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Perioperative risk factors and outcomes

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Stockholm 2020

Published by Karolinska Institutet.
Printed by US-AB Tryckeriet 2020

ISBN 978-91-7831-951-0

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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The thesis will be defended in public at Thorsten Gordh Auditorium, S2:02, Norrbacka, Karolinska. Friday the 18th of December 2020.

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To family and friends

Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less.

Marie Curie

ABSTRACT

Perioperative complications is an increasing issue worldwide, as surgical volume continues to grow. Myocardial and kidney injury, and myocardial infarction (MI), are known complications in non-cardiac surgery. Hemodynamic instability during anaesthesia and surgery, the association with perioperative complications, and optimal blood pressure threshold in the perioperative period, have been topics of increasing interest since this thesis idea was formed.

The thesis aime is to increase our knowledge of perioperative organ injury and to understand its aetiology: to evaluate the relation between preoperative risk factors – comorbid burden – and intraoperative risk factors, with a special focus on intraoperative hemodynamic variability.

All studies are observational by design and epidemiologically approached. Regional and national registers, and medical records, are used in the data collection. *Study I* is a descriptive, registry-based, cohort study of more than 400 000 operated adult patientes in 22 Swedish hospitals between 2007 and 2014. *Study II* and *III* are cohort studies enrolling adult patients undergoing major non-cardiac surgery att the Karolinska University Hospital, 2012 to 2013 and 2015 to 2016. *Study IV* use a case-control study design, nested within the cohort collected in *study I*.

In summary, this thesis illuminates how comorbid patients, undergoing major non-cardiac surgical procedures, are at increased risk of perioperative cardiac and kidney morbidity. Development of myocardial or kidney injury, or clinically significant MI in the perioperative period is associated with short- and longterm mortality. This elderly, high-risk surgical population should be targeted to improve perioperative outcomes. Intraoperative hypotension is associated with myocardial and kidney injury and is a major contributor to clinically significant perioperative MI. The high absolute risk of MI development associated with intraoperative hypotension, among a growing population of patients with a high risk-burden, suggests that increased vigilance of blood pressure control in these patients is beneficial.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers:

I. **Myocardial infarction after non-cardiac surgery in Sweden: a national, retrospective cohort study.**
Hallqvist L, Granath, Bell M.
Br J Anaesth. 2020 Jul;125(1): 47-54

II. **Intraoperative hypotension is associated with myocardial damage in noncardiac surgery: An observational study.**
Hallqvist L, Mårtensson J, Granath F, Sahlén A, Bell M.
Eur J Anaesthesiol. 2016 Jun;33(6):450-6

III. **Intraoperative hypotension is associated with acute kidney injury in noncardiac surgery: An observational study.**
Hallqvist L, Granath F, Huldt E, Bell M.
Eur J Anaesthesiol. 2016 Jun;33(6):450-6

IV. **Intraoperative hypotension and MI-development in high-risk patients undergoing non-cardiac surgery: A nested case-control study.**
Hallqvist L, Granath, Fored M, Bell M.
Submitted to Anesthesia&Analgesia. Sept 2020.

CONTENTS

LIST OF ABBREVIATIONS

AF	Atrial fibrillation
AKI	Acute kidney injury
ASA classification	The American Society of Anaesthesiologists physical status classfication
ß-blockers	ß-adrenergic receptor antagonists
BP	Blood Pressure
BMI	Body mass index
CCI	Charlson comorbidity index
CI	Confidence interval
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
DM	Diabetes Mellitus
ICU	Intensive Care Unit
ICD	International classification of diseases
IOH	Intraoperative hypotension
IHD	Ischemic heart disease
IQR	Interquartile range
GFR	Glomerular filtration rate
HR	Hazard ratio
KDIGO	Kidney disease improving global outcomes
MACE	Major adverse cardiac events
MAP	Mean arterial blood pressure
MI	Myocardial infarction
MINS	Myocardial injury after non-cardiac surgery
NBHW	National Board of Health and Welfare
NPR	National Patient Register
OR	Odds Ratio
PMI	Perioperative myocardial injury
SAP	Systolic Arterial Pressure
SBP	Systolic Blood Pressure
SPDR	Swedish Prescribed Drug Register

Chapter 1. Introduction

Epidemiology

In Sweden, more than 800 000 patients undergo surgery each year.[1] Worldwide, the number of surgical procedures yearly is over 310 million.[2] Surgical care is an essential part of the advancement in treating disease, associated with increased life expectancy and improved quality of life. However, as surgical volume continues to grow, the number of patients who suffer postoperative complications will also increase. Older surgical patients with multimorbidity sustain complications more frequently, an important determinant of decreased postoperative survival.[3,4] In a large international study of postoperative outcomes, evaluating the global incidence and risk factors for complications and death after elective inpatient surgery in adults, 1 out of 6 patients developed complications with associated five-fold increased mortality rates.[5]

Anaesthesia-related mortality has dramatically declined over the past half century. In a global meta-analysis, 34 deaths per million surgeries were attributed to the anaesthesia in developed and developing countries.[6] Despite major advances in the delivery of safe anaesthesia, perioperative morbidity and mortality remain a major public health problem.[7] In a study of an inpatient surgical population for the year 2006, perioperative death prior to discharge or within 30 days following elective open surgery was the 3rd leading cause of death,[8] exceed only by heart disease and cancer in the general population.

This thesis aims to increase our knowledge of perioperative organ injury and to understand its aetiology: to evaluate the relation between preoperative risk factors – comorbid burden – and intraoperative risk events, with a special focus on intraoperative hemodynamic variability.

Perioperative organ injury

Regardless of many advances in the perioperative care, acute organ injury leading to single or multiple organ failure remains a serious consequence following surgery. Systemic inflammatory response syndrome due to the surgical trauma has been suggested as a trigger in surgical patients.[8] A number of studies have shown associations with patient preoperative comorbidities and intraoperative factors, such as hemodynamic stability, blood- and fluid administration.[9-11] Stroke, myocardial infarction (MI), acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), and acute gut injury (AGI) are among the most common morbidities and causes of mortality in surgical patients.[8,12-15]

Perioperative myocardial injury and infarction

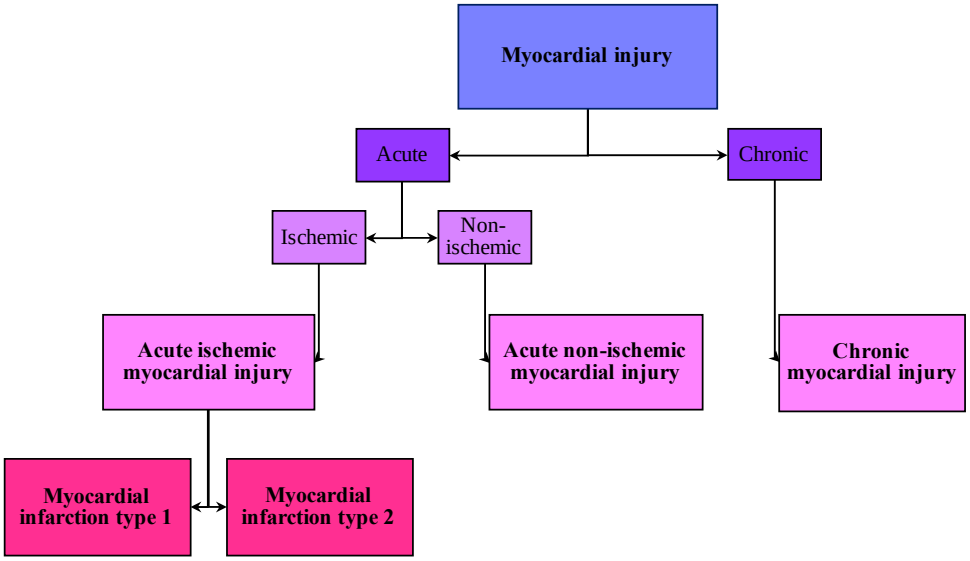
MI is traditionally divided into different types; *MI type 1* is due to occlusive coronary artery disease, plaque rupture and thrombosis, whilst *MI type 2* is characterised by an oxygen supply-demand imbalance, when other conditions than atherosclerotic disease and the usual thrombotic plaque rupture contributes to oxygen insufficiency.[16] Even as MI type 1 and 2 have different underlying mechanisms, both conditions are traditionally associated with ischemia in the myocardium. Myocardial ischemia is by definition the result of disturbances in myocardial perfusion due to an imbalance in oxygen demand and delivery, the myocardial cells are not receiving enough oxygen to perform their work optimally. If oxygen delivery is not increased and/or workload reduced, and the imbalance restored, myocardial necrosis and cell death will follow.

Table 1. Classification of myocardial injury, derived from the fourth universal definition of acute MI.[16,17]

Classification	**Definition**
Acute MI	Clinical evidence of acute MI: - Symptoms of myocardial ischemia - New ischemic ECG changes and/or Q waves - Imaging evidence of new loss of vialbe myocardium or regional abnormalities consistent with ischemic aetiology - Coronary thrombus identification by angiography/autopsy
MI type 1	Atherothrombotic coronary artery disease, usually precipitated by atherosclerotic plaque disruption.
MI type 2	Mismatch between oxygen supply and demand by a pathophysiological mechanism other than coronary atherothrombosis.
Acute non-ischemic myocardial injury	Acute myocardial injury (rise and fall of cardiac biomarkers) in the absence of a primary ischemic cause (i.e. MI)
Chronic myocardial injury	Chronic myocardial injury (hs-cTnT >99th percentile) without an acute change

However, *MI type 2* may arise in various *non-ischemic* medical and surgical conditions.[18] This type of infarction is frequent in critically ill patients, or in patients undergoing anaesthesia and surgery, where high levels of catecholamines and/or direct toxic effects of endogenous toxins might be the cause.[16] The term *MI type 2* has been questioned for many reasons, one being that there are no evidence-based treatment strategies. Cardiac troponin elevation, without other features of infarction, i.e. ECG changes or symptoms, is formally entitled *myocardial injury*, an even more vague diagnosis. These cardiac conditions are frequently confused. *Secondary myocardial injury*, followed by a description of the underlying cause, ischemic/non-ischemic, has been an alternative suggested terminology.[19]

Figure 1. Classification of myocardial injury.[17]



Patients with cardiovascular and atherosclerotic disease, with underlying fixed atherosclerotic plaques and/or endothelial dysfunction, are at particularly high risk in the perioperative period, due to the high risk of tachycardia, hypotensive and/or hypoxic episodes, contributing to the oxygen supply/demand imbalance. Defining myocardial ischemia and infarction in the perioperative setting is particularly difficult due to the absence of classic ischemic symptoms. Most perioperative MI's occur during or closely (24-48 hours) after surgery,[20] when patients receive analgesics and sedatives, limiting their ability to recognize and communicate symptoms. Postoperative signs, like hypotension and tachycardia, or symptoms, as shortness of breath or nausea, are non-specific for myocardial ischemia and may be (mis-)interpreted as

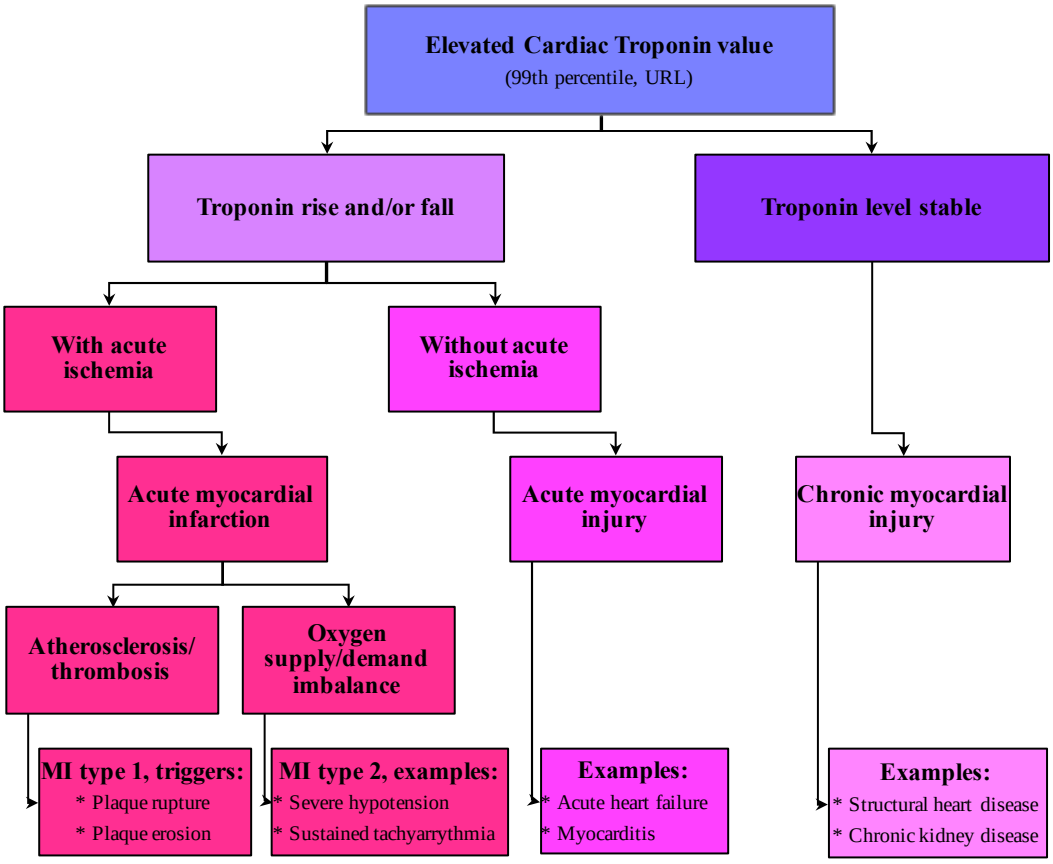
other complications, such as atelectasis, pneumonia, hypovolemia or medication side effects.[21] Nevertheless, myocardial infarction, symptomatic or asymptomatic, has an equally poor prognosis.[20]

There are several definitions of myocardial injury (damage) in the perioperative setting in the literature; perioperative myocardial injury (PMI), major adverse cardiac events (MACE) and myocardial injury after non-cardiac surgery (MINS) being the most established. Independently of the terminology, they are united by the fact that their definition relies on biomarkers. The incidence varies because of lack of consensus in the definition as described below. An incidence of 2-3% within 30 days after non-cardiac surgery has been reported,[22] approximately affecting more than 10 million patients each year worldwide. In a recent study of high-risk non-cardiac surgical patients, an incidence of 16% was found and followed by a substantial association with short- and long-term mortality.[23]

Cardiac biomarkers

Troponins are the biomarkers of choice in diagnosing myocardial injury and infarction. They are proteins expressed both in skeletal and cardiac muscles and exist in several different isoforms, such as troponin I and troponin T. In addition, there are many different assays with varying cut-off levels for diagnosing MI.[24] Since perioperative myocardial injury and infarction often are detected solely by biomarkers, comparison between different studies is challenging. The newest high-sensitivity cardiac troponin-T (hs-cTnT) assay is the most cardiac-specific biomarker and has improved identification of clinically silent myocardial ischemia, as in the perioperative period. Hs-cTnT improves risk assessment and enables identification of more patients with – or at risk of – myocardial injury and new cardiac ischemic events.[25] However, improvements in assay sensitivity may lead to over-diagnosis. Coupled with a decreased specificity this calls for consideration of differential diagnoses. Even though hs-cTnT is highly specific for myocardial injury, the underlying cause might be related to many different chronic conditions without cardiomyocyte necrosis.[26] Elevated levels are often detected, in absence of acute coronary syndrome, in elderly[27] and in patients with chronic renal dysfunction, septic conditions, atrial fibrillation and congestive heart failure. Therefore higher cut-off levels have been suggested in these patients.[24,28] Although the aetiology of increased levels of hs-cTnT in plasma remains uncertain, whether from increased production or decreased clearance, elevated levels are associated with poor prognosis.[29] Recent studies suggest that postoperative elevated troponin levels are independently associated with increased mortality after non-cardiac surgery.[30]

Figure 2. Classification of myocardial ischemia, definitions based on cardiac troponins.[31]



Perioperative kidney injury

Acute kidney injury (AKI) is characterised by a sudden decline in renal function and diagnosed by a rise in serum creatinine or a decrease in urine output. AKI is associated with short- and long term mortality and morbidity.[32] The KDIGO criteria is a classification system of AKI, categorizing the condition into three different stages depending on increase in serum creatinine or decrease of urine output.[33]

Table 2. Staging of acute kidney injury (AKI) according to KDIGO criteria.[33]

Stage	Serum creatinine	Urine output
1	1.5 to 1.9 times baseline *or* ≥0.3 mg/dl (≥26.5 µmol/l) increase	<0.5 ml/kg/hour for 6 to 12 h
2	2.0 to 2.9 times baseline	<0.5 ml/kg/hour for ≥12 h
3	3.0 times baseline *or* increase in serum creatinine to ≥4.0 mg/dl (≥353.6 µmol/l) *or* initiation of renal replacement therapy *or* in patients <18 years a decrease in GFR to <35 ml/minute per 1.73 m^2	<0.3 ml/kg/hour for ≥24 h *or* anuria for ≥12h

Perioperative AKI is common, with a recent study of major abdominal surgery showing an incidence of 13 percent.[34] Incidence of AKI after cardiac surgery has been studied more, using the KDIGO criteria in a retrospective analysis 42% of the patients developed AKI postoperatively.[35] In a systematic review and meta-analysis, including 91 observational studies and 320 086 cardiac surgery patients, a pooled AKI incidence rate of 22.3% (95% CI 19.8 to 25.1) was reported.[36]

The aetiology of AKI is complex. A common feature of many processes causing AKI is a reduction in regional renal oxygen delivery, leading to inflammation, ischemia and, possibly, necrosis.[37,38] A surgical inflammatory trauma likely increases the risk of AKI and intraoperative factors like hypotension, bleeding and hypoxia may add insult to injury. A decrease in haemoglobin concentration during surgery has been identified as a risk event associated with post-operative AKI.[10] In patients with severe anaemia, the independent effect of hypotension on AKI in the perioperative period was more pronounced, supporting the pathophysiological theory above, where additive harmful factors lead to a more aggravated outcome. Some of these events are modifiable in the perioperative setting.

In addition, fluid overload has been suggested as an important contributor to AKI.[39] Increased renal venous pressure could theoretically result in a reduction of the trans-renal pressure gradient for renal blood flow. The subsequent elevated interstitial and tubular pressure might affect - diminish - the net glomerular filtration pressure gradient. Whilst there are troves of observational data supporting the association between fluid overload and AKI,[39] standard treatment of low cardiac output and hypotension involving fluid bolus therapy makes this confounder especially confounding. Nevertheless, a recent review suggested that the hemodynamic management of the elderly surgical patient should focus on avoiding hypotension and high central venous pressures to minimise risk of postoperative AKI.[40]

Intraoperative hypotension

Hemodynamic instability in the perioperative period is common and there has been a cumulative interest in this area, and the relation to organ failure, over the recent years. Hypotensive episodes are particularly frequent during the anaesthetic induction, related to the cardio-depressant and vasodilating effect of anaesthetic agents.[41,42] Inhalational anaesthesia with Sevoflurane has previously been regarded as cardio-protective,[43,44] although the evidence is questioned. A comparison with Propofol-maintained anaesthesia revealed an

advantage in maintaining hemodynamic stability during surgery with Sevoflurane.[45] Intraoperative hypotension may also be the result from blood loss, fluid shifts and cytokine release during surgery.[46]

There are several studies showing results of associations between intraoperative hypotensive events and perioperative cardiac, kidney and cerebral injury, and increased mortality in in high-risk surgical patients.[9,11,22,47-50] However, consensus is still lacking regarding optimal blood pressure thresholds to achieve adequate perfusion and oxygenation in critical organs during anaesthesia and surgery and there are no general recommendations regarding lowest acceptable perioperative blood pressure. Numerous different definitions of hypotension in a perioperative setting exist in the literature, a review of intraoperative hypotension identified as many as 140 definitions in 130 studies.[51] Binary cut-offs are commonly used to define intraoperative hypotension, as mean arterial pressure (MAP) below 55mmHg or systolic blood pressure (SPB) below 80mmHg, and associations with increased risk of organ damage and mortality have been shown.[9,11,47] But these binary cut-offs may introduce a distortion and individually based intraoperative hypotension definitions have been proposed.

Importantly, perioperative hemodynamic instability can be avoided, or at least minimized, in most clinical situations. Through attentive medical treatment, with vasoactive drugs, and the use of protocolized hemodynamic algorithms, to guide delivery of intravenous fluids and maximize stroke volume, it is often possible to maintaining adequate intravascular volume and organ perfusion pressure.

Aims of the thesis

The overall aim of this project was to increase our knowledge of perioperative organ injury and to understand its aetiology: to evaluate the relation to preoperative risk – comorbid burden – and intraoperative risk factors, with a special focus on intraoperative hemodynamic variability.

Specific aims were:

I. To report the incidence of MI, defined according to the universal definition,[16] after non-cardiac surgery in Sweden and to study the association with preoperative risk factors.

II. To investigate how intraoperative events, with focus on hypotension, are related to perioperative myocardial injury, to evaluate the impact of preoperative risk factors and to study the association with MI.

III. To examine how intraoperative hypotension is related to perioperative AKI and to evaluate the impact of other potential risk factors including; comorbidities, blood loss and fluid overload.

IV. To test the hypothesis that IOH is an independent risk factor for clinically significant perioperative MI in a high-risk non-cardiac surgical population.

Chapter 2. Methods

ETHICAL CONSIDERATIONS

All studies, I-IV, included in this thesis have ethical permission approved by the Regional Ethics Committee of Stockholm, Sweden. The studies are conducted in accordance with the Helsinki declaration and good clinical practice. This is registry-based research, which carries no deviation from clinical routine nor does it involve any direct contact with the study participants, hence, no personal consent is needed from the study participants to obtain approval.[52] All studies are observational, there are no procedures involving pain, discomfort or risk of complications. Potential ethical aspects of the project are related to the risk of violating patients' integrity when collecting data from the medical chart. However, individuals usually benefit from registry-based research since knowledge about personal history and risk factors associated with their disease is increased. One could argue that individuals participating have more to gain more than they have to lose, since registry-based research does not involve any liabilities to the study participants. Data included in these studies are stored pseudonymized, there is a key and a possibility to define the true identity of individuals in a dataset, and, subsequently, an opportunity to link these individuals to new data or to update their medical history, if needed. The key file (between the personal identity number and serial number) is stored at the agency responsible for the data matching, the National Board of Heatlh and Welfare.

DATA SOURCES

The Orbit Register

Orbit is a software program to administer surgical procedures used by approximately 40% of Swedish hospitals of all levels (university, county and district hospitals). The Orbit registry obligatory includes the Swedish identity number, patient demographics, elective or non-elective status, type-, extent- and duration of anaesthesia and surgery. Orbit was used to identify the surgical study population in these studies.

The National Board of Health and Welfare

In Sweden, the tradition of registry establishment and high-quality record keeping extends far back. The National Board of Health and Welfare (NBHW), a Swedish government agency, is responsible for maintaining health data registers and official statistics of health, medical care and social services.[53] The statistical database includes statistics on a number of diseases,

including acute myocardial infarctions, causes of death and in-patient care diagnoses. Statistics are presented by year, age and geographical area.[54] The unique personal identity number assigned to all Swedish citizens at birth, or at immigration, allows linkage to all national registers.[55]

The National Patient Register, established in 1964 and maintained by the NBHW, contain information on all in-patient somatic and psychiatric care with complete coverage since 1987.[56,57] Discharge diagnosis is registered according to the International Classification of Diseases (ICD-SE) coding, the 10th version has been used in Sweden since 1997.[58]

The *Swedish Cause of Death Registry*, established in 1961, includes the deaths of all Swedish citizens and residents with a national identity number; it is highly reliable with over 99% of all deaths reported.[59,60] The primary cause of death, defined as the disease of condition leading to death, is registered according to ICD-10 codes, acquired from the obligatory death report submitted to the NBHW by the responsible physician. Misclassifications exist, a report from 2010 estimated the risk to approximately 20%, with an age-dependent variation.[61]

The *Swedish Prescribed Drug Register*, another registry managed by the NBHW, became operational in July 2005 and contain data on all dispensed prescriptions of drugs in Sweden.[62,63]

The Total Population Register

Statistics Sweden (SCB) is responsible for coordinating the system for official statistics in Sweden. The Total Population Register (TPR) is maintained by SCB[64] and contain data on birth and death (100% reported to the population register within 30 days), name change, family relationships, migration and immigration. Through the personal identity number, data from TPR can be used for medical purposes and allows identification of general population controls and participants in cohort studies.[65]

National Quality Registries

In Sweden, a number of Quality Registries have been developed. These registries contain patient data information on individual level, including background factors, diagnoses, medical interventions and outcome after treatment. All data is annually monitored and approved by an Executive Committee. National Quality Registries in Sweden provide a unique possibility for research and quality development in healthcare.[66]

Swedeheart

Swedeheart (National Quality Registry for Enhancement and Development of Evidence-Based Care in Heart Disease) is a national quality registry containing data on acute coronary care, coronary angiography, cardiac surgery, secondary prevention and genetic cardiovascular diseases. The Swedeheart registry provide a platform for continuous improvement measures that, in the long-term, may contribute to a reduction in cardiovascular morbidity and mortality. Swedeheart contains, among others, data on all patients with acute myocardial infarction and all patients undergoing angiographic coronary intervention and heart surgery.[67]

DEFINITIONS

Perioperative MI was defined according to the universal definition by the joint European Society of Cardiology (ESC) and American College of Cardiology (ACC) consensus,[31] occurring within 30 days of surgery. MI diagnoses were identified using ICD-10-SE diagnosis codes (I21.0-I21.4), acute *transmural*, *subendocardial* and *unspecified* MI, thus including both MI type I and type II.

Myocardial injury (damage) was defined as elevated levels of the cardiac biomarker, hs-cTnT >14 ng/L, on postoperative day one.

Perioperative AKI, was determined, according to the KDIGO criteria,[33] as a rise in creatinine; >1.5 times or ≥26.5 μmol/l, increase from individual baseline preoperative creatinine, within the first two postoperative days. Hence, the highest creatinine value on postoperative morning 1-3 was used for the AKI staging.

Intraoperative hypotension was defined as a decrease in SBP from patients' individual baseline lasting >5 minutes.

The ASA classification, the American Society of Anaesthesiologists physical status classification, is a simple five-degree categorization of a patient's physical status, developed to be helpful in predicting operative risk.[68] The ASA classification originated in 1941, after several revisions the latest version was approved 2014, it is used in clinical praxis in Swedish hospitals.

Table 3. The American Society of Anaesthesiologists physical status classification.[68]

Classification	Definition
ASA 1	A normal healty patient, non-obese (BMI <30), nonsmoking with good exercise capacity.
ASA 2	A patient with a mild (well-controlled) systemic disease, with no functional limitations; (e.g. treated hypertension, obesity with BMI <35, frequent social drinker or smoker).
ASA 3	A patient with a severe systemic disease, with functional limitations but not life-threatening; (e.g. poorly treated hypertension or diabetes, morbid obesity, chronic renal failure, bronchospastic disease with intermittent exacerbations, stable angina, implanted pacemaker).
ASA 4	A patient with severe systemic disease, with severe functional limitations and constant threat to life; (e.g. unstable angina, poorly controlled COPD, symptomatic CHF, recent (less than three months ago) myocardial infarction or stroke.
ASA 5	A moribund patient, not expected to survive beyond 24 hours without surgery; (e.g. ruptured abdominal aortic aneurysm, massive trauma, and extensive intracranial haemorrhage with mass effect).
ASA 6	A brain-dead patient whose organs are being removed with the intention of transplanting them into another patient

STUDY DESIGN AND OUTCOME MEASURES

-Study I

In this cohort study, data was obtained from 23 hospitals using the Orbit surgical planning system software, which covers approximately 40% of Sweden. Patients >18 years, undergoing non-cardiac surgery between January 1, 2007, and December 31, 2014, were included. To acquire information on discharge dates, covariates and drug exposure, surgical records were linked to the *National Patient Register*, the *Swedish Prescribed Drug Register* and *Swedish Cause of Death Registry* using the personal identification number assigned to all at birth or at immigration. Exclusion criteria were; ambulatory care surgery, cardiac-, obstetric- and minor surgery, surgeries performed before 2007 or after 2014, and if a valid surgery code in Orbit – or a corresponding surgery code in NPR – was lacking. Data collection included individual-level information of demographics and medical history; age, sex, geographic region of residence, ASA-classification, hospital diagnoses and dispensed drug prescriptions within five years of surgery. This made it possible to identify comorbidities in patients treated in outpatient care, to validate preoperative hospital diagnoses

and calculation of Charlson comorbidity index.[69] Statistics of the incidence of acute MI per 100 000 inhabitants by year, age and geographical were extracted from the NBHW statistical database[70] and used to calculate standardized incidence ratios (SIR).

Perioperative characteristics included date, type and duration of surgery. Based on surgical codes, procedures were clustered into 13 subtypes: gastrointestinal, endocrine, ophthalmic, ENT, dental, thoracic, neuro, breast, urologic, gynaecologic, orthopaedic, vascular and dermatologic surgery. To identify all cases of myocardial infarctions <30 days after surgery, both Swedeheart and NPR was used. The cohort inclusion and exclusion procedure is detailed in the participant flowchart, *Figure 3*.

Main exposure was surgical procedures requiring anaesthesia and in-hospital care.

Primary outcome was incidence of MI, fulfilling the universal criteria,[16] diagnosed within 30 days after surgery. Secondary endpoints sought to illuminate characteristics and predictors of perioperative MI, to evaluate if major non-cardiac surgery increases risk of MI compared to matched non-hospitalized controls and to report associations with short- and long-term mortality.

Study II

An observational cohort study of all adult patients undergoing major elective non-cardiac surgery at Karolinska University Hospital, Stockholm, Sweden, from October 2012 to May 2013, who, in advance, were planned for an overnight admission at the postoperative unit. Patients undergoing pheochromocytoma surgery were excluded. Preoperative risk factors (comorbidities), intraoperative events (hypotension, tachycardia and hypoxia) and postoperative data (blood loss and fluid balance) were collected from medical records. Levels of high sensitivity cardiac Troponin T (hs-cTnT) were measured on postoperative day 1. Myocardial damage was defined as an increase in the hs-cTnT value above 14 ng/L. Cases of MI within 30 days of surgery were adjucated by a cardiologist.

Main exposure was intraoperative hypotension, defined as a percentage decrease in SBP relative each patient's baseline, lasting >5 minutes. Baseline BP was determined as the patient's habitual value measured as an estimate of all BPs, documented within two months prior to surgery, obtained from the surgical ward, preoperative anaesthetic consultation or documentations from the primary health care.

Primary outcome was perioperative myocardial damage, defined as elevated hs-cTnT >14 ng/L on postoperative day one. Secondary outcomes were MI, defined according to the fourth universal definition,[16] and 30-day mortality.

Study III

An observational cohort study of adult patients undergoing major elective non-cardiac surgery at Karolinska University Hospital, Stockholm, Sweden, from Oct 2012 to May 2013 and Jan 2015 to April 2016, who, in advance, were planned for an overnight admission at the postoperative unit. Preoperative risk factors (comorbidities), intraoperative events and postoperative data were collected from medical records. Plasma creatinine were measured before, on the first, second and third day after surgery.

Main exposure was intraoperative hypotension, defined as a percentage decrease in SBP relative each patient's baseline, lasting >5 minutes. Baseline BP was determined as the patient's habitual value measured as an estimate of all BPs, documented within two months prior to surgery, obtained from the surgical ward, preoperative anaesthetic consultation or documentations from the primary health care.

Primary outcome was AKI stage 1, or higher, within the first two postoperative days, determined according to the KDIGO criteria.[33] Secondary outcomes were to study the impact of other potential risk factors including; comorbidities, blood loss and fluid overload.

Study IV

A nested case-control study of patients developing MI within 30 days of surgery, matched with non-MI-patients from the same source population, the cohort in *study I*. Study participants were adults undergoing non-cardiac surgery at 3 hospitals in Sweden; Karolinska, Lund, and Malmö university hospital, from 2007 to 2014. Control subjects were sampled among patients alive and without MI diagnosis at day 30, i.e. *cumulative incidence sampling.*[71] Matching criteria were: age, sex, ASA-class, cardiovascular disease, hospital, year-, type- and extent of surgical procedure. Matching variables were selected based on risk factors of MI identified *in study I*, except hospital, which was chosen for convenience. Regarding 10% of the sampled cases, an exact matched control could not be identified and matching on calendar year and knife-time was relaxed, resulting in a slight imbalance on these factors. Description of the source population and the selection of cases and controls is detailed in *Figure 4*, Flowchart. Medical records were reviewed to validate MI diagnoses and retrieve information on comorbid history, baseline BP and laboratory values. Intraoperative data were collected from anaesthetic charts.

Main exposure was intraoperative hypotension (IOH), defined as at least one event of an absolute decrease in SBP, from patient preoperative baseline, lasting >5 minutes. Baseline BP was determined as the patient's habitual value measured as an estimate of all BPs, documented within two months prior to surgery, obtained from the surgical ward, preoperative anaesthetic consultation or documentations from the primary health care. IOH was categorized into quartiles in accordance with incidence among controls; <20 mmHg, 21-40 mmHg, 41-50 mmHg or >50 mmHg drop from individual baseline. Notably, different definitions of IOH was further analysed, including a comparison between absolute thresholds and relative decreases from baseline, detailed under statistics.

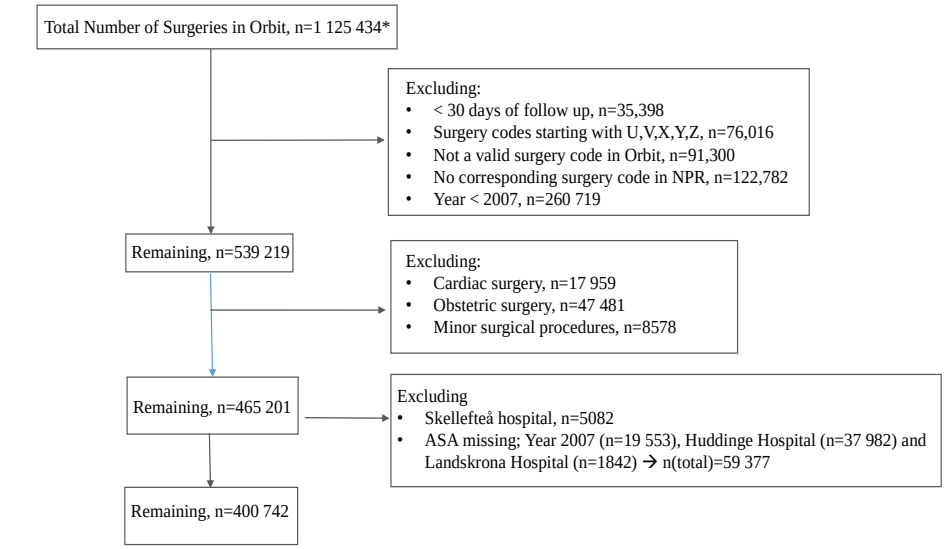
Primary outcome was to evaluate the effect of IOH on acute perioperative MI, fulfilling the universal criteria,[16] occurring within 30 days of surgery. Secondary outcomes were frequency of MI type 1 vs type 2, postoperative day of MI and mortality beyond 30 days among case- and control-patients.

Table 4. Summary of studies I-IV

Study	**I**	**II**	**III**	**IV**
Study design	Multicenter, cohort	Cohort	Cohort	Nested case control
Data source	Orbit	Orbit	Orbit	Orbit
	NBHW	Medical records	Medical records	NBHW
	National Patient Register			National Patient Register
	Prescribed Drug Register			Prescribed Drug Register
	Cause of Death Register			Cause of Death Register
	Swedeheart			Swedeheart
				Medical records
Study population	Registry-linked surgical cohort	Prospectively collected surgical cohort	Prospectively collected surgical cohort	Registry-linked surgical cohort
Sample size	400 742	300	470	Cases: 326
				Controls: 326
Study period	2007-2014	2012-2013	2012-2013	2007-2014
			2015-2016	
Exposure	Surgery	Intraoperative hypotension	Intraoperative hypotension	Intraoperative hypotension
Outcome measures	MI <30 days of surgery	Hs-cTnT >14 ng/L (myocardial damage)	AKI	IOH as risk factor of perioperative MI

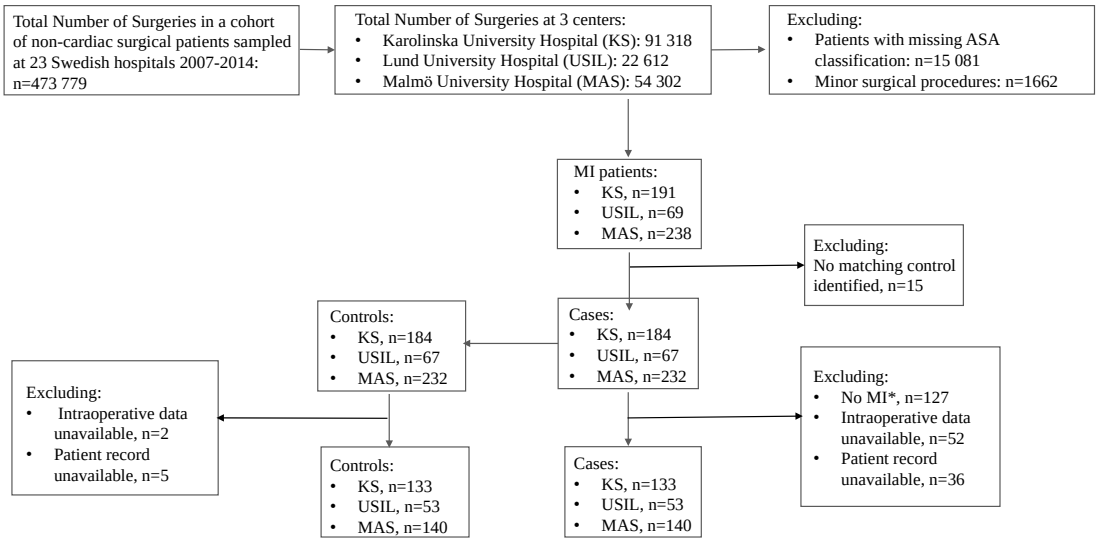
AKI = Acute Kidney Injury, IOH = Intraoperative hypotension, MI = Myocardial infarction, NBHW = National Board of Health and Welfare, Orbit = National Surgical Register, Swedeheart = National Quality Register

Figure 3. Participant Flowchart, study I.



*Surgeries in ambulatory care and individuals <18 years old excluded

Figure 4. Participant Flowchart, study IV.



*No myocardial infarction (MI), recent MI <30 days preoperatively or >30 days after surgery, cardiac surgery or no surgery.

STATISTICS

Data was analysed using STATA version 14.2 (Stata Corp., College Station, TX, USA). In general, all statistical analysis followed a pre-set analysis plan according to the priori defined hypotheses. Continuous variables are presented as medians with interquartile range (IQR) and categorical variables as percentages. For comparison of continuous data, the Mann–Whitney U-test or Kruskal-Wallis test was used, binary variables were compared using the χ^2 test. Statistical tests are two-sided and *p*-values below 0.05 considered to be significant. In the multivariable analyses, covariates were considered as potential confounders based on clinical perspective, results in the bivariate analyses, and on whether the addition to the multivariable models changed the relative risk estimates. Directed acyclic graphs (DAGs) were used to assess the association between covariates and the relation to exposures and outcomes, in order to evaluate, and differentiate, between confounding and effect modification. Sensitivity analyses and tests for interaction were performed, in all studies, to test the robustness of the results.

-Study I

In the multivariable analyses, logistic regression was used to analyse the association between risk factors and MI development, results presented as odds ratios (OR) with 95% CI. The relative risk of MI after different surgical procedures were calculated and the surgeries were divided into three risk groups; *low* (endocrine, ENT, ophthalmic dental, breast and gynaecological surgery), *medium* (GI, neuro, urologic, orthopaedic and dermatologic surgery) and *high* (vascular and thoracic surgery) risk surgery, based on odds ratios (OR). The following risk factors were entered into the model; age (six categories), sex, ASA-classification, cardiovascular- renal-, cerebrovascular- and pulmonary comorbidity, diabetes mellitus (DM), Charlson comorbidity score, surgical risk group and year. The risk factors found in the multivariable model indicated that MI-risk varied substantially between individuals. To illustrate risk differences, the cohort was divided into different strata using significant parameters to create quantiles. Absolute risk measures were calculated in these five risk groups. Mortality after postoperative day 30 was compared with stratified Cox' regression, crude and adjusted hazard ratios (HR) with 95% CI are presented. Standardized incidence ratios (SIR) were calculated as the ratio of the observed and expected number of cases using direct standardisation method. The expected number of cases was calculated according to the yearly incidence rate for all individuals in the statistical database provided by the National Board of Health and Welfare. The SIRs were standardized by 5-year age group, sex, 1-year time period and geographic region. 95% confidence intervals (CIs) were

produced. Sensitivity analyses and tests for interaction were performed. Most importantly to evaluate if missing information of ASA-classification was associated with systematic errors. There were no significant differences when patients with missing ASA were analysed separately. Restriction of these surgeries, or hospitals with high percentage of missing ASA-information, had no impact on crude or adjusted relative risks in the remaining cohort. All indicating that ASA-classification were missing completely at random. Moreover, the percentage of patients with missing ASA- was below 10%: no imputation of data was considered needed. Further analyses, adjusting for time trends and potential clustering by centre, and restriction of the cohort by age, were conducted.

Study II & III

Logistic regression was used to analyse the association between intraoperative hypotensive events and perioperative hs-cTnT elevation (*study II*) and AKI development (*study III*), results presented as odds ratios (OR) with 95% CI. The final models included the following significant adjustment variables: age, preoperative creatinine, abnormal ECG, ASA>2, and congestive heart failure (*study II*) and male sex, ASA>2, preoperative creatinine, treated hypertension and FLB (*study III*). In study II, patients were divided into tertiles reflecting underlying risk, using the significant parameters, in order to analyse the effect of hypotension in different risk strata. In study III, the influence of preoperative high creatinine, intraoperative blood loss and fluid balance on the association between a hypotensive event and AKI was further explored, and tests of interaction between IOH and pre-existing hypertension evaluated.

Study IV

Conditional logistic regression was used in the multivariable analysis to assess the association between predefined risk covariates and perioperative MI development in cases and controls, results presented as odds ratios (OR) with 95% CI. Preoperative, unmatched, risk factors; preoperative BP, DM and IHD (since there were remaining significant incidence difference between cases and controls) and intraoperative risk factors; blood loss, low Hb-value and fluid balance, were entered into the model. Three definitions of the main exposure, IOH, were explored; relative to baseline (mmHg), relative to baseline (%) and absolute intraoperative thresholds. All three definitions were subdivided into 4 categories, in accordance with incidence among controls. The multivariable models yielded were compared using Akaike information criterion (AIC) test. The population attributable fractions (PAFs), the proportion (fraction) of all cases in the population that can be attributed to the exposure, were calculated

using information of the proportion of exposed subjects in the entire surgical population and the relative risks.

To illustrate the overall low absolute risks, cases and controls were distributed to different risk strata, according to five risk-groups created in the original Orbit cohort, used in study I; very low (1)-, low (2)-, median (3)-, high (4)-, and very high (5) risk-group. Absolute risks in these risk-groups in relation to hypotensive events were calculated using absolute risks of MI in *study I* and the relative risks associated with IOH in this study. These calculations rely on the assumption that the estimated odds ratios apply to the source population, the *study I* cohort, and that the estimated incidence of IOH events among our sampled controls estimates of the corresponding incidence in the whole cohort.

Controls were selected using cumulative incidence sampling,[71] all controls were bound to be alive at 30 days, thus differences in 30-day mortality between cases and controls could not be assessed. Mortality from day 31-90 and day 91-365 was compared with stratified Cox' regression, crude and adjusted hazard ratios (HR) with 95% CI are presented. The IOH related risk of fatal MI within 30 days, among cases, was analysed with logistic regression, as were the association with MI type 1 and 2. We assessed possible effect modification by preoperative BP, risk group, day of MI and tachycardia. Internal stratified analyses of preoperative BP, postoperative day of MI diagnose, risk group and tachycardia were performed together with interaction tests

Chapter 3. Results

STUDY I

The final surgical cohort consisted of 400 742 patients, participant characteristics presented in *table 5*. The number of patients suffering MI <30 days of surgery was 1605 (0.41%). Multivariable logistic regression identidfied risk elevation associated with increasing age, surgical procedure, and preoperative cardiovascular comorbidity *(Table 6*). ASA-classification excelled as an independent risk predictor, reflecting how combinations of risk factors result in extensive risk elevation of MI and mortality.

Table 6. Predictors of MI <30 days after surgery.

Risk factor	**OR (Unadjusted)**	**OR (Adjusted*)**
Non-elective	3.15 (2.84-3.51)	1.75 (1.55-1.97)
Male	1.35 (1.22-1.50)	1.13 (1.02-1.27)
Age, y <65	Ref	ref
65-69	3.03 (2.38-3.87)	1.64 (1.28-2.10)
70-74	4.78 (3.83-5.97)	2.22 (1.76-2.79)
75-79	7.57 (6.15-9.31)	2.97 (2.39-3.69)
80-84	11.4 (9.37-14.0)	3.82 (3.09-4.72)
≥85	20.4 (17.0-24.5)	5.47 (4.48-6.69)
ASA 1	ref	ref
2	8.24 (5.34-12.7)	3.38 (2.15-5.32)
3	37.0 (24.2-56.5)	7.65 (4.86-12.1)
4	158 (102-245)	23.2 (14.5-37.1)
Cardiovascular† Disease, No	ref	ref
Yes, excl MI	5.91 (4.97-7.03)	1.75 (1.45-2.12)
Yes, incl MI	26.4 (21.9-31.9)	4.41 (3.54-5.50)
Renal‡ Disease	2.67 (2.29-3.13)	1.05 (0.89-1.24)
Cerebrovascular§ Disease	2.86 (2.46-3.32)	0.97 (0.83-1.13)
Pulmonary‖ Disease	2.88 (2.52-3.29)	1.00 (0.87-1.16)
Diabetes	2.68 (2.38-3.02)	1.28 (1.13-1.46)
Charlson score: 0	ref	ref
1	2.60 (2.16-3.13)	0.93 (0.76-1.13)
≥2	3.31 (2.92-3.75)	0.86 (0.74-1.01)
Surgery: Low[1] Risk	ref	ref
Medium[2] Risk	6.66 (5.04-8.79)	2.22 (1.66-2.96)
High[3] Risk	16.8 (12.4-22.7)	4.40 (3.21-6.02)
Year: 2013-2014	ref	
2011-2012	1.14 (0.99-1.31)	1.19 (1.04-1.37)
2009-2010	1.13 (0.97-1.31)	1.29 (1.11-1.50)
2007-2008	1.44 (1.24-1.67)	1.88 (1.62-2.19)

* Mutually adjusted for all variables in the table

Table 5. Participant baseline characteristics and proportion of MI <30 days after surgery.

Patient and Perioperative Characteristics		Total N= 400 742(%)	MI<30d N=1605 (0,4%*)	P value
Type of Surgery	Elective	281 507 (70)	687 (0.24)	<0.001
	Acute	119 235 (30)	918 (0.77)	
Gender	Female	220 434 (55)	763 (0.35)	<0.001
	Male	180 308 (45)	842 (0.47)	
ASA	1	96 583 (24)	22 (0.02)	<0.001
	2	159 092 (40)	298 (0.19)	
	3	96 977 (24)	810 (0.84)	
	4	8038 (2)	280 (3.5)	
	Missing	40 052 (9.9)	195 (0.49)	
Age, y		64 (49, 75)	81 (72, 86)	<0.001
Age, y	<65	201 500 (50)	181 (0.09)	<0.001
	65-69	49 810 (12)	131 (0.26))	
	70-74	44 992 (11)	185 (0.41)	
	75-79	39 194 (10)	247 (0.63)	
	80-84	32 246 (8)	304 (0.94)	
	≥85	33 090 (8)	557 (1.7)	
Preoperative data	Cardiovascular† Disease;			<0.001
	yes, excl MI	189 980 (47)	983 (0.52)	
	yes, incl MI	19 453 (5)	456 (2.3)	
	no	191 309 (48	166 (0.09	
	Renal‡ Disease; yes	21 038 (5)	211 (1.0)	<0.001
	no		1394 (0.37)	
	Cerebrovascular§ Disease; yes	22 787 (6)	241 (1.1)	<0.001
	no		1364 (0.36)	
	Pulmonary‖ Disease; yes	30 545 (8)	297 (0.97)	<0.001
	no		1308 (0.35)	
	Diabetes; yes	45 613 (11)	420 (0.91)	<0.001
	no		1185 0.33)	
	Charlson score 0	198 082 (49)	372 (0.19)	<0.001
	1	38 617 (10)	188 (0.49)	
	≥2	164 043 (41)	1045 (0.64)	
Perioperative data	Knife time ≥2h	110 914 (28)	412 (0.37)	0.072
	<2h		1193 (0.41)	
Surgery	Low risk[1]	87 141 (22)	69 (0.08)	<0.001
	Medium risk[2]	291 505 (73)	1284 (0.44)	
	High risk[3]	22 096 (6)	252 (1.14)	
Year of surgery	2007-2008	71 377 (18)	361 (0.51)	<0.001
	2009-2010	90 635 (23)	366 (0.40)	
	2011-2012	111 929 (28)	440 (0.39)	
	2013-1014	126 801 (32)	438 (0.35)	
Mortality	30-day; Dead	7152 (1.8)	420 (5.9)	<0.001
	Alive		1185 (0.3)	
	90-day; Dead	13 818 (3.5)	562 (4.1)	<0.001
	Alive		1043 (0.27)	
	1-year; Dead	29 571 (7.4)	728 (2.5)	<0.001
	Alive		877 (0.24)	

* Percentage of MI<30d within the horizontal subpopulation of the cohort.
† Chronic ischemic heart disease, Angina pectoris, Hypertensive disease, Cardiac arrest, Heart failure, Cardiomyopathy, Conduction disorders/Cardiac arrhythmias, Diseases of arteries, arterioles and capillaries.
‡ Acute renal failure/unspecified renal failure, Chronic renal failure, Other renal disease
§ Cerebrovascular disease
‖ Pneumonia, COPD
1) Endocrine, ENT, ophthalmic, dental, breast, gynaecologic surgery
2) GI, neuro, urologic, orthopaedic, dermatologic surgery
3) Vascular, non-cardiac thoracic surgery

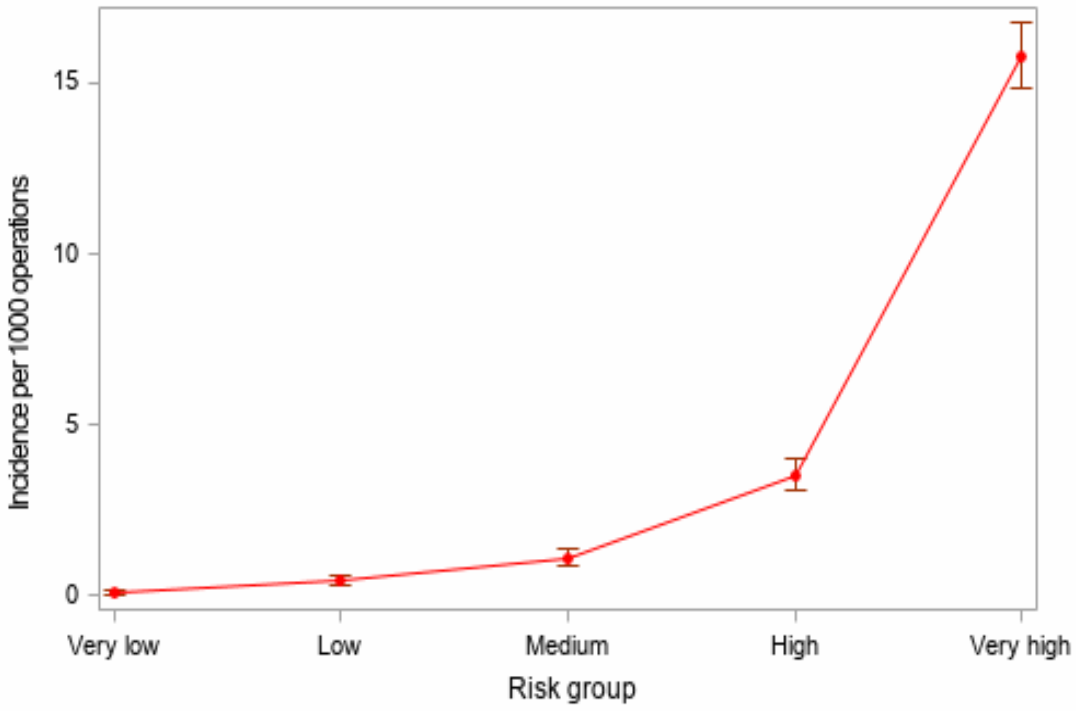
As detailed in methods, patients were divided into five equally sized groups based on risk, incidences per 1000 surgeries are illustrated in *table 7* and *figure 5*. A small subset, consisting of high-risk patients, were found to be the main drivers of perioperative cardiac morbidity. Among two thirds of the cohort, perioperative MI is infrequent, less than 1 in 1000, and 75% of the events occur in one fifth.

Table 7. Risk of MI < 30 days after surgery. Cohort divided into 5 equally sized risk groups.

Risk group 1-5	**Total N (%)**	**MI<30d N (%)**	**OR (95% CI)**	**Inc/1000 (95% CI)**
1. Very Low	77 628 (22)	5 (0.0064)	Ref	0.064 (0.02-0.12)
2. Low	75 348 (21)	31 (0.041)	6.39 (2.48-16.4)	0.41 (0.27-0.56)
3. Medium	77 132 (21)	85 (0.11)	17.1 (6.95-42.2)	1.10 (0.87-1.34)
4. High	63 178 (18)	223 (0.35)	55.0 (22.7-133)	3.53 (3.07-3.99)
5. Very High	67 404 (19)	1066 (1.58)	249 (104-601)	15.8 (14.9-16.8)

1. Very low risk: Age<65 y, ASA 1, low risk surgery, no cardiovascular comorbidity or diabetes.
2. Low risk: Same as risk group 1, but with 2 or 3 factors described in risk group 3 below.
3. Medium risk: Age 65-79 y, ASA 2, medium risk surgery, cardiovascular comorbidity without previous MI, diabetes.
4. High risk: Same as risk group 3 but with 2 or 3 factors described in risk group 5 below.
5. Very high risk: Age ≥80 y ASA>2, high risk surgery, cardiovascular comorbidity with previous MI.

Figure 5. MI incidence per 1000 operations. Cohort divided into 5 equally sized risk groups.



Compared to the Swedish population risk increase was five-fold, standardized by age, sex, geographical region and year (*Table 8*). There were correlations with short- and long-term mortality; 5-fold increased 30-day mortality, doubled risk at 3 months and 30% risk-increase remaining one year after surgery (*Table 9*).

Table 8. MI risk in surgical patients, with the Swedish population as reference

	Observed Cases	**SIR* (95% CI)**	**Observed cases /100 000**	**Expected cases /100 000**
Total	1605	5.35 (5.09-5.61)	401	75
Female	763	6.06 (5.63-6.49)	190	31
Male	842	4.83 (4.51-5.17)	210	43

* Standardized by 5-year age group, gender, 1-year time period and geographic region.

Table 9. Mortality rates in patients developing MI within 30 days after surgery; Odds ratios presented for 30-day mortality, Hazard ratios presented for mortality day 31-90 and day 91-365 after surgery.

		OR (Unadjusted)	**OR (Adjusted*)**	**HR (Unadjusted)**	**HR (Adjusted*)**
Mortality	<30 Days	22.2 (19.7-25.1)	5.49 (4.76-6.32)		
	Day 31-90			8.03 (6.72-9.58)	2.05 (1.72-2.46)
	Day 91-365			4.29 (3.63-5.06)	1.37 (1.16-1.62)

* Adjusted for 5-year age group, gender, ASA-class, cardiovascular disease, previous MI, renal-cerebrovascular- and pulmonary disease, diabetes, Charlson comorbidity index, surgical risk group, acute vs elective status and year of surgery.

STUDY II

Of the final cohort of 300 patients, 90 (30%) had elevated levels of hs-cTnT on the first postoperative morning, as an indication of myocardial damage. Baseline and perioperative characteristics of patients are presented in *table 10*. For the entire cohort, average age was 67 years and 53% were women. The most common surgery was gastrointestinal surgery (40%), followed by urological (29%) and gynaecological (17%) surgery. Patients with elevated levels of hs-cTnT on postoperative day 1 were older with more cardiovascular risk factors, one third of had an abnormal preoperative ECG, compared to 8% with normal hs-cTnT levels ($p < 0.001$). More than twice as many, 38% vs 17%, had chronic treatment with beta blockers ($p<0.001$). Moreover, they had more intraoperative adverse events and worse outcome, with significantly more MI's.

Intraoperative hypotension, defined as a fall in systolic blood pressure >50% from baseline for >5 min, was associated with high troponin values on the first postoperative day (OR, 4.4; 95% CI 1.8-11.1). As patients were divided into three equally sized groups based on risk estimates; low risk-, median- and high-risk group, the risk of hs-cTnT elevation after surgery increased considerably in the presence of an intraoperative hypotensive event in all three risk groups. Results detailed in *table 11* and *figure 6*.

Table 10. Characteristics of the cohort and the proportion of myocardial damage (injury), defined as hs-cTnT>14 ng/l, on postoperative day 1.

Patient and perioperative characteristics		Total n=300	Hs-cTnT ≤14 ng/l n=210	Hs-cTnT >14 ng/l n=90	p
	Age	67 (57, 74)	63 (54, 70)	73 (67, 78)	0.0000
Gender n(%)	Female	159 (53)	119 (57)	40 (44)	0.052
	BMI	26 (23, 29)	26 (23, 28)	25 (22, 29)	0.61
	Smokers	45 (15)	34 (16)	11 (12)	0.38
ASA	1	31 (10)	26 (12)	5 (6)	0.075
	2	138 (46)	111 (53)	27 (30)	0.000
	3	130 (43)	72 (34)	58 (64)	0.000
	4	1 (0.3)	1 (0.5)	0	0.000
Comorbidity	Hypertension	128 (43)	75 (36)	53 (59)	0.000
	Atrial fibrillation	23 (7.7)	8 (4)	15 (17)	0.000
	Congestive heart failure	9 (3)	2 (1)	7 (8)	0.001
	Ischemic heart disease	26 (9)	12 (6)	14 (16)	0.005
	Insulin-dependent diabetes mellitus	23 (8)	12 (6)	11 (12)	0.052
Chronic medication	ACE inhibitors	42 (14)	27 (13)	15 (17)	0.38
	Beta blockers	69 (23)	35 (17)	34 (38)	0.000
	Calcium channel blockers	39 (13)	22 (10)	17 (19)	0.047
Preoperative data	Creatinine (µmol/L)	71 (60, 87)	68 (59, 79)	86 (65, 103)	0.0000
	Abnormal ECG	45 (15)	29 (8)	16 (32)	0.0000
Surgical procedure	Gastrointestinal surgery	121 (40)	82 (39)	39 (43)	0.49
	Urology	87 (29)	62 (30)	25 (28)	0.76
	Gynecology	50 (17)	36 (17)	14 (16)	0.74
	Vascular surgery	8 (3)	2 (1)	6 (7)	0.005
	Plastic surgery	6 (2)	5 (2)	1 (1)	0.47
	Head- and neck surgery	21 (7)	18 (9)	3 (3)	0.10
	Orthopedics	7 (2,3)	5 (2)	2 (2)	0.93
Type of anesthesia	General	117 (39)	88 (42)	29 (32)	0.12
	Regional	7 (2,3)	0	7 (8)	0.13
	General and regional	175 (58)	121 (58)	54 (60)	0.70
	Local	1 (0.3)	1 (0.5)	0	0.51
Intraoperative events	Hypotension	43 (38, 48)	42 (38, 46)	46 (39, 50)	0.0004
	Hypotension >40%	190 (63)	126 (60)	64 (71)	0.067
	Hypotension >50%	34 (12)	13 (6)	21 (23)	0.000
	Tachycardia	33 (11)	21 (10)	12 (13)	0.40
	Hypoxia	2 (0,68)	0	2 (2)	0.029
	Intraoperative blood loss (ml)	500 (200, 1300)	500 (200, 1300)	600 (300, 1250)	0.15
	Intraoperative blood loss (%)	11 (5, 27)	10 (4, 27)	12 (6, 27)	0.15
Postoperative data	Fluid balance	2940 (2115, 3700)	2810 (2050, 3430)	3300 (2280, 4180)	0.0091
	AKI	69 (23)	42 (20)	27 (30)	0.059
Outcome	MI <30 days	15 (5)	4 (2)	11 (12)	0.0000
	Mortality <30 days	5 (1.7)	2 (1.0)	3 (3.3)	0.14
	Mortality <6 month	12 (4)	6 (2.9)	6 (6.7)	0.12

BMI – body mass index, ECG – electrocardiography, Hs-cTnT – high sensitivity cardiac troponin T, AKI – acute kidney injury, ASA - the American Society of Anesthesiologists physical status

* Decrease in systolic blood pressure relative to baseline; continuous, 40 and 50% respectively.

Table 11. Risk estimates in combination with intraoperative hypotensive event* and the effect on myocardial damage (hs-cTnT >14 ng/l).

Risk group	Hypotensive event	Hs-cTnT >14 ng/l		Total	RR
		No (n=210)	Yes (n=90)	n=300	
Low†	No	100 (94)	6 (6)	106	
	Yes	5 (71)	2 (29)	7	4.8
Medium‡	No	61 (76)	19 (24)	80	
	Yes	3 (38)	5 (63)	8	2.6
High§	No	36 (45)	44 (55)	80	
	Yes	5 (26)	13 (74)	19	1.3

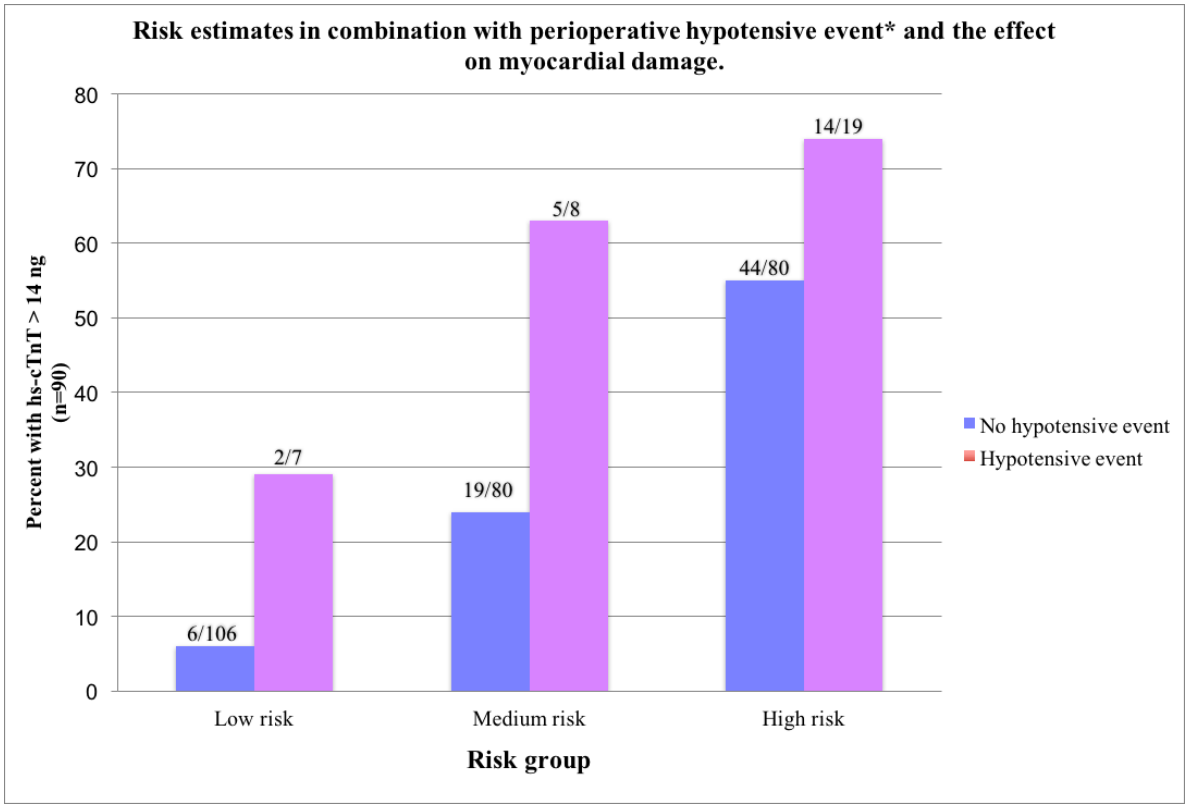
* Decrease in systolic arterial pressure >50% relative to baseline for >5 min

Low risk† (1/3) = no risk factor or only; abnormal ECG or ASA >2 or preop creatinine <59 µmol/L

Medium risk‡ (1/3) = only age >70 y and/or preop creatinine ≥79 µmol/L; combinations of two risk factors: ASA >2 and (preop creatinine <59 µmol/L or >79 µmol/L or age 70-79 y or abnormal ECG) or preop creatinine <59 µmol/L and abnormal ECG

High risk§ (1/3) = remaining combinations

Figure 6.



* Decrease in systolic arterial pressure >50% relative to baseline for >5 min

Low risk† (1/3) = no risk factor or only; abnormal ECG or ASA >2 or preop creatinine <59 µmol/L

Medium risk‡ (1/3) = only age >70 y and/or preop creatinine ≥79 µmol/L; combinations of two risk factors: ASA >2 and (preop creatinine <59 µmol/L or >79 µmol/L or age 70-79 y or abnormal ECG) or preop creatinine <59 µmol/L and abnormal ECG

High risk§ (1/3) = remaining combinations

Within 30 days of surgery, 15 patients (5%) developed MI, two thirds had their MI diagnosed within the first 4 postoperative days and the majority (87%) within a week. Of all 300 patients, 34 (12%) had an intraoperative fall in SBP of more than 50% from baseline, 21 of those had myocardial damage and 8 patients were diagnosed with perioperative MI (p <0.001). The relation between the combination of a hypotensive event, hs-cTnT elevation and myocardial infarction is presented in *table 12*. The combination of several factors lead to a higher likelihood of the event, indicating a 24 % MI incidence as compared to 0.5% with and without the aforementioned risk factors.

Table 12. Association between the combination of hypotensive event*, myocardial damage (hs-cTnT >14 ng/l) and MI <30 days.

Hypotensive event	**Hs-cTnT >14 ng**	**MI <30 days**		**Total**
		No (n=285)	Yes (n=15)	n=300
No	No	196 (99.5)	1 (0.5)	197
No	Yes	63 (91)	6 (9)	69
Yes	No	10 (77)	3 (23)	13
Yes	Yes	16 (76)	5 (24)	21

* Decrease in systolic arterial pressure >50% relative to baseline for >5 min.

STUDY III

During the study time frame a total of 470 patients fulfilled the inclusion criteria in this observational cohort study of high risk elective non-cardiac surgerical patients. 127 patients, or 27%, developed AKI within two days of surgery. A number of unalterable characteristics, such as male gender, preoperative creatinine elevation, treated hypertension and ASA-class >2 were associated with risk of AKI. Baseline characteristics of the study cohort are shown in *table 13* and results from the multivariable logistic regresssion are presented in *table 14*. An intraoperative hypotensive event, defined by a 40% and 50% drop from SBP baseline for a minimum of five minutes, using each patient as control, was associated with an elevated risk of AKI, even after adjustment of aforementioned characteristics. Further adjustment for blood loss in quartiles, as detailed in *table 15*, had no considerate effect on the association.

As preoperative creatinine was associated with elevated risk of AKI, sensitivity analysis was performed with restriction of patients in the quartile with highest preoperative creatinine. This yielded an OR of 2.85 (95% CI 1.31 to 6.23), as shown in *table 15*, indicating a more pronounced effect of an intraoperative hypotensive event on AKI risk in patients without lowered glomerular filtration rate. This was strengthened in a further interaction analysis illustrating a clear risk gradient of AKI in the presence of an increasing hypotensive event when creatinine was <90 µmol/L, but among patients with preoperative creatinine >90 µmol/L, there was a consistently high risk, with or without a hypotensive event, but no gradient.

Table 14. Preoperative predictors and odds ratios of AKI in relation to an intraoperative hypotensive event* and the influence of intraoperative blood loss.

Risk factor	**OR (unadjusted) (95% CI)**	**OR (adjusted†) (95% CI)**	**OR (adjusted‡) (95% CI)**
Hypotensive event* (>40-≤50%) vs ≤40%	1.56 (0.98-2.48)	1.64 (1.015-2.66)	1.50 (0.92-2.47
Hypotensive event* (>50%) vs ≤ 40%	2.38 (1.30-4.36)	2.46 (1.31-4.62)	2.18 (1.14-4.18)

*Decrease in systolic blood pressure in percent relative to baseline for >5 min.
†Adjusted for the covariates: gender (male), ASA>2, treated hypertension, pre-operative creatinine >90 µmol/L.
‡Adjusted for the covariates mentioned above and blood loss in quartiles.

Table 15. Sensitivity analyses of the association hypotensive event and AKI; restriction of the cohort, excluding patients with preoperative creatinine >90 µmol/L (75th percentile).

Risk faktor	**OR† (95% CI)**
Hypotensive event* (>40-≤50%) vs ≤40%	2.03 (1.15-3.69)
Hypotensive event* (>50%) vs ≤ 40%	2.85 (1.31-6.23)

*Decrease in systolic blood pressure in percent relative to baseline for >5 min.
†Adjusted for the covariates: gender (male), ASA>2 and treated hypertension.

Table 13 – Baseline characteristics of the cohort in *study III* and the proportion of AKI.

Patient and perioperative characteristics		Total n=470	No AKI n=343	AKI n=127	*P*
	Age	67 (58 to 74)	67 (58 to 75)	67 (58 to 73)	0.54
Sex n(%)	Female	223 (47)	180 (52)	43 (34)	0.000
	BMI	25 (23 to 28)	25 (23 to 28)	26 (23 to 29)	0.086
	Smokers	60 (13)	39 (11)	21 (17)	0.14
ASA	1	47 (10)	34 (10)	13 (10)	0.92
	2	221 (45)	166 (48)	45 (35)	0.012
	3	208 (44)	141 (41)	67 (53)	0.024
	4	4 (0.009)	2 (0.06)	2 (0.02)	0.060
	>2	212 (45)	143 (42)	69 (54)	0.014
Comorbidity	Hypertension	206 (44)	137 (40)	69 (54)	0.005
	Atrial fibrillation	43 (9)	29 (8)	14 (11)	0.39
	Congestive heart failure	19 (4)	14 (4)	5 (4)	0.94
	Ischemic heart disease	38 (8)	25 (7)	13 (10)	0.30
	Insulin-dependent diabetes mellitus	29 (6)	18 (5)	11 (9)	0.17
Chronic medication	ACE inhibitors	71 (15)	45 (13)	26 (20)	0.048
	Beta blockers	115 (24)	74 (22)	41 (32)	0.016
	Calcium channel blockers	70 (15)	40 (12)	30 (24)	0.001
Preoperative data	Creatinine (µmol/L)	75 (62 to 91)	73 (61 to 89)	81 (67 to 100)	0.0033
Surgical procedure	Gastrointestinal surgery	238 (51)	165 (48)	73 (57)	0.071
	Urology	136 (29)	96 (28)	40 (31)	0.46
	Gynaecology	54 (11)	44 (13)	10 (8)	0.14
	Vascular surgery	8 (2)	5 (1)	3 (2)	0.50
	Plastic surgery	6 (1)	6 (2)	0	0.13
	Head- and neck surgery	21 (4)	20 (6)	1 (1)	0.02
	Orthopaedics	7 (1)	7 (2)	0	0.11
Type of anaesthesia	General	148 (31)	114 (33)	34 (27)	0.18
	Regional	13 (3)	10 (3)	3 (2)	0.75
	General and regional	308 (66)	218 (64)	90 (71)	0.14
Intraoperative events	Hypotension*	43 (37 to 48)	43 (38 to 50)	42 (36 to 47)	0.012
	Hypotension >40% *	286 (61)	197 (57)	89 (70)	0.013
	Hypotension >50% *	68 (14)	42 (12)	26 (20)	0.024
	Tachycardia	50 (10)	36 (10)	14 (11)	0.87
	Hypoxia	4 (0.009)	3 0.009)	1 (0.008)	0.93
	Intraoperative blood loss (ml)	500 (200 to 1200)	400 (150 to 1095)	800 (300 to 1800)	0.0001
Postoperative data	Fluid balance	2825 (2045 to 3585)	2700 (1962 to 3390)	3123 (2364 to 4178)	0.0002
	Hs-cTnT	11 (7 to 17)	10 (6 to 16)	14 (9 to 21)	0.0000
Outcome	Myocardial injury**	156 (33)	98 (29)	58 (46)	0.000
	Mortality <30 days	9 (2)	4 (1)	5 (4)	0.0046

BMI – body mass index ($kg/m^{2)}$, ECG – electrocardiography, Hs-cTnT – high sensitivity cardiac troponin T, AKI – acute kidney injury, ASA - the American Society of Anesthesiologists physical status

* Decrease in systolic blood pressure relative to baseline; % from baseline, 40 and 50% respectively.

** Myocardial injury on postoperative day 1, defined as hs-cTnT >14 ng l^{-1}

STUDY IV

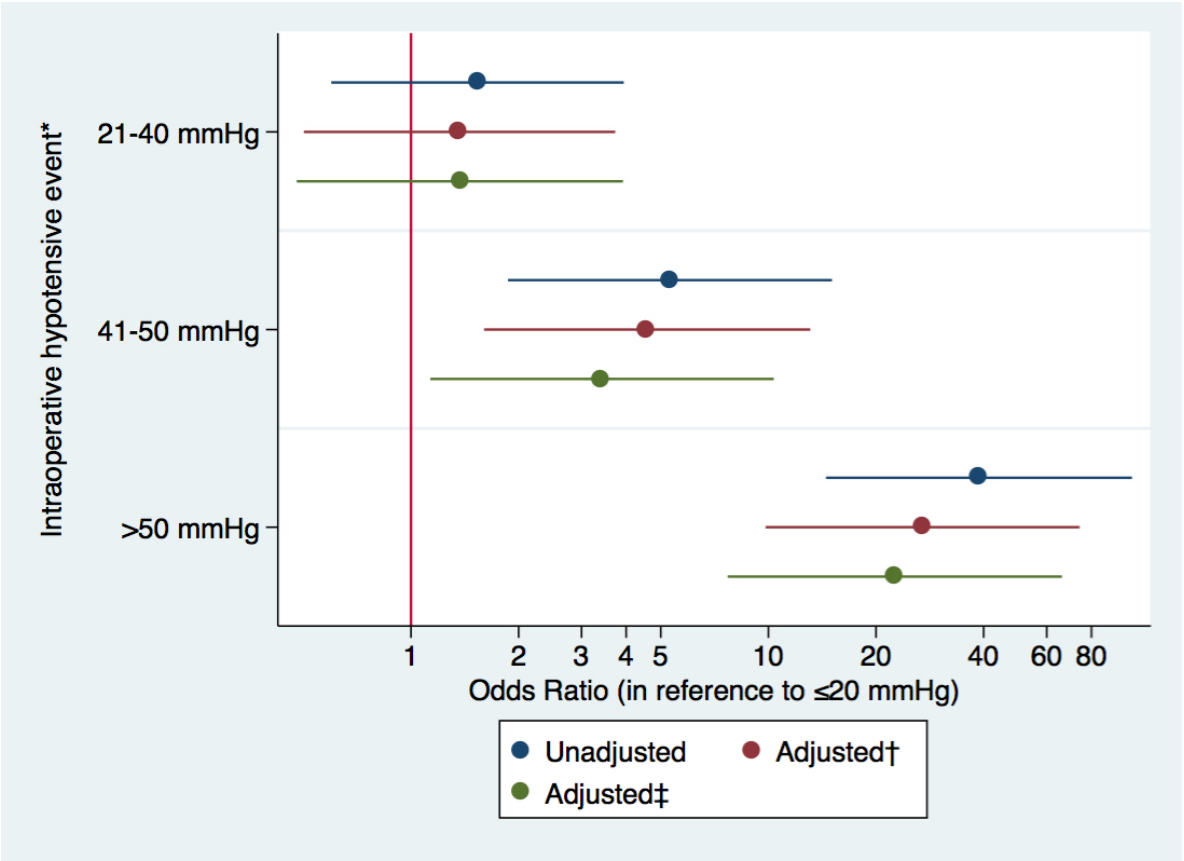
In this case-control study, nested within a well-defined large cohort of high-risk patients undergoing non-cardiac surgery, 326 cases met the inclusion criteria and were successfully matched with 326 controls (see Flowchart, *Fig 4* for details in the selection process). Conditional logistic regression identified IOH as an important risk factor for MI-development <30 days of surgery (*table 16*, *Fig 7*). An intraoperative hypotensive reduction of 41-50 mmHg, from individual baseline SAP, was associated with a more than tripled MI risk, OR 3.42 (95% CI, 1.13 to 10.3), and a hypotensive event >50 mmHg with a *considerable* risk increase, OR 22.6, (95% CI, 7.69 to 66.2). These risk estimates are derived after adjustment for preoperative covariates, high BP (SAP ≥140 mmHg), DM, and IHD and intraoperative risk events; blood loss (>1800 mL), Hb <85 g/L, hypoxia (SaO2 <90%) and fluid balance (>2000 mL). The absolute decrease in mmHg, from individual preoperative BP baseline, was selected as main IOH definition. Multivariable comparison of the three final models based on different IOH definitions yielded similar odds estimates. The AIC test favoured the models with IOH defined as a relative to baseline measure, ahead of the model with absolute blood pressure thresholds (AIC value 226), while data do not clearly support a discrimination between the models based on absolute and relative change from baseline blood pressure (AIC value 214 vs 210), results shown in *table 17*.

Table 16. Odds ratios of MI in relation to intraoperative hypotension.

Risk factor		Cases n(%)	Controls n(%)	OR (unadjusted) (95% CI)	OR (adjusted†) (95% CI)	OR (adjusted‡) (95% CI)
Hypotensive event*	≤20	13 (4)	84 (26)	ref	ref	ref
(mmHg)	21-40	22 (7)	105 (32)	1.53 (0.60-3.94)	1.37 (0.50-3.73)	1.37 (0.48-3.92)
	41-50	31 (10)	64 (19)	5.30 (1.87-15.1)	4.58 (1.60-13.1)	3.42 (1.13-10.3)
	>50	260 (80)	73 (22)	38.8 (14.5-104)	27.0 (9.82-74.1)	22.6 (7.69-66.2)

* Decrease in SBP from baseline for >5 min
† Adjusted for preoperative risk factors; IHD and DM
‡ Further adjusted for intraoperative risk factors; blood loss (>1800 mL), Hb <85 g/L, hypoxia (SaO2 <90%) and fluid balance (>2000 mL)

Figure 7. Odds ratios (log scale) of MI in relation to intraoperative hypotension.



* Decrease in SBP (mmHg) from baseline for >5 min
† Adjusted for preoperative risk factors; SBP, IHD and DM
‡ Further adjusted for intraoperative risk factors; blood loss (>1800 mL), Hb <85 g/L, hypoxia (SaO2 <90%) and fluid balance (>2000 mL)

Table 17. Adjusted Odds ratios of MI in relation to different definitions of intraoperative hypotension, categorized into quartiles.

Risk factor		OR* (95% CI)	OR† (95% CI)	OR‡ (95% CI)
Hypotensive event	Q1	ref	ref	ref
	Q2	1.37 (0.48-3.92)	1.73 (0.62-4.86)	2.43 (1.11-5.31)
	Q3	3.42 (1.13-10.3)	3.72 (1.41-9.83)	4.15 (1.74-9.90)
	Q4	22.6 (7.69-66.2)	26.8 (9.53-75.6)	24.2 (9.08-64.3)
AIC§		214	210	226

* Decrease in SBP from baseline for >5 min, defined as an absolute decrease (mmHg) relative to baseline; ≤20, 21-40, 41-50, >50 (mmHg)
† Decrease in SBP from baseline for >5 min, defined as a percentage decrease relative to baseline; ≤20, 21-30, 31-40, >40 (%)
‡ Decrease in SBP for >5 min, defined as absolute thresholds; ≥110, 90-110, 80-90, <80 (mmHg)
§ Akaike Information Criterion

The right panel of *table 18* displays the absolute risks of MI in relation to IOH together with the estimated incidence of IOH in different risk groups. High absolute excess risks were observed among patients with a SBP drop >50 mmHg as compared to patients with a SBP drop ≤40 mmHg, where patients with *very high* baseline risk increased their risk from 3.6 to 68 per 1000 operations, patients with *high* risk increased from 0.5 to 10 and the corresponding increase in lower risk patients was 0.1 to 1.8. We could also show that the incidence of high-risk hypotensive events (i.e. SBP drop>50 mmHg) decreased significantly with increasing risk factor burden *(p=0.005).* In the left panel of *table 16*, displaying published results from *study I*, it is shown that 19% of all non-cardiac surgeries are characterized by very high risk, and that 76% of MI's occur among these patients. Overall PAF was 82%, hence four out of five MI's were attributable to a serious IOH. For patients in the highest risk group, the associated absolute excess risk was estimated to about 6 percent.

Table 18. MI risk in relation to intraoperative hypotensive events and preoperative risk group.

	Orbit study†			**Case-Control study**				
Risk group [1-5]	No of operations (%)	No of MI (%)	MI per 1000	No of MI (%)	MI risk per 1000 operations *(% with hypotensive event in the population‡)*			PAF % (95% CI)
Hypotensive event*					≤40	41-50	>50	
Relative risk (OR)					ref	2.81	18.6	
Low[1+2]+Medium[3]	230 108 (64)	121 (8)	0.8	33 10)	0.1 *(38)*	0.3 *(23)*	1.8 *(38)*	89 (81-94)
High[4]	63 178 (17)	223 (16)	3.5	48 (15)	0.5 *(49)*	1.5 *(20)*	10 *(31)*	84 (75-90)
Very High[5]	67 404 (19)	1066 (76)	15.8	245 (75)	3.6 *(64)*	10 *(19)*	68 *(17)*	80 (74-85)
Overall PAF§								82 (75-87)

* Decrease in SBP (mmHg) from baseline for >5 min
† Data from Orbit (*study I*)[72]
‡ Estimated from the controls in this study (P=0.005 for difference between risk groups)
§ Population attributable fraction

Risk groups
1+2. Low risk: Age<65 y, ASA 1, low-risk surgery, no cardiovascular comorbidity or diabetes, with 2 or 3 factors described in risk group 2 below.
3. Medium risk: Age 65-79 y, ASA 2, medium risk surgery, cardiovascular comorbidity without previous MI, diabetes.
4. High risk: Same as risk group 3 but with 2 or 3 factors described in risk group 5 below.
5. Very high risk: Age ≥80 y ASA>2, high risk surgery, cardiovascular comorbidity with previous MI.

In *table 19*, results from mortality analyses are presented. At 30 days postoperatively, 88 of 326 (27%) cases were deceased. There was no difference in IOH occurrence among patients with fatal (<30 days) and non-fatal MI, adjusting for age, sex, ASA-class and comorbidities in logistic regression (*p=0.84*). Day 91-365, 39 cases (20%) and 25 controls (9%) died. Crude HR was 2.12 (95% CI, 1.27 to 3.55), adjustment for DM and IHD resulted a HR of 2.01 (95% CI, 1.19 to 3.38). During 31 to 90 days, there was no difference in mortality between cases and controls.

Table 19. Mortality rates in patients developing MI <30 days after surgery; Hazard ratios presented for mortality day 31-90 and day 91-365 after surgery.

Mortality	**Case n=326 (%)**	**Controls n=326 (%)**	**OR (Adjusted*)**	**HR (Unadjusted)**	**HR (Adjusted†)**
<30 Days*	88 (27)	N/A	5.49 (4.76-6.32)		
Day 31-90	17 (7)	18 (8)		1.14 (0.57-2.29)	1.02 (0.47-2.19)
Day 91-365	39 (20)	25 (9)		2.12 (1.27-3.55)	2.01 (1.19-3.38)

* Data from study I. OR adjusted for 5-year age group, gender, ASA-class, cardiovascular disease, previous MI, renal- cerebrovascular- and pulmonary disease, diabetes, Charlson comorbidity index, surgical risk group, acute vs elective status and year of surgery.

†Adjusted for diabetes and ischemic heart disease.

Results yielded from the sensitivity analyses are detailed in *table 20*. There was no evidence of effect modification between preoperative BP or intraoperative tachycardia and IOH. Although not significant, a more pronounced effect of IOH in higher risk-patients compared to lower risk-patients was observed, as in MI development on postoperative day 1 to 2 compared to later diagnosed MI cases. None of the interaction tests involving these covariates were significant.

Table 20. Risk of MI in relation to hypotension. Odds Ratios after adjusted for intraoperative risk factors; blood loss >1800 mL, postop Hb <85 mg/L, fluid balance >2000 mL, hypoxia.

Risk factor	**Preoperative BP†**		**Day of MI‡**		**Risk group§**		**Tachycardia‖**	
Hypotensive event*	<140 mmHg	≥140 mmHg	1-2	>2	Low	High	No	Yes
≤20 mmHg (ref)								
21-40 mmHg	1.12 (0.22-5.64)	1.75 (0.39-7.74)	1.77 (0.38-8.21)	1.04 (0.25-4.28)	0.53 (0.06-4.36)	1.70 (0.50-5.82)	2.68 (0.22-5.64)	0.57 (0.58-12.3)
41-50 mmHg	3.23 (0.65-16.0)	3.60 (0.84-15.5)	4.37 (0.75-25.4)	2.89 (0. 69-12.1)	1.74 (0.26-11.8)	3.78 (0.97-14.8)	5.97 (0.65-16.0)	14.5 (1.26-28.2)
>50 mmHg	31.9 (6.19-164)	20.9 (5.83-75.2)	43.7 (7.83-244)	13.3 (3.47-50.6)	7.08 (1.24-40.5)	38.7 (9.68-155)	47.1 (6.19-164)	52.8 (10.2-217)
P-value**	0.74		0.62		0.47		0.42	

* Decrease in SBP, defined as an absolute decrease (mmHg) relative to baseline, for >5 min
† Stratified by preoperative BP (<140 mmHg vs ≥140 mmHg)
‡ Stratified by postoperative day of MI (day 1-2 vs > day 2)
§ Stratified by risk group (low; risk group 1 to 3 vs high; risk group 4 to 5)
‖ Stratified by intraoperative tachycardia; >110 bpm >5 minutes
** P-value from interaction tests

Chapter 4. Discussion

SUMMARY OF FINDINGS

In this thesis of observational studies, risk factors of myocardial and kidney outcome in patients undergoing non-cardiac studies were evaluated. Overall incidence of perioperative MI, fulfilling the universal definition.[16] was 0.41%, a small subset of high-risk patients was identified as the main drivers and should be targeted in order to improve perioperative outcomes. Compared to the Swedish population, the standardized risk increase of MI was five-fold and there was a strong association with short- and long-term mortality. Intraoperative hypotension was a major contributor to perioperative cardiac troponin elevation, AKI and clinically significant MI. The high absolute MI-risk associated with IOH, among a growing population of patients with a high risk-burden undergoing surgery, suggests that increased vigilance of BP control during anaesthesia and surgery in these patients may be beneficial.

METHODOLOGICAL CONSIDERATIONS

Study design

Observational, epidemiologic studies are historically regarded as lower grade evidence in the methodological hierarchy of research designs.[73] However, observational study designs are important in medical research as experimental studies not always are possible to implement, due to ethical reasons or clinical feasibility. Moreover, the general consensus about study design hierarchy, that observational studies have less validity and may overestimate causal relations, is challenged. Observational studies, either cohort or case-control design, if well-performed, have been shown to yield results similar to prospective randomized trials, with even less heterogeneity in point estimates.[74,75]

Study I is an observational descriptive cohort study with patients extracted from a nationwide surgical register and linked to several national and quality registries, enabling an extensive data collection. *Study II* and *III* are single-centre, prospective observational cohort studies with patients undergoing major non-cardiac surgery within a specified time-period and data collected from medical records and anaesthetic charts. *Study IV* use a *nested* case-control study design, conducted within the cohort used in *study I*, allowing random sampling of cases and controls. In cohort studies, patients are followed over time allowing frequencies and associations of risk factors and outcomes to be observed during this time period, an appealing

study design when multiple exposures and/or outcomes are evaluated. The case-control study design is generally preferred when rare outcomes, that develops over of long time, are studied, due to practical and economic reasons. In *study IV*, control subjects were sampled using the *cumulative incidence (exclusive) sampling* method, hence odds ratios correspond, on average, exactly to OR in the full cohort and would approximate risk ratio and rate ratio using the *rare disease assumption*.[71] Two alternative options to sample controls in nested case-control studies are *case-cohort (inclusive) sampling* and *risk-set (density) sampling*. An important consideration is that cases and controls were sampled from a well-defined surgery cohort, characterized in *study I*. This allows estimation of the proportion of patients exposed to IOH events in the population, from controls, and, thus, enables a transfer of the relative risk to a corresponding absolute risk increase, even though this is a case-control designed study. An alternative approach to explore the effect of intraoperative risk factors on perioperative outcome, the ideal study design for providing evidence of causal relations, would have been a randomized controlled trial. However, from an ethical perspective, possible benefits yielded from the study could be outweighed by the disadvantages. To randomize patients to a protocolized intraoperative algorithm, in order to minimize hemodynamic instability, compared to standard, less careful, anaesthetic management, would be controversial. Even more problematic would be the difficulty of keeping the involved staff blinded to the purpose of the study and, by that means, the risk of Hawthorn effect[76,77] influencing the results. Also, conduction of an RCT would be time-consuming and expensive, and the nested case-control design was considered a fair option.

External validity

The meaning of external validity - generalizability – is the possibility to draw general conclusions from research, i.e. to apply the results to other populations than the study sample. *Study I* was a nation-wide study, with a study cohort identified from 23 hospitals of all levels (university-, county and district) representing approximately 40% of Swedish hospitals. All adult patients undergoing various non-cardiac surgical procedures were included. Generalizability should be high and the possibility to make inferences regarding other surgical populations legitimate. The results are considered applicable to other countries with similar healthcare standard, and to patients with equivalent comorbid burden and comparable surgical risk profile. *Study II and III* were single-centre studies, the study cohorts were well-defined but smaller, limiting the possibility to generalize these results to other surgical population. These studies are conceptually more hypothesis generating by design. However, the use of an individual, relative to baseline, definition of IOH has advantages; patients with

preoperative normal BP could be included, thus increasing the generalizability of the study results to low-BP patients. Moreover, patients with preoperative elevated creatinine were included in the *study III* cohort, the influence of hypotension on patients with pre-existing renal insufficiency could therefore be explored and conclusions drawn regarding this patient group. In *study IV*, the main results could safely be generalized to a surgical population with the same risk profile. This study was multi-centre and the sample was drawn from a large well-defined cohort. However, the majority of cases were patients with an elevated risk factor burden, and the ability to estimate the IOH associated MI risk among patients with a low underlying risk was limited. Sensitivity analysis illustrated a lower relative impact of IOH in low risk patients and a higher impact among high risk patients, suggesting that we may underestimate the absolute excess in patients with a high-risk profile. Correspondingly, in low risk patients, the effect of intraoperative hypotensive events may be overestimated.

Internal validity

Internal validity is related to *systematic error*s, in methodology or study design.[78] Systematic errors, or *bias*,[77,79] are the consistent deviations of measurements away from the true path, unrelated to sample size.

Misclassification bias

In epidemiological research, there is an inherent risk of *misclassification*, or *information bias*.[79] Quality of data, often dependent on registry accuracy and coverage, variable definition and categorization, are potential areas. Random misclassifications, unrelated to exposure or outcome, generally result in dilution of effects, i.e. *bias towards the null*. *Differential* misclassifications, of exposure or outcome, may have an important impact on the results, either by creating false – or concealing existing – associations. In *study I*, data were obtained from large registries and databases, with possible reporting bias and errors in coding and subsequent risk of misclassification of both outcome, MI diagnosis, and risk factors, i.e. comorbidities. Although the NPR have close to complete coverage of in-patient data, information from primary care is lacking. To maximise the coverage of comorbid history, data linkage to the *Swedish Prescribed Drug Register*,[62] for information of dispensed drug prescriptions within five years before surgery, was performed. In the *Swedish Cause of Death Registry*, over 99% of all deaths are reported,[59] so mortality rates reported in *study I* are reliable. In *study IV*, dates of death were validated in electronic medical records. *Study I* was not a prospective study, it cannot be ensured that all physicians across Sweden who diagnosed cases of MI included in this study used the universal definition,[31] which may influence the estimated MI-incidence. In *study II*, *III* and *IV*, parts of the data collection were

performed manually, preoperative BP and laboratory values were obtained from electronic medical records and intraoperative data from paper charts, with risk of errors. The accuracy of the recordings of the main exposure, IOH, was followed, to test how well hypotensive events during surgery and anesthesia were transferred to paper records. The validation trial showed that 13 out of 30 patients had major hypotensive events captured by the electronic monitors, 9 patients had hypotensive events recorded in the anaesthetic paper records. Thus, there were no overestimated hypotensive events, rather a trend that the anaesthetic staff was underestimating the lower limit of intraoperative BP recordings.

Selection bias

Selection bias is a systematic error[79,80] related to the selection process of study participants. All four studies are registry-based, with pre-defined inclusion- and exclusion criteria, and participation was not voluntary, reducing risk of selection bias. However, in *study I*, the lack of cardiac biomarker information in all patients introduce a potential bias; with cardiac troponins, the possibility of identifying all cases of myocardial injury and infarction would be increased, since many of these incidents are clinically silent.[81] These limitations also apply to *study IV*, since cases and controls were obtained from the same source population. Troponins may be analysed more readily in elderly/high-risk patients, possibly leading to an over-representation of more severe and frail patients among cases. In addition, an observed episode of IOH may increase the likelihood of a MI being diagnosed, leading to over-estimation of the risk. In *study II* and *III*, the pre-set strict inclusion criteria of all adult patients undergoing major elective non-cardiac surgery, within a specific time frame, and who, in advance, were planned for an overnight admission at the postoperative unit, reduce risk of selection bias.

Confounding

Confounding factors are, by definition, covariates related to exposure and outcome without partaking in the causal pathway. Confounding is inevitable in all research.[79] Strategies to handle, and minimize, the impact and distortion of study results includes using the correct study design approach, by randomization, restriction and matching when possible, and, in the analysis phase, by stratification and regression.

In *Study I*, confounding was handled statistically using regression analyses, stratification and restriction. The large study cohort freely enabled variable categorization and adjustment for all potential confounders, without risk of losing power. The selection of covariates was based on clinical consideration and on whether the addition to the multivariable models changed the relative risk estimates. *Confounding by indication* refers to when a determinant of the

outcome that is present in patients at high risk, with estimated poor prognosis, leads to differences in care between the exposed and non-exposed, and between cases and non-cases.[82] The outcome may, in fact, be caused by the indication for which the exposure was used. Confounding by severity is a variant, when disease severity acts as confounders. There is a risk of confounding by indication in *study I*, troponins may be more frequently analysed in elderly/high-risk patients in the perioperative period, possibly identifying and diagnosing more clinically silent MIs in this patient group.

Study II and III were smaller and dependent on the rule of ten in the modelling process.[83] Even if this rule of thumb, that logistic and proportional hazard models should be used with a minimum of 10 outcome events per predictor variable, has been questioned.[84] Thumb rules are valuable tools and useful signals for potential trouble but there are statistical situations when this rule may be too rigid, as in sensitivity analyses undertaken to explore the influence of confounding in observational studies. In *study II and III*, the selection of potentially confounding factors was based on clinical experience in conjunction with p-values in the bivariate analysis. However, there is risk of residual confounding.

In *study IV*, control subjects were matched to cases by age, comorbidities and surgical risk factors, reducing risk of confounding and increasing the possibility to evaluate the effect of the main exposure on the primary outcome.

Effect modification and interaction

Effect modification has to be considered when the association between an exposure and outcome variable is affected by another variable. Unlike a confounder, the effect modifier takes part in the causal pathway and may affect the magnitude the exposure effect on the outcome of interest. Interaction (synergistic) is when the joint effect of two covariates is higher than the individual effects on a specific outcome.[78,85] Stratification and interaction tests are valuable statistical tools to handle potential effect modifying – and interacting - influence.

In *study I*, the large amount of data and different risk assessments entail existence of interaction, and multicollinearity, which was taken into account in the statistical analyses and the result interpretation. Pre- and intraoperative risk factors were carefully evaluated in all studies using interaction tests and stratified analyses. Furthermore, with regards to BP levels during surgery, intraoperative blood loss is a risk factor closely associated with hemodynamic instability and has to be considered both as an effect modifying risk factor and a confounder, discussed in more detail under *clinical interpretations*. In *study IV*, effect modification by

preoperative BP, risk group, day of MI diagnosis and tachycardia were thoroughly assessed using internally stratified analyses (*table 20)*.

Reverse causation

In *study IV*, reverse causality must be considered as a potential bias. From data, we were statistically unable to exclude the possibility that the hypotensive event was a consequence of a major MI occurring on the operating table. However, from a clinical perspective, MI following a fall in BP is a more probable course. Moreover, all cases with a major hypotensive episode during surgery, leading to cardiac biomarker-analysis after surgery despite absence of other clinical signs and subjective ischemic symptoms, were excluded. This was done to minimize the risk of reverse causation.

Immortal time bias

In *study IV*, controls were selected using cumulative incidence sampling, all controls were bound to be alive at 30 days. Differences in 30-day mortality could not be analysed, due to immortal time bias in controls; this sampling scheme precludes estimation of 30-day mortality related to MI.

Precision

The accuracy and replicability of research results depends on internal validity, as described above, and precision. All research, as life in general, is inevitably affected by chance. Risk of random errors are related to study sample size. A measure of the unpredicted variability in a study finding is p-values and CI. The p-value stands for the probability that the difference between groups in a population is caused by chance, if the null hypothesis comprises that the groups are equal. The meaning of CI intervals is to illustrate what 95% of the point estimates would be if a new study population was sampled from the same source population, i.e. the likelihood that the *true* value lies within this interval.

In *study I*, the risk of random errors should be minimal due to the large sample size. The accurate sampling procedure of cases and controls from the *study I* cohort, reduce risk of random errors in *study IV*. *Study II* and *III* are conducted with smaller study samples, hence precision is lower and the results more susceptible to chance.

INTERPRETATIONS OF FINDINGS

Perioperative MI – incidence and risk factors

Myocardial infarction, fulfilling the universal definition, occurring in the perioperative period is an overall rare condition. Our study results indicate that the risk elevation is associated with increasing age, surgical procedure, and preoperative cardiovascular comorbidity. A small subset of high-risk patients is especially affected by perioperative cardiac morbidity.[72] In the *study I* cohort, the perioperative MI incidence was half of the incidence (0.9%) reported in a large study of MI in non-cardiac surgical patients.[86] The age inclusion cut-off was higher (≥45y) but median age in the cohorts similar, as were patient factors and surgical procedures carrying highest risk. Restriction of our cohort to patients ≥45y resulted in an incidence of 0.5%. There was a major difference how MI patients were identified, MI diagnosis reported *during the surgical inpatient hospitalization* were defined as cases without a specified pre- or postoperative time span, with consequential risk of reversed causality and confounding by indication, potentially leading to higher incidence. Using the unique Swedish Quality Registry (Swedeheart) and the National Patient Register, all MIs within a pre-specified period (30 days) after surgery, including patients with MI type 2, not referred to cardiology clinics or subject for cardiac intervention, could be identified. However, since these incidents often are clinically silent,[81] the lack of cardiac biomarkers in all patients is vital; with cardiac troponins, the possibility of identifying all cases of myocardial injury and infarction would be increased.

Reports on long-term mortality after perioperative MI are lacking. In a smaller study of patients with perioperative myocardial injury in non-cardiac surgery, 8.9% died <30 days and 22.5% <1 year after surgery. Adjusted HR for 30-day and 1-year mortality was 2.73 and 1.58.[23] This cohort constituted of high-risk patients, defined by age and comorbidities, explaining the higher overall mortality (30-day- and 1-year mortality was 2.8% vs 11.2%), and the subsequent lower relative risks, compared to ours. A large multinational study reported overall an mortality of 1.2-1.8% in major non-cardiac surgical patients (equal to our cohort mortality) and tripled 30-day mortality in patients with perioperative myocardial injury (adjusted HR, 3.69).[30,87] In a recent study evaluating MI incidence in a US surgical cohort, in-hospital mortality was 18% in patients with in-hospital MI, and corresponding adjusted OR 5.76.[86]

In *study I*, a high death-rate was identified among patients developing MI <30 days; 26% at 30-days, 35% at 90-days and 45% one year after surgery. Elevated absolute risks were related to extensive preoperative comorbid burden and high age. After adjustment for demographic

variables and comorbidities, patients with perioperative MI had five-fold increased risk of dying within 30 days after surgery, in-line with the in-hospital mortality following perioperative MI previously reported[86] and higher compared to the doubled - and tripled - 30-day mortality after myocardial injury described above.[23,87] A plausible explanation would be that only patients with a verified MI diagnosis fulfilling the universal criteria[16] are cases in our study, some myocardial injuries are diagnosed as MI type 2, and included, but *asymptomatic myocardial injuries* are not. One could credibly argue that this would result in a worse outcome, although there are studies implying that MI, symptomatic or asymptomatic, carries equally poor prognosis.[20] Long-term mortality was increased, as expected. Mortality rates beyond 30 days were doubled in patients with MI up to 90 days after surgery, then the risk-increase declined. Between day 91-365, there was a remaining 37% increased mortality. Hence, the major risk elevation of death following perioperative MI occur within the first 3 postoperative months, possibly because of depletion of susceptible individuals. Since elderly, diseased patients who develop perioperative MI are more likely to die early, patients surviving the first 90 days are a more resistant population. Residual confounding, interaction factors remaining after adjustment, could be another explanation. As the fact that MI is a heterogenic diagnosis, with a spectrum from fatal types to more benign myocardial injuries.

Intraoperative hypotension and perioperative MI risk

As mentioned, hemodynamic instability is common in a perioperative setting and associated with perioperative cardiac injury, and increased mortality in high-risk surgical patients.[9,11,22,47,48] Results presented in *study IV* are in line with previous studies,[9,11,48,88-91] but with a more pronounced effect of the intraoperative hypotensive events. The nested case-control design, and the use of a well-characterized cohort of high-risk surgical patients as source population, gives reliable estimates of associations even in rare outcomes, reducing risk of residual confounding. Further possible reasons for the strong association are the outcome – and exposure – definitions. Only symptomatic MIs, fulfilling the universal definition, are included, myocardial injuries are not. Regarding exposure; both pre- and intraoperative BP values were accessible which enabled the comparison between different hypotension definitions: relative to baseline (mmHg), relative to baseline (%) and absolute intraoperative thresholds. All resulted in similar risk estimates with a gradual elevation of MI-risk in relation to an increasing fall in BP. Statistically, a relative drop in mmHg from individual baseline was favoured. From a clinical perspective, the reduction in mmHg from individual baseline is an appealing definition, a lowest acceptable threshold could be easily determined in the OR, before the anaesthetic induction.

There is scarce evidence of optimal blood pressure (BP) thresholds to maintain adequate perfusion and oxygenation in critical organs during anaesthesia and surgery. Various definitions of perioperative hypotensive events exist in the literature.[51] Previous investigations are limited by the use of specific systolic- or mean BP and may underestimate IOH as a risk factor. Individualized hypotension definitions are theoretically better when investigating the risk of perioperative organ injury. In patients with a pre-existing hypertension diagnosis the auto-regulatory capacity in the kidney and brain, an essential mechanism to preserve optimal blood perfusion when systemic BP fluctuates, is likely affected.[92,93] Thus higher BP may be beneficial for certain high-risk patients.[9,47,88,90] The advantage of using individual IOH definitions was also strengthened by a randomized controlled trial evaluating BP targets in patients with septic shock, where outcomes were improved by high BP targets only in patients with known hypertension.[94] However, there are studies showing that absolute and relative thresholds are comparable in their ability to discriminate patients with myocardial and kidney injury from those without.[88] A randomized study showed that targeting an individualized SBP, as compared with standard management, reduced risk of postoperative organ dysfunction.[91] Patients in the individualized treatment group had significantly lower rates of renal dysfunction and a lower risk for altered consciousness and confusion than patients in the standard treatment group.

The underlying mechanisms of hypotension occurring closely after the induction and episodes later during surgery are most certainly completely different. The former being related to the cardio-depressant effect of the anaesthetic agents (and possibly an un-attentive anaesthetist) and the latter rather associated with other intra-surgical events, such as excessive bleeding, etc. In *study IV*, various intraoperative events, such as tachycardia, hypoxia, blood loss, low Hb-values and fluid overload were associated with MI. However, no significant effect on the strong association between hypotension and MI was seen. Increased heart rate is a physiological consequence of low BP, and a response to pain and insufficient anaesthesia, but doesn't act as a cause of hypotension. Tachycardia was therefore considered as a contributor in the causal pathway between hypotension and MI, rather than a confounder. Intraoperative heart rate >100 bpm has previously been identified as a risk factor of perioperative myocardial injury and infarction (OR 1.27 and 1.34) and an indication of a slightly stronger association in combination with an intraoperative SBP <100 mmHg has been shown[95], in line with the results in *study IV*. The stratified analyses also highlighted a more pronounced effect of hypotension in higher risk patients and on MI-development closely after surgery.

Importantly, even though the relative risk of clinically manifested MI associated with a large fall in BP was 20-fold, this corresponds to a low absolute excess risk for the vast majority of operated patients. However, for patients with a very high preoperative risk factor burden the associated absolute excess risk was considerable.

Intraoperative hypotension - perioperative myocardial and kidney injury

Elevated levels of the cardiac biomarkers hs-cTnT, as an indication of myocardial injury, following non-cardiac surgery is now a well-known warning flag. In a large, recent study, one in 10 patients with myocardial injury after non-cardiac surgery were deceased within 30 days and more than 80% of these patients would not have been identified without the postoperative troponin measurement.[96] Associations between peak postoperative fourth generation TnT and 30-day mortality have been reported previously.[30] In a small study of 140 patients, cardiac troponin I was associated to major adverse cardiac events but no differences during the perioperative course was found.[97] Two meta-analyses in recent years have detailed the relationship between postoperative leakage of troponin and mortality. One included nine studies to investigate how elevation of troponin below the diagnostic threshold for perioperative MI, without symptoms or ischemic electrocardiography changes or echocardiography signs, was predictive of all-cause mortality at 30 days after vascular surgery.[98] In the other, fourteen studies were analysed, enrolling 3,318 patients with 459 deaths, demonstrating increased troponin postoperatively to be an independent predictor of all-cause mortality one year after non-cardiac surgery.[99]

Interestingly, the association between intraoperative hypotension and myocardial injury, in *study II*, was consistent independently of baseline comorbidity.[48] Chronic antihypertensive medications were not independently associated with myocardial injury or intraoperative hypotensive events. Since ACE inhibitors are known to increase intraoperative BP instability, national guidelines recommend patients to discontinue this treatment on day of surgery. Furthermore, preoperative comorbidity risk factors were more prevalent in cases with high hs-cTnT (>14 ng/l) after surgery as well as in patients with perioperative MI. Notably, almost one in four of the patients with perioperative MI had a negative hs-cTnT in the early postoperative phase, possibly indicating later adverse events during hospitalization. In line with previous findings,[20] most MI's occurred within 48 hours of surgery.

Despite uncertainties regarding BP thresholds, we do know that over 10 of the 200 million adults undergoing major non-cardiac surgery annually will suffer elevation of troponin within 30 days.[30,100] In a randomized control trial of over 8000 patients, 1.4% suffered vascular

death, 0.5% suffered stroke, 0.5% nonfatal cardiac arrest and 5.7% suffered myocardial injury in the first 30 postoperative days.[101] Most researchers have focused on association between postoperatively elevated biomarkers and adverse outcomes, suggesting a systematic use of biomarkers, such as cardiac troponins, to find patients at risk.

The findings in *study III* confirm published data on the association between hypotension and AKI.[9,11,47,102-104] In a review of 20 studies receiving perioperative hemodynamic optimization indeed were at decreased risk of renal impairment.[105] In a study investigating outcomes of 5,127 patients showed that time spent under different levels of lowered MAP were associated with AKI.[47] However, in that study, patients with baseline MAP <65 were excluded, making it impossible to study the effect of IOH in patients with preoperative normal BP. As mentioned above, a comparable ability to discriminate patients with myocardial or kidney injury using both absolute and relative MAP thresholds was identified. MAP <65 mmHg, or a relative decrease of 20% below baseline, were related to myocardial and kidney injury, with an increased risk at lower absolute thresholds, and prolonged hypotension. Notably, when a IOH definition close to ours was used, MAP below 50% of preoperative values, lasting for 5 minutes, significantly increased the risk for myocardial and kidney injury.[88] In contrast to that study, with a 5.6% AKI incidence, our cohort had five times that. This is likely explained by our cohort being subjected to high risk surgery, where all patients were scheduled for an overnight admission to the postoperative unit. As previously highlighted, a large systematic review, including 91 observational studies, reported an AKI incidence rate of 22.3% (95% CI 19.8 to 25.1).[36]

Since patients with preoperative elevated creatinine were included in the *study III* cohort, in contrast to others studies,[9] the influence of hypotension on patients with pre-existing renal insufficiency could be explored. Interestingly, the findings in *study III* showed that patients with an elevated preoperative creatinine had an elevated risk of perioperative AKI with or without hypotension, whilst the risk among those without a preoperative lowered glomerular filtration rate were more negatively affected of an intraoperative hypotensive event.

As addressed in *methodological considerations*, intraoperative blood loss must be considered both as a potential effect modifying risk factor and a confounder, when the association between intraoperative hypotension and organ injury is evaluated. A sudden substantial bleeding during surgery is most often associated with a period of lower BP readings, before that is corrected with crystalloid fluids, blood transfusion, inotropes, or vasopressors. It may therefore be difficult to distinguish if the increased risk of organ ischemia is because of the fall in BP or if it could be related to the loss of haemoglobin and the reduced capacity of

oxygen transport.[10] In *study III*, there was a strong association between the estimated intraoperative blood loss and AKI in the bivariate analyses but, since we are unable to determine the temporal relationship between the two, our findings cannot contribute to the reasoning above. The addition of this variable to the multivariable model resulted only in a slight attenuation in the relative risk, suggesting there was no significant effect on the association between IOH and perioperative AKI.

The relation between fluid balance and AKI is complex, since fluid overload can be the cause, as in renal compartment syndrome or renal venous congestion,[106] or rather a consequence of a symptomatic AKI when administered (incorrectly) as a treatment of anuria. As for blood loss, we have insufficient data on the timing of fluid administration, to which extent it is given intra- or postoperatively, and can therefore not discuss the relation to the exposure or outcome any further.

CLINICAL PERSPECTIVE

As we are entering an era of individualized medicine,[107,108] where the aim is to optimize clinical decisions about a patient's care by utilizing all available data, the application of baseline individual information on physiological parameters is paramount. Results yielded in this thesis, and in multiple previous studies, show that hypotension intraoperatively matters and that dangerously low levels of hypotension, especially when it comes to patients-at-risk, exist. An elderly person with known hypertension is likely to have higher risk for adverse events at differing thresholds than patients with normal baseline BP. The next important step is to determine if individualized, goal directed anaesthesia can minimise these risks.

This is the first project that describe the incidence and characteristics of perioperative MI among patients undergoing non-cardiac surgery in Sweden. Furthermore, the definition of a hypotensive event as a relative decrease from each patients' individual baseline, rather than an absolute threshold, is unique. As mentioned, previous studies may be limited by the use of specific systolic- or mean blood pressure, which may have underestimated intraoperative hypotension as a risk factor.

MI, myocardial and kidney injury after non-cardiac surgery are clinical realities and have a significant impact on postoperative morbidity and mortality. In patients developing a perioperative – clinically significant – MI, 30-day mortality is increased 5-fold and the risk increase remains; non-fatal perioperative MI-patients have a doubled risk of death within 3 month, and a persistent 37% excess mortality at one year after surgery. Patients developing MI after surgery are at increased risk of other types of complications, such as respiratory failure, pneumonia, wound infection, deep venous thrombosis and confusion. They also have a prolonged postoperative length of stay and more commonly need treatment at the intensive care unit.[21,22,30,81,109] The studies included in this thesis identified IOH as a possible contributor to MI, irrespective of MI type, and associated with myocardial and kidney injury. IOH was equally common among patients with fatal and non-fatal MI, suggesting that IOH is merely a trigger and that the mortality is a result of other risk factors. Overall, four out of five MI's were attributable to a serious IOH in the study population. Perioperative MI is an overall rare condition explaining why these findings have not been identified previously.

Notably, IOH was significantly more frequent in lower risk- than in higher risk-groups, implying more vigilant anaesthesia in comorbid and fragile patients. Importantly, perioperative hemodynamic instability can be prevented in most clinical situations. Adequate intravascular volume and organ perfusion pressure can be maintained through attentive medical treatment using vasoactive drugs, and protocolized hemodynamic algorithms to

guide delivery of intravenous fluids and maximize stroke volume. An increasing number of elderly patients, with cardiovascular risk factors, are undergoing extensive surgery. Avoiding IOH, by an attentive anaesthetic caretaking, during and after surgery, could lower the risk of perioperative MI, as well as other postoperative complications, improving quality of life for these patients and reducing costs for the society. These findings are important, as individualized perioperative medicine moves from bench to bedside and anaesthetic management to minimise hypotension is doable. Large scale clinical trials are needed to confirm if tailored BP targets could reduce risk of organ injury and other adverse events.

Conclusions

- Comorbid patients, undergoing high-risk non-cardiac surgery, are at increased risk of perioperative cardiac morbidity. This high-risk population should be targeted to improve perioperative outcomes.
- Intraoperative hypotension may be an important event contributing to cardiac and kidney injury in the perioperative period. Patients with myocardial injury are possibly at increased risk of developing myocardial infarction.
- Intraoperative hypotension may be a important contributor to clinically significant perioperative MI. The high absolute MI-risk associated with IOH, among a growing population of patients with a high risk-burden undergoing surgery, suggests that increased vigilance of BP control in these patients may be beneficial.
- Prospective studies are desirable, where patients are randomised to having an anesthesiologic procedure with avoidance of intraoperative hypotension. This will enhance our understanding and enable a causal relation to be investigated.

Acknowledgements

My research interest developed in 2013, when an injured skiers thumb, needing surgery, prevented me from working clinically as an anaesthesiologist. Since then, this has been an overall amazing journey and I am deeply grateful to so many people who made it possible.

In particular, I would like to acknowledge the following:

Max, main supervisor and friend. I run out of superlatives when I speak of you; your sharp mind, exuberant energy, visionary enthusiasm is a true inspiration. Your ability to stay cool when it storms is admirable, nothing upsets your opinions, or values, and your loyal support has meant everything to me. There is always time for kind words, encouraging messages, when needed most. I am lucky to have you by my side.

Fredrik Granath, my fantastic co-supervisor. You have the rare and amazing capability of being a complete brilliant statistician who still think as a clinician. Your praiseworthy patience, kindness and generosity with time, and knowledge, have been invaluable to me. Thank you for opening my eyes to the world of statistics!

Anders Sahlen, my Singapore-based co-supervisor, who helped me immensely in my first study. I am still looking forward to that Singapore sling.

Lars Eriksson, **Eddie Weitzberg** and **Anders Oldner**, for creating an exceptional research ambience, for your support and encouragement. It's a great feeling to know that any question can be asked and will be answered with an expert opinion, together with a warm and friendly smile.

Gabriella Bröms, **Anders Ekbom** and **Michael Fored**, for providing an inspirational environment, and an outstanding education, at the Karolinska Intstitute research school in Clinical Epidemiology.

Jonas Blixt, and **Johan Petersson**, for giving me the opportunity to complete this thesis in parallel to clinical work.

David Konrad, Björn Persson and **Caroline Hällsjö** for providing resources and an organization in which research is possible, and encouraged.

Kristina Hambraeus-Jonzon, for recruiting me to Karolinska, and for being an amazingly warm and caring Head of Education at PMI.

Kirsi Dolk, for your sensitivity and consideration that made it possible for me to survive three pregnancies during the combined residency and doctoral student time. And many thanks to **Peter Sigurjónson**, **Maria Nilsson**, **Linda Rydén** and **Daniel Ringby** for your tireless work in creating the best possible time schedule for us all.

Malin Jonsson Fagerlund, for your support in 2016, when I was very close to abandon it all.

Eva Selldén, for introducing me to perioperative care and encouraging me to initiate this project.

Anil Gupta, for your kindness and genuine support, for choosing the chair next to me at a conference when I felt very lonely.

Johan Mårtensson, for introducing me to the world of STATA, even though my initial scepticism was evident, it very soon changed to true enthusiasm.

To the fantastic secretaries at PMI; **Magdalena Brohmée**, **Marie Stenbeck** and **Noomi Forsberg**, without you the organization would collapse.

Sofia Petersson at FyFa, for keeping everything organised, for your availability and help with the billions of questions, registrations, forms and papers.

Anna Milton, my dear, intelligent and thoughtful friend, who has been by my side all the way from high school in Uppsala. Many years ago, over a coffee, you inspired me to choose medical school, after graduation, you advised me to start as an anaesthesiologist and, then, when you registered as a PhD student, and applied to the research school, I did likewise. You are my leading star, thank you for always being genuinely supportive.

To all colleagues at PMI, it is an honour to be a part of what we do and a fantastic feeling to work among so many super-competent people. **Mads**, **Ida-Maria**, **Anna Sundelin**, I am looking forward to the days to come, when we have time for a coffee and croissant at Vetekatten.

Malin Rundgren, for your warmth and generosity, for taking valuable time to help me when I arrived in Lund. For letting me use your room, your computer, if it had not been for your pragmatic approach to things, the data collection would still be ongoing… And thank you, **Andreas Hvarfner**, for the introduction.

Our colleagues in Lund, Malin's room-mates in particular, for giving me a friendly welcome, for your cheering support and deliberating small talks when I was fed up with numbers and data trouble.

To my beloved **mum**, I cannot believe that ten years have passed. There hasn't been a single day when I haven't a thought of you. I wish you were here.

To my dad, **Johan**, for your love and inspiration, for opening my eyes to world of research when I was a teenager.

To my dear brothers, **Mathias** and **Elias**. And to my beloved sister, **Siri**, for always, patiently, listing to my thoughts of the intricacies of life and for being a lovely aunt to my children. You are the best!

My wonderful family, I am so unbelievably fortunate to be a part of you. **Calle,** your patience and loyal support, your ability to always choose the bright side is admirable. **Alva**, **Elis**, **Edvin**. You are the reason I wake up every morning with a smile inside. You are miracles. My love for you is endless.

This research has received funding from the Swedish Heart-Lung Foundation, and Swedish National Quality Registries, SKL.

Finally, I would like to express my deepest gratitude to patients undergoing surgery, who are anonymously represented in every number, every calculation and interpretation, and I sincerely hope that this thesis may contribute to improving future perioperative care.

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