Belangrijker is dat statines niet gestopt worden in de postoperatieve periode, aangezien dit gepaard gaat met een verhoogde kans op hartinfarcten en cardiale sterfte. Het tweede gedeelte van dit hoofdstuk beschrijft potentiële toepassingen voor statines in de toekomst. Experimentele studies zijn hoopgevend en tonen goede resultaten in vaak voorkomende ziektes op de intensive care (o.a. nierfalen, neurovasculaire ziekten en bloedvergiftiging).
Hoofdstuk acht toont aan dat epidurale analgesie, in combinatie met algehele anesthesie, leidt tot minder postoperatieve complicaties bij COPD patiënten die grote buikchirurgie ondergaan. Het resultaat van deze studie laat zien dat COPD patiënten

die een epidurale catheter ontvingen, een kleinere kans hadden op het krijgen van een postoperatieve longontsteking. Het gebruik van epidurale analgesie lijkt niet alleen gerelateerd te zijn aan een betere uitkomst op korte termijn, maar kan ook positieve effecten hebben op de overleving tot een jaar na chirurgie.

Publications



Publications

Papers related to the thesis

van Lier F, Schouten O, van Domburg RT, van der Geest PJ, Boersma E, Fleisher LA, Poldermans D. Effect of chronic beta-blocker use on stroke after noncardiac surgery. Am J Cardiol. 2009 Aug 1;104(3):429-33.

Poldermans D, Schouten O, van Lier F, Hoeks SE, van de Ven L, Stolker RJ, Fleisher LA. Perioperative strokes and beta-blockade. Anesthesiology. 2009 Nov;111(5):940-5.

van Lier F, Schouten O, Hoeks SE, van de Ven L, Stolker RJ, Bax JJ, Poldermans D. Impact of prophylactic beta-blocker therapy to prevent stroke after noncardiac surgery. Am J Cardiol. 2010 Jan 1;105(1):43-7.

van Lier F, van Gestel YRBM, Hol JW, Hoeks SE, Grüne F, Stolker RJ, Fleisher LA, Poldermans D. Intraoperative cardiac arrest during noncardiac surgery: a single center case-control study. Submitted.

van Lier F, van der Geest PJ, Hoeks SE, Hol JW, Sin DD, Poldermans D. Pulmonary embolism after noncardiac surgery: derivation of a risk model. Submitted.

van Lier F, van der Geest PJ, Hoeks SE, van Gestel YRBM, Hol JW, Sin DD, Stolker RJ, Poldermans D. Epidural analgesia is associated with improved health outcomes of surgical patients with chronic obstructive pulmonary disease. Submitted.

van Lier F, Schouten O, Poldermans D. Statins in Intensive Care Medicine: still too early to tell. Review. Netherlands Journal of Intensive Care Medicine. In press.

Presented abstracts related to the thesis

Poldermans D, Schouten O, Hoeks SE, Dunkelgrun M, van Lier F, Durazzo AE, Bax JJ, Boersma E. Perioperative Stroke in Non-Cardiac Surgery; The Impact of Prophylactic Beta-Blocker Therapy. (Annual Scientific Session of the American-Heart-Association, New Orleans 2008)

van Lier F, Schouten O, van Domburg RT, van der Geest PJ, Boersma E, Fleisher LA, Poldermans D. Effect of chronic beta-blocker use on stroke after noncardiac surgery. (Annual Scientific Sessions of the American Society of Anesthesiology, New Orleans 2009)

van Lier F, van der Geest PJ, Hoeks SE, Sin DD, Poldermans D. Timing of thrombosis prophylaxis in relation to postoperative pulmonary embolism. (European Society of Cardiology, Stockholm 2010)

PhD Portfolio

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Dankwoord

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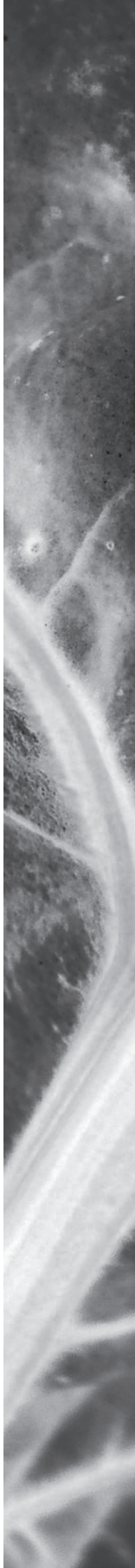
Curriculum Vitae



Erasmus MC
University Medical Center Rotterdam

PhD Portfolio Summary
Summary of PhD training and teaching activities

Name PhD student: Felix van Lier Erasmus MC Department: Anesthesiology Research School: COEUR	PhD period: 2007-2011 Promotor(s): Prof. dr. D. Poldermans

1. PhD training

	Year	Workload (Hours/ECTS)
Courses		
- NIHES 'Principles of research and medicine', 'Biostatistics for Clinicians'	2008 - 2009	2.9
- COEUR course Papendal	2008	6
- Intensive care research	2009	3
Seminars and workshops		
- Journal Club	2007 - 2010	1
- COEUR, Research seminars	2007 - 2010	0.1
Presentations		
- National Conferences	2007 - 2010	1
- International Conferences	2009 - 2010	4
International conferences		
- European Society of Cardiology Congress	2010	1
- American Society of Anesthesiology annual meeting	2009 - 2010	2

2. Teaching activities

	Year	Workload (Hours/ECTS)
Lecturing		
- Clinical training Anesthesiology	2009 - 2010	0.1
Supervising practicals and excursions		
- MSc students EUR	2010	0.1
Supervising Master's theses		
- MSc students EUR	2007 - 2010	4

Dankwoord

Een proefschrift schrijf je nooit alleen. Mijn dank gaat naar de volgende personen die een grote bijdrage hebben geleverd bij het tot stand komen van dit proefschrift.

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Curriculum Vitae

Felix van Lier werd op 27 augustus 1977 geboren in Utrecht. Nadat hij het eindexamen gymnasium behaalde in 1995 heeft hij een jaar scheikunde en een jaar medische biologie gestudeerd aan de Universiteit Utrecht. In 1997 begon hij aan de studie Geneeskunde aan dezelfde Universiteit. In 2003 werd het artsexamen behaald. Aansluitend werkte hij een jaar als arts op de chirurgische intensive care van het Universitair Medisch Centrum Utrecht (Prof. dr. L.P.H. Leenen). In 2006 werd gestart met de opleiding tot Anesthesioloog in het Erasmus Medisch Centrum te Rotterdam (Prof. dr. J. Klein en Prof dr. RJ Stolker). Vanaf juni 2010 is hij werkzaam op de intensive care van het Universitair Medisch Centrum Utrecht als fellow intensive care (Prof. dr. J. Kesecioglu). Felix is getrouwd met Bepje van den Burg, samen hebben zij een prachtige zoon: Tjebbe.