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**Perioperative Myocardial Damage
&
Cardiac Outcome
in Patients-at-Risk undergoing
Non-Cardiac Surgery**

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To the patients involved in the studies

Abstract

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Despite increasingly sophisticated perioperative management, cardiovascular complications continue to be major challenges for the clinician. As a growing number of elderly patients with known coronary artery disease (CAD) or with risk factors for CAD are undergoing non-cardiac surgery, cardiovascular complications will remain a significant clinical problem in the future.

The overall objective of this thesis was to study the incidence of myocardial damage and perioperative adverse cardiac events, to determine predictors of poor outcome and to assess the effect of a medical intervention in patients at risk undergoing non-cardiac surgery.

The studies in this thesis were conducted on a total of 952 patients undergoing non-cardiac surgery. Studies I and IV were multicenter studies; whereas the patients included in studies II and III underwent non-cardiac surgery at Linköping University Hospital, Sweden.

The correlation between postoperative myocardial damage and short- and long-term outcome were studied in 546 patients, aged 70 years or older undergoing non-cardiac surgery of at least 30 minutes duration. This study showed a close correlation between postoperative myocardial damage and poor short- as well as long-term outcome. Elevated Troponin T was a strong independent predictor of mortality within one year of surgery. In 186 patients with ASA physical status classification III or IV undergoing non-elective surgery, the incidence of myocardial damage was 33%. In this study preoperative myocardial damage was an independent predictor of major adverse cardiac events in the postoperative period. In 69 patients with ASA physical status classification III & IV undergoing acute hip surgery, we found a close correlation between elevated NT-proBNP value prior to surgery and cardiac complications in the postoperative period. To study the effect of acetylsalicylic acid on postoperative myocardial damage and cardiovascular events, 220 patients at risk were randomized to receive 75 mg of acetylsalicylic acid or placebo 7 days prior to surgery until the third postoperative day. This study showed that treatment with acetylsalicylic acid resulted in an 8% (95% CI 1-15%) absolute risk reduction of having a postoperative major adverse cardiac event. No statistically significant differences of bleeding complications were seen between the groups.

In conclusion, this thesis contributes to the understanding of the clinical relevance of elevated cardiac markers (with or without clinical or ECG signs of myocardial damage) in patients undergoing elective or emergency surgery. Moreover, we have identified predictors of poor outcome in the perioperative period that could be used as tools for identifying patients at risk. Finally, we have shown that continuing acetylsalicylic acid in the perioperative period reduced the risk of major adverse cardiac events within 30 days of surgery.

Keywords: Myocardial damage, troponin I, troponin T, myocardial infarction, mortality, major adverse cardiac event, outcome, cardiac complication, NT-proBNP, left ventricular systolic dysfunction, aspirin, acetylsalicylic acid.

List of original papers

This thesis is based on the following studies, which will be referred to in the text by their Roman numerals:

- I. Oscarsson A, Eintrei C, Anskär S, Engdahl O, Fagerström L, Blomqvist P, Fredrikson M, Swahn E. Troponin T-values provide long-term prognosis in elderly patients undergoing non-cardiac surgery. *Acta Anaesthesiol Scand* 2004; 48: 1071-1079.
- II. Oscarsson A, Fredrikson M, Sörliden M, Anskär, S Gupta A, Swahn E, Eintrei C. Predictors of cardiac events in high-risk patients undergoing emergency surgery. *Acta Anaesthesiol Scand* 2009; 53: 986-994.
- III. Oscarsson A, Fredrikson M, Sörliden M, Anskär S, Eintrei C. N-terminal fragment of pro-B-type natriuretic peptide is a predictor of cardiac events in high-risk patients undergoing acute hip fracture surgery. *British Journal of Anaesthesia* 2009; 103: 206-212.
- IV. Oscarsson A, Gupta A, Fredrikson M, Järhult J, Nyström M, Pettersson E, Darwish B, Krook H, Swahn E, Eintrei C. Aspirin: To continue or discontinue in the perioperative period. A prospective, controlled, clinical trial. *Submitted*.

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Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
ASA	American Society of Anaesthesiology
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CI	Confidence Interval
CK-MB	MB isoenzyme of Creatine kinase
ECG	Electrocardiogram
IHD	Ischaemic Heart Disease
MACE	Major Adverse Cardiac Event
MET	Metabolic Equivalent
MI	Myocardial Infarction
NSTEMI	Non ST segment Elevation Myocardial Infarction
NT-proBNP	N-terminal fragment of B-type natriuretic peptide
PCI	Percutaenous Coronary Intervention
PMI	Perioperative Myocardial Infarction
RCRI	Revised Cardiac Risk Index
TnI	Troponin I
TnT	Troponin T

Introduction

Despite increasingly sophisticated monitoring techniques and improved treatment, management of myocardial damage and cardiovascular complications in the perioperative period continues to be a major challenge for the clinician. Approximately 100 million adults undergo non-cardiac surgery worldwide yearly ¹ and up to 40% of these patients have or are at risk of coronary artery disease (CAD) ². Four million patients per year have been estimated to have a major perioperative cardiovascular complication, including cardiac death, non-fatal myocardial infarction or cardiac arrest ¹. In high-risk patients, the incidence of major perioperative cardiac complications varies from 4 to 25 % depending on patient population and type of surgery ³⁻⁵.

In addition, several studies have shown that perioperative myocardial infarction (PMI) is associated with an in-hospital mortality of 15-25% ⁶⁻⁹. These high mortality rates could result from difficulty in detecting PMI due to the absence of classical symptoms in the perioperative period ¹⁰. It has been found that only 14% of patients with a PMI have typical chest pain and consequently 53% of the PMI will not be diagnosed if the physician relies only on symptoms or clinical signs ¹¹. Therefore, cardiac markers (primarily the cardiac-specific troponins) are important for detecting perioperative myocardial damage. The appropriate cut-off levels for detecting myocardial damage using troponins in a surgical setting are still debated. However, elevated troponin with or without clinical or ECG signs of ischaemia are known to be associated with poor outcome both in patients with acute coronary syndrome ¹² as well as patients undergoing non-cardiac surgery ^{13, 14}.

Despite extensive research on strategies for risk assessment, preoperative testing, perioperative monitoring, as well as management of myocardial damage in cardiac risk patients, cardiovascular complications remain the leading causes of death in surgical patients ^{2, 15}. Apart from the suffering caused to the individual, perioperative cardiovascular complications are associated with a dramatic increase in resource utilization and, therefore, result in a major burden to the health care system ^{15, 16}. The World Health Organization estimates that, in the second half of the 21st century, 25% of the population will be ≥ 65 years of age, a group of patient with a high prevalence of ischaemic heart disease. As a growing number of elderly patients with known coronary artery disease (CAD) or with risk factors for CAD are undergoing non-cardiac surgery, cardiovascular complications will remain a significant clinical problem even in the future.

Background

Pathogenesis of Coronary Artery Disease

Ischaemic heart disease can be divided into stable coronary artery syndrome (presenting as angina pectoris) and acute coronary syndrome (unstable angina or myocardial infarction). The primary cause of different manifestations of coronary artery disease (CAD) including acute coronary syndrome (ACS), myocardial infarction, and angina pectoris is atherosclerosis. The vascular endothelium plays a central role in the initiation of early changes in atherosclerosis and plaque formation. Risk factors such as smoking, hypertension, high plasma levels of low-density lipoproteins (LDL), and diabetes mellitus disturb the normal function of the endothelium which results in an impairment of local control of vascular tone and maintenance of an anti-thrombotic surface within the coronary vessel ¹⁷.

The earliest evidence of the formation of an atherosclerotic plaque is a fatty streak consisting of foam cells i.e., activated macrophages containing low-density lipoproteins (LDL) ¹⁸. Smooth muscle cells migrate to the primary lesion to form a fibrous cap which is stabilized through deposition of collagen and calcium. The consequences of the plaque formation include loss of elasticity of the blood vessel and stenosis of the artery. Due to the decreased lumen of the affected coronary artery, the balance between oxygen supply and demand could be disrupted and myocardial ischaemia may occur ¹⁹.

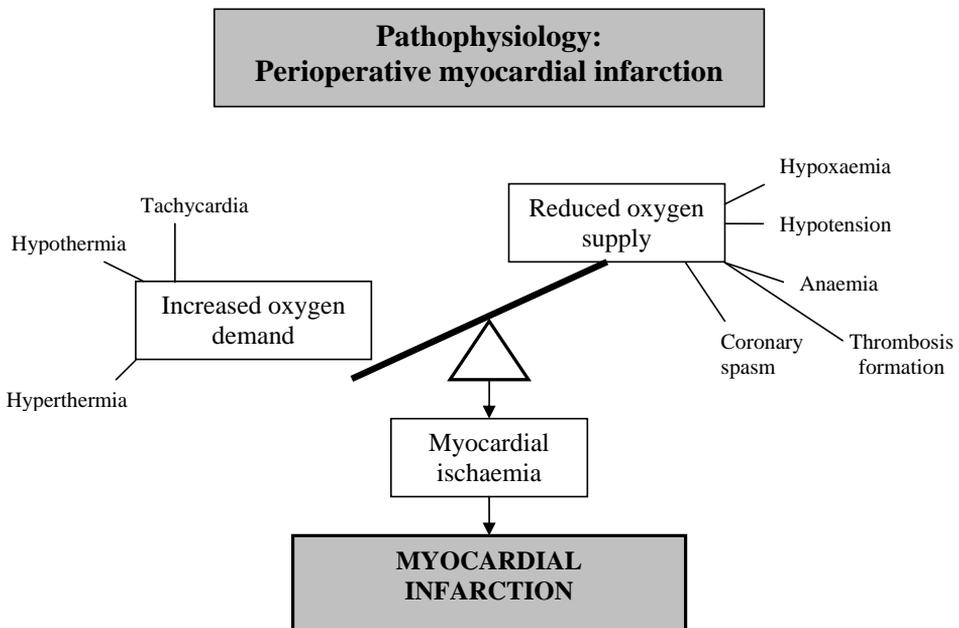
In contrast to stable coronary artery disease, acute coronary syndrome is characterized by plaque inflammation and rupture ²⁰. Erosion of the plaque results in an exposure of collagen and the von Willebrand factor which activates platelets and the coagulation cascade. Platelets adhere to collagen which leads to further platelet activation and release of calcium within the cell. Increased levels of intracellular calcium result in release of ADP (adenosine diphosphate) from the platelet which in turn triggers activation of other platelets. In addition, calcium induces a change in glycoprotein IIb/IIIa receptor on the surface of the platelet thereby facilitating binding of fibrinogen as well as increasing the production of arachidonic acid ²¹. This results in the formation of a thrombus. The clinical consequences of the thrombus depend on the depth of the injury, the composition of the plaque, the extent of platelet activation, and the site of the thrombus ²². In acute coronary syndrome, the plaque often contains inflammatory cells and the inflammatory process is central in the development of CAD ²³.

Pathophysiology of Perioperative Myocardial Ischaemia & Infarction

Myocardial infarction is defined as myocardial cell necrosis due to prolonged ischaemia²⁴. The pathophysiology of perioperative myocardial infarction (PMI) differs to some extent from myocardial infarction in a non-surgical setting. Plaque rupture and thrombus formation occur only in approximately 50% of PMI compared to 64-100% in non-surgical myocardial infarctions²⁵. The pathophysiology of PMI without coronary artery thrombosis is, to some extent, still unclear. It is believed that an imbalance between oxygen supply and demand could be a major cause of myocardial ischaemia and infarction in patients with stable CAD undergoing non-cardiac surgery¹³. Surgical stress with pain, hypothermia, and anaemia results in catecholamine/cortisol release and an increase in heart rate and oxygen demand^{26, 27}; at the same time, perioperative hypotension, hypoxaemia, and anaemia decrease the oxygen supply to the myocardium. This mismatch between oxygen supply and demand results in myocardial ischaemia and infarction, Figure 1.

Furthermore, the surgical trauma also initiates inflammation which has an important role in plaque injury²⁸ and creates a pro-thrombotic state including platelet activation and reduced fibrinolytic activity^{29, 30}.

Figure 1:



Perioperative infarction is preceded, in the majority of cases, by episodes of myocardial ischaemia³¹. The ischaemic episodes are most common in the early postoperative period with a peak at 6-12 hours after the surgical procedure³². This suggests that the postoperative stress with shivering, pain, and tachycardia are of major importance for the occurrence of cardiac complications. Over 90% of the ischaemic episodes are asymptomatic³² and the typical ECG sign of myocardial ischaemia in the perioperative period is ST segment depression. The duration of the perioperative myocardial ischaemia has been shown to be of major importance for the development of myocardial infarction. One study has shown that 78% of the patients with cardiac complications had at least one period with prolonged myocardial ischaemia (>30 min) before the cardiac complication³³. Perioperative myocardial infarction is most common 24 to 48 hours after surgery³³. The majority of PMI's are non-ST segment elevation myocardial infarctions (NSTEMI) and only half of the patients that develop a PMI have clinical signs or symptoms of an ongoing infarction and will go unnoticed unless cardiac markers and ECG are obtained in the perioperative period^{3, 7, 32}. Recent studies also suggest two different types of PMI that depend on the debut of symptoms. Early onset of troponin release may indicate acute coronary occlusion; whereas prolonged low-level release of cardiac markers may suggest ongoing myocardial ischaemia resulting in later cardiac complications³⁴.

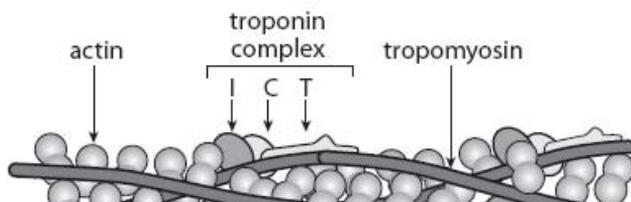
Detection of myocardial damage

Cardiac Markers

Troponins

The cardiac proteins Troponin T, I and C are located on the actin filament and are, together with tropomyosin, essential for regulation of skeletal and cardiac muscle contraction³⁵, Figure 2.

Figure 2:



The troponins are a complex of three polypeptides; Troponin T, I and C. The complex regulates the response of the myofilament to calcium. (Illustration by Per Lagman)

Troponin T, C and I have different isoforms for skeletal and cardiac muscle tissue^{36, 37}.

However, the cardiac isoform of Troponin C (TnC) is shared by skeletal muscle and TnC is therefore not used as a marker for myocardial damage. TnI has one isoform in cardiac muscle cells³⁶; whereas myocardial tissue contains four isoforms of TnT. One of these four isoforms is characteristic of the adult myocardial tissue³⁷. Due to the fact that a re-expression of fetal isoforms of TnT are expressed in injured skeletal muscle cells, a cross-reactivity had been observed in the first assays used for detection of the cardiac isoforms of TnT³⁸. However, more specific monoclonal antibodies have eliminated the risk of false positive TnT elevations³⁹. TnI is not expressed in skeletal muscle during development and therefore no cross-reactivity has been identified in this analysis⁴⁰. The assay used today for measurement of cardiac TnT has the same cardiac specificity as assays used for detection of TnI.

As a result of the high specificity in detection of myocardial damage, troponin I (TnI) and T (TnT) have replaced CK-MB as the gold standard for detection of myocardial injury in non-surgical as well as surgical settings^{24,41}. Table 1 shows a comparison of the performance of the assays for troponin I versus troponin T.

Table 1: Troponin I versus Troponin T

Troponin I	Troponin T
23500kD	33500kD
No increase in patients with skeletal myopathies	Possibility of false-positive results in patients with myopathies?
Different assays	One manufacturer
No standardization between assays	Standardized results
Difficult to compare results from different assays	

Table 1: A comparison of the performance of TnI and TnT

Troponin elevation appears approximately 6 hours after the myocardial injury and peaks after 12-24 hours. Troponin I remains elevated for 5-9 days and Troponin T for up to 14 days after the myocardial damage⁴². The majority of TnI and TnT are bound to the myofibrils. However, 3% of TnI and 6% of TnT are free in the cytoplasm. After myocardial damage, the free pool in the cytoplasm is released. The more prolonged increase in troponin levels seen after myocardial cell necrosis is caused by the constant release from injured myofibrils⁴³, Figure 3.

Figure 3:

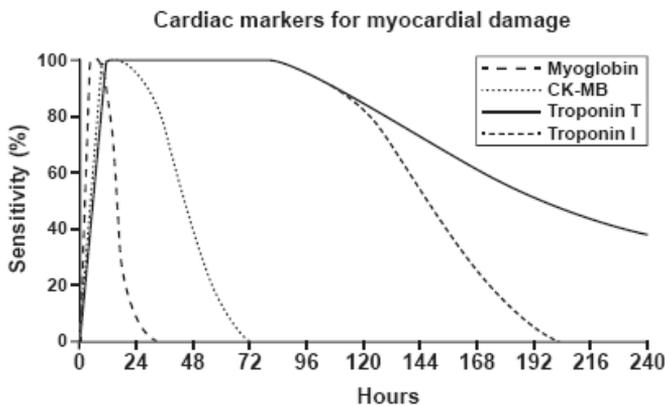


Illustration by Per Lagman

In 2000, new criteria for the diagnosis of myocardial infarction were published. In these guidelines, an elevation of cardiac markers, specifically Troponin I and T, play a central roll in the detection the of myocardial infarction ²⁴, Figure 4.

Figure 4:

European Society of Cardiology and American College of Cardiology’s criteria’s for acute or recent myocardial infarction:

1. Typical rise and gradual fall of biochemical markers (troponins or CK-MB) of myocardial necrosis with at least one of the following:
 - Ischaemic symptoms
 - Development of pathological Q waves on ECG
 - ECG changes indicative of myocardial ischaemia
 - Coronary artery intervention
2. Pathological findings of myocardial infarction

Alpert JS, Thygesen K, Antman E et al. J Am Coll Cardiol 2000; 36: 959-69.

It was also agreed that the 99th percentile of a reference control group should be used as the cut-off level for the diagnosis of myocardial infarction. These decision limits are also recommended for detecting a myocardial infarction in the perioperative period ⁴⁴. The cut-off values for the two assays used in this thesis are presented in Table 2 ⁴⁵.

Table 2:
Cut-off levels for troponin assays used in this thesis

	Lower limit of detection (µg/l)	99th percentile	10% CV
Stratus CS, Dade Behring (TnI)	0.03	0.07	0.06
Elecsys 2010, Roche Diagnostics (TnT)	0.01	<0.01	0.035

The recommended reference interval for each assay is defined as the 99th percentile of a reference population. Acceptable imprecision (coefficient of variation: CV) at the 99th percentile for each assay is ≤10%.

Apart from being sensitive and specific tools in diagnosing myocardial damage and infarction, evidence suggests that troponin I and T are strong independent predictors of

outcome in patients with acute coronary syndrome, severe pulmonary embolism, chronic obstructive lung disease, heart failure, and renal failure⁴⁶⁻⁵².

Previous studies have also reported a good correlation between cardiac troponins and mortality after non-cardiac^{13, 53} as well as cardiac surgery^{54, 55}. In one meta-analysis of the literature, it was found that the troponins had a sensitivity of 76% and a specificity of 88% in predicting short-term adverse outcome in patients undergoing non-cardiac surgery⁵⁶.

An elevated level of troponin I or T does not explain the cause of myocardial damage and this is not necessarily indicative of ischaemic myocardial injury. Increase in cardiac troponins could be detected in a wide variety of conditions leading to cardiac stress such as cardiac trauma, congestive heart failure, renal failure, sepsis, critical illness, amyloidosis, drug toxicity etc. However, increased levels of troponins in these conditions are also associated with poor outcome⁴⁸⁻⁵².

Other biomarkers

The use of biochemical markers other than troponins for diagnosis of perioperative myocardial damage is not recommended today because of the release of these markers from damaged skeletal muscle in the perioperative period. Creatine kinase (CK) has three isoforms distributed in different tissues. CK-MB is primarily present in the myocardium, but is also found in skeletal muscle. The ratio of CK-MB to total CK has been used to improve specificity for myocardial injury. However, skeletal muscle injury will also increase this ratio in a surgical setting⁵⁷.

Myoglobin is located in the cytoplasm in all muscle cells and is rapidly released in response to muscle cell injury. After myocardial injury, an increase in myoglobin is seen in plasma after 2-3 hours. It is therefore used as an early marker of myocardial damage⁵⁸. In the perioperative period, myoglobin has little value due to its lack of cardiac specificity.

To summarize, CK, CK-MB, aspartate aminotransferase (AST), lactate dehydrogenase (LD), and myoglobin are not recommended for the diagnosis of myocardial damage in the perioperative setting^{56, 59}.

Electrocardiogram

ECG is one of the key tools in assessment of patients with suspected myocardial ischaemia. ECG signs of myocardial ischaemia are defined as ST segment elevation or depression ≥ 0.2 mV in one lead or ≥ 0.1 mV in at least two adjacent leads. Due to the fact that ECG disturbances are common in the perioperative period, some studies have shown that the sensitivity of ECG in a surgical setting is low. Martinez *et al.* showed that routine postoperative ECG surveillance had a sensitivity of 12% (95% CI 7-17%) and a specificity of 98% (95% CI 95-100%)⁶⁰. Other studies have verified this high specificity in a perioperative setting and have shown that ECG signs of myocardial ischaemia are associated with poor outcome. In addition, a postoperative ECG demonstrating ischaemia directly after surgery is predictive of major cardiac complications⁶¹.

In 2002, the American Heart Association and the American College of Cardiologists published new guidelines for perioperative monitoring of myocardial ischaemia and infarction. They recommended that, in patients with known or suspected CAD who are undergoing high-risk procedures, ECG should be obtained at baseline, immediately after surgery, and on the first 2 days after surgery⁶².

Other predictors of perioperative cardiac events

NT-proBNP

B-type natriuretic peptide (BNP) and its prohormone, N-terminal fragment of BNP (NT-proBNP) are produced by ventricular cardiomyocytes and have a vasodilatory and natriuretic function⁶³. These cardiac peptides are released from the ventricular myocardium in response to an increase in filling pressure and wall tension. Thus, circulating concentrations of BNP and NT-proBNP are increased in patients with left ventricular systolic dysfunction and congestive heart failure. Several studies have established a dose-dependent correlation between increased levels of BNP and left ventricular systolic dysfunction^{64, 65}.

In addition to cardiac failure, a wide variety of clinical conditions can lead to elevated levels of BNP and NT-proBNP such as myocardial ischaemia, sepsis, pulmonary hypertension, and renal failure⁶⁵⁻⁶⁸.

B-type natriuretic peptide and NT-proBNP also have prognostic value in

patients with congestive heart failure as well as acute coronary syndrome. Elevated BNP has been demonstrated to be more accurate than clinical examination in identifying patients with cardiac failure as a cause of dyspnoea in the emergency department⁶⁵. The natriuretic peptides have also been established as important independent predictors of major adverse cardiac events^{69, 70}.

Recent studies have suggested that BNP and NT-proBNP have prognostic value in cardiac as well as in non-cardiac surgical settings^{68, 71-75}. Specifically, results from investigations in patients undergoing vascular surgery suggest that both BNP and NT-proBNP are useful in predicting postoperative adverse outcome in high risk patients undergoing surgery⁷⁵⁻⁷⁷.

NT-proBNP has also been shown to be as reliable as preoperative dobutamine stress test, echocardiography, and the Revised Cardiac Risk Index in the prediction of major adverse cardiac events^{74, 78}.

Risk assessment in non-cardiac surgery

The main aim of preoperative assessment is to reduce risk and to influence outcome. In recent years, focus has shifted from preoperative testing to treatment strategies with the aim of increasing the oxygen supply and stabilizing the coronary plaque. One reason for this shift is that the non-invasive stress and imaging tests in general have a low positive predictive value for predicting PMI and death in the perioperative period and do not provide any further information than clinical risk assessment⁷⁹. Recent guidelines only recommend preoperative stress tests if the test results will influence the perioperative management of the patient⁷⁹. According to the 2007 guidelines of the American College of Cardiology and the American Heart Association, preoperative testing is only recommended in patients with several risk factors or a poor functional capacity and who are undergoing vascular surgery⁷⁹.

In the preoperative risk assessment, the clinician has to:

1. Identify risk factors in the medical history,
2. Evaluate the functional capacity of the patient,
3. Assess the risk of the surgical procedure.

1. In recent years several risk indices have been developed. In 1999 Lee *et al.* published the Revised Cardiac Risk Index (RCRI), which is now the most widely used and recommended risk index for risk assessment of perioperative risk in non-cardiac surgery⁸⁰.

Lee identified six predictors of cardiac complications: Ischaemic heart disease, congestive heart failure, cerebro-vascular disease, insulin-dependent diabetes mellitus, renal failure (Serum-creatinine levels > 170 $\mu\text{mol}\cdot\text{l}^{-1}$), and high risk surgery. In the presence of more than one of these factors, the risk of a major cardiac event increases dramatically, Table 3.

Table 3: Cardiac complication rates by the Revised Cardiac Risk Index

Risk factors	Complication rate	95% CI
0	0.4%	0.05-1.5%
1	0.9%	0.3-2.1%
2	6.6%	3.9-10.3%
≥ 3	11.0%	5.8-18.4%

Cardiac complications include myocardial infarction, cardiac arrest, pulmonary edema, and complete heart block.

High risk surgery include intraperitoneal, intrathoracic surgery or suprainguinal vascular surgery

2. Assessment of the functional capacity has been established as an important factor in the preoperative risk assessment. One metabolic equivalent (MET) is defined as the amount of oxygen consumed while sitting at rest and is equal to 3.5 ml O_2/kg body weight/min⁶², Table

4. Patients with $\text{MET} \leq 4$ are at higher risk of cardiac complication in the postoperative period⁸¹. Studies have also shown that patients who are unable to climb one flight of stairs have a very high incidence of postoperative cardiopulmonary complications following high-risk surgery^{82, 83}.

Table 4 :Metabolic Equivalents (MET)

1 MET	Getting dressed Walk indoors Walk a block at 3.2-4.8 km/h
4 MET	Climbing one flight of stairs Light house work Walk on level ground at 6.4 km/h
>10 MET	Participate in strenuous sport activities

Examples of energy expenditures for physical activities

1 MET = 3.5 ml $\text{O}_2/\text{kg}/\text{min}$

3. Surgery-specific risk can be divided into three groups: High, intermediate, and low risk surgery. High-risk surgery includes major emergency surgery, vascular surgery, and procedures that are associated with major blood loss or fluid shifts. High-risk surgery is associated with a cardiac risk of > 5% in the perioperative period. Intermediate risk surgery includes procedures such as intraperitoneal and intrathoracic surgery, carotid endarterectomy, orthopaedic surgery, prostate surgery, and head and neck surgery and has a cardiac risk of 1-5%. In low risk surgery the cardiac risk is estimated to be <1% and includes all other minor procedures ⁶².

A compilation of the three steps in the preoperative risk assessment gives the clinician a good idea of the cardiac risk at hand and is a prerequisite for the optimal planning of perioperative care of the patient.

Interventions to reduce perioperative cardiac complications

Preoperative revascularization

The value of coronary artery bypass grafting prior to non-cardiac surgery has been debated. Eagle *et al.* showed in the CASS (coronary artery surgery study) trial that preoperative CABG in patients planned for high-risk non-cardiac surgery, a preoperative intervention was associated with better outcome compared to medical treatment ⁸⁴. In contrast, the CARP (coronary artery revascularization prophylaxis) trial, a prospective randomized trial studying the risk/benefit of CABG prior to elective vascular surgery, did not show a reduced incidence of PMI or death within 30 days of surgery. In this study, patients with 1- or 2-vessel disease were included ⁸⁵. Poldermans *et al.* verified these latter results in patients with 3-vessel disease undergoing vascular surgery ⁸⁶. ACC/AHA guidelines therefore do not recommend prophylactic CABG in patients with stable CAD. However, if there is an indication for CABG, e.g. significant left coronary artery stenosis or unstable angina, the same indications for surgery apply as in a non-surgical setting ⁷⁹.

Preoperative percutaneous coronary intervention

In recent years, advances in interventional cardiology have resulted in a shift from surgical intervention of coronary artery stenosis to the more frequent use of percutaneous interventions. Over 90% of the PCIs include the placement of an intracoronary stent. In 2000, the first reports of a catastrophic outcome in non-cardiac surgical patients that had recently received a drug-eluting stent were published⁸⁷. This investigation showed that, in patients with a drug-eluting stent placement less than 6 weeks before the surgical procedure, 20% of the patients died, 18% had a myocardial infarction, and 28% had major bleeding complications. Other studies have verified this high incidence of cardiac events in patients with intracoronary stents^{88,89}. The cause for the high complication rate was the development of perioperative stent thrombosis; itself caused by a discontinuation of antiplatelet therapy. Therefore, the current recommendations are to delay elective surgery for 4-6 weeks in patients with bare metal stents and for up to one year in patients with drug-eluting stents. If surgery is essential, aspirin should be continued in the perioperative period⁷⁹.

Medical treatment

Beta-blocker therapy

The effect of beta-blockers in the perioperative period is to prevent an increase in heart rate in response to increased levels of catecholamines and thereby decrease the myocardial oxygen demand⁹⁰. During the last decade, several guidelines have been published recommending continuing beta-blocker therapy in patients with or at risk of CAD undergoing non-cardiac surgery. These guidelines were primarily based on two randomized trials showing a significant decrease in cardiac complications and death in patients treated with beta-blockers compared to patients treated with placebo^{91,92}. However, in recent years, the use of beta-blockers in the perioperative period has been questioned. The two randomized trials that these guidelines were based upon were rather small (a total of 312 patients) and have been shown to be underpowered. In addition, in these two studies, patients with reduced left ventricular systolic function were excluded. There is no consensus on the duration of beta-blocker treatment and it is unclear if all beta-blocker agents have a similar effect. A recently published randomized controlled trial (POISE : perioperative ischaemic evaluation), including 8351

patients with or at risk of CAD undergoing non-cardiac surgery, showed that the incidence of major adverse cardiac events (MACE) were reduced in patients treated with metoprolol in the perioperative period. However, there was a significantly higher risk of all-cause mortality and stroke in patients treated with beta-blockers compared to placebo⁹³. The indications for continuing beta-blockers perioperatively are now restricted to those patients who are already taking this medication preoperatively (for treatment of angina, hypertension, or symptomatic arrhythmias) and to those with myocardial ischaemia on preoperative cardiac testing and are undergoing vascular surgery.⁷⁹

Statin therapy

The beneficial effect of statins in patients with CAD in non-surgical setting is well established⁹⁴. In addition to a lipid lowering ability, statins have been shown to have a plaque-stabilizing effect^{95,96}. Statins may therefore also have a positive effect on perioperative outcome in a surgical setting. In a large meta-analysis of 223010 patients undergoing surgery, statin therapy was associated with a 44% reduction in mortality⁹⁷. However, a majority of studies included in this meta-analysis were retrospective studies. Large randomized trials are needed to verify the effect of statins in the perioperative period. Current recommendations suggest that statin treatment should be continued in perioperatively⁷⁹.

Calcium channel blockers

Little data exists on the effect of calcium channel blockers in reducing cardiac events in the surgical setting. A meta-analysis including 11 randomized trials did not show any conclusive evidence of the benefit of calcium channel blockers in the perioperative period⁹⁸. Calcium channel blockers have not been evaluated in the recent guidelines for perioperative assessment and care.

α_2 -adrenergic agonist

α_2 -adrenergic agonist treatment reduces the release of catecholamines. A meta-analysis of the use of α_2 -adrenergic agonists in vascular surgery showed a significant reduction in PMI and mortality⁹⁹. In contrast, no effect was seen in patients undergoing non-vascular, non-cardiac surgery. No large prospective randomized trial exists on the effect of α_2 -adrenergic agonists in reducing MACE during non-cardiac surgery.

Acetylsalicylic acid (Aspirin)

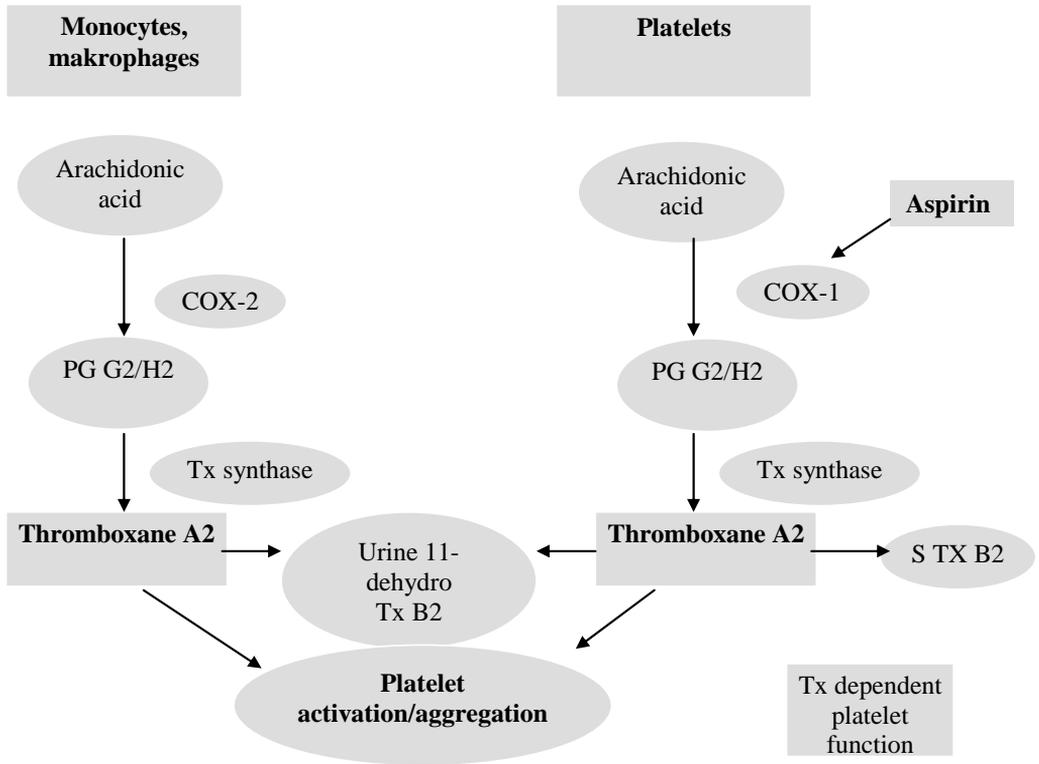
Acetylsalicylic acid irreversibly blocks cyclo-oxygenase-1 thereby inhibiting the synthesis of thromboxane A2. A reduction of thromboxane A2 reduces platelet aggregation by ADP and collagen¹⁰⁰, Figure 5.

Platelet aggregation tests have shown a reduction in platelet aggregation after a single dose of acetylsalicylic acid for up to 10 days, i. e. the lifespan of the platelet. Acetylsalicylic acid has been used for decades in the prevention of myocardial injury or stroke in patients with ischaemic heart or cerebro-vascular disease and its efficacy has been well documented.

The 2002 Antithrombotic Trialists' Collaboration reported that antiplatelet therapy reduced the risk of non-fatal myocardial infarction by one third, non-fatal stroke by one fourth, and vascular events by one sixth¹⁰¹. Acetylsalicylic acid is therefore strongly recommended for secondary prevention as a life-long therapy after coronary or cerebro-vascular events^{101,102}.

Despite extensive data on the benefit of acetylsalicylic acid in patients at risk for cardiovascular accidents, treatment with acetylsalicylic acid is often discontinued in the perioperative period because of the risk of bleeding. Recent studies, on the risk of discontinuing anti-platelet therapy in patients with coronary stents, have focused on the use of acetylsalicylic acid in the perioperative period^{87,89}. As a result of these studies, the routine withdrawal of acetylsalicylic acid 7-10 days prior to surgery has been questioned and several review articles published recently recommend that aspirin treatment should not be stopped routinely in the perioperative period^{79 103-105}. However, these recommendations are not based on evidence from controlled trials elucidating the risk/benefit of acetylsalicylic acid in a non-cardiac surgical setting.

Figure 5:



Arachidonic acid is converted to Thromboxane A2 in a reaction that is catalysed by the enzymes cyclooxygenase-1 (COX-1) and Thromboxane synthase (Tx synthase). Thromboxane A2 augments platelet activation, increases the expression of fibrinogen receptors on the surface of the platelets and acts as a potent vasoconstrictor.

Aspirin irreversibly acetylates COX-1 and thereby reduces Thromboxane A2.

Perioperative Myocardial Damage & Outcome

The consequence of perioperative myocardial damage and its influence on outcome depends on several factors such as the patient's cardiac function prior to surgery, the functional capacity of the patient, the size of the cardiac injury, and whether the myocardial damage is

detected or not. Since approximately 50% of all PMI's are asymptomatic, it is likely that a large proportion of these go unrecognized in the perioperative period¹¹. As described above, myocardial damage usually occurs early in postoperative period when the patients have received narcotic analgesics for treatment of surgical pain that blunt the symptom of chest pain. In addition, other symptoms of ongoing myocardial ischaemia such as nausea, tachycardia, and hypotension can be misinterpreted as side effects of surgery and anaesthesia. Therefore, it is a challenge for the clinician to evaluate an elevated troponin without any other symptoms or clinical signs of cardiac disease. Studies on the incidence of perioperative myocardial damage and its influence on cardiac complications and outcome in patients undergoing non-cardiac surgery are presented in Table 5^{7, 13, 14, 27, 53, 75, 76, 80, 106-118}. These studies all show that myocardial damage, defined as a troponin elevation, is significantly correlated to adverse perioperative outcome. The problems in interpreting these data are that there is neither consensus on the troponin levels used for cut-off level in detecting perioperative myocardial damage, nor a commonly accepted definition of cardiovascular complications. As described in Table 5, most studies on myocardial damage and outcome are undertaken in patients undergoing vascular surgery. There are very few large studies that have been published in the literature that have focused on non-cardiac, non-vascular surgery.

Table 5: Myocardial damage & MACE in patients undergoing noncardiac surgery

Authors	Patient population	Troponin	Myocardial Damage	Cut-off level $\mu\text{g}\cdot\text{l}^{-1}$	MACE
Adams et al	108 vascular/spinal surgery	TnI	8%	3.1	7.4%
Lee et al	1175 major non-card surgery	TnT	6%	0.1	1.4%
Neill et al	80 vasc or orthopaedic surgery	TnT	7.5%	0.1	10% (a)
Badner et al	323 risk patients > 50 yrs	TnT	na	0.2	5.6%
Metzler et al	67 cardiac risk patients	TnT	19.5%	0.2	11.9% (b)
Lopez-Jimenez et al	772 patients	TnT	12%	0.1	2.5%
Kim et al	229 vascular patients	TnI	12%	1.5	7.4% (c)
Ausset et al	88 patients hip surgery	TnI	12.5%	0.08	9% (d)
Barbagallo et al	75 patients vascular surgery	TnI	33%	0.06	12% MI
Cuthbertson et al	40 patients emergency surgery	TnI	37% preop	0.1	28% (e)
Cuthbertson et al	204 major non-cardiac surgery	TnI	13%	0.1	6% MI
Filipovic et al	173 risk patients	TnI	16%	2.0	16% (f)
Howell et al	65 patients vascular surgery	TnI	65%	0.06	20% MI
Kertai et al	393 patients vascular surgery	TnT	14%	0.1	na
Landesberg et al	447 major vascular surgery	TnT	24%	0.03	8.7% TnT<0.1
Martinez et al	467 high risk patients	TnI	13%	1.5	10% MI
Landesberg et al	185 patients vascular surgery	TnI	6.5%	3.1	6.5% MI
Jules-Elysee et al	85 risk pts orthopaedic surgery	TnI	6%	3.1	6% MI
Dawson-Bowling et al	108 patients with hip fracture	TnT	39%	0.03	29% (g)
Feringa et al	272 vascular patients	TnT	16%	0.1	24% (h)
Mahla et al	67 risk patients	TnT	19%	0.2	na

a. MACE, unstable angina, CHF or cerebrovascular accident

b. MACE or severe arrhythmia, unstable angina, CHF

c. Death or MI

d. Cardiac death, MI or cardiac failure

e. MI, death or TnI elevation

f. 1year mortality

g. Arrhythmia, pulm embolism, cardiac failure, myocardial ischaemia

h. Long-term mortality

Aims of the study

The overall objective of this thesis was to study the incidence of myocardial damage and perioperative adverse cardiac events, to determine predictors of poor outcome, and to assess the effect of a medical intervention in patients at risk undergoing non-cardiac, non-vascular surgery. Therefore, the aims of this thesis were:

- I. To assess the long-term prognostic importance of myocardial damage in elderly patients undergoing non-cardiac surgery.
- II. To investigate the incidence of myocardial damage and major adverse cardiac events in high-risk patients undergoing emergency surgery and to identify predictors of poor outcome.
- III. To study the incidence and consequence of elevated NT-proBNP in high-risk patients undergoing unscheduled hip surgery.
- IV. To evaluate the effect of continuing as opposed to withdrawing low-dose aspirin on myocardial damage and cardiovascular events as well as bleeding in patients at risk, undergoing non-cardiac surgery.

Material and methods

Study population and design

All patients included in this thesis underwent non-cardiac surgery. Studies I and IV were multi-centre studies, whereas the patients included in studies II and III underwent non-cardiac surgery at Linköping University Hospital, Sweden.

Study I (POMI=PeriOperative Myocardial Injury), a prospective observational study, which comprised 568 patients aged 70 years or older undergoing non-cardiac surgery of at least 30 minutes duration. Twenty-two patients were excluded due to incomplete data. Patients were recruited between November 1998 and March 2000 at three centres; Örebro University Hospital, Ryhov Hospital, Jönköping and Linköping University Hospital.

In **Study II (A-POMI= Acute Surgery and PeriOperative Myocardial Injury)**, 211 patients in ASA physical status classification 3 or 4 undergoing emergent or urgent non-cardiac surgery at Linköping University Hospital were included. This prospective observational investigation was conducted over a one-year period from April 15th 2007 until April 14th 2008. Fifteen patients were excluded due to incomplete data and 10 patients were lost to follow-up. A total of 186 patients completed the study.

Study III is a sub-group analysis of study II in which 69 patients in ASA physical status classification 3 or 4 undergoing acute hip fracture surgery were included.

Study IV (ASINC=Aspirin in Non-Cardiac Surgery) is a prospective randomized double-blinded placebo-controlled multi-centre study where 220 patients undergoing elective high or intermediate risk non-cardiac surgery with at least one of the following cardiac risk factors in their medical history were included: ischaemic heart disease, congestive heart failure, renal impairment ($S\text{-creatinine} > 170 \mu\text{mol}\cdot\text{l}^{-1}$), cerebro-vascular accident, and insulin-dependent diabetes mellitus. After giving written informed consent, the patients were randomly assigned to receive 75 mg of aspirin or placebo in a one-to-one ratio using a computer-generated algorithm. The study product as well as reference product was produced by APL, Stockholm. Both products were of identical shape, weight and appearance. Study medication was started 7 days before surgery and continued until the third postoperative day. Patients were recruited from 7 centres (Linköping University Hospital, Örebro University Hospital, Ryhov Hospital, Jönköping, Vrinnevi Hospital, Norrköping, Motala Hospital, Södertälje Hospital and

Stockholm South General Hospital) between November 2005 and December 2008. Exclusion criteria included: unstable coronary artery disease, uncompensated congestive heart failure, allergy to aspirin, age under 18 years, a history of gastrointestinal or intracranial haemorrhage, and treatment with warfarin, clopidogrel or methotrexate. In 2006, an amendment was made and the presence of an intra-coronary stent was added as an exclusion criteria.

Patient characteristics in the 4 studies are presented in Table 6.

Table 6: Patient characteristics

	Study I		Study II		Study III		Study IV	
	n=546	n (%)	n=186	n (%)	n=69	n (%)	n=220	n (%)
Age	77±5		80±11		86±7		72±8	
BMI	24.3		24.9		23.1		27.4	
Gender: male	293(54)		67(36)		27(39)		139(63)	
Ischaemic Heart Disease	104(19)		112(60)		46(67)		152(69)	
Congestive Heart Failure	64(12)		85(46)		35(51)		31(14)	
Insulin dep. Diabetes Mellitus	61(11)		43(23)		6(9)		50(23)	
Creatinine > 170 µmol/l	15(3)		60(32)		11(16)		8(4)	
Cerebrovascular disease	61(11)		59(32)		30(43)		49(22)	
ASA classification								
1	91(17)		NA		NA		1(0.5)	
2	327(60)		NA		NA		126(57)	
3	123(22)		170(91)		66(96)		82(37)	
4	5(1)		16(9)		3(4)		1(0.5)	
Medication:								
Betablockers	159(29)		121(65)		50(72)		134(61)	
Calcium channel blockers	65(12)		37(20)		17(25)		59(27)	
ACE inhibitors	89(16)		86(46)		30(43)		92(42)	
Diuretics	157(29)		119(64)		47(68)		83(38)	
Organic Nitrates	67(12)		56(30)		25(36)		40(18)	
Aspirin	77(14)		91(49)		41(59)		197(90)	
Insulin	25(5)		42(23)		4(6)		49(22)	
Statins	NA		63(34)		21(30)		125(57)	
Type of surgery								
Abdominal	181(33)		58(31)				52(24)	
Urology	150(27)		3(2)				61(28)	
Orthopaedics	131(24)		112(60)		69(100)		96(44)	
Gynaecology	63(12)		2(1)				11(5)	
Vascular	21(4)							
Spinal			5(3)					
Neurosurgery			1(1)					
Reconstructive								
surgery			2(1)					
Ophthalmological			3(2)					
Type of anaesthesia								
General	259(47)		91(49)		4(6)		49(22)	
Regional	231(42)		95(51)		65(94)		108(49)	
GA + epidural							48(22)	
Local	56(10)							

Data collection

Data was collected prospectively according to protocol in all 4 studies.

Observational studies (Study I-III)

Demographic data included: age, gender, BMI (body mass index) ASA classification, history of ischaemic heart disease, previous myocardial infarction, CABG, PCI, congestive heart failure, renal failure (S-Creatinine $> 170 \mu\text{mol}\cdot\text{l}^{-1}$), stroke, insulin-dependent diabetes mellitus, and chronic medication. In studies II & III, the New York Heart Association (NYHA) functional classification, the Revised Cardiac Risk Index (RCRI), as well as the priority classification for non-elective surgery were also documented.

The perioperative characteristics that were included were: Type of surgery, type of anaesthesia, duration of surgery, peroperative blood loss, as well as peroperative complications. Peroperative complications were defined as: tachycardia (heart rate $>30/\text{min}$ from baseline for $> 5 \text{ min}$), bradycardia (heart rate $<30/\text{min}$ from baseline or < 50 beats per minute for $> 5 \text{ min}$), haemodynamic instability (systolic blood pressure $\pm 30 \%$ of baseline), or hypoxaemia ($\text{SpO}_2 < 90\%$ for $> 5 \text{ min}$). These complications were also documented in the postoperative period in study II and III.

Randomized controlled trial (Study IV)

Demographic and perioperative characteristics described in studies II & III were also collected in study IV. In addition, perioperative bleeding complications, and the need for fluids, packed red blood cells, plasma, and platelet transfusions were recorded. Furthermore, the attending surgeon made a subjective assessment of intra-operative bleeding by using a scale from 1 to 5 (where 1 was normal surgical bleeding and 5 was greatly increased surgical bleeding). Severe bleeding was defined as bleeding that resulted in re-operation, gastrointestinal bleeding, intracranial haemorrhage, or spinal/epidural haematoma within 30 days of surgery.

Laboratory tests

Troponins

In studies I & IV, Troponin T was used for detection of myocardial damage, whereas Troponin I was the assay used in studies II & III. Troponin T was determined by Elecsys 2010® immunoassays (Roche Diagnostics, Mannheim, Germany) and troponin I was analyzed by using the Stratus® CS Acute Care™ Diagnostic System (Dade International Holding GmbH, Lieberbach, Germany). The reason for this diversity was that studies I & IV were multi-centre studies and, since there is only one method of analysis of Troponin T, the use of this marker made it easier to compare the results between the centres. In addition, studies I & IV commenced prior to the purchase of Stratus® CS Acute Care™ Diagnostic System at our institution.

Study I: Troponin T was measured one hour prior to surgery and on the 5th to 7th postoperative days.

Study II & III: Blood was obtained for assays of Troponin I one hour preoperatively and 24 and 48 hours after surgery.

Study IV: Troponin T was analyzed prior to surgery and 12, 24 and 48 hours postoperatively.

In case of an elevated troponin preoperatively in any of the four studies, the attending anaesthetist, cardiologist, and surgeon evaluated the risk/benefit of the surgical procedure and surgery was delayed when deemed necessary.

NT-proBNP

NT-proBNP was measured one hour prior to surgery in patients included in studies II-IV.

Electrocardiogram

In all four studies, the ECG data were analyzed by a cardiologist or clinical physiologist blinded to clinical symptoms, the laboratory data, as well as the treatment initiated. ECG signs of myocardial ischaemia were defined as ST segment elevation or depression ≥ 1 -mm or presence of new Q waves lasting ≥ 0.04 s and ≥ 1 -mm deep in at least two adjacent leads.

Study I: Resting ECG was obtained preoperatively and on the 5th to 7th days after surgery.

Study II & III: Resting electrocardiograms was taken preoperatively in all patients. In the postoperative period, an additional 12-lead ECG was done in case of an elevated TnI.

Study IV: A 12-lead ECG was recorded preoperatively, immediately after surgery, and 24 and 48 hrs postoperatively.

Clinical decisions and anaesthetic or surgical management were not controlled by any of the study protocols throughout the study period.

Definition of end-points

The main endpoints in this thesis were: incidence of myocardial damage, perioperative cardiac events, and both short-term (30 days) and long-term outcome (1 year). However, the exact definitions of these outcome variables differ between the four investigations.

Study I: The primary endpoint in this observational study was death within the first postoperative year. The secondary endpoint was a major cardiac event which was defined as non-fatal myocardial infarction or the need of invasive coronary intervention (CABG or PCI). Myocardial infarction was defined according to the joint European Society of Cardiology (ESC) and the American College of Cardiology (ACC) consensus document²⁴, Figure 4. Myocardial damage was defined as $TnT > 0.02 \mu\text{g}\cdot\text{l}^{-1}$.

Study II was done on high-risk patients undergoing non-elective surgery and the primary endpoint was myocardial damage (defined as an increase in TnI above $0.06 \mu\text{g}\cdot\text{l}^{-1}$). The secondary endpoints were postoperative major adverse cardiac events (MACE), all-cause mortality, and the clinical value of preoperatively elevated NT-proBNP. The definition of a major adverse cardiac event (MACE) was acute myocardial infarction, and/or cardiovascular death. In this study, MACEs were limited to within 30 days and 3 months following surgery.

Study III is a subgroup analysis of patients undergoing surgery for fractured hip who were included in study II. In this study, we were interested in determining the prognostic value of NT-proBNP in patients undergoing unscheduled hip surgery. The primary endpoint was NT-proBNP level $> 3984 \text{ ng}\cdot\text{l}^{-1}$. The secondary endpoints were myocardial damage, perioperative cardiac complications (defined as: $TnI > 0.06 \mu\text{g}\cdot\text{l}^{-1}$, acute myocardial infarction, or death) within 30 days and 3 months postoperatively.

Study IV: The primary endpoint here was postoperative myocardial damage, which was defined as TnT level $\geq 0.04 \mu\text{g}\cdot\text{l}^{-1}$ on at least one occasion in the postoperative period.

Secondary endpoints were: Major adverse cardiac events (MACEs) (defined as acute myocardial infarction, cardiac arrest, severe arrhythmia or cardiovascular death within the first 30 postoperative days), cardio-cerebro-vascular complications (defined as MACE or TIA/stroke within 30 days of surgery), as well as the incidence of haemorrhagic complications (defined as postoperative bleeding resulting in re-operation, gastrointestinal bleeding, intracranial haemorrhage, or spinal/epidural haematoma within 30 days of surgery).

Follow-up

In **study I**, 108 patients without TnT elevation were used as control and compared to patients with a TnT level $> 0.02 \mu\text{g}\cdot\text{l}^{-1}$. The control group was representative for all patients without TnT elevation and comparable with respect to age, chronic medication, medical history, and type of surgery to patients with TnT elevation. Complications within 30 days and 1 year after surgery were identified through medical records. Death was confirmed from medical records, death certificates, or autopsy reports.

Follow-up in **studies II & III** were conducted by telephone interviews undertaken 30 days and 3 months after surgery. If the patient died during the follow-up period, death certificates, medical records, and autopsy reports were examined in order to determine the cause of death.

In **the randomised trial (study IV)**, follow-up interviews were conducted 30 days after surgery by telephone. New cardiovascular and cerebro-vascular events as well as bleeding complications were documented. If a patient died during the follow-up period, information on the cause of death was obtained from medical records, death certificates, and autopsy reports.

In all four investigations, the causes of death were classified as cardiovascular, malignancy, or other.

Statistical methods

In **study I-IV** the association between baseline and perioperative characteristics and the predefined outcome variables was explored by using un-paired t -test or Mann-Whitney U test for continuous variables, and χ^2 test or Fisher's Exact test for dichotomous data.

Study I: Perioperative myocardial damage and outcome in elderly patients undergoing non-cardiac surgery.

Logistic regression analyses were undertaken to identify predictors of myocardial damage (TnT > 0.02 $\mu\text{g}\cdot\text{l}^{-1}$). Odds ratios (OR) and their 95% confidence interval (CI) were calculated. Stepwise logistic regression analysis was thereafter used to detect independence among the predictors. To find determinants of death, Cox regression analysis was calculated. The results are presented as Hazard ratios (HR) and their 95% CI. Stepwise Cox regression analysis was undertaken to predict independence. In this analysis, variables with OR or HR >2.0, <0.5 or p-value <0.05 were entered. Kaplan-Meier methods were used for estimation of survival in patients with or without TnT elevations. Comparison of survival was performed with log-rank test.

Study II: Predictors of cardiac events in high-risk patients undergoing emergency surgery

Uni- and multivariate logistic regression analysis was used to detect variables predictive of myocardial damage and major adverse cardiac events.

Stepwise logistic regression analysis was undertaken to detect independence among the predictors. The covariates with a $p < 0.10$ were entered into the model. Odds ratios (OR) and their corresponding 95% confidence interval (CI) were calculated. Receiver operating characteristic (ROC) curves was used to identify TnI and NT-proBNP cut-off values for prediction of major adverse cardiac events and the area under the curve (AUC) was calculated. Survival at 30 days and 3 months was compared between patients with different TnI levels by using Kaplan–Meier methods.

Study III: Predictors of outcome in high-risk patients undergoing hip fracture surgery

For identification of NT-proBNP values predictive of perioperative cardiac complications, ROC curves were plotted and the AUC estimated. Univariate and multivariate logistic regression analysis were also used in this study for identification of independent predictors of

perioperative cardiac complication. In the stepwise logistic regression analysis variables with $p < 0.10$ were entered.

Study IV: The effect of aspirin on perioperative cardiovascular events.

Absolute and relative risk ratios for perioperative major adverse cardiac events were calculated and presented with their 95% confidence intervals. In addition, numbers needed to treat for prevention of MACE was calculated.

In all analyses a $p \leq 0.05$ were considered statistically significant.

Statistical software

All analyses were performed by using STATA (Stata Corp LP; College Station, Tx, USA). In Study I version 8.0 was used while in the remaining three investigations version 10.1 was used.

Ethical considerations

The Regional Ethics Committees approved the protocols for all four investigations which were conducted in accordance to the Declaration of Helsinki. In studies I & IV the patients gave written informed consent. In studies II & III the ethics committee accepted verbal informed consent from patients since these studies were observational studies and did not involve any interventions. In addition, the local ethics committee considered that the benefit of a more intense cardiac monitoring in the perioperative period outweighed the possible risk of the extra blood samples in this high-risk patient population.

External monitors ensured the quality of data in Study IV. After 100 included patients, an independent multidisciplinary Data Management & Safety Board performed an interim analysis. The trial was to be stopped if there was a significant difference between the groups in either the number of patients with increased TnT level ($\geq 0.04 \mu\text{g}\cdot\text{l}^{-1}$) or bleeding complications requiring re-operation. No significant differences were seen between patients

taking aspirin and placebo. No other interim analysis was planned or performed throughout the study period.

Results

Per- and postoperative characteristics for the patient populations in Studies I-IV are presented in Table 7.

Table 7: Per- & postoperative characteristics of the study populations

	Study I	Study II	Study III	Study IV
Duration of surgery	73±93	77±42	65±30	131±99
Blood loss	414±1010	210±244	265±249	450±540
Perop complications				
Tachycardia	13(2%)	5(3%)	2(3%)	7(3%)
Bradycardia	41(8%)	4(2%)	2(3%)	22(10%)
Hypertension	21(4%)	7(4%)	3(4%)	7(3%)
Hypotension	135(25%)	59(32%)	15(22%)	106(48%)
Hypoxaemia	7(1%)	9(5%)	4(6%)	1(0.5%)
Postop complications				
Tachycardia		20(11%)	4(6%)	8(4%)
Bradycardia		2(1%)	1(1%)	11(5%)
Hypertension		15(8%)	4(6%)	7(3%)
Hypotension		17(9%)	4(6%)	26(12%)
Hypoxaemia		13(7%)	6(9%)	3(1%)

Perioperative myocardial damage and long-term outcome in elderly undergoing non-cardiac surgery (Paper I)

Myocardial Damage

Fifty-three patients (9.7%) had a myocardial damage (defined as TnT >0.02 µg·l⁻¹) on day 5 to 7 after surgery. The patients with a TnT elevation were significantly older, had a lower BMI, higher ASA classification, a history of ischaemic heart disease, congestive heart failure, or peripheral vascular disease more frequently compared to control. Patients with elevated TnT were significantly more often treated with diuretics and anticoagulants compared to the control group. Perioperative characteristics of patients with myocardial damage and the control group are shown in Table 8.

Table 8:**Perioperative characteristics in Study I**

	Troponin T > 0,02 µg/l (n=53)	%	Troponin T ≤ 0,02 µg/l (n=108)	%	p value
Surgical procedure					
Gynaecology	1	1.9%	10	9.3%	p=0.06
General surgery	16	30.2%	32	29.6%	p=0.94
Vascular surgery	9	17.0%	5	4.6%	p=0.004
Orthopaedics	10	18.9%	19	17.6%	p=0.84
Urology	17	32.1%	42	38.9%	p=0.40
Total	53		108		
Type of anaesthesia					
General	19	35.8%	43	39.8%	p=0.51
Regional	30	56.6%	52	48.1%	p=0.31
Local	4	7.5%	13	12.0%	p=0.38
Perioperative bleeding					
	975±1984		268±609		p=0.01
Perioperative complications					
Tachycardia	4	7.5%	0	0.0%	p=0.004
Bradycardia	4	7.5%	11	10.1%	p=0.59
Hypotension	19	35.8%	22	20.4%	p=0.03
Hypertension	1	1.9%	6	5.6%	p=0.28
Hypoxaemia	3	5.7%	0	0.0%	p=0.01

Patients with elevated TnT underwent vascular surgery significantly more often compared to controls. Episodes of perioperative tachycardia, hypotension, or hypoxaemia were more frequent in patients with myocardial damage. Patients with elevated TnT had an increased blood loss during surgery compared to the control group.

Independent predictors of myocardial damage were: Treatment with diuretics (OR 3.2; 95% CI 1.4-7.2), insulin (OR 5.7; 95% CI 1.3-25.2), or anticoagulants (OR 2.6; 95% CI 1.1-6.1) and perioperative tachycardia (OR 11.5; 95% CI 1.8-73.7).

Outcome

The overall cardiac events rate (MI, CABG, PCI, cardiovascular death) during the first postoperative year was 19 (36%) in patients with elevated TnT compared to three (2.8%) in the control group (p<0.05). Five patients (9.4%) with elevated TnT died within 30 days of surgery. During the same period of time, no deaths were seen in the control group.

Fifty-three patients (9.7%) died within the first postoperative year. Of these, 17 (32%) patients with elevated TnT in the postoperative period died compared to 5 patients (4.6%) in the control group ($p < 0.001$). The causes of deaths are listed in Table 9.

Table 9: Causes of death during the first postoperative year

Study I	Troponin T > 0,02 µg/l (n=53)	Controls (n=108)	p value
Cardiovascular	10	2	0.02
Malignancy	6	2	<0.001
Other	1	1	0.33
Total	17	5	<0.001

TnT elevation was an independent predictor of one-year mortality; (Hazard ratio (HR) 14.9; 95% CI 3.7-60.3). Adjusted predictors of one-year all-cause mortality are listed in Table 10.

Table 10: Predictors of one year mortality in Study I

	Hazard ratio (adjusted)	(95% CI)	p
Baseline characteristics			
Age	1.11	1.03-1.20	0.01
Body Mass Index	0.88	0.83-0.95	<0.005
ASA 4	8.16	1.32-50.05	0.02
Medication			
Betablocker	0.14	0.03-0.56	0.006
Diuretics	4.21	1.29-13.76	0.02
Perioperative characteristics			
Reoperation	6.39	1.10-36.89	0.04
Tachycardia	14.95	3.45-64.76	<0.001
Postoperative findings			
TnT >0.02 µg/l	14.89	3.67-60.27	<0.001

In addition to elevated TnT, perioperative episodes of tachycardia were strong independent predictors of death within one-year of surgery (HR, 14.9; 95% CI 3.4-64.8).

It is important to note here that we had *a priori* decided to include treatment with beta-blockers in our Cox regression analysis. Chronic medication with beta-blockers significantly reduced the risk of death within the first postoperative year (HR 0.14; 95% CI 0.03-0.56). Using Cox regression analysis, we found that the only independent predictor for *cardiovascular* mortality was TnT > 0.02 $\mu\text{g}\cdot\text{l}^{-1}$ (HR 9.4; 95% CI 2.0-43.4). Moreover, we found a dose-dependent relationship between elevated TnT and all-cause mortality. Troponin T level greater than 0.10 $\mu\text{g}\cdot\text{l}^{-1}$ was associated with a higher risk of death within the first postoperative year compared to TnT level between 0.02 and 0.10 $\mu\text{g}\cdot\text{l}^{-1}$.

Perioperative myocardial damage & predictors of major adverse cardiac events in high-risk patients undergoing emergency surgery (Paper II)

Myocardial damage

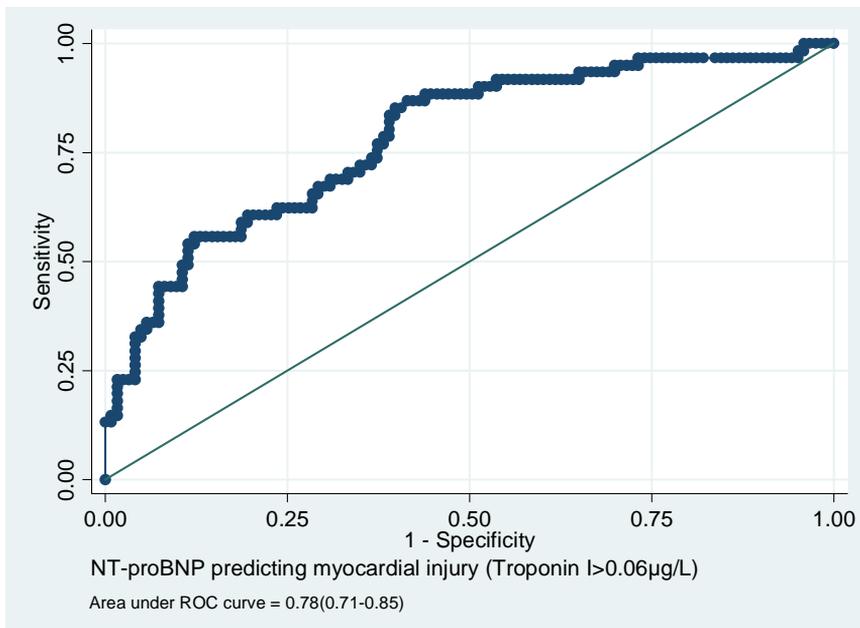
In this high-risk group of patients (ASA classification 3 or 4), 62 patients (33%) had a Troponin I elevation (TnI >0.06 $\mu\text{g}\cdot\text{l}^{-1}$) 12 hours after surgery. Forty of these patients (64%) already had a myocardial damage prior to surgery. Sixteen patients with elevated TnI (26%) were diagnosed to have a perioperative myocardial infarction.

Patient who had a TnI elevation in the postoperative period were significantly older (84 ± 10 vs. 78 ± 10 , $p<0.001$), had a history of ischaemic heart disease (73% vs. 54%, $p=0.02$), and renal impairment (creatinine clearance 44 ± 28 $\text{ml}\cdot\text{min}^{-1}$ vs. 60 ± 31 $\text{ml}\cdot\text{min}^{-1}$, $p=0.001$) compared to patients without myocardial damage. Patients who had a myocardial damage also had significantly higher Revised Cardiac Risk Index Score (Risk factors ≥ 3 : 66% vs. 49%, $p=0.05$), had a preoperative NT-proBNP >1800 $\text{ng}\cdot\text{l}^{-1}$ (88% vs. 45%, $p<0.001$), and were treated with organic nitrates (44% vs. 24%, $p=0.005$) and/or diuretics (74% vs. 59%, $p=0.04$) more often compared to patients with normal TnI levels. However, patients without TnI elevation had a history of malignant disease significantly more often than patients who had myocardial damage. Patients that had elevated Troponin I levels 12 hours after surgery had a lower priority classification (priority class 4 6% versus 21%, $p=0.04$), underwent surgery more frequently in regional anaesthesia (68% versus 43%, $p=0.001$), and had a shorter duration of surgery (66 ± 33 versus 81 ± 46 , $p=0.02$) compared to patients without TnI elevation. Patients with postoperative myocardial damage also had postoperative episodes of

tachycardia more frequently than patients without myocardial damage (19% *versus* 6%, $p=0.007$).

After adjusting for covariates, independent predictors of myocardial damage were NT-proBNP $>1800 \text{ ng}\cdot\text{l}^{-1}$ (OR, 6.2; 95% CI 2.1-18.0), medication with organic nitrates (OR, 2.8; 95% CI 1.1-6.8), intraoperative hypertension (OR, 8.0; 95% CI 1.3-50.7), and postoperative tachycardia (OR, 7.0; 95% CI 1.9-25.7). Figure 6 shows the Receiver operating characteristics (ROC) curve and the ability of NT-proBNP in predicting perioperative myocardial damage. The area under the curve was 0.78 (95% CI 0.71-0.85).

Figure 6:



Receiver operating characteristic curve for ability of preoperative NT-proBNP to predict myocardial injury. Sensitivity and 1-specificity are plotted for various NT-proBNP.

Outcome

MACE

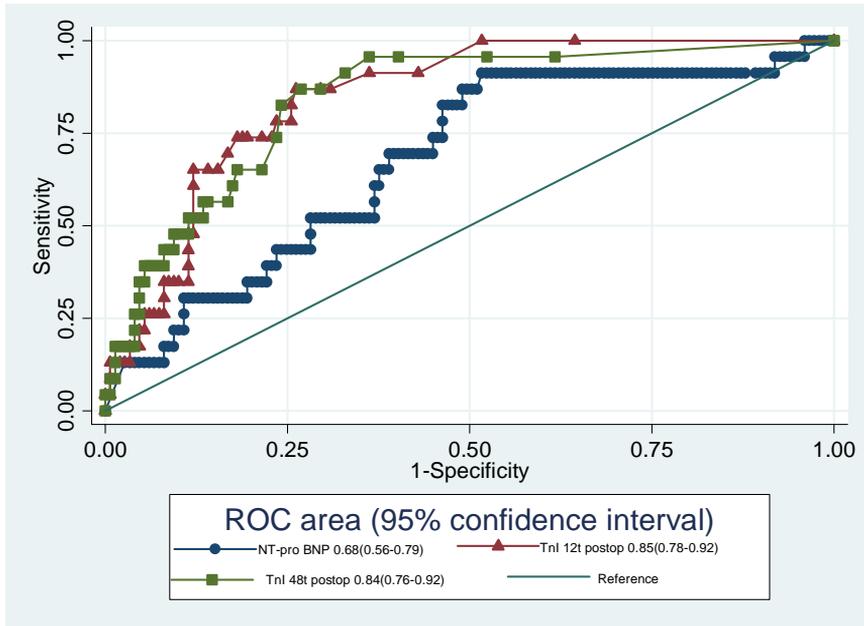
The incidence of major adverse cardiac events and all-cause mortality at 30 days and 3 months are presented in Table 11. The overall incidence of major adverse cardiac events (MACE) was 14%. Twenty-two patients (35%) with elevated TnI 12 hours after surgery had a MACE during the first 30 days postoperatively compared to 4 patients (3%) without a TnI elevation ($p < 0.001$).

Table 11: Outcome in Risk Patients undergoing Emergency Surgery

Study II	TnI > 0.06 $\mu\text{g}\cdot\text{l}^{-1}$ n=62	TnI \leq 0.06 $\mu\text{g}\cdot\text{l}^{-1}$ n=124	p
Major Adverse Cardiac Events	22(35%)	4(3%)	<0.001
30 days mortality	14(23%)	9(7%)	0.003
3 months mortality	23(37%)	20(16%)	0.001

The only independent predictor of a postoperative MACE, when postoperative TnI elevation was not entered into the model, was TnI elevation prior to surgery (OR 4.8; 95% CI 1.5-15.5). The utility of Troponin I and NT-proBNP in predicting a MACE is presented in Figure 7. The best cut-off level of TnI for predicting MACE was 0.21 $\mu\text{g}\cdot\text{l}^{-1}$ with a sensitivity of 67%, a specificity of 89%, and an area under the curve of 0.85 (95% CI 0.78-0.92). The area under the curve for NT-proBNP was 0.68 (95% CI 0.56-0.79) with the best cut-off level at 2107 $\text{ng}\cdot\text{l}^{-1}$.

Figure 7:



Receiver operating characteristics curve of TnI 12 hours , 48 hours postoperatively as well as preoperative NT-proBNP for prediction of major adverse cardiac events within 30 days of surgery.

Mortality

Thirty days after surgery, 23 patients (12%) had died. Fourteen patients (23%) who had TnI $>0.06 \mu\text{g}\cdot\text{l}^{-1}$ 12 hours postoperatively did not survive compared to 9 patients (7%) with normal TnI levels postoperatively who died within 30 days of surgery ($p=0.003$), Table 11.

Three months postoperatively, a total of 43 patients (23%) had died, 23 patients (37%) with elevated TnI compared to 20 patients (16%) without TnI elevation ($p=0.001$). Independent predictors of MACE and mortality are shown in Table 12.

We had decided *a priori* to investigate the importance of aspirin on outcome in this high-risk patient population. As shown in Table 12, there was a trend towards a protective effect of aspirin treatment on 3 month mortality (OR, 0.39; 95% CI 0.14-1.0).

Table 12: Predictors and Odds ratios of Outcome variables**Study II**

Outcome	Odds ratio (adjusted)	(95% CI)	p
Cardiac events:			
Elevated TnI preop	4.8	1.5-15.5	0.008
Organic nitrates	3.0	0.97-9.3	0.057
30 days mortality:			
Creatinine >170 $\mu\text{mol}\cdot\text{l}^{-1}$	1.0	1.0-1.01	0.004
Hypoxaemia postop	11.7	2.1-64.0	0.005
3 months mortality:			
Malignancy	5.9	1.8-18.9	0.003
Inotropes perop	4.2	1.6-10.9	0.004
TnI 12 t postop	4.6	1.5-13.6	0.006
Acetylsalicylic acid	0.4	0.14-1.0	0.06

NT-proBNP as a predictor of outcome in high-risk patients undergoing surgery for fractured hip (Paper III)*Myocardial damage*

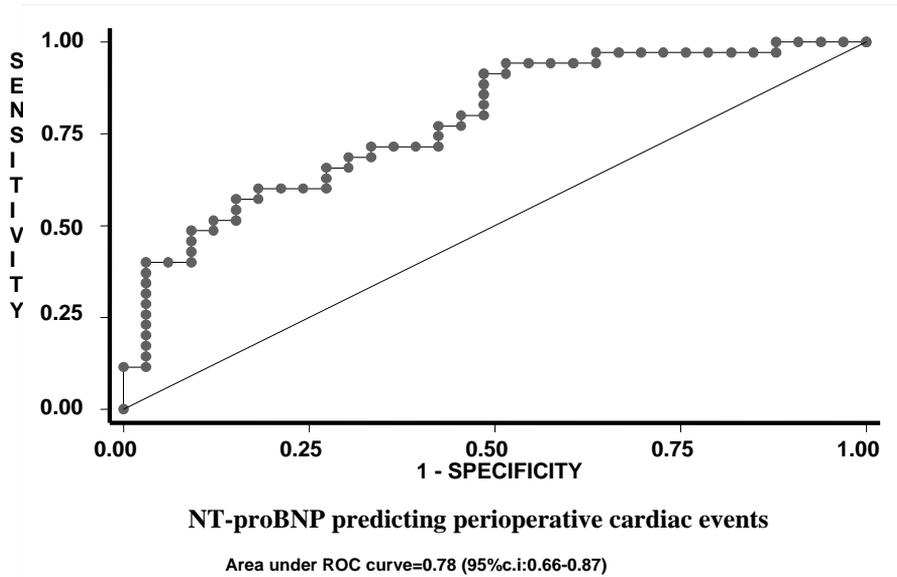
In this subgroup analysis of 69 patients in the ASA physical status classification 3 or 4 undergoing acute hip surgery, 31 patients (45%) had a TnI >0.06 $\mu\text{g}\cdot\text{l}^{-1}$ 48 hours after surgery.

NT-proBNP

For identification of the NT-proBNP cut-off value that best predicted perioperative cardiac events, receiver operating characteristic (ROC) curve was used and the area under the curve was calculated (Figure 8).

A NT-proBNP of $\geq 3984 \text{ ng}\cdot\text{l}^{-1}$ had a sensitivity of 69%, a specificity of 71% for predicting adverse cardiac events, and a likelihood ratio of 2.27. The area under the ROC curve was 0.78 (95% CI 0.66-0.87).

Figure 8:



Receiver operating characteristic curve for the ability of N-terminal pro-brain natriuretic peptide (NT-proBNP) to predict perioperative adverse cardiac events. Sensitivity and 1-specificity are plotted for various NT-proBNP. A NT-proBNP of $\geq 3984 \text{ ng}\cdot\text{l}^{-1}$ had a sensitivity of 69% and a specificity of 71%, likelihood ratio 2.27. The area under the ROC curve was 0.78 (95% CI 0.66-0.87).

Thirty-four patients (49%) had an NTproBNP $\geq 3984 \text{ ng}\cdot\text{l}^{-1}$ prior to surgery. Table 13 shows the baseline characteristics of patients with NT-proBNP above and below $3984 \text{ ng}\cdot\text{l}^{-1}$.

Table 13: NTproBNP		≥3984 ng·l⁻¹	<3984 ng·l⁻¹	p
Study III		n=34	n=35	
Gender	Female	20(59%)	22(63%)	0.73
Age		87.0±5.7	84.1±7.2	0.07
BMI		21.6±3.1	24.5±3.8	<0.01
ASA				
	3	32(94%)	34(97%)	
	4	2(6%)	1(3%)	0.54
Ischaemic heart disease		23(68%)	23(66%)	0.86
Congestive heart failure		18(53%)	17(49%)	0.61
Insulin dep.diabetes mellitus		5(15%)	1(3%)	0.08
Creatinine (μmol·l ⁻¹) mean (SD)		133±73	102±36	0.03
RCRI				
	1-2	3(9%)	2(6%)	
	3	9(26%)	11(31%)	
	>3	22(65%)	22(63%)	0.90
Previous stroke		10(29%)	20(57%)	0.02
Malignancy		5(15%)	4(11%)	0.69
NYHA				
	1-2	17(50%)	24(69%)	
	3-4	17(50%)	11(31%)	0.12
<i>Medication</i>				
Betablockers		25(74%)	25(71%)	0.84
Calciumchannel blockers		9(26%)	8(23%)	0.73
ACE inhibitors		16(47%)	14(40%)	0.55
Diuretics		25(74%)	22(63%)	0.34
Organic nitrates		14(41%)	11(31%)	0.40
Acetylsalicylic acid		20(59%)	21(60%)	0.92
Insulin		3(9%)	1(3%)	0.29
Statins		10(29%)	11(31%)	0.86
<i>Lab tests preop</i>				
TnI > 0.06 μg·l ⁻¹		11(32%)	7(20%)	0.24
NT-proBNP ng·l ⁻¹ median (range)		7942 (5030-14170)	1786 (893-2690)	<0.01

Patients with NT-proBNP above the diagnostic threshold had statistically significant lower BMI and higher creatinine levels than patients with NT-proBNP below 3984 ng·l⁻¹. In addition, patients with NT-proBNP below the cut-off level had a known history of stroke more frequently than patients with NT-proBNP above the cut-off level. No statistically significant differences between the groups were seen regarding type of anaesthesia, type of surgery, duration of surgery, or per-operative bleeding.

Outcome

Cardiac complications

A perioperative cardiac complication in this study was defined as TnI $>0.06 \mu\text{g}\cdot\text{l}^{-1}$, myocardial infarction, and/or mortality within 30 days of surgery. Thirty-four patients (49%) had a perioperative cardiac event within 30 days after surgery. Twenty-four patients with cardiac events (71%) had NT-proBNP above the diagnostic threshold compared to 12 patients (34%) without NT-proBNP elevation ($p<0.01$). The only baseline characteristic associated with a cardiac complication was age (87.3 ± 6.5 vs. 83.8 ± 6.4 , $p=0.02$). Table 14 presents pre- and postoperative characteristics of patients, with and without perioperative cardiac complications.

Table 14: Per- & postoperative characteristics

Cardiac events in Study III		Yes n=34	No n=35	p
Anaesthesia	Regional	34(100%)	31(89%)	0.04
Type of surgery	Bipolar hemiarthroplasty	18(53%)	12(34%)	
	Osteosynthesis with hooked pins	7(21%)	9(26%)	
	Intertrochanteric nail	6(18%)	6(17%)	
	Twinhook sliding nail	3(9%)	8(23%)	0.30
Duration of surgery		65±29	66±31	0.85
Peroperative bleeding		252±208	279±289	0.67
Peroperative events	Tachycardia perop	1(3%)	1(3%)	0.98
	Bradycardia perop	1(3%)	1(3%)	0.98
	Hypertension perop	2(6%)	1(3%)	0.54
	Hypotension perop	8(24%)	7(20%)	0.72
	Hypoxaemia perop	4(12%)	0(0%)	0.04
	Inotropes perop	11(32%)	10(28%)	0.92
Temperature postop		36.1±0.7	35.8±0.8	0.20
Postoperative events	Tachycardia	3(9%)	1(3%)	0.29
	Bradycardia	1(3%)	0(0%)	0.30
	Hypertension	2(6%)	2(6%)	0.98
	Hypotension	3(9%)	1(3%)	0.29
	Hypoxaemia	5(15%)	1(3%)	0.09
	Acute kidney failure	3(9%)	0(0%)	0.08

Patients who had a cardiac complication underwent surgery under regional anaesthesia and had intraoperative episodes of hypoxaemia more frequently than patient without events. No other baseline or peri-operative characteristics were significantly correlated to perioperative cardiac events. After adjusting for covariates two independent predictors of perioperative cardiac events remained: a) preoperative NT-proBNP $\geq 3984 \text{ ng}\cdot\text{l}^{-1}$ (OR 3.0; 95% CI 1.0-8.9) and b) congestive heart failure (OR 3.0; 95% CI 1.0-9.0).

Mortality

Eight patients (12%) had died within 30 days of surgery. Four patients who died had NT-proBNP $\geq 3984 \text{ ng}\cdot\text{l}^{-1}$ prior to surgery and four patients had NT-proBNP below the diagnostic threshold. At three months postoperatively, 13 patients (19%) had died - ten patients with a perioperative cardiac event (29%) compared to three patients (9%) without a perioperative cardiac event ($p=0.03$). No statistical significant difference was seen in the 3 months mortality rate in patients above and below the diagnostic NT-proBNP threshold.

Table 15: Outcome in patients with NTproBNP	$>3984 \text{ ng}\cdot\text{l}^{-1}$	$\leq 3984 \text{ ng}\cdot\text{l}^{-1}$	p
Study III	n=34	n=35	
Myocardial damage: TnI $>0.06\mu\text{g}\cdot\text{l}^{-1}$ 12 hours postop	21(62%)	8(23%)	<0.01
Cardiac events	24(71%)	12(34%)	<0.01
Length of stay	11 \pm 4.9	11 \pm 6.2	0.71
30 days mortality	4(12%)	4(12%)	1.00
3 months mortality	6(18%)	7(20%)	0.80

Cardiac events are defined as TnI $> 0.06 \mu\text{g}\cdot\text{l}^{-1}$, acute myocardial infarction, and/or death within 30 days of surgery

Effect of acetylsalicylic acid on myocardial damage & cardiovascular events in risk patients undergoing non-cardiac surgery (Paper IV)

Of the planned 540 patients, the study was ended after 220 patients were included. The study was terminated prior to full enrolment for several reasons.

1. During the study period, new guidelines were published on patients-at-risk taking acetylsalicylic acid. These guidelines recommended a continuation of acetylsalicylic acid in the perioperative period.
2. We had difficulties in finding eligible patients for inclusion - especially after an amendment in 2006, requiring exclusion of patients with intra-coronary stents.
3. We estimated that it would take another five years before the study was completed if recruitment continued at the same rate.

Of note: The study was terminated without any further statistical analysis.

The 220 included patients were randomized to receive 75 mg of aspirin or placebo from 7 days prior to surgery until the third postoperative day. One hundred and nine patients were treated with acetylsalicylic acid whereas 111 patients received placebo. In seven of these patients surgery was postponed (4 patient taking acetylsalicylic acid and 3 patients taking placebo) and 10 patients did not comply with the treatment (4 patients in the acetylsalicylic group and 6 patients in the placebo group). All analyses were performed on an intention-to-treat basis. There were no significant differences in baseline patient characteristics between the patients treated with acetylsalicylic acid compared to those treated with placebo.

Myocardial Damage

Fourteen patients (6.4%) had a TnT $\geq 0.04 \mu\text{g}\cdot\text{l}^{-1}$ on at least one occasion within the first 48 hours postoperatively. Ten patients (9%) who were treated with placebo had a myocardial damage compared to 4 patients (3.7%) in the acetylsalicylic acid group ($p=0.10$). There were no differences in the type of surgery, type of anaesthesia, or duration of surgery between the groups, Table 16.

However, patients who were treated with acetylsalicylic acid had significantly more episodes of bradycardia at the postanesthesia care unit compared to the placebo group. In contrast, patients who received placebo had more episodes of tachycardia compared to patients who received acetylsalicylic acid, Table 16.

Table 16: Per- & postoperative characteristics in Study IV

	Aspirin n=109	%	SD or IQR	Placebo n=111	%	SD or IQR	p
Perop complications							
Tachycardia	1	1.0		6	5.4		0.06
Bradycardia	13	11.9		9	8.1		0.34
Hypertension	3	2.7		4	3.6		0.72
Hypotension	48	44.0		58	52.2		0.22
Hypoxaemia	0	0		1	0.9		1.00
Use of vasoactive drugs	52	47.7		64	57.6		0.14
Temperature postop	36.0		0.67	36.1		0.70	0.11
Postop complications							
Tachycardia	0	0		8	7.2		0.007
Bradycardia	9	8.2		2	1.8		0.03
Hypertension	3	2.7		4	3.6		0.68
Hypotension	13	11.9		13	11.7		0.96
Hypoxaemia	0	0		3	2.7		0.25

Outcome

Twelve patients (5.4%) had a MACE during the first 30 postoperative days. Two of these patients (1.8%) were treated with acetylsalicylic acid and ten patients (9%) were taking placebo (p=0.02).

Thirteen patients (6 %) had a cardio-cerebro-vascular event (defined as MACE or TIA/Stroke) within 30 days of surgery. Of these 13 patients, 10 patients (9%) received placebo and 3 patients (2.7%) had acetylsalicylic acid (p =0.049), Table 17.

Table 17: Myocardial damage and cardiovascular events

	Aspirin n=109	%	Placebo n=111	%	p
Troponin T $\geq 0.04 \mu\text{g}\cdot\text{l}^{-1}$	4	3.7	10	9.0	0.10
MACE	2	1.8	10	9.0	0.02
Cardio-cerebro-vascular events	3	2.7	10	9.0	0.049

MACE is defined as myocardial infarction, cardiac arrest, severe arrhythmia or cardiovascular death within 30 days of surgery.

Cardio-cerebro-vascular events are defined as: MACE or TIA/Stroke

Treatment with acetylsalicylic acid resulted in a 79% relative risk reduction (95% CI 8-95%) for postoperative major adverse cardiac events within the first 30 days after surgery. The absolute risk reduction was 8% (95% CI 1.0-15%). Number needed to treat was calculated to be 12 (95% CI 7-100).

Four patients (2%) died within the first 30 postoperative days. No significant differences were seen between the groups.

Bleeding complications

Severe bleeding was defined as postoperative bleeding resulting in reoperation, or gastrointestinal bleeding, or intracranial haemorrhage, or spinal/epidural haematoma within 30 days after surgery. The overall incidence of severe bleeding was 1%.

Two patients (2%) in the acetylsalicylic acid group had postoperative bleeding resulting in reoperation. None in the placebo group had severe bleeding ($p=0.24$).

During the study period, a total of five cases of bleeding were documented including milder complications (e.g. tendency to bruising, or larger peroperative bleeding than expected). Three of these complications were in the acetylsalicylic acid group and two in the placebo group. In addition, neither significant difference in the amount of per- or postoperative bleeding nor in the surgeons' opinion of the tendency of bleeding was identified between the groups.

Discussion

This thesis adds to the understanding of the clinical relevance of elevated cardiac markers without clinical or ECG signs of myocardial damage in patients undergoing elective and emergency non-cardiac surgery. Moreover, we have identified predictors of poor outcome in the perioperative period, which could be used as tools for identifying patients at risk. Finally, we have shown that perioperative treatment with acetylsalicylic acid protects patients at-risk from cardiovascular complications.

The Incidence of Perioperative Myocardial Damage

Table 20 summarizes the incidence of myocardial damage and outcome in studies I-IV.

	Patients No	Type of patients	Type of surgery	Troponin	Cut-off $\mu\text{g/l}$	MD n(%)	Outcome n(%)
Study I	546	> 70 yrs	> 15 min duration	TnT	>0.02	53(10%)	22(4%)
Study II	186	ASA 3 or 4	Non-elective	TnI	>0.06	62(33%)	26(14%)
Study III	69	ASA 3 or 4	Hip fracture	TnI	>0.06	31(45%)	34(49%)
Study IV	220	≥ 1 RCRI	High/intermed risk	TnT	>0.03	14(6%)	12(5.4%)

MD= Myocardial damage
Study I Outcome =MI, CABG, PCI, cardiovascular death within one year
Study II Outcome =MACE within 30 days of surgery
Study III Outcome=TnI $>0.06 \mu\text{g}\cdot\text{l}^{-1}$, myocardial infarction and/or mortality within 30 days of surgery
Study IV Outcome=MACE within 30 days of surgery.

In this thesis we saw a wide variation in the incidence of myocardial damage between the studies. In **Study I**, in patients undergoing elective surgery, the incidence of TnT elevation was approximately 10%. In **Study II**, on high-risk patients undergoing non-elective surgery, a significantly higher incidence of Troponin elevation (33%) at 12 hours after surgery was found. In the subgroup analysis (**Study III**) of patients at-risk undergoing surgery for

fractured hip, myocardial damage was even more frequent (45%). The incidence of myocardial damage in the literature varies widely between studies (6-65%), depending on the type of surgery, patient population, time for measurements, and the cut-off levels of biochemical markers used for the diagnosis of myocardial damage, Table 5. High-risk surgery, including emergency surgery, is associated with a greater risk for myocardial damage than elective surgery, Table 5. The differences in the incidence of myocardial damage between Studies II/III and I are therefore not surprising. However, in all four studies we were surprised by the incidence of troponin elevation in the perioperative period. All four studies showed that intermittent ECGs and clinical signs were poor instruments for the identification of myocardial damage in the perioperative period. The detection of perioperative myocardial damage is therefore strongly dependent on surveillance using sensitive cardiac markers. In **Studies I-III**, we found perioperative clinical events that were associated with elevated troponin and myocardial damage. In addition to high-risk surgery, these included: tachycardia, hypoxaemia, hypotension, as well as large perioperative bleeding in **Study I**. These findings are consistent with earlier data^{10, 91, 92}. In **Study II**, independent predictors of myocardial damage in the postoperative period were: NT-proBNP >1800 ng·l⁻¹ prior to surgery, medication with organic nitrates, tachycardia at recovery, and intraoperative hypertension. Therefore we believe that clinical events including tachycardia, hypotension/hypertension, and hypoxaemia in the perioperative period should be aggressively treated in order to reduce the risk of myocardial damage.

Previous studies have shown that myocardial damage usually occurs towards the end of surgery or within the first 24-48 hours postoperatively³². Interestingly, we found that a proportionately large number of patients with elevated troponins in the postoperative period also had laboratory signs of myocardial damage prior to surgery. The incidence of preoperative myocardial damage was dependent on the type of surgery and the patient population. In **Study I**, in patients > 70 years old undergoing elective surgery in 90% of the cases, we found preoperatively elevated TnT in 26% of the patients with TnT elevation in the postoperative period. In **Study II** where all patients underwent emergency or urgent surgery, 64% of the patients with TnI elevation 12 hours after surgery already had a TnI elevation prior to surgery. This was remarkably high. However, our findings are consistent with earlier data on patients undergoing emergency surgery where the authors also found a high incidence of myocardial damage in patients undergoing major emergency non-cardiac surgery (38%)

¹¹². Compared to the latter study our patients were older and had a higher ASA physical status classification, which could explain why the incidence of preoperative myocardial damage was higher.

One of the main reasons for the differences between preoperative myocardial damage in elective versus non-elective surgery could be that patients who undergo emergency surgery are often under a lot of stress due to pain and dehydration prior to anaesthesia and surgery. In addition to these factors, the patients who underwent non-elective surgery were generally older and at higher risk than patients undergoing elective procedures in our studies.

Interestingly, the majority of patients with preoperative myocardial injury were asymptomatic. Therefore, we believe that cardiac monitoring including analyses of troponins and NT-proBNP in high-risk patients should start prior to surgery. In this way, we might be able to identify patients with pathological TnI levels preoperatively, and these patients could then receive optimal perioperative management thereby limiting postoperative cardiac complications. In addition, surveillance with troponins should continue throughout the postoperative period and at least until 48 hours after surgery in order to detect asymptomatic cardiac events.

The Impact of Myocardial Damage on Outcome in Non-Cardiac Surgery

Our studies have established the negative influence of perioperative elevated troponin on both short-term (Study II) and long-term (Study I) outcome.

The objective of **Study I** was to assess the long-term prognostic importance of myocardial damage in elderly patients undergoing non-cardiac surgery. Our investigation showed that an elevated TnT was a powerful, independent predictor for both 30-day and 1-year mortality in elderly patients undergoing non-cardiac surgery. Patients with TnT levels $>0.02 \mu\text{g}\cdot\text{l}^{-1}$ were ten-times more likely to die within 30 days of surgery compared to patients with normal TnT values. One year after surgery, 32% of the patients with elevated TnT had died. Increased TnT levels on the 5th to 7th postoperative day resulted in a 15-fold increase in mortality risk (HR 14.9; 95% CI, 3.7-60.3).

In **Study II**, the primary objective was to assess the incidence of myocardial damage and major adverse cardiac events in high-risk patients undergoing emergency surgery. As in Study I, in this study too, we found the same strong correlation between myocardial damage and

outcome. Outcome was defined as major adverse cardiac events (MACEs) in this study. In patients with a MACE during the first 30 postoperative days, the incidence of myocardial damage was 35% compared to 3% in patients without troponin elevation ($p < 0.001$). The only independent predictor of MACE identified in this study was preoperative elevated TnI (OR 4.8; 95% CI 1.5-15.5). Furthermore, we also found that myocardial damage without clinical symptoms or ECG signs of ongoing myocardial ischaemia was associated with poor outcome in both Study I and II. Therefore, increases in troponins just above the diagnostic threshold in patients undergoing non-cardiac surgery should be considered to be early warning signs and appropriate therapy started immediately.

Our data on the correlation between myocardial damage and outcome was consistent with other studies in patients undergoing cardiac^{54,55} as well as non-cardiac surgery^{53,109}.

However, there are several difficulties in comparing results from different studies: a) the definition of perioperative cardiac events and perioperative myocardial infarction as well as, b) the diagnostic thresholds for cardiac markers that vary between the different studies, Table 5. In addition, the age, sex, type of surgery, and the pre-existing diseases that are also known to alter the risk of a cardiac event vary between the studies.

Predictors of outcome in non-cardiac surgery

During the last decades, a variety of risk indices have been developed for prediction of cardiac complications in patients undergoing non-cardiac surgery. The one most commonly used is the Revised Cardiac Risk Index (RCRI),⁸⁰ Table 4. In this thesis, we have used the risk factors included in the RCRI as inclusion criteria for patients in Study IV. In addition, the RCRI has been calculated for patients with and without TnI elevation (Study II) and with or without cardiac complications (Study II & III). Patients who developed a TnI elevation had significantly more risk factors than patients without TnI elevation (as assessed by the RCRI), Study II. However, we did not find any significant correlation between cardiac complications and RCRI in either Study II or Study III.

In order to find independent predictors of the various outcome variables in Studies I-III, uni- and multivariate logistic regression analyses were performed.

In **study I** we identified five independent predictors of one year all-cause mortality in addition to elevated TnI: 1) peroperative episodes of tachycardia (HR, 14.9; 95% CI, 3.45

-64.8), 2) ASA classification 4 (HR, 8.1; 95% CI, 1.3-50.0), 3) reoperation (HR, 6.4; 95% CI, 1.1-36.9), 4) age (HR 1.1 (95% CI 1.0-1.2) as well as 5) the use of diuretics (HR, 4.2; 95% CI, 1.3-13.8).

In **Study II**, independent predictors of 30 days mortality were renal impairment and episodes of hypoxaemia at the postanaesthesia care unit; whereas independent correlates for 3 months mortality included elevated TnI postoperatively, malignancy, and the use of inotropes intraoperatively. In addition, we also found a close correlation between NT-proBNP and myocardial damage, but we could not verify elevated NT-proBNP as a predictor of MACE or death in this study. However, we did find a close correlation between NT-proBNP and perioperative cardiac complications in Study III. Thus, a NT-proBNP > 3984 ng⁻¹ prior to surgery was an independent predictor of adverse cardiac events in patients undergoing acute hip surgery. The reason for this difference in results could partly be due to the fact that myocardial injury was included in the definition of a cardiac complication in Study III but not in Study II. Since a large number of clinical conditions are associated with elevated NT-proBNP, we could not verify that elevated NT-proBNP in Studies II & III were due to cardiac failure. However, a majority of our patients had a history of congestive heart failure, were significantly more often treated with diuretics, and had a higher NYHA classification. All of these data would suggest that a major proportion of the NT-proBNP elevation was most likely due to cardiac failure.

As described above, at least half of all predictors of poor outcome are perioperative clinical complications such as tachycardia and hypoxaemia. This suggests that at least some of the events could have been avoided. More consideration should therefore be taken to reduce the risk of perioperative complications in patients-at-risk undergoing non-cardiac surgery. An improved optimisation preoperatively as well as a more intense perioperative management should be profitable even though it may increase resource utilization in the perioperative period. Study II and III also showed that a combination of TnI and NT-proBNP monitoring in the perioperative period could be used to supplement the risk assessment together with validated risk scores such as Revised Cardiac Risk Index. The combination of these relatively inexpensive and rapid point-of-care tests is a reliable way of monitoring patient at high-risk perioperatively.

Acetylsalicylic acid for Reduction of Cardiac Risk in Non-Cardiac Surgery

As a consequence of the high incidence of myocardial damage and its impact on outcome demonstrated in Study I, we wished to identify interventions that reduced the risk of myocardial damage and cardiovascular events.

Acetylsalicylic acid has been used for decades in the treatment of patients with cardiovascular disease and the efficacy of aspirin in reducing major cardiovascular events has been well elucidated. Despite evidence of the benefit of anti-platelet drugs in the management of patients with ischaemic heart disease, there has been reluctance in continuing acetylsalicylic acid therapy in the perioperative period due to the risk of bleeding. The trend in most hospitals in Sweden has been to stop acetylsalicylic acid 4-10 days prior to non-cardiovascular surgery. Recent data on the risk of discontinuing anti-platelet therapy in patients with coronary stents has focused on the continuation of aspirin in the perioperative period^{87, 89}. As a result of these studies, the routine withdrawal of acetylsalicylic acid 7-10 days prior to surgery has been questioned and review articles published recently recommend that acetylsalicylic acid treatment should not be stopped routinely in the perioperative period^{79, 103-105}. However, these recommendations are not based on evidence from controlled trials elucidating the risk/benefit of acetylsalicylic acid in a non-cardiovascular surgical setting. Therefore, **Study IV** was undertaken with the primary aim of investigating the incidence of myocardial damage in patients at-risk and treated with aspirin compared to placebo in the perioperative period. In addition, we wanted to study the effect of low-dose acetylsalicylic acid on cardiovascular events and perioperative bleeding complications.

In this randomized controlled trial we found that treatment with low-dose acetylsalicylic acid in the perioperative period reduced the risk of MACE within 30 days of surgery. A trend was also seen towards a reduction in myocardial injury postoperatively which, however, did not reach statistical significance. Furthermore, we found no significant differences between the groups in perioperative bleeding complications.

Two main questions have to be discussed when considering these results. Is there any risk in discontinuing acetylsalicylic acid in the perioperative period? The surgical trauma by itself creates a pro-thrombotic and pro-inflammatory state, including platelet activation/aggregation and reduced fibrinolytic activity^{29, 30}. In addition, acute withdrawal of acetylsalicylic acid results in an increase in thromboxane A₂ activity and a decrease in fibrinolysis, resulting in increased platelet adhesion and aggregation^{119, 120}.

Our present study has shown that there is an increased risk of MACE within 30 days after surgery when acetylsalicylic acid is stopped as opposed to its continuation in the perioperative period.

Is there any harm in continuing acetylsalicylic acid therapy in the perioperative period? A meta-analysis of 474 studies showed that the use of acetylsalicylic acid increased intraoperative bleeding by a factor of 1.5¹²¹. However, no increased risk in morbidity or mortality was found in this review. In our present study, there was no evidence of an increase in severe bleeding complications, perioperative blood loss, packed red blood cells, plasma transfusions, or in the surgeon's assessment of the operative bleeding tendency. Two patients in the acetylsalicylic acid group required to be re-operated due to bleeding. However, the overall incidence of perioperative bleeding was low and there were no statistical differences between the groups. Of note; our study was not designed to detect differences in bleeding complications between the groups.

Study IV was stopped before the intended 540 patients were included. The main reason was that during the study period, new recommendations on acetylsalicylic acid in high-risk patients undergoing non-cardiac surgery were published which urged physicians to continue acetylsalicylic acid therapy in the perioperative period^{79, 103}. Many of our investigators were therefore reluctant to randomize high-risk patients into this study. Since our study is underpowered, it is difficult to draw definite conclusions from our results. However, based on the fact that no harm was seen in continuing aspirin therapy perioperatively and that a trend towards improved outcome was evident, we believe that our study adds to the earlier evidence from non-controlled trials of the benefit of continuing acetylsalicylic acid perioperatively in high-risk patients.

Clinical Implications & Future Perspectives

This thesis has established a close correlation between perioperative myocardial damage and poor short- and long-term outcome in patients undergoing non-cardiac surgery. Therefore, the question should not be if a perioperative troponin elevation has any clinical importance.

Instead, the focus should move towards interventions and treatments that should be initiated in order to reduce the risk of myocardial damage in the perioperative period. Many therapeutic interventions are already available for this purpose, which essentially optimize the

myocardial oxygen supply/demand equation. Other modalities that could be recommended include the continuation of statins⁹⁷ and beta-blockers⁷⁹ in patients already on this medication. Treatment with beta-blocker could reduce episodes of tachycardia and hypertension. However, the risk/benefit of perioperative beta-blocker treatment remains to be fully established⁸⁶.

Study IV showed that acetylsalicylic acid treatment could be continued throughout the perioperative period in order to reduce the risk of coronary thrombosis without any increased risk of bleeding. Our results have to be verified by larger randomized controlled trials in patients with ischaemic cardio-cerebro-vascular disease. In addition, evidence on the effect of other medical treatments, such as ACE inhibitors, calcium channel blockers, or α_2 -adrenergic agonists in reducing myocardial damage and improving postoperative outcome remains unclear.

Our studies have also shown that the clinical management and surveillance in the perioperative period could be improved - especially in patients undergoing emergency surgery. Due to the high incidence of preoperative elevated TnI in this type of surgery, we need to consider strategies to optimize management prior to the surgical procedure in these high-risk patients. Should these patients be managed in high-dependency unit prior to surgery? Should invasive monitoring be used to optimize cardiac status perioperatively? Should Anaesthesiologists be more actively involved in patient management in the preoperative period? These questions need to be answered in future studies.

Finally, the health-economical implications of perioperative cardiac complications remain to be elucidated. With an aging population undergoing increasingly sophisticated surgical procedures, myocardial damage and cardiovascular complications will remain a major problem for any clinician involved in perioperative management and treatment in the future.

Conclusions

The results from the studies included in this thesis have led to the following conclusions:

- Postoperative myocardial damage is an independent predictor of death within one year of surgery in elderly patients undergoing non-cardiac surgery. Perioperative TnT values provide important prognostic information and routine TnT surveillance in the postoperative period is useful for detecting patients with increased risk of adverse outcome.
- Perioperative myocardial damage is common in high-risk patients undergoing non-elective surgery. An asymptomatic preoperative increase in TnI is an independent predictor of perioperative major adverse cardiac events. An elevated NT-proBNP prior to surgery is an independent predictor of perioperative myocardial damage.
- Elevated NT-proBNP prior to surgery is frequent in elderly high-risk patients undergoing hip fracture surgery. NT-proBNP was found to be an independent predictor of perioperative adverse cardiac outcome in this group of patients. The use of NT-proBNP as a routine test in high-risk patients undergoing emergency surgery could be a useful tool in assessing perioperative risk and an aid to clinical decisions on pre-, per-, and postoperative treatment and monitoring.
- Perioperative treatment with acetylsalicylic acid reduces the risk of cardiovascular events within 30 days of surgery compared to placebo.

Summary in Swedish (Sammanfattning på svenska)

Globalt genomgår 100 miljoner vuxna årligen icke-hjärtkirurgi, och cirka 40 % av dessa har riskfaktorer för eller har diagnostiserad hjärt-kärlsjukdom. Omkring fyra miljoner patienter utvecklar årligen en allvarlig hjärtkomplikation, som infarkt, i samband med kirurgiska ingrepp. Trots alltmer avancerad övervakning och behandling av patienter, som genomgår icke-hjärtkirurgi, så fortsätter hjärt-kärlkomplikationer att vara den primära dödsorsaken efter ett kirurgiskt ingrepp.

Fler äldre genomgår alltmer avancerad kirurgi, varför hjärtmuskelskador och hjärt-kärlkomplikationer i samband med icke-hjärtkirurgi kommer att fortsätta utgöra ett problem. Forskare vid Anestesi- & Operationscentrum, Universitetssjukhuset i Linköping, arbetar med att identifiera riskfaktorer för hjärt-kärlkomplikationer och att utveckla åtgärder, som minskar komplikationsfrekvensen. Föreliggande avhandling fokuserar på detta område.

Avhandlingen studerar andelen hjärtmuskelskador hos äldre, som genomgår icke-hjärtkirurgi och hos högriskpatienter, som genomgår akuta operationer. Vidare identifieras faktorer, som indikerar försämrad överlevnad och hjärt-kärlkomplikationer hos dessa patientkategorier. Man undersöker även, huruvida behandling med acetylsalicylsyra dagarna före och efter det kirurgiska ingreppet påverkar andelen hjärtmuskelskador och hjärt-kärlkomplikationer hos riskpatienter som genomgår kirurgi.

Avhandlingen visar, att av patienter, 70 år eller äldre, som genomgick icke-hjärtkirurgi, utvecklade 10 % tecken på hjärtmuskelskada på femte till sjunde dagen efter det kirurgiska ingreppet. Detta visades genom ett förhöjt värde av hjärtskademarkören Troponin T. En tredjedel av de patienter, som utvecklade hjärtmuskelskada, avled inom ett år efter kirurgi, jämfört med cirka 1/20 av dem, som inte hade några tecken på hjärtmuskelskada. Analys av hjärtskademarkören Troponin T kan således underlätta identifiering av patienter med ökad risk för att avlida inom ett år efter ingreppet.

Av patienter, som var tvungna att genomgå en akut operation och som samtidigt hade en allvarlig och känd grundsjukdom, utvecklade 33 % tecken på hjärtmuskelskada i samband med kirurgi. Av de patienter, som hade förhöjda troponinvärden, utvecklade 33 % en allvarlig hjärtkomplikation efter kirurgi, jämfört med 3 % av de patienter, som inte hade tecken på hjärtmuskelskada. Även dödligheten 30 dagar respektive 3 månader efter ingreppet var högre

hos de patienter, som hade troponinförhöjning i samband med kirurgi. Det konstaterades även, att 2 av 3 patienter med förhöjda Troponinvärden efter operationen, redan hade tecken på hjärtmuskelskada före det kirurgiska ingreppet.

Vidare studerades komplikationsfrekvensen hos svårt sjuka patienter, som genomgick operation på grund av höftfraktur. I denna studie fokuserades på andelen förhöjda NT-proBNP (en hjärtsviktsmarkör). Ett förhöjt NT-proBNP före operationen visades vara klart associerat med hjärt-kärlkomplikationer efter ingreppet.

Eftersom redan den första studien kunde konstatera att andelen hjärtmuskelskador efter kirurgi var hög, studerades även åtgärder, som kunde reducera hjärt-kärlkomplikationer i samband med icke-hjärtkirurgi. Ett stort antal studier har påvisat, att acetylsalicylsyras effektivt reducerar frekvensen hjärt-kärlkomplikationer hos patienter med känd hjärt-kärlsjukdom.

Trots starka bevis för acetylsalicylsyras (ASA) fördelar hos hjärtsjuka patienter, sätts ASA ofta ut 7-10 dagar före planerad kirurgi hos kärlsjuka patienter på grund oro för blödningskomplikationer. Denna studie belyste, huruvida ASA-terapi i samband med kirurgi kan:

1. Reducera andelen hjärtmuskelskador och hjärt-kärlkomplikationer i samband med icke-hjärtkirurgi.
2. Påverka risken för blödningskomplikationer.

220 riskpatienter deltog. 109 patienter behandlades med 75 mg acetylsalicylsyra, och 111 patienter erhöll placebo. Behandlingen startade 7 dagar före kirurgi och fortsatte till och med den tredje postoperativa dagen. 9 % av de patienter, som erhöll placebo, utvecklade en allvarlig hjärt-kärlkomplikation inom 30 dagar efter det kirurgiska ingreppet, jämfört med 1.8% av dem, som behandlades med acetylsalicylsyra. Detta innebär, att behandling med acetylsalicylsyra gav en reduktion av risken att utveckla hjärt-kärlkomplikation i samband med kirurgi. Någon skillnad avseende blödningskomplikationer kunde inte ses mellan grupperna.

Sammanfattningsvis har avhandlingsarbetet visat att det föreligger en stor andel hjärtmuskelskador i samband med icke-hjärtkirurgi. En troponinstegring, som tecken på hjärtmuskelskada, även utan kliniska symtom eller EKG förändringar, innebär ökad risk för

allvarlig hjärt-kärlkomplikation i efterförloppet. Analys av hjärtskademarkörerna Troponin T/I, respektive hjärtsviktsmarkören NT-proBNP före operation är välfungerande hjälpmedel för att lättare kunna identifiera patienter med ökad risk för postoperativa hjärtkomplikationer. Att bibehålla behandling med acetylsalicylsyra hos riskpatienter i samband med kirurgi reducerar risken för hjärt-kärlkomplikationer utan att öka risken för blödningsproblem. Ytterligare studier behövs för att bättre kunna belysa åtgärder och behandlingar, som kan minska frekvensen av hjärtkomplikationer i samband med icke-hjärtkirurgi.

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