Monitoring of myocardial injury after noncardiac surgery

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Colophon

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Monitoring of myocardial injury after noncardiac surgery

Monitoring van myocardschade na niet-cardiale chirurgie

(met een samenvatting in het Nederlands)

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Contents

Chapter 1

Introduction

Introduction

This chapter will give some background information about myocardial infarction and myocardial injury in the non-perioperative setting, about myocardial injury and infarction after noncardiac surgery, and about postoperative monitoring of these entities. Finally, it describes the objectives and outline of this thesis.

Myocardial infarction

Coronary heart disease, including myocardial infarction (MI), is one of the most important causes of morbidity and mortality in Western countries.[1,2]with a particular focus on coronary heart disease (CHD The overall prevalence of MI is estimated at 2.8%, and is >10% in men above 65 years of age.[3]

MI is defined as myocardial cell death due to prolonged ischemia.[4] After the onset of ischemia, it takes about 30-40 minutes before myocardial cells undergo structural cell changes and several hours before complete necrosis occurs.[5] MI is classified into five distinct types, based on different etiological mechanisms, clinical characteristics and treatment strategies:[4]

- Spontaneous MI (type 1): this is caused by intraluminal thrombus formation in a coronary artery due to rupture, ulceration, fissuring, erosion or dissection of an atherosclerotic plaque, leading to ischemia by decreased myocardial blood flow and/or distal platelet emboli. Most patients have underlying severe coronary artery disease, but it may also occur in absence of obstructive coronary artery disease.
- MI secondary to an ischemic imbalance (type 2): this is caused by an imbalance between myocardial oxygen supply and demand due to a condition other than coronary artery disease, such as coronary vasospasm, endothelial dysfunction, coronary embolism, arhythmias, anaemia, respiratory failure, hypotension, hypertension and left ventricular hypertrophy.
- Cardiac death due to MI (type 3): this is diagnosed in patients with symptoms and electrocardiographic (ECG) changes suggestive of myocardial ischemia, but in whom death occurs before elevated biomarkers can be identified. In fact, these patients may have suffered from one of the other MI types.
- MI associated with coronary revascularization (MI types 4 and 5): this is caused by instrumentation of the myocardium during percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), or by stent thrombosis and restenosis after PCI.

MI is diagnosed when a rise and/or fall of cardiac biomarker values with at least one value above the upper reference limit is detected, and with at least one of the following: symptoms of ischemia (e.g. angina pectoris), new ECG changes suggestive of ischemia (i.e. ST-segment or T-wave changes or new left bundle branch block), development of pathological Q waves in the ECG, imaging evidence of new loss of viable myocardium or new regional wal lotion abnormalities, or identification of an intracoronary thrombus by angiography or autopsy.[4] A rising and/or falling pattern in cardiac biomarkers is required to distinguish chronic elevated biomarker levels, e.g. in patients with chronic heart failure, from elevations caused by myocardial infarction.[6]

Myocardial injury

Injury to myocardial cells leads to release of structural proteins from the myocardium, some of which may be measured in the blood as cardiac biomarkers, including phosphocreatine kinase MB (CKMB), cardiac troponin I (TnI) and cardiac troponin C (TnT).[7]

When elevated levels of such biomarkers are detected, this is considered evidence of injury of myocardial cells. Release of myocardial proteins may result from cell death caused by ischemia, but also from normal turnover of myocardial cells, apoptosis, cellular release of troponin degradation products, increased cellular wall permeability, and release of membranous vesicles.[8] Unlike other cardiac biomarkers, troponin may be released in reversible myocardial injury that does not lead to necrosis.[9,10] Hence, myocardial injury as detected by cardiac biomarkers is not always myocardial infarction. Several other pathologic conditions than myocardial infarction may be accompanied by myocardial injury, e.g. heart failure, renal failure, myocarditis, arrhythmias, pulmonary embolism, cardiac contusion, stress cardiomyopathy, and sepsis.[11–13] Myocardial injury also occur in healthy patients undergoing strenuous exercise.[14] Only when the myocardial injury is the result of ischemia, it is designated as MI.[4]

Myocardial infarction after noncardiac surgery

MI that occurs after a surgical procedure, either a cardiac or noncardiac procedure, is designated as postoperative myocardial infarction (POMI).[4,15] It is an important complication after noncardiac procedures that is associated with a poor prognosis.[16] The incidence of POMI in patients undergoing intermediate- to high risk surgery is estimated at 3-5%.[17,18] As it is estimated that about 200 million patients undergo major noncardiac surgery each year, about 3 million patients suffer from POMI.[19,20]described their distribution, and assessed the importance of surgical care in global public-health policy. Methods: We gat-

hered demographic, health, and economic data for 192 member states of WHO. Data for the rate of surgery were sought from several sources including governmental agencies, statistical and epidemiological organisations, published studies, and individuals involved in surgical policy initiatives. We also obtained per-head total expenditure on health from analyses done in 2004. Major surgery was defined as any intervention occurring in a hospital operating theatre involving the incision, excision, manipulation, or suturing of tissue, usually requiring regional or general anaesthesia or sedation. We created a model to estimate rates of major surgery for countries for which such data were unavailable, then used demographic information to calculate the total worldwide volume of surgery. Findings: We obtained surgical data for 56 (29% Patients suffering from POMI have a markedly increased risk of mortality within 30 days after surgery.[16] A problem in the diagnosis of POMI is that most of the patients with POMI do not experience any symptoms.[18] Typical symptoms such as chest pain or discomfort may be masked by postoperative analgesics and distracting pain from the surgical wound. Moreover, symptoms such as nausea, dyspnea and fatigue that may be caused by myocardial ischemia may be easily interpreted as resulting from other common postoperative problems such as atelectasis, pneumonia, hypovolemia, bleeding, or medication side effects.[21] Consequently, in many patients POMI is not recognized and not treated.[18] Importantly, patients who do not experience any symptoms of ischemia carry the same risk of mortality as patients with ischemic symptoms.[16] In contrast with non-perioperative MI, POMI is suspected to be caused mainly through an imbalance of myocardial oxygen supply and demand, i.e. type 2 MI. Several common perioperative factors that are the result of a stress respons to surgery, may contribute to this imbalance, including tachycardia, anaemia, hypovolemia, hypotension and hypertension.[15]

Postoperative monitoring of myocardial injury and infarction

In the postoperative phase, cardiac troponin is the preferred biomarker to diagnose POMI because it is highly specific for the myocardium, whereas CKMB may be released from skeletal muscle due to surgical trauma.[22,23]24 and 48 h after surgery. The CK/CK-MB ratio was measured where cTnI was detectable. RESULTS: Some 14 of 24 emergency and ten of 35 elective patients had detectable cTnI (greater than 0.5 ng/ml

In 1994, Adams and colleagues were the first to describe the role of troponin in the diagnosis of POMI. They obtained troponin measurements before surgery and every 6 hours for at least 36 hours after surgery, and pre- and postoperative ECGs and echocardiograms. They concluded that measurement of troponin was an accurate method to confirm or exclude the diagnosis of perioperative cardiac injury, and that its use should be simpler and more cost effective than the routine use of echocardiography.[24]

After that, several authors have studied the use of troponin in the perioperative phase, and found that troponin was an independent predictor of mortality.[25] Because of the difficulties in recognizing POMI and the excellent prognostic value of troponin, several experts advocated to monitor cardiac biomarkers routinely after noncardiac surgery, in order to better risk stratify and manage patients at risk for POMI.[21,25–29]

Therefore in January 2011, routine troponin monitoring and subsequent cardiology consultation was implemented in the University Medical Center Utrecht in patients above 60 years of age undergoing intermediate- to high risk surgery, as part of the postoperative care protocol. However by that time, evidence of a beneficial effect of troponin monitoring was lacking, as its effect was not yet evaluated.[30,31]

Cardiac troponin

Troponin is a protein that is part of the cardiac muscle contractile apparatus. The subunits troponin I, C, and T form a complex that regulates the calcium-modulated interaction of actin and myosin in order to enable muscle contraction. As described above, troponin may be released into the blood when myocardial cells are injured. Serum elevations of TnI and TnT are highly specific for myocardial injury.[24,32]

Since the introduction of the first analytical assay to measure troponin, assays have become more and more sensitive. Currently, contemporary sensitive and high-sensitive troponin assays are being used.[33] With increasing sensitivity, assays are capable of detecting smaller amounts of troponin. Consequently, nowadays troponin levels far below the upper reference limit may be detected. The upper reference limit is defined as the 99th percentile of a healthy population with a coefficient of variation <10%, and may therefore vary among assays.[4,33] In this thesis, a contemporary sensitive TnI assay was used with an upper reference limit of 60 ng/L (= 0.06 mcg/L).[34,35]the UniCel Dxl 800 and the Access 2 (Beckman Coulter

Objectives

The objectives of this thesis were 1) to evaluate the effect of routine troponin monitoring after noncardiac surgery, 2) to explore determinants of myocardial injury, and 3) to define patient selection criteria for routine troponin monitoring.

Outline of the thesis

Part I, Chapters 2 and 3, describes the prognostic relevance of routine troponin monitoring to predict mortality after noncardiac surgery. As myocardial injury as measured by troponin elevation was found to be an independent predictor of mortality, in **Chapter 3** the causes of death in patients with myocardial injury are reported. Furthermore, in this chapter the effect of troponin monitoring in term of cardiology consultations and cardiac interventions is described. Because the kinetics of troponin were considered important in the evaluation of myocardial injury, **Chapter 4** describes the prognostic relevance of postoperative troponin kinetics.

Part II is about determinants of myocardial injury: **Chapter 5** describes the association between intraoperative hypotension and myocardial injury, and **Chapter 6** reports the prevalence of coronary artery disease and incidence of pulmonary embolism in patients with myocardial injury.

Part III, Chapter 7, describes selection criteria for patients with the highest risk of POMI, who may benefit from troponin monitoring.

Part IV, Chapter 8, discusses the findings from the previous chapters in a broader context, as well as the future role of troponin monitoring.

References

1. Yeh RW, Sidney S, Chandra M, Sorel M, Selby J V, Go AS: Population Trends in the Incidence and Outcomes of Acute Myocardial Infarction. N. Engl. J. Med. 2010; 362:2155–65
2. Nichols M, Townsend N, Scarborough P, Rayner M: Cardiovascular disease in Europe 2014: epidemiological update. Eur. Heart J. 2015; 36:2696–705
3. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Ferranti S De, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, et al.: Heart disease and stroke statistics-2015 update : A report from the American Heart Association. 2015
4. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand J-P, Menasché P, Ravkilde J, Ohman EM, Antman EM, et al.: Third universal definition of myocardial infarction. Circulation 2012; 126:2020–35
5. Jennings RB, Ganote CE: Structural changes in myocardium during acute ischemia. Circ. Res. 1974; 35:III – 156 – III – 172
6. Jaffe AS: How Low Can You Go if You Can See the Rise? J. Am. Coll. Cardiol. 2006; 48:9–10
7. Park JP, Park MK, Yun JW: Proteomic biomarkers for diagnosis in acute myocardial infarction. Biomarkers 2011; 16:1–11
8. White HD: Pathobiology of troponin elevations. J. Am. Coll. Cardiol. 2011; 57:2406–8
9. Baig MA, Ali S, Khan MU, Rasheed J, Qadir A, Vasavada BC, Khan IA: Cardiac troponin I release in non-ischemic reversible myocardial injury from parvovirus B19 myocarditis. Int. J. Cardiol. 2006; 113:109–10
10. Mather AN, Fairbairn TA, Artis NJ, Greenwood JP, Plein S: Relationship of cardiac biomarkers and reversible and irreversible myocardial injury following acute myocardial infarction as determined by cardiovascular magnetic resonance. Int. J. Cardiol. 2013; 166:458–64
11. Jaffe AS, Ravkilde J, Roberts R, Naslund U, Apple FS, Galvani M, Katus H: It's Time for a Change to a Troponin Standard. Circulation 2000; 102:1216–20
12. Roongsritong C, Warraich I, Bradley C: Common causes of troponin elevations in the absence of acute myocardial infarction: Incidence and clinical significance. Chest 2004; 125:1877–84
13. Jeremias A, Gibson CM: Review Narrative Review : Alternative Causes for Elevated Cardiac Troponin. Ann. Intern. Med. 2008:1024–30
14. Gresslien T, Agewall S: Troponin and exercise. Int. J. Cardiol. 2016; 221:609–21
15. Landesberg G, Beattie WS, Mosseri M, Jaffe AS, Alpert JS: Perioperative myocardial infarction. Circulation 2009; 119:2936–44
16. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Málaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P: Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008; 371:1839–47

17. Devereaux PJ, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, Leslie K, Purnima R-M: Characteristics and Short-Term Prognosis of Perioperative Myocardial Infarction in Patients Undergoing Noncardiac Surgery. Ann. Intern. Med. 2011; 154:523–8

18. The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Writing Group: Myocardial Injury after Noncardiac Surgery: A Large, International, Prospective Cohort Study Establishing Diagnostic Criteria, Characteristics, Predictors, and 30-day Outcomes. Anesthesiology 2014; 120:564–78

19. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, Gawande AA: An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet 2008; 372:139–44

20. Longo DL, Devereaux PJ, Sessler DI: Cardiac Complications in Patients Undergoing Major Noncardiac Surgery. N. Engl. J. Med. 2015; 373:2258–69

21. Devereaux PJ, Goldman L, Yusuf S, Gilbert K, Leslie K, Guyatt GH: Surveillance and prevention of major perioperative ischemic cardiac events in patients undergoing noncardiac surgery: a review. CMAJ 2005; 173:779–88

22. Haggart PC, Adam DJ, Ludman PF, Bradbury AW: Comparison of cardiac troponin I and creatine kinase ratios in the detection of myocardial injury after aortic surgery. Br J Surg 2001; 88:1196–200

23. Jules-Elysee K, Urban MK, Urquhart B, Milman S: Troponin I as a diagnostic marker of a perioperative myocardial infarction in the orthopedic population. J. Clin. Anesth. 2001; 13:556–60

24. Adams JE, Bodor GS, Dávila-Román VG, Delmez JA, Apple FS, Ladenson JH, Jaffe AS: Cardiac troponin I. A marker with high specificity for cardiac injury. Circulation 1993; 88:101–6

25. Levy MM, Heels-Ansdell D, Hiralal R, Bhandari M, Guyatt G, Yusuf S, Cook D: Prognostic Value of Troponin and Creatine Kinase Muscle and Brain Isoenzyme Measurement after Noncardiac Surgery. Anesthesiology 2011; 114:796–806

26. Oscarsson A, Eintrei C, Anskär S, Engdahl O, Fagerström L, Blomqvist P, Fredriksson M, Swahn E: Troponin T-values provide long-term prognosis in elderly patients undergoing non-cardiac surgery. Acta Anaesthesiol. Scand. 2004; 48:1071–9

27. Kim LJ, Martinez EA, Faraday N, Dorman T, Fleisher LA, Perler BA, Williams GM, Chan D, Pronovost PJ: Cardiac Troponin I Predicts Short-Term Mortality in Vascular Surgery Patients. Circulation 2002; 106:2366–71

28. Gandhi R, Petruccelli D, Devereaux PJ, Adili A, Hubmann M, Beer J de: Incidence and timing of myocardial infarction after total joint arthroplasty. J. Arthroplasty 2006; 21:874–7

29. Martinez EA, Nass CM, Jermyn RM, Rosenbaum SH, Akhtar S, Chan DW, Malkus H, Weiss JL, Fleisher LA: Intermittent Cardiac Troponin-I Screening is an Effective Means of Surveillance for a Perioperative Myocardial Infarction. J. Cardiothorac. Vasc. Anesth. 2005; 19:577–82

30. Archan S, Fleisher LA: From creatine kinase-MB to troponin: the adoption of a new standard. Anesthesiology 2010; 112:1005–12

31. Muehlschlegel JD: If a troponin falls in a forest but no one measures it, does it really matter? Anesthesiology 2011; 114:732–3

32. Jaffe AS, Babuin L, Apple FS: Biomarkers in Acute Cardiac Disease. The Present and the Future. J. Am. Coll. Cardiol. 2006; 48:1–11

33. Apple FS, Ler R, Murakami MM: Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population. Clin. Chem. 2012; 58:1574–81

34. Zaninotto M, Mion MM, Novello E, Moretti M, Delprete E, Rocchi MB, Sisti D, Plebani M: Precision performance at low levels and 99th percentile concentration of the Access AccuTnI assay on two different platforms. Clin. Chem. Lab. Med. 2009; 47:367–71

35. Moretti M, Pieretti B, Sisti D, Rocchi M, Gasperoni S: Analytical performance and clinical decision limit of a new release for cardiac troponin I assay. Ann. Clin. Biochem. 2015; 52:169–72

cTnI
78/54
MMHG
cTnI
cTnI
90/65
mmHg
cTnI
cTnI
type 1 MI
type 2 MI
/65
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mmol/l
ischemia
Hb 5.7
78/54
MMHG
cTnI
cTnI
cTnI
type 1 MI
cTnI
HR 96 bpm
85/40
mmHg
90/65
mmHg
78/54
mmHg
cTnI

PART I

PROGNOSTIC RELEVANCE AND CLINICAL EFFECTS OF MONITORING OF MYOCARDIAL INJURY AFTER NONCARDIAC SURGERY

Chapter 2

Myocardial injury after noncardiac surgery and its association with short-term mortality

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Abstract

Background

To identify patients at risk for postoperative myocardial injury and death, it has been suggested to measure cardiac troponin routinely after noncardiac surgery. Such monitoring was implemented in our hospital. The aim of this study was to determine the predictive value of postoperative myocardial injury, as measured by troponin elevation, on 30 day mortality after noncardiac surgery.

Methods and results

This observational single center cohort study included 2,232 consecutive intermediate to high risk noncardiac surgery patients aged 60 and above operated in 2011. Troponin was measured on the first three postoperative days. Log binomial regression analysis was used to estimate the association between postoperative myocardial injury (troponin I level >0.06 mcg/L) and all-cause 30-day mortality.

Myocardial injury was found in 315 of 1627 patients in whom troponin I was measured (19%). All-cause death occurred in 56 (3%) patients. The relative risk of a minor increase in troponin (0.07-0.59 mcg/L) was 2.4 (95% CI 1.3-4.2, p<0.01), and the relative risk of a 10-100 fold increase in troponin (≥0.60mcg/L) was 4.2 (95% CI 2.1-8.6, p<0.01). A myocardial infarction according to the universal definition was diagnosed in 10 patients (0.6%), of which one (0.06%) had ST-elevation myocardial infarction.

Conclusion

Postoperative myocardial injury is an independent predictor of 30-day mortality after noncardiac surgery. Implementation of postoperative troponin monitoring as standard of care is feasible and might be helpful to improve the prognosis of patients undergoing noncardiac surgery.

Introduction

Perioperative adverse cardiovascular events are the leading cause of morbidity and mortality after noncardiac surgery.[1] Despite efforts to prevent the occurrence of such events,[2,3] the incidence of postoperative myocardial infarction (POMI) after noncardiac surgery is still high and varies depending on the definition used.[4,5] Using the latest universal definition of myocardial infarction in a large cohort of patients undergoing noncardiac surgery, the incidence of POMI was as high as 5%.[4,5,6] Because symptoms such as chest pain are easily masked by adequate postoperative pain management including opioids, the clinical course of POMI is mainly silent [6]. As a result, POMI is recognized late or not recognized at all, but remains strongly associated with mortality. [1,6-9] The mortality rate in patients with asymptomatic POMI is similar to that of patients who experience ischemic symptoms.[6] Moreover, even patients with minor elevations of troponin after surgery, without any symptoms of ischemia or signs of myocardial infarction, seem to have a comparably high risk of cardiovascular complications and death. [6,10-13]

Although the pathophysiology of such isolated postoperative troponin elevation is not yet fully understood,[1,14] a meta-analysis of studies in predominantly high risk surgery patients showed that isolated troponin elevation was a strong independent predictor of mortality within the first year after surgery.[10] Of note, troponin elevation was associated with a six fold increase in mortality.[10] In addition, the recently published VISION study including over 15,000 surgical patients showed a strong association between peak troponin levels after surgery and 30 day mortality.[11] Time to death after the peak troponin values was reported to vary between one and two weeks, potentially allowing for interventions to alter a patients risk of death.[11] The accumulating evidence from VISION and other studies, suggests that implementation of postoperative troponin monitoring as care as usual in patients undergoing noncardiac surgery might be useful for better risk stratification and management of patients.[6,10-13]

Therefore, we implemented routine troponin measurement monitoring on the first three days after surgery as part of our standard postoperative care in patients aged 60 or above undergoing all types of intermediate to high risk noncardiac surgery. We hypothesized that the results of this routine monitoring would improve risk stratification of patients at risk for early postoperative death. The aim of the present study therefore was to determine the predictive value of postoperative troponin elevation as a marker of myocardial injury on 30 day mortality after noncardiac surgery.

Methods

Patients

This observational cohort study included consecutive patients undergoing noncardiac surgery between January 3rd and December 15th 2011 at the University Medical Center Utrecht, The Netherlands, a 1,000 bed tertiary referral hospital. Patients were eligible if they were aged 60 years or older, were undergoing intermediate to high risk noncardiac surgery under general or spinal anesthesia and had an expected postoperative length of hospital stay of at least 24 hours. For patients who underwent surgery more than once during the study period, the first surgery was included in the analyses for all patients. A reoperation was included as a novel case if this surgery took place during another hospital admission and at least 30 days after the first surgery. Patients were excluded if they were lost to follow-up within 30 days after surgery.

The local medical ethics committee approved the study protocol. The need for informed consent was waived, as only routinely collected patient data were used and data were anonymized before analysis (UMC Utrecht Medical Research Ethics Committee 11-120/C).

Data collection

All preoperative and postoperative data were obtained from electronic medical and administrative records. Data collected in all patients included patient characteristics, preoperative physical status, comorbidities and death within 30 days. In those patients with postoperative TnI measurements, TnI levels were collected. Additionally, data on postoperative symptoms, ECG changes, the incidence of POMI and the treatment initiated by the consultant cardiologist were collected in those patients who had a cardiology consultation. The unique hospital patient identifier was used to merge databases. For data on 30-day mortality the municipal personal records database was consulted.

Troponin measurements

According to the hospital protocol, cardiac troponin I (TnI) measurements were ordered for the first three days after surgery by the attending anesthesiologist immediately after completing the case in the operating room. In case of a TnI elevation above the clinical cut-off level during the first three days after surgery, the ward physician was notified. As the optimal treatment of patients with postoperative troponin elevation is not yet known and obviously has to be interpreted in consistency with a patient's clinical course, it was left at the discretion of the treating physician whether further diagnostic procedures including an ECG or a consultation of the cardiologist was indicated in individual patients. In this, troponin elevation was considered simply as a marker for myocardial injury, warranting for additional attention.

In this study, myocardial injury was defined as a TnI > 0.06mcg/L, which was the lowest value measurable with a 10% coefficient of variation above the 99th percentile of 0.04mcg/L of the assay used.[15] TnI was analyzed using the third-generation enhanced AccuTnI assay (Beckman Coulter, Brea, California). For each patient, the highest value of all routine TnI measurements was used in the analysis.

Outcomes

The primary outcome was defined as all-cause mortality within 30 days after surgery. Secondary outcomes included the incidence of POMI and length of hospital stay. Myocardial infarction was defined according to the universal definition.[15]

Statistical analysis

The analysis was performed by using SPSS (release 20.0 for Windows). In advance of data analysis we were aware that TnI results would not be available in all patients, as adherence to a new protocol in daily clinical practice takes time. Therefore, we compared baseline characteristics and the incidence of death in patients in whom TnI was measured to those in whom it was not, in order to determine whether the missing TnI measurements could be considered as missing at random. To check whether excluding the missing values from the analysis influenced the association between postoperative myocardial injury and death, we repeated the multivariable regression analysis after multiple imputations of the missing TnI values. Five datasets were imputed using the method of fully conditional specification. The baseline characteristics were used as predictors of the TnI values. In the primary analysis, we first looked at the distribution of the first TnI elevation over the postoperative days. Second, the primary outcome and the incidence of POMI were compared for patients with and without myocardial injury using the Chi-square test, and relative risks (RR) with 95% confidence intervals were calculated. In this, TnI was included both as a continuous as well as a categorical variable. In the latter, TnI was categorized into four groups on a logarithmic scale: TnI ≤0.06, 0.07-0.59, 0.60-5.99, ≥6.00 mcg/L. The median time to death was calculated, and the median length of stay in the hospital of both groups was compared using the Mann-Whitney test. Kaplan-Meier survival analysis was used to determine the survival of patients in each category of TnI elevation. Subsequently, a log binomial multivariable regression model was developed to adjust the association between myocardial injury and death for preoperative variables known to predict postoperative cardiovascular events.[16] We used log binomial regression analysis to facilitate presenting effect measures as relative risks. In this we used model-based covariance estimates. The model included TnI and age, sex, emergency surgery and renal failure (preoperative glomerular filtration rate <50ml/h). [16] Emergency surgery was defined as surgery required within 72 hours. Because the number of patients with a TnI level >6.00mcg/L was considered too small to obtain relevant results, in this

analysis the two upper TnI categories were merged into one (i.e. with TnI ≥0.60mcg/L). We compared the predictive value of a model with only preoperative variables to a model in which TnI was added to these variables using the area under the receiver operating characteristic curve (AUROC) and integrated discrimination improvement (IDI) analysis. We preferred the latter method over using the net reclassification improvement (NRI) because it does not require (arbitrary) classification of the mortality risk.[17]

Results

In total 2,232 patients were eligible for inclusion. Sixteen patients (0.7%) were lost to follow-up and excluded from the analysis: three patients were transferred to another hospital on the day of surgery, six patients died on the day of surgery (i.e. TnI could not be measured in these patients) and in seven patients mortality data could not be obtained as they were not known by the municipal personal records database. Baseline characteristics of the 2,216 remaining patients are given in Table 2.1.

TnI was measured in 1627 (73.4%) patients. It was measured consecutively on all three postoperative days in 907 (55.7%) patients and elevated at least once in 315 (19.4%) patients. Within the group of patients with myocardial injury, the first elevated TnI was found on the first postoperative day in 162 (51.4%) patients (Figure 2.1). Stratification of the patients into decades of age showed that the incidence of postoperative myocardial injury increased with age (Figure 2.2).

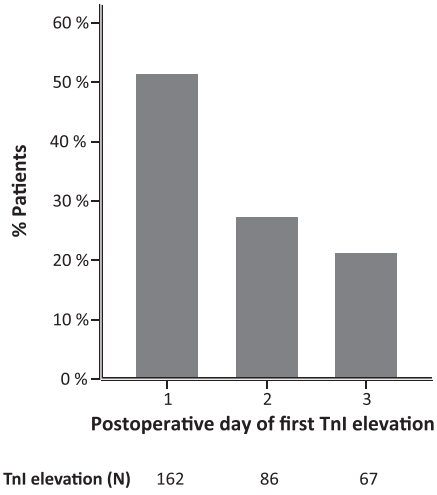

Figure 2.1
Distribution of the first troponin elevations over the first three postoperative days.

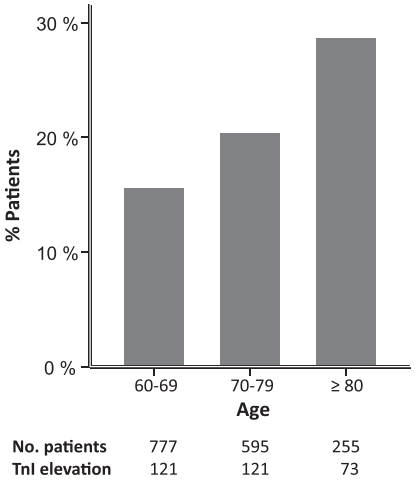

Figure 2.2
Distribution of myocardial injury over age.

Table 2.1 *Baseline characteristics.*

	Troponin measured N=1627		Troponin not measured N=589		p-value
Male	844	(51.9)	303	(51.4)	0.86
Mean age (SD*)	71.0	(7.7)	70.2	(7.4)	0.02
RCRI† factors					
High risk surgery	501	(30.8)	120	(20.4)	<0.01
History of ischemic heart disease	264	(16.2)	80	(13.6)	0.13
History of heart failure	35	(2.2)	16	(2.7)	0.43
History of cerebrovascular disease	242	(14.9)	88	(14.9)	0.97
Renal failure	166	(10.2)	68	(11.5)	0.36
Preoperative insulin use	92	(5.7)	35	(5.9)	0.80
Smoking‡	286	(18.2)	97	(17.4)	0.68
Hypertension	829	(51.0)	291	(49.4)	0.52
Diabetes	288	(17.7)	106	(18.0)	0.87
COPD	167	(10.3)	48	(8.1)	0.14
Peripheral vascular disease	180	(11.1)	46	(7.8)	0.03
ASA class§					
1	197	(12.1)	89	(15.1)	0.06
2	1043	(64.1)	357	(60.6)	0.13
3	366	(22.5)	141	(23.9)	0.48
4	21	(1.3)	2	(0.3)	0.05
General anesthesia	1514	(93.1)	537	(91.2)	0.14
Emergency surgery	306	(18.8)	157	(26.7)	<0.01
Re-operation within 30 days	163	(10.0)	49	(8.3)	0.23
Surgical specialty					
General	369	(22.7)	113	(19.2)	0.08
Neuro	355	(21.8)	123	(20.9)	0.64
Vascular	255	(15.7)	76	(12.9)	0.11
ENT|| and dental	206	(12.7)	76	(12.9)	0.88
Orthopedic	193	(11.9)	96	(16.3)	<0.01
Gynaecology	128	(7.9)	46	(7.8)	0.97
Urologic	84	(5.2)	36	(6.1)	0.38
Plastic	37	(2.3)	23	(3.9)	0.04

Figures are numbers of patients (%), unless indicated otherwise.
** Standard Deviation; † Revised Cardiac Risk Index; ‡ N=1568 and 556 respectively, due to some missing values for smoking status; § Physical status classification by the American Society of Anesthesiologists; \|\| Ear Nose Throat*

Postoperative myocardial injury was associated with an increased risk of death. Twenty-seven of the 315 patients (8.6%, 95% CI: 6.0-12.2%) with myocardial injury died within 30 days, compared to 29 of the 1,312 patients (2.2%, 95% CI: 1.5-3.2%) with normal TnI levels ($p<0.01$). The median time to death after TnI elevation was 12 days (interquartile rage 13). Patient characteristics of the three categories of troponin elevation are given in Table 2.2.

Table 2.2 *Baseline characteristics of patients in each category of troponin elevation.*

	Troponin ≤ 0.06 mcg/L N=1312		Troponin 0.07-0.59 mcg/L N=258		Troponin ≥ 0.60 mcg/L N=57		p-value
Male	660	(50.3)	148	(57.4)	36	(63.2)	0.03
Mean age (SD*)	70.6	(7.5)	72.7	(8.0)	73.1	(8.8)	<0.01
RCRI† factors							
High risk surgery	372	(28.4)	103	(39.9)	26	(45.6)	<0.01
History of ischemic heart disease	192	(14.6)	53	(20.5)	19	(33.3)	<0.01
History of heart failure	21	(1.6)	11	(4.3)	3	(5.3)	<0.01
History of cerebrovascular disease	182	(13.9)	47	(18.2)	13	(22.8)	0.05
Renal failure	104	(7.9)	39	(15.1)	23	(40.4)	<0.01
Preoperative insulin use	66	(5.0)	18	(7.0)	8	(14.0)	0.01
Smoking‡	226	(17.8)	50	(20.4)	10	(19.2)	0.61
Hypertension	649	(49.5)	148	(57.4)	32	(56.1)	0.05
Diabetes	221	(16.8)	51	(19.8)	16	(28.1)	0.06
COPD	134	(10.2)	28	(10.9)	5	(8.8)	0.89
Peripheral vascular disease	133	(10.1)	35	(13.6)	12	(21.1)	0.01
ASA class§							
1	174	(13.3)	21	(8.1)	2	(3.5)	<0.01
2	858	(65.4)	158	(61.2)	27	(47.4)	0.01
3	270	(20.6)	73	(28.3)	23	(40.4)	<0.01
4	10	(0.8)	6	(2.3)	5	(8.8)	<0.01
General anesthesia	1211	(92.3)	246	(95.3)	57	(100.0)	0.02
Emergency surgery	215	(16.4)	69	(26.7)	22	(38.6)	<0.01
Re-operation within 30 days	112	(8.5)	39	(15.1)	12	(21.1)	<0.01
Surgical specialty							
General	276	(21.0)	79	(30.6)	14	(24.6)	<0.01
Neuro	302	(23.0)	44	(17.1)	9	(15.8)	0.06
Vascular	186	(14.2)	47	(18.2)	22	(38.6)	<0.01
ENT|| and dental	169	(12.9)	33	(12.8)	4	(7.0)	0.43
Orthopedic	154	(11.7)	33	(12.8)	6	(10.5)	0.85
Gynaecology	116	(8.8)	10	(3.9)	2	(3.5)	0.01
Urologic	73	(5.6)	11	(4.3)	0	(0)	0.14
Plastic	36	(2.7)	1	(0.4)	0	(0)	0.03

Figures are numbers of patients (%), unless indicated otherwise.
** Standard Deviation; † Revised Cardiac Risk Index; ‡ N=1271, N=245 and N=52 respectively, due to some missing values for smoking status; § Physical status classification by the American Society of Anesthesiologists; || Ear Nose Throat*

The unadjusted relative risk of death was 3.0 in case of a minor increase in TnI (0.07-0.59 mcg/L), and 7.9 in case of a 10-fold increase or higher in TnI (≥0.60mcg/L) (Table 2.3).

The survival in each of these categories is shown in Figure 2.3. The analysis including TnI on a continuous scale showed an increase in relative risk for each 0.1mcg/L increase in TnI level (RR 1.003, 95% CI 1.001-1.004).

Table 2.3 Association of postoperative troponin and 30 day mortality, adjusted for age, sex, emergency surgery and preoperative renal failure.

	Unadjusted analysis			Adjusted analysis		
	RR*	95% CI†	p-value	RR*	95% CI†	p-value
Age (per year increase)	1.04	1.01 – 1.07	<0.01	1.01	0.98 – 1.04	0.33
Female sex	1.08	0.64 – 1.80	0.64			
Emergency surgery	5.76	3.44 – 9.63	<0.01	4.46	2.62 – 7.58	<0.01
Renal failure (preoperative)	2.67	1.46 – 4.85	<0.01	1.37	0.74 – 2.53	0.32
Troponin elevation, categorical						
Troponin ≤ 0.06 mcg/L	*ref*			*ref*		
Troponin 0.07-0.59 mcg/L	2.98	1.66 – 5.34	<0.01	2.36	1.31 – 4.22	<0.01
Troponin ≥ 0.60 mcg/L	7.94	4.07 – 15.5	<0.01	4.19	2.06 – 8.55	<0.01

** Relative Risk; † Confidence interval*

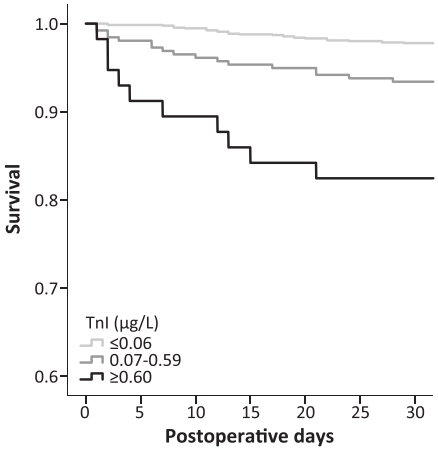

Figure 2.3
Survival curve of each category of TnI elevation.

After adjustment of the association between myocardial injury and death for variables known to predict postoperative cardiovascular events, only emergency surgery and TnI remained significantly related to death within 30 days. The relative risk of death was 2.4 (95% CI 1.3-4.2, p<0.01) in case of a minor increase in TnI (0.07-0.59 mcg/L), and 4.2 (95% CI 2.1-8.6, p<0.01) in case of a 10-fold increase or higher in TnI (≥0.60mcg/L) (Table 2.3). The AUROC of the model with only preoperative predictors was 0.75 (95% CI 0.68-0.83), compared to 0.78 (95% CI 0.71-0.85) of the model in which TnI was added. The integrated discrimination improvement index of the model including TnI was 0.02 (p < 0.001).

The median length of stay in the hospital was 10 days (interquartile range (IQR) 12) in patients with myocardial injury compared to 5 days (IQR 6) in patients without myocardial injury (p <0.01).

Ten of the 315 (3.2%) patients with troponin elevation had typical chest pain and ECG changes suggestive of new ischemia were found in 30 (9.5%) patients. One (0.3%) of these ECGs showed ST elevation (≥1 mm), 14 (4.4%) showed ST depression (≥ 1 mm) and 15 (4.8%) showed minimal ST depression (<1 mm) and/or repolarization changes.

A cardiologist was consulted in 110 of the 315 (34.9%) patients. In most of these 110 patients the clinical course was awaited without any intervention (N=67, 60.9%) and in 43 (39.1%) patients, cardiovascular medication was changed or added (statins and aspirin). Eight (7.3%) patients were transferred to a coronary care unit for continuous ECG monitoring. Coronary angiography was performed in 7 (6.4%) patients, and significant coronary stenoses were found in 6 (5.4%) of these patients. A percutaneous coronary intervention was performed in 4 (3.6%) patients, one (0.9%) patient underwent coronary bypass surgery, and in one other patient (0.9%) a coronary intervention was considered not to be beneficial because of a poor clinical condition.

POMI according to the criteria of the universal definition was diagnosed in 10 of the 1,627 (0.6%) patients. This concerned a non-ST-elevation myocardial infarction (NSTEMI) in 9 patients (0.6%) and a STEMI in one (0.06%) patient. Because the STEMI was considered to have sustained more than six hours coronary angiography was not performed immediately. This patient was initially treated with medication, and percutaneous coronary intervention for a non-significant coronary stenosis was performed in an outpatient setting.

In order to determine whether the missing TnI measurements could be considered as missing at random, patients in whom TnI was measured were compared to those in whom it was not. Death occurred in 56 of the 1,627 (3.4%, 95% CI: 2.7-4.4) patients in whom troponin was measured, compared to 20 of the 589 (3.4%, 95% CI: 2.2-5.2) patients in whom troponin was not measured (p=0.96). After imputation of the missing TnI values, multivariable regression analysis showed a comparable association between postoperative myocardial injury and death (Table 2.4).

Table 2.4 *Association of postoperative troponin and 30 day mortality after multiple imputation of missing troponin values and adjusted for age, sex, emergency surgery and preoperative renal failure.*

	Unadjusted analysis			Adjusted analysis		
	RR*	**95% CI†**	**p-value**	**RR***	**95% CI†**	**p-value**
Age (per year increase)	1.05	1.02 – 1.07	<0.01	1.02	1.00 – 1.05	0.12
Female sex	1.02	0.65 – 1.58	0.94			
Emergency surgery	6.87	4.34 – 10.9	<0.01	5.06	3.09 – 8.25	<0.01
Renal failure (preoperative)	2.63	1.58 – 4.38	<0.01	1.33	0.77 – 2.29	0.30
Troponin elevation, categorical						
Troponin ≤ 0.06 mcg/L	*ref*			*ref*		
Troponin 0.07-0.59 mcg/L	2.98	1.66 – 5.34	<0.01	1.93	1.06 – 3.54	0.03
Troponin ≥ 0.60 mcg/L	7.94	4.07 – 15.5	<0.01	3.47	1.67 – 7.21	<0.01

** Relative Risk; † Confidence interval*

Discussion

This cohort study estimated the incidence of myocardial injury after noncardiac surgery and its predictive value on the risk of death within 30 days, using data from routine postoperative monitoring of troponin. TnI was elevated in 19% of the patients and TnI elevation was an independent predictor of 30-day mortality. This association with the risk of death was dependent on the degree of the TnI elevation (RR between 2.4 and 4.2), but independent of preoperative factors known to be associated with postoperative death.[16] As suggested previously, implementation of postoperative monitoring of troponin as standard of care is feasible and may improve risk stratification and reclassification of patients at risk for early postoperative death, even when daily care clinical protocols are not always followed.

This study is one of the first studies describing the results of the implementation of routine postoperative monitoring of troponin as part of a standard postoperative care protocol. The study has some obvious limitations. First, since we measured TnI only on the first three days after surgery, myocardial injury that may have occurred after that time interval has been missed. However, previous research has shown that myocardial injury mostly occurs within the first three postoperative days.[18-20] Second, TnI was not measured in all patients due to the fact that it takes time to fully implement a new protocol in daily clinical practice. Patients in whom TnI was not measured seemed somewhat healthier at baseline and high risk surgery was less frequent in these patients. In contrast, these patients without TnI measurements underwent more often emergency surgery and reoperations with a higher incidence of death (Table 2.1). This apparent discrepancy of healthier patients who were more likely to die may be explained by the fact that TnI measurements were more often (unintentionally) not ordered after emergency surgery. To check whether these baseline differences resulted in a biased association between myocardial injury and death, we compared the results of the complete case analysis to the results of a sensitivity analysis including all patients after multiple imputations of the missing TnI values. This analysis showed comparable results, indicating that imputation of missing data did not change the association between myocardial injury and short-term death. Third, as we did not measure TnI before surgery, we could not adjust the results for pre-existent TnI elevations. Pre-existent TnI elevations may occur in patients with renal failure or other cardiovascular conditions. The cause of the higher preoperative levels of cardiac biomarkers in these patients is not completely clear, but it is thought to be caused by subclinical cardiac damage from silent myocardial ischemia or microinfarction, mild heart failure, left ventricular hypertrophy, or increased cardiac apoptosis.[21] We hypothesize that patients with a pre-existent TnI elevation may have an additional increase of TnI because of ischemia caused by surgical stress. Although some patients with a preoperative acute coronary syndrome

in whom TnI levels decreased to normal values after surgery may have been missed, we do not expect that this has influenced the obtained results significantly. Moreover, although myocardial injury may already have occurred before surgery in some patients, postoperative troponin elevations may still predict short-term mortality.

The improved risk discrimination of patients with mostly asymptomatic myocardial injury, together with the time interval between TnI elevation and death (median almost two weeks) may potentially allow physicians to modify prognosis. First, we showed that in most patients with postoperative TnI elevation, TnI was only slightly (up to tenfold) to moderately (up to hundredfold) increased, suggesting minor myocardial injury. In addition, only 3.2% of the patients with TnI elevation had typical chest pain and in only 9.5% (minor) ECG changes suggestive for myocardial ischemia were found. Still, these patients with minor myocardial injury had a higher risk of death. This risk seems comparable to the detrimental risk on survival of spontaneous acute coronary syndrome, suggesting a comparable pathophysiological mechanism in patients with isolated troponin elevation after surgery. Given the numerous plaque destabilizing and thrombogenic factors that are present in the perioperative period, troponin elevation may be a consequence of coronary plaque rupture with distal embolization of thrombus or, alternatively, thrombosis of small coronary arteries.[22-27] In these patients further myocardial damage may be prevented by adequate treatment during the time interval between troponin elevation and death. Although many studies have addressed prevention of postoperative myocardial injury and death, a major shortcoming is the insufficiently resolved pathophysiology of such myocardial injury and POMI. [2-6] Myocardial injury may be caused by regional ischemia due to preexistent significant coronary artery disease or plaque rupture with thrombosis (acute coronary syndrome, type 1 MI), or as a consequence of diffuse myocardial ischemia due to an imbalance between myocardial oxygen supply and demand, caused by pre-existent stable coronary stenosis or non-coronary factors such as deep anemia or hemodynamic instability (type 2 MI).[1] The treatment benefits and possible harms in patients with postoperative myocardial injury remain to be evaluated, particularly those harms associated with invasive treatment options. A recent study in which 70 patients with postoperative troponin elevation were randomized to cardiology care consisting of monitoring, investigations and changes to medications, versus standard ward treatment showed no difference in one year mortality.[28] However, this study was performed in a limited number of patients.

The results of our evaluation of the data from routine postoperative monitoring of troponin are comparable to those obtained under research circumstances. Until recently, research was done in smaller cohorts of patients undergoing mainly vascular and other high risk but elective surgical procedures, showing an incidence of postoperative myocardial injury of 8–52%. [4,12,13,29-39] Studies with a follow-up time of 12 months or less found a two- to twentyfold increased mortality risk. Studies including emergen-

cy surgery reported an incidence of 33-53% of postoperative myocardial injury, and four- to twelvefold increased mortality risk.[40,41] We found a similar association in our routine troponin measurement cohort including elective and emergency patients. Like in previous studies, in most patients myocardial injury was found on the first postoperative day.[18-20] The recently published VISION study including over 15,000 patients reported that elevation of troponin T after non-cardiac surgery was strongly associated with 30-day mortality, with adjusted hazard ratio's comparable to the adjusted relative risks of our protocol. The eligibility criteria of this study were comparable to those of our clinical protocol, except for the age criterion above 45 years instead of 60 years in our protocol. Thus, the predictive value of our standard of care postoperative troponin monitoring is markedly concordant with that found in a large cohort of patients included in the VISION study. The VISION investigators demonstrated that clinically relevant troponin thresholds existed below the value that corresponded to a 10% co-efficient of variation of the troponin assay used. We considered the sample size of our study not sufficient to confirm this finding. Nevertheless, the strengths of our study are that it focused on patients at higher age and that patients from a single center were included within a shorter time period. In addition, we made an attempt to validate that the missing data were missing at random by imputation of missing troponin values. Moreover, in our study we used troponin-I as compared to troponin-T in the VISION study. Since troponin-I compared to troponin-T is less influenced by renal dysfunction [42,43], the results from our study may be more representative in patients with renal dysfunction. Finally, the VISION study did not include renal failure in the multivariable analysis, while in our study the association between postoperative myocardial injury and death was adjusted for preexistent renal failure.

We found a strong association between postoperative myocardial injury, as measured by TnI, and death in noncardiac surgery patients. We therefore conclude that patients at risk for early death after noncardiac surgery are easily identified by routine postoperative troponin measurements. The time interval between troponin elevation and death potentially allows physicians to modify prognosis. Obviously, for this purpose the underlying pathophysiological mechanisms of postoperative myocardial injury have to be explored. In addition, it has to be elucidated whether there is a causal relationship between myocardial injury and mortality or whether myocardial injury merely indicates a worse outcome, and next, whether patients with myocardial injury may benefit from postoperative cardiovascular treatment.

References

1. Landesberg G, Beattie WS, Mosseri M, Jaffe AS, Alpert JS. Perioperative myocardial infarction. *Circulation.* 2009;119:2936-44.
2. Lindenauer PK, Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. *N Engl J Med.* 2005;353:349-61.
3. Brady AR, Gibbs JS, Greenhalgh RM, Powell JT, Sydes MR; POBBLE trial investigators. Perioperative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial. *J Vasc Surg.* 2005;41:602-9.
4. Landesberg G, Shatz V, Akopnik I, Wolf YG, Mayer M, Berlatzky Y, Weissman C, Mosseri M. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. *J Am Coll Cardiol.* 2003;42:1547-54.
5. Wu WC, Schifftner TL, Henderson WG, Eaton CB, Poses RM, Uttley G, Sharma SC, Vezeridis M, Khuri SF, Friedmann PD. Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. *JAMA.* 2007;297:2481-8.
6. Devereaux PJ, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, Leslie K, Rao-Melacini P, Chrolavicius S, Yang H, Macdonald C, Avezum A, Lanthier L, Hu W, Yusuf S; POISE (PeriOperative ISchemic Evaluation) Investigators. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. *Ann Intern Med*. 2011;154:523-8.
7. Mangano DT, Browner WS, Hollenberg M, Li J, Tateo IM. Long-term cardiac prognosis following noncardiac surgery. The Study of Perioperative Ischemia Research Group. *JAMA.* 1992;268:233-9.
8. Ashton CM, Petersen NJ, Wray NP, Kiefe CI, Dunn JK, Wu L, Thomas JM. The incidence of perioperative myocardial infarction in men undergoing noncardiac surgery. *Ann Intern Med.* 1993;118:504-10.
9. Badner NH, Knill RL, Brown JE, Novick TV, Gelb AW. Myocardial infarction after noncardiac surgery. *Anesthesiology.* 1998;88:572-8.
10. Levy M, Heels-Ansdell D, Hiralal R, Bhandari M, Guyatt G, Yusuf S, Cook D, Villar JC, McQueen M, McFalls E, Filipovic M, Schünemann H, Sear J, Foex P, Lim W, Landesberg G, Godet G, Poldermans D, Bursi F, Kertai MD, Bhatnagar N, Devereaux PJ. Prognostic value of troponin and creatine kinase muscle and brain isoenzyme measurement after noncardiac surgery: a systematic review and meta-analysis. *Anesthesiology.* 2011;114:796-806.
11. The Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators, Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, Villar JC, Wang CY, Garutti RI, Jacka MJ, Sigamani A, Srinathan S, Biccard BM, Chow CK, Abraham V, Tiboni M, Pettit S, Szczeklik W, Lurati Buse G, Botto F, Guyatt G, Heels-Ansdell D, Sessler DI, Thorlund K, Garg AX, Mrkobrada M, Thomas S, Rodseth RN, Pearse RM, Thabane L, McQueen MJ, VanHelder T, Bhandari M, Bosch J, Kurz A, Polanczyk C, Malaga G, Nagele P, Le Manach Y, Leuwer M, Yusuf S. Association Between Postoperative Troponin Levels and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. *JAMA.* 2012;307:2295-2304.
12. Kim LJ, Martinez EA, Faraday N, Dorman T, Fleisher LA, Perler BA, Williams GM, Chan D, Pronovost PJ. Cardiac troponin I predicts short-term mortality in vascular surgery patients. *Circulatio.n* 2002;106:2366-71.

13. Oscarsson A, Eintrei C, Anskär S, Engdahl O, Fagerström L, Blomqvist P, Fredriksson M, Swahn E. Troponin T-values provide long-term prognosis in elderly patients undergoing non-cardiac surgery. *Acta Anaesthesiol Scand*. 2004;48:1071-9.

14. Biccard BM, Rodseth RN. The pathophysiology of peri-operative myocardial infarction. *Anaesthesia*. 2010;65:733-41.

15. Thygesen K, Alpert JS, White HD, Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Circulation*. 2007; 27;116:2634-53.

16. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, Ludwig LE, Pedan A, Goldman L. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;100:1043-9.

17. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27:157-172.

18. Longhitano S, Coriat P, Agrò F. Postoperative myocardial infarction: pathophysiology, new diagnostic criteria, prevention. *Minerva Anestesiol*. 2006;72:965-83.

19. Le Manach Y, Perel A, Coriat P, Godet G, Bertrand M, Riou B. Early and delayed myocardial infarction after abdominal aortic surgery. *Anesthesiology*. 2005;102:885-91.

20. Martinez EA, Nass CM, Jermyn RM, Rosenbaum SH, Akhtar S, Chan DW, Malkus H, Weiss JL, Fleisher LA. Intermittent cardiac troponin-I screening is an effective means of surveillance for a perioperative myocardial infarction. *J Cardiothorac Vasc Anesth*. 2005;19:577-82.

21. Desai AS, Toto R, Jarolim P, Uno H, Eckardt KU, Kewalramani R, Levey AS, Lewis EF, McMurray JJ, Parving HH, Solomon SD, Pfeffer MA. Association between cardiac biomarkers and the development of ESRD in patients with type 2 diabetes mellitus, anemia, and CKD. Am J Kidney Dis. 2011;58:717-28.

22. Breslow MJ, Parker SD, Frank SM, Norris EJ, Yates H, Raff H, Rock P, Christopherson R, Rosenfeld BA, Beattie C. Determinants of catecholamine and cortisol responses to lower extremity revascularization. The PIRAT Study Group. *Anesthesiology*. 1993;79:1202-1209.

23. Sametz W, Metzler H, Gries M, Porta S, Sadjak A, Supanz S, Juan H. Perioperative catecholamine changes in cardiac risk patients. *Eur J Clin Invest*. 1999;29:582-587.

24. Fukumoto Y, Hiro T, Fujii T, Hashimoto G, Fujimura T, Yamada J, Okamura T, Matsuzaki M. Localized elevation of shear stress is related to coronary plaque rupture: a 3-dimensional intravascular ultrasound study with in-vivo color mapping of shear stress distribution. *J Am Coll Cardiol*. 2008;51:645-650.

25. Gibbs NM, Crawford GP, Michalopoulos N. Postoperative changes in coagulant and anticoagulant factors following abdominal aortic surgery. *J Cardiothorac Vasc Anesth*. 1992;6:680-685.

26. Rosenfeld BA, Faraday N, Campbell D, Dorman T, Clarkson K, Siedler A, Breslow MJ, Bell W. Perioperative platelet reactivity and the effects of clonidine. *Anesthesiology*. 1993;79:255-261.

27. Kluft C, Verheijen JH, Jie AF, Rijken DC, Preston FE, Sue-Ling HM, Jespersen J, Aasen AO. The postoperative fibrinolytic shutdown: a rapidly reverting acute phase pattern for the fast-acting inhibitor of tissue-type plasminogen activator after trauma. *Scand J Clin Lab Invest*. 1985;45:605-610.

28. Chong CP, van Gaal WJ, Ryan JE, Profitis K, Savige J, Lim WK. Does cardiology intervention improve mortality for post-operative troponin elevations after emergency orthopaedic-geriatric surgery? A randomised controlled study. *Injury.* 2012;43:1193-8.

29. Filipovic M, Jeger R, Probst C, Girard T, Pfisterer M, Gürke L, Skarvan K, Seeberger MD. Heart rate variability and cardiac troponin I are incremental and independent predictors of one-year all-cause mortality after major noncardiac surgery in patients at risk of coronary artery disease. *J Am Coll Cardiol.* 2003;42:1767-76.

30. Kertai MD, Boersma E, Westerhout CM, Klein J, Van Urk H, Bax JJ, Roelandt JR, Poldermans D. A combination of statins and beta-blockers is independently associated with a reduction in the incidence of perioperative mortality and nonfatal myocardial infarction in patients undergoing abdominal aortic aneurysm surgery. *Eur J Vasc Endovasc Surg.* 2004;28:343-52.

31. Lopez-Jimenez F, Goldman L, Sacks DB, Thomas EJ, Johnson PA, Cook EF, Lee TH. Prognostic value of cardiac troponin T after non-cardiac surgery: 6-month follow-up data. *J Am Coll Cardiol.* 1997;29:1241-1245.

32. Godet G, Dumerat M, Baillard C, Ben Ayed S, Bernard MA, Bertrand M, Kieffer E, Coriat P. Cardiac troponin I is reliable with immediate but not medium-term cardiac complications after abdominal aortic repair. *Acta Anaesthesiol Scand.* 2000;44:592-7.

33. Higham H, Sear JW, Sear YM, Kemp M, Hooper RJ, Foex P. Peri-operative troponin I concentration as a marker of long-term postoperative adverse cardiac outcomes. A study in high-risk surgical patients. *Anaesthesia.* 2004;59:318-23.

34. Bursi F, Babuin L, Barbieri A, Politi L, Zennaro M, Grimaldi T, Rumolo A, Gargiulo M, Stella A, Modena MG, Jaffe AS. Vascular surgery patients: perioperative and long-term risk according to the ACC/AHA guidelines, the additive role of post-operative troponin elevation. *Eur Heart J.* 2005;26:2448-56.

35. Blecha MJ, Clark ET, Worley TA, Salazar MR, Podbielski FJ. Predictors of electrocardiographic change, cardiac troponin elevation, and survival after major vascular surgery: a community hospital experience. *Am Surg.* 2007;73:697-702.

36. McFalls EO, Ward HB, Moritz TE, Apple FS, Goldman S, Pierpont G, Larsen GC, Hattler B, Shunk K, Littooy F, Santilli S, Rapp J, Thottapurathu L, Krupski W, Reda DJ, Henderson WG. Predictors and outcomes of a perioperative myocardial infarction following elective vascular surgery in patients with documented coronary artery disease: results of the CARP trial. *Eur Heart J.* 2008;29:394-401.

37. Bolliger D, Seeberger MD, Lurati Buse GA, Christen P, Rupinski B, Gürke L, Filipovic M. A preliminary report on the prognostic significance of preoperative brain natriuretic peptide and postoperative cardiac troponin in patients undergoing major vascular surgery. *Anesth Analg.* 2009;108:1069-75.

38. Kouvelos GN, Milionis HJ, Arnaoutoglou EM, Chasiotis G, Gartzonika C, Papa NK, Tzimas P, Matsagkas MI. Postoperative levels of cardiac troponin versus CK-MB and high-sensitivity C-reactive protein for the prediction of 1-year cardiovascular outcome in patients undergoing vascular surgery. *Coron Artery Dis.* 2011;22:428-34.

39. Nagele P, Rao LK, Penta M, Kallogjeri D, Spitznagel EL, Cavallone LF, Nussenbaum B, Piccirillo JF. Postoperative myocardial injury after major head and neck cancer surgery. *Head Neck.* 2011;33:1085-91.

40. Dawson-Bowling S, Chettiar K, Cottam H, Worth R, Forder J, Fitzgerald-O'Connor I, Walker D, Apthorp H. Troponin T as a predictive marker of morbidity in patients with fractured neck of femur. *Injury.* 2008;39:775-80.

41. Chong CP, Lam QT, Ryan JE, Worth R, Forder J, Fitzgerald-O'Connor I, Walker D, Apthorp H. Incidence of post-operative troponin I rises and 1-year mortality after emergency orthopaedic surgery in older patients. *Age Ageing.* 2009;38:168-74.

42. Apple FS, Murakami MM, Pearce LA, Herzog CA. Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. Circulation. 2002;106:2941-5.

43. Hamm CW, Giannitsis E, Katus HA. Cardiac troponin elevations in patients without acute coronary syndrome. Circulation. 2002;106:2871-2.

Chapter 3

One-year mortality, causes of death, and cardiac interventions in patients with postoperative myocardial injury

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Abstract

Background

To evaluate the role of routine troponin surveillance in patients undergoing major noncardiac surgery, unblinded screening with cardiac consultation per protocol was implemented at a tertiary care center. This study evaluated one-year mortality, causes of death, and consequences of cardiac consultation of this protocol.

Methods

This observational cohort included 3,224 patients ≥60 years of age undergoing major noncardiac surgery. Troponin I was measured routinely on the first three postoperative days. Myocardial injury was defined as troponin I >0.06 mcg/L. Regression analysis was used to determine the association between myocardial injury and one-year mortality. The causes of death, the diagnoses of the cardiologists and interventions were determined for different levels of troponin elevation.

Results

Postoperative myocardial injury was detected in 715 patients (22%) and was associated with one-year all-cause mortality (RR 1.4, p=0.004; RR 1.6, p<0.001; and RR 2.2, p<0.001 for minor, moderate and major troponin elevation respectively). Cardiac death within one year occurred in 3%, 5% and 11% of patients respectively, as compared to 3% of the patients without myocardial injury (p=0.059). A cardiac consultation was obtained in 290 of the 715 patients (41%). In 119 (41%) of these patients, the myocardial injury was considered to be due to a predisposing cardiac condition, and in 111 (38%) an intervention was initiated.

Conclusions

Postoperative myocardial injury was associated with an increased risk of one-year all-cause, but not cardiac mortality. A cardiac consultation with intervention was performed in less than half of these patients. The low number of interventions may be explained by a low suspicion of a cardiac etiology in most patients and lack of consensus for standardized treatment in these patients.

Introduction

Postoperative adverse cardiovascular events are a leading cause of morbidity and mortality after noncardiac surgery.[1] The reported incidence of postoperative myocardial infarction (POMI) among patients undergoing noncardiac surgery is between 3 and 6%.[2–4] Prevention of POMI by perioperative suppression of the compensatory sympathetic effects of surgery or the inhibition of platelet function have showed no beneficial effect in several major clinical trials.[2,3,5] Failure of such preventive strategies has led to strategies aimed at early recognition and subsequent treatment of POMI after surgery.[1,6,7] Therefore, routine monitoring of cardiac biomarkers has been advocated to identify patients at risk of postoperative cardiovascular events early after surgery.[8]

Routine troponin I (TnI) measurements on the first three days after surgery, followed by a cardiac consultation in patients with troponin elevation were implemented in our hospital. This clinical protocol was part of our standard postoperative care in patients aged 60 years or older undergoing all types of intermediate to high risk noncardiac surgery. In a previous study, we showed that postoperative myocardial injury as measured by troponin elevation above the clinical cut-off level of 0.06 mcg/L with or without clinical symptoms occurred in 19% of these patients. Myocardial injury was strongly associated with short-term mortality, and troponin elevation improved risk stratification of patients at risk for death.[7] Consequently, we hypothesized that this clinical protocol would facilitate cardiovascular optimization to prevent further myocardial injury, POMI and long-term cardiovascular mortality.

The primary aim of this study was therefore to determine the association between myocardial injury and long-term death, and to assess the causes of death in patients with myocardial injury. Furthermore, we aimed to evaluate the effects of implementing routine postoperative troponin measurements by studying their impact on cardiologists consultation recommendations and whether specific interventions were implemented in such patients.

Methods

Patients

This observational cohort study included consecutive patients undergoing noncardiac surgery between January 1st 2011 and December 31st 2012 at the University Medical Center Utrecht, The Netherlands, a 1,000 bed tertiary referral hospital. Some of this cohort was used in a previous study.[7] Patients were eligible if they were aged 60 years or older, were undergoing intermediate to high risk noncardiac surgery under general or spinal anesthesia and had an expected postoperative length of hospital stay of at

least 24 hours. For patients who underwent surgery more than once, the first surgery was included in the analyses. A reoperation was included as a novel case if this surgery took place at least one year after the first surgery. Patients were excluded if they were lost to follow-up within one year after surgery.

The local medical ethics committee approved the study protocol. The need for informed consent was waived, as only routinely collected patient data were used and data were anonymized before analysis (UMC Utrecht Medical Research Ethics Committee 11-120/C).

Routine Postoperative Troponin Measurements

Routine troponin measurements were implemented as part of the standard postoperative care protocol on January 1st, 2011. According to this protocol, troponin was measured daily on the first three days after surgery. In the first phase of the protocol implementation, troponin measurements were ordered by the attending anesthesiologist. In case of a troponin elevation above the clinical cut-off level of 0.06 mcg/L, the ward physician was notified. As the optimal treatment of patients with postoperative troponin elevation was not protocolized, it was left at the discretion of the treating physician (surgical specialist) whether further diagnostic procedures including an ECG or cardiology consult was indicated. Thus, troponin elevation was simply considered as a marker for myocardial injury, warranting additional attention.

The logistics of the protocol were changed on May 2012 as troponin was not consistently measured in all eligible patients previously, and cardiology consultations were not performed in all patients with troponin elevation. Thus, troponin measurements were subsequently ordered by dedicated anesthesiology nurses, who also requested a postoperative ECG and a cardiology consultation in positive patients. Further diagnostic procedures such as cardiac or pulmonary CT-angiography, and coronary angiography (CAG) were only performed if indicated according to the consultant cardiologist. Cardiac interventions including prescription of medication were carried out in concurrence with the treating physician.

Myocardial injury

Troponin was analyzed using the third-generation enhanced AccuTnI assay (Beckman Coulter, Brea, California). Myocardial injury was defined as a TnI above the clinical cut-off level of 0.06 mcg/L, which was the lowest value measurable with a 10% coefficient of variation above the 99th percentile of 0.04 mcg/L.[7] For each patient, the highest value of all routine troponin measurements was used in the analysis.

Data collection

All preoperative and postoperative data were obtained from electronic medical and administrative records. Data collected in all patients included patient characteristics, preoperative physical status, comorbidities including factors from the Revised Cardiac Risk Index,[9] postoperative troponin measurements and death within one year. Additionally, data on postoperative symptoms, ECG changes, the occurrence of in-hospital POMI and other diagnoses, and the treatment initiated by the consultant cardiologist were collected in those patients who had a postoperative cardiac consult. The unique hospital patient identifier was used to merge databases. The municipal personal records database was consulted for one-year mortality data. Causes of death were obtained from general practitioners.

Outcomes

The primary outcome was defined as all-cause mortality within one year after surgery. Secondary outcomes included cardiac death within one year and the incidence of in-hospital POMI. Cardiac death was defined as death resulting from a cardiac arrest or heart failure. Myocardial infarction was defined according to the third universal definition of myocardial infarction.[8]

Cardiac consultations

In patients with a cardiology consultation, we determined the suspected etiology of the troponin elevation as proposed by the consultant cardiologist. These were divided into predisposing cardiac conditions and perioperative triggers.[1,10] Predisposing cardiac conditions included tachyarrhythmias (supraventricular or ventricular tachycardia), pre-existent coronary artery disease, cardiomyopathy, left ventricular hypertrophy and cardiac contusion. Perioperative triggers included tachycardia, anemia, hypertension, sympathetic storm in the presence of intracranial pathology, hypotension, inflammation and sepsis, pulmonary embolism, renal failure, fluid overload and hypoxia. Furthermore, we recorded the interventions recommended by the cardiologist.

Statistical analysis

Baseline characteristics were compared between patients with and without postoperative myocardial injury using the Chi-square test or two-sample t-test, as appropriate. The incidence of one-year mortality was compared using the Chi-square test, and a relative risk with 95% confidence interval was calculated. The median time to death was compared using the Mann-Whitney-U test.

Multivariable log-binomial regression analysis was used to adjust the association between myocardial injury and one-year mortality for patient and surgery characteristics and comorbidities. For this purpose, univariable regression analysis was used to

identify variables that were associated with one-year mortality. Variables with a p-value of 0.10 or less were included in the multivariable model. In this model, patients were classified according to their highest postoperative troponin value. Therefore, we defined more or less equally sized groups for the patients with troponin elevation, based on one, two and ten times the TnI cut-off level: TnI ≤0.06 mcg/L, TnI 0.07-0.12 mcg/L (minor elevation), TnI 0.13-0.60 mcg/L (moderate elevation) and TnI >0.60 mcg/L (major elevation). High risk surgery was defined as intra-abdominal, intrathoracic, or suprainguinal vascular surgery[9], and emergency surgery was defined as surgery required within 72 hours after the indication for surgery was set. Ischemic heart disease was defined as previous myocardial infarction and/or coronary revascularization, heart failure was defined as a left ventricular ejection fraction <40%, and preoperative renal failure was defined as a glomerular filtration rate <45 mL/min/1.73m^2. Next, we checked for interaction of troponin with any of the significant variables in the multivariable model by including interaction terms. We used log binomial regression analysis to facilitate presenting effect measures as risks ratios.[11]

A Kaplan-Meier survival analysis was used to determine the survival of patients in each category of troponin elevation. Survival was compared using the log rank test. Furthermore, causes of death were compared between these groups. Finally, we recorded the number of cardiology consultations and the diagnoses and interventions by the cardiologist.

All hypothesis testing was conducted two-sided and throughout the analyses we used a level of significance of 0.05. The analysis was performed using SPSS (release 21.0.0 for Windows).

Results

During the study period 4,099 patients were eligible for inclusion, of which 49 patients (1%) were excluded from the analyses (Figure 3.1). Of the remaining 4,050 patients, 826 patients (20%) were excluded because troponin was not measured during the first three postoperative days. Thus, 3,224 patients were included in this study (Table 3.1).

Myocardial injury occurred in 715 patients (22%): 344 (11%) had minor troponin elevations (TnI 0.07-0.12 mcg/L), 255 (8%) had moderate troponin elevations (TnI 0.13-0.60 mcg/L), and 116 (4%) had major troponin elevations (TnI >0.60 mcg/L).

Table 3.1 *Baseline characteristics in patients with and without postoperative myocardial injury.*

	No myocardial injury N=2509		Myocardial injury N=715		p-value
Male	1282	(51)	424	(59)	<0.001
Mean age (SD)	70	(7)	73	(8)	<0.001
Smoking[a]	446	(19)	122	(20)	0.452
Hypertension	1243	(50)	434	(61)	<0.001
Diabetes	404	(16)	150	(21)	0.002
COPD	233	(9)	76	(11)	0.282
History of myocardial infarction	193	(8)	106	(15)	<0.001
History of coronary revascularization	251	(10)	130	(18)	<0.001
History of heart failure	56	(2)	38	(5)	<0.001
(Paroxysmal) atrial fibrillation	262	(10)	107	(15)	0.001
Pacemaker/Implantable Cardioverter Defibrillator	50	(20)	36	(5)	<0.001
History of cerebrovascular disease	361	(14)	135	(19)	0.003
Renal failure	223	(9)	151	(21)	<0.001
Peripheral vascular disease	245	(10)	111	(16)	<0.001
Medication use					
Beta blockers	722	(29)	268	(38)	<0.001
Calcium antagonists	414	(17)	134	(19)	0.159
RAS[b] inhibitors	845	(34)	294	(41)	<0.001
Diuretics	630	(25)	219	(31)	0.003
Aspirin	688	(27)	264	(37)	<0.001
Warfarins	264	(11)	100	(14)	0.010
Statins	863	(34)	300	(42)	<0.001
Insulin	130	(5)	55	(8)	0.011
Oral anti-diabetics	309	(12)	99	(14)	0.278
ASA class[c]					<0.001
1	355	(14)	58	(8)	
2	1641	(65)	401	(56)	
3	497	(20)	237	(33)	
4	16	(1)	19	(3)	
General anesthesia	2333	(93)	693	(97)	<0.001
High risk surgery	725	(29)	311	(44)	<0.001
Emergency surgery	437	(17)	256	(36)	<0.001
Re-operation within one year	408	(16)	172	(24)	<0.001
Surgical specialty					<0.001
General surgery	517	(21)	240	(34)	
Neurosurgery	630	(25)	147	(21)	
Vascular surgery	365	(15)	145	(20)	
ENT and dental surgery	339	(14)	65	(9)	
Orthopedic surgery	267	(11)	78	(11)	
Gynaecology / Urology	391	(16)	40	(6)	

Figures are numbers of patients (%), unless indicated otherwise. a N=2354 and N=601 respectively, due to missing data on smoking. b Renin angiotensin system inhibitors; c Classification system by the American Society of Anesthesiologists.

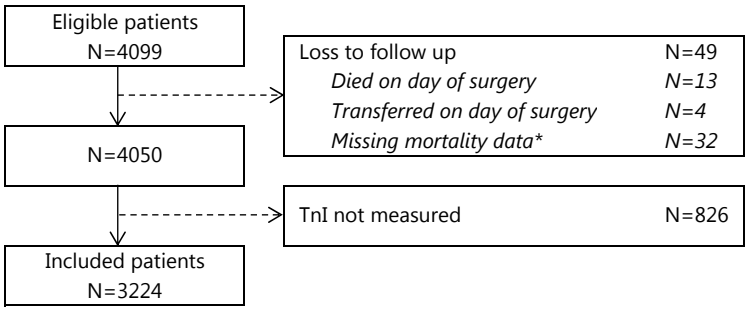

Figure 3.1 *Flow chart of patient inclusion.*
** These patients were not known by the municipal personal records database.*

One-year all-cause mortality

Of the 715 patients with myocardial injury, 182 patients (26%) died within one year after surgery, as compared to 318 (13%) of the 2,509 patients without myocardial injury (RR 2.0, 95% CI 1.7-2.4, p<0.001). The median time to death was 55 days (interquartile range (IQR) 11-173) in patients with myocardial injury as compared to 135 days (IQR 47-236) in patients without myocardial injury (p<0.001). The one-year survival in patients with minor, moderate and major troponin elevations was 21%, 25% and 40%, respectively (p<0.001) (Figure 3.2).

After adjustment for variables that are known to predict death, the RR of one-year mortality was 1.4 (95% CI 1.1 – 1.8, p=0.004) in patients with minor troponin elevations, 1.6 (95% 1.3-2.1, p<0.001) in patients with moderate troponin elevations, and 2.2 (95%

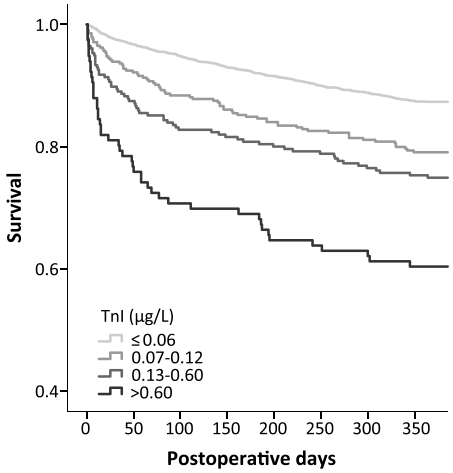

Figure 3.2
Kaplan Meier plot of patients with different levels of troponin elevation.

Table 3.2 *The association between postoperative myocardial injury for different categories of troponin elevation, and one-year mortality, adjusted for age, comorbidities and surgery characteristics.*

	Unadjusted analysis			Adjusted analysis		
	RR[a]	**95% CI[b]**	**p-value**	**RR[a]**	**95% CI[b]**	**p-value**
TnI[c] (mcg/L)						
≤0.06	*ref*			*ref*		
0.07-0. 12	1.7	1.3 – 2.1	<0.001	1.4	1.1 – 1.8	0.004
0.13-0.60	2.0	1.6 – 2.5	<0.001	1.6	1.3 – 2.1	<0.001
>0.60	3.1	2.4 – 4.0	<0.001	2.2	1.7 – 2.8	<0.001
Age (per 10 years increase)	1.4	1.2 – 1.5	<0.001	1.2	1.1 – 1.3	<0.001
Female sex	0.9	0.8 – 1.1	0.920			
Ischemic heart disease	1.0	0.8 – 1.2	0.877			
Hypertension	0.9	0.8 – 1.1	0.203			
(Paroxysmal) atrial fibrillation	1.3	1.0 – 1.6	0.022	1.1	0.9 – 1.4	0.383
Heart failure	1.3	0.9 – 2.0	0.190			
Pacemaker and/or ICD[d]	1.2	0.8 – 1.9	0.414			
Cerebrovascular disease	1.1	0.9 – 1.4	0.217			
Preoperative renal failure	1.8	1.5 – 2.2	<0.001	1.3	1.1 – 1.6	0.014
Preoperative insulin use	1.7	1.3 – 2.3	<0.001	1.4	1.1 – 1.7	0.012
COPD	1.0	0.8 – 1.4	0.730			
Peripheral vascular disease	1.0	0.8 – 1.3	0.851			
High risk surgery	1.0	0.9 – 1.2	0.728			
Emergency surgery	1.9	1.6 – 2.2	<0.001	1.5	1.3 – 1.8	<0.001
Reoperation within one year	1.3	1.1 – 1.6	0.002	1.2	1.0 – 1.4	0.111

Figures are numbers (%) of patients.[a] Relative Risk; [b] Confidence Interval; [c] Troponin I; [d] Implantable Cardioverter Defibrillator

CI 1.7-2.8, p<0.001) in patients with major troponin elevations, as compared to patients without myocardial injury (Table 3.2).

Other independent predictors of death were age, preoperative renal failure, preoperative insulin use and emergency surgery. Interaction terms for each of these predictors with troponin in the multivariable model were not statistically significant.

Causes of death

Data on the cause of death were available for 358 of the 500 patients (72%) who died within one year (Table 3.3).

Cardiac death occurred in 2 (3%), 3 (5%) and 5 patients (11%) with minor, moderate and major troponin elevations respectively, as compared to 9 patients (3%) without myocardial injury (p=0.059). Predominant causes of death in patients with major troponin elevations were sepsis (20%), cerebrovascular (15%), and cardiac causes (11%), whereas most of the patients without myocardial injury died of cancer (43%).

Table 3.3 *Causes of death within one year after surgery for each category of troponin elevation (total N=500).*

	TnI[a] (mcg/L)								p-value
	<0.06 N=318		0.07-0.12 N=72		0.13-0.60 N=64		>0.60 N=46		
Cardiac	9	(3)	2	(3)	3	(5)	5	(11)	0.059
Cardiac arrest	6	(2)	2	(3)	3	(5)	2	(4)	
Heart failure	3	(1)	0	(0)	0	(0)	3	(7)	
Pulmonary embolism	3	(1)	0	(0)	2	(3)	0	(0)	0.249
Other pulmonary	10	(3)	8	(11)	5	(8)	4	(9)	0.024
Cerebrovascular/brain injury	19	(6)	10	(14)	13	(20)	7	(15)	0.001
Malignancy	135	(43)	22	(31)	10	(16)	1	(2)	<0.001
Infection/sepsis	23	(7)	6	(8)	10	(16)	9	(20)	0.018
Other	18	(6)	5	(7)	8	(13)	11	(24)	<0.001
Unknown	101	(32)	19	(26)	13	(20)	9	(20)	0.125

Figures are numbers (%) of patients. a Troponin I

ECG results

A postoperative ECG was performed in 424 of the 715 patients (59%) with myocardial injury. ECG changes suggestive of new ischemia were found in 96 of the 424 patients (23%), and were more frequent in patients with major troponin elevations (43 of 112 patients, 38%), as compared to patients with moderate troponin elevations (32 of 187 patients, 17%) or minor troponin elevations (21 of 135 patients, 16%). Three (0.7%) of these ECGs showed ST elevation ≥1mm, 52 (12%) ECGs showed ST depression ≥1mm, and 41 (10%) ECGs showed ST depression <1mm or T-wave inversion, respectively. Twenty-five of the 715 patients (3%) with myocardial injury had typical chest pain.

Cardiology consultations

A cardiology consultation followed in 290 of the 715 patients (41%) with myocardial injury (i.e. 9% of the total study population). The proportion of patients with a cardiac consultation was 18%, 54% and 79% in patients with a minor, moderate and major troponin elevation, respectively.

For the 290 patients who had cardiology consultation, the suspected etiologies of myocardial injury as determined by the consultant cardiologist, are given in Figure 3.3. In 119 of the 290 patients (41%) with a cardiac consultation, the myocardial injury was considered to be due to predisposing cardiac conditions, including tachyarrhythmia and pre-existent coronary artery disease, and in 81 patients (28%) the myocardial injury was considered to be due to perioperative triggers. In 126 patients (43%) the etiology of myocardial injury was not specified. Of note, the number of patients within the different groups of suspected etiologies exceeds the total number of patients, as 36 patients (12%) were assigned to more than one group (e.g. a patient with myocardial injury due to anemia in the presence of left ventricular hypertrophy).

Suspected etiology of myocardial injury		Real-time diagnosis of POMI*	Intervention
All patients	**N=290**	**N=23**	**N=111**
Predisposing cardiac conditions	**119 (41)**	**23 (100)**	**72 (65)**
Tachyarrythmia	46		
Pre-existent coronary artery disease	38		
Cardiomyopathy	19		
Left ventricular hypertrophy	14		
Cardiac contusion	5		
Recent myocardial infarction	1		
Perioperative triggers	**81 (28)**	**9 (39)**	**45 (41)**
Anemia	19		
Hypertension/sympathetic storm	19		
Tachycardia	17		
Hypotension	12		
Sepsis/Inflammation	10		
Fluid overload	7		
Pulmonary embolism	7		
Renal failure	7		
Hypoxia	3		
Not specified	**126 (43)**	**0 (0)**	**20 (18)**

Figure 3.3 *Suspected etiologies of myocardial injury, postoperative myocardial infarction and interventions in the 290 patients with a cardiac consultation. The suspected etiologies as determined by the consultant cardiologist were classified as predisposing cardiac conditions and perioperative triggers. The number of patients with postoperative myocardial infarction and the number of patients with a cardiac intervention are given for each of these groups. Of note, the number of patients in each column exceeds the total number of patients, because in 36 patients the myocardial injury was suspected to be due to both a predisposing cardiac condition and perioperative triggers.*
*Figures are numbers (%) of patients. *Postoperative myocardial infarction.*

POMI

POMI defined according to the third universal definition occurred in 97 of the 715 patients (14%) with myocardial injury: STEMI in 3 patients and NSTEMI in 94 patients, i.e. 3% of the total study population. However, only 18 of them who were in the group that received cardiologist consultation, were diagnosed by the cardiologist in real time as having POMI, including the 3 patients with STEMI. In addition, 5 patients who in retrospect did not fulfill the criteria of the third universal definition of myocardial infarction were diagnosed in real time as having POMI, because of high TnI values with a rise-and-fall pattern in four patients and high TnI values with ventricular tachycardia in one patient. In total 23 patients were diagnosed by the cardiologist with POMI. In all of these 23 patients POMI was considered to be due to a predisposing cardiac condition, and in 9 of these 23 patients a perioperative trigger was suspected as well.

Interventions

A cardiac intervention was initiated in 111 of the 290 patients (38%) with a cardiology consultation. In the remaining 179 patients (62%) only follow-up of troponin was carried out, and the clinical course was further awaited without any intervention. Interventions were more often done in patients with a major troponin elevation (48 of 92 patients, 52%), as compared to patients with a moderate troponin elevation (45 of 138 patients, 33%) or a minor troponin elevation (18 of 60 patients, 30%). In patients in whom the myocardial injury was considered to be due to predisposing cardiac conditions or perioperative triggers, a cardiac intervention was initiated in 72 of 119 patients (61%) and 45 of 81 patients (56%) respectively, whereas when the etiology of myocardial injury was not specified, a cardiac intervention was done in 20 of 126 patients (16%) (Figure 3.3).

The cardiac interventions consisted of the following: in 104 of the 290 patients (36%), new medication or a dose increase was prescribed. This included beta-blockers in 52 patients (18%), other antihypertensive agents including renin angiotensin inhibitors, diuretics and calcium channel blockers in 21 patients (7%), aspirin in 34 patients (12%), other antiplatelet agents in 15 patients (5%), (low molecular weight) heparin in 28 patients (10%), statins in 22 patients (8%) and other medication in 25 patients (9%). In 14 patients (5%), red cell transfusion was advised by the cardiologist. Seventeen patients (6%) were transferred to the coronary care unit or medium care for cardiac monitoring. Coronary angiography (CAG) was performed in 15 patients (5%). The median time to CAG was 10 days (IQR 4-62). Significant coronary artery stenoses were found in 12 patients (4%). Nine patients (3%) underwent percutaneous coronary intervention (PCI), and one patient (0.3%) underwent coronary artery bypass graft surgery. Finally, in two patients (0.7%) coronary revascularization was not performed because the risk of intervention was considered too high, or because it was considered to be not beneficial because of the patients' poor condition.

Of the three patients with STEMI, only one underwent CAG and PCI. In this patient, CAG and PCI were not performed in the acute phase because of an initial diagnostic delay (>6 hours), but 14 and 33 days after STEMI was diagnosed, respectively. This patient survived the follow-up time of one year. In one STEMI patient who underwent neurosurgery, CAG (and PCI) was not performed because the risk of intracranial bleeding with antiplatelet and anticoagulant therapy was considered too high. This patient died 15 days later of cerebral empyema. In another STEMI patient a diagnostic delay occurred because of difficulties in interpreting the ECG (pre-existent ST elevation in the anterior leads due to a prior anterior wall myocardial infarction). By the time STEMI was diagnosed, the ECG was normalized and CAG was not considered beneficial anymore. The patient was admitted to the medium care for cardiac monitoring and treated with antiplatelet therapy, and survived the follow-up time of one year.

Discussion

This study determined the association between postoperative myocardial injury and one-year mortality in a large cohort of patients, and assessed causes of death in patients with myocardial injury. In addition, we studied the diagnoses and cardiac interventions in these patients. Postoperative myocardial injury, as detected by troponin elevation, was found in 22% of the patients, and was associated with a 1.5 to 3-fold increased risk of one-year mortality. The protocol led to a cardiac intervention in only 111 (16%) of the 715 patients with myocardial injury.

Our hospital is one of the first that implemented routine troponin measurements after noncardiac surgery, in order to improve early identification of patients with myocardial injury who are at risk of (silent) POMI and death. Because data from clinical care obtained in the implementation period of a new protocol were used in this study, the results represent daily care, instead of a controlled research setting.

Limitations

Several limitations must be addressed. First, because troponin was only measured on the first three days after surgery, myocardial injury that may have occurred after the third postoperative day was missed. However, previous research has shown that myocardial injury occurs primarily within the first three postoperative days.[12–14]our ability to identify and quantify myocardial infarction in the postoperative period has been greatly enhanced. Even small elevations of cTnI should be considered as a myocardial infarction. Small increases in cTnI postoperatively have indeed been found to be associated with worse short and long-term outcomes, the higher the cTnI level the worse the outcome. Studies undertaken in the 1980s when postoperative myocardial infarction (PMI Second, as troponin was not measured in 20% of patients, selection bias may be present. However, we showed in a previous report including a part of this cohort that there were no large differences between patients with and without troponin measurements, and that imputation of the missing troponin values did not alter the association between myocardial injury and death.[7] Third, exclusion of patients who were lost to follow-up (1%) may have introduced potential bias. Fourth, troponin was not measured prior to surgery; hence the results could not be adjusted for possible preexisting troponin elevations. [15–17]2, and 3. RESULTS: At baseline before surgery, 599 patients (98.5% Fifth, in evaluating postoperative troponin measurements, the occurrence of complications of resulting interventions (e.g. bleeding caused by anticoagulants) [3,18,19]both among patients who are already on an aspirin regimen and among those who are not. METHODS: Using a 2-by-2 factorial trial design, we randomly assigned 10,010 patients who were preparing to undergo noncardiac surgery and were at risk for vascular complications to receive aspirin or placebo and clonidine or placebo. The results of the as-

pirin trial are reported here. The patients were stratified according to whether they had not been taking aspirin before the study (initiation stratum, with 5628 patients would have been valuable to report, but these data were not available for all patients. Finally, data on the cause of death were not available for all patients. As the cause of death may have been reported as 'unknown' in some patients with sudden death, the incidence of sudden cardiac death may be underestimated.

Literature

The association between postoperative myocardial injury and long-term mortality has previously been assessed in several smaller cohort studies that included patients undergoing major surgery. Myocardial injury as measured by troponin elevation was reported to be associated with a two- to 41-fold increased risk of death within one year after surgery, which is consistent with the result of our study.[20–33]"author" In the VISION trial, even troponin levels below the upper limit of normal were found to be related to mortality.[4] Cardiac death occurred in 19 of the 3,224 patients (0.6%) in our study, which is in accordance with the incidence of cardiovascular death in the POISE-2 trial (0.7%).[3] Furthermore, Chong and colleagues reported that cardiovascular death occurred more frequent in patients who suffered from postoperative myocardial injury after orthopedic surgery, like in our study.[20]

The incidence of POMI according to the third universal definition of myocardial infarction (3%) is comparable to previous reports (3-6%).[2–4] It should be noted that only 0.7% of patients were diagnosed with POMI in real time by the cardiologist. This implies that - in clinical practice - myocardial injury in the postoperative phase is evaluated differently than outside the perioperative setting, e.g. in patients who are suspected of myocardial infarction in the emergency department. Also, POMI appears to be less often diagnosed in a daily clinical care setting than in a controlled research setting, even if routine postoperative monitoring of troponin is used.

Because many of the patients with postoperative myocardial injury do not fulfill the criteria of myocardial infarction, a new diagnosis of MINS (Myocardial Injury after Noncardiac Surgery), defined as prognostically relevant myocardial injury due to ischemia that occurs during or within 30 days after noncardiac surgery, was proposed to guide timely diagnosis and intervention.[34] Current guidelines concur that early postoperative troponin measurements could have therapeutic consequences and therefore that it may be considered in high risk patients,[35] but it is emphasized that its usefulness is uncertain in the absence of established risks and benefits of a defined management strategy,[36] which is confirmed by our study.

Although many causes of postoperative myocardial injury have been put forward, including noncardiac causes,[1,10] it is not known in how many patients and to what extent perioperative factors contribute to the development of myocardial injury. Fur-

thermore, if POMI is diagnosed, there is uncertainty whether this is mainly caused by plaque rupture with thrombosis (type 1 myocardial infarction) or an imbalance between myocardial oxygen supply and demand (type 2 myocardial infarction),[37–40] which hampers the initiation of proper treatment options. Moreover, even in patients with type 2 myocardial infarction outside the perioperative setting no established treatment guidelines exist.[41]

Few studies evaluated cardiac treatment initiated after surgery in patients with postoperative myocardial injury. Foucrier and colleagues studied the effect of cardiovascular medical optimization in 667 patients undergoing elective major vascular surgery. They reported that patients with treatment optimization, consisting of prescription or a dose increase of antiplatelet drugs, beta blockers, angiotensin converting enzyme inhibitors and statins, had a lower risk of adverse cardiac events than patients without treatment optimization.[42]death, myocardial infarction, coronary revascularization, or pulmonary edema requiring hospitalization Treatment interventions were much more frequent (65%) than in our study (16%), which may be explained by the type of patients included, i.e. those at higher risk of cardiovascular complications who may have had more benefit from cardiovascular optimization. Chong and colleagues randomized 70 patients with troponin elevation after orthopedic surgery to cardiology care, consisting of assessment by a cardiologist and admission to a coronary care unit, versus standard treatment. Prescription of new medication, mainly beta blockers and aspirin, was more frequent (83% of the patients), as compared to our study (36% of the patients with cardiology consultation). However, cardiology care had no effect on in-hospital cardiac complications and one-year mortality.[43]

Clinical implications

Several strategies to prevent the occurrence of POMI, including suppression of the sympathetic nervous system and antiplatelet therapy, have failed to show an effect or the beneficial effect was outweighed by severe side effects.[3,5] As an alternative strategy, in those patients in whom postoperative myocardial injury has occurred, further myocardial injury and infarction may be prevented by adequate treatment early after surgery and consequently prognosis in terms of survival may be improved.[6,7] Indeed, we found that among patients with postoperative myocardial injury, the most common causes of death were cardiac, cerebrovascular and sepsis (Table 3.3), whereas among the patients without myocardial injury most patients died of cancer. Although we showed that it is feasible to identify these patients at risk early after surgery by routine troponin measurements, this resulted in treatment interventions in less than half (38%) of the patients who had a cardiac consultation. In patients in whom the myocardial injury was considered to be due to predisposing cardiac conditions, a cardiac intervention was carried out in 60% of patients. However, in many patients (43%) the etiology of the

myocardial injury was not clear, hence it was likely not known what treatment should be initiated to prevent further injury and death. Furthermore, in about half of the patients with perioperative triggers for troponin elevation, no treatment was initiated. In a part of these patients who were at high risk of death, the myocardial injury may have been inherent to the underlying disease, e.g. in patients with myocardial injury due to sympathetic storm in the presence of intracranial pathology, or in patients with severe sepsis. Hence, it is conceivable that cardiac interventions were not carried out in these patients because this may not have been beneficial.

The findings from the current study support that attempts to improve prognosis in patients with myocardial injury are limited by insufficient knowledge of the underlying pathophysiology and adequate treatment options in individual cases, and by insufficient capability to select those patients in whom cardiac treatment may be beneficial. It is likely that one single intervention is not simply beneficial in all patients. Given the high mortality rate in patients who suffer from postoperative myocardial injury, future research efforts should first and foremost focus on unraveling the pathophysiology of postoperative myocardial injury in order to guide treatment options, and on identifying the patients who may benefit from (different) treatments. As long as these questions are not answered, we would recommend carefully weigh the benefits and risks of measuring troponin routinely in all patients after noncardiac surgery.

Conclusion

Postoperative myocardial injury as detected by routine troponin measurements is associated with one-year mortality. However, implementation of a clinical protocol including a cardiology consultation in patients with postoperative myocardial injury in order to improve prognosis in these patients, resulted in a cardiac consultation and intervention in less than half of the patients with myocardial injury. The low number of interventions may be explained by the suspicion of a cardiac condition in only a minority of the patients, and the lack of a standardized treatment protocol in our study, which in turn is attributable to a lack of knowledge of the underlying pathophysiology and treatment options in patients with postoperative myocardial injury.

References

1. Landesberg G, Beattie WS, Mosseri M, Jaffe AS, Alpert JS. Perioperative myocardial infarction. Circulation 2009;119:2936–44.
2. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Málaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008;371:1839–47.
3. Devereaux PJ, Mrkobrada M, Sessler DI, Leslie K, Alonso-Coello P, Kurz A, Villar JC, Sigamani A, Biccard BM, Meyhoff CS, Parlow JL, Guyatt G, Robinson A, Garg AX, Rodseth RN, Botto F, Lurati Buse G, Xavier D, Chan MT V, Tiboni M, Cook D, Kumar PA, Forget P, Malaga G, Fleischmann E, Amir M, Eikelboom J, Mizera R, Torres D, Wang CY, et al. Aspirin in patients undergoing non-cardiac surgery. N Engl J Med 2014;370:1494–503.
4. The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators. Association Between Postoperative Troponin Levels and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. JAMA 2012;307:2295–304.
5. Devereaux PJ, Sessler DI, Leslie K, Kurz A, Mrkobrada M, Alonso-Coello P, Villar JC, Sigamani A, Biccard BM, Meyhoff CS, Parlow JL, Guyatt G, Robinson A, Garg AX, Rodseth RN, Botto F, Lurati Buse G, Xavier D, Chan MT V, Tiboni M, Cook D, Kumar PA, Forget P, Malaga G, Fleischmann E, Amir M, Eikelboom J, Mizera R, Torres D, Wang CY, et al. Clonidine in patients undergoing noncardiac surgery. N Engl J Med 2014;370:1504–13.
6. Devereaux PJ, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, Leslie K, Purnima R-M. Characteristics and Short-Term Prognosis of Perioperative Myocardial Infarction in Patients Undergoing Noncardiac Surgery. Ann Intern Med 2011;154:523–8.
7. Waes JAR van, Nathoe HM, Graaff JC de, Kemperman H, Borst GJ de, Peelen LM, Klei WA van. Myocardial injury after noncardiac surgery and its association with short-term mortality. Circulation 2013;127:2264–71.
8. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand J-P, Menasché P, Ravkilde J, Ohman EM, Antman EM, et al. Third universal definition of myocardial infarction. Circulation 2012;126:2020–35.
9. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KKL, Ludwig LE, Pedan A, Goldman L. Derivation and Prospective Validation of a Simple Index for Prediction of Cardiac Risk of Major Noncardiac Surgery. Circulation 1999;100:1043–9.
10. Nathoe HM, Klei WA van, Beattie WS. Perioperative troponin elevation: always myocardial injury, but not always myocardial infarction. Anesth Analg 2014;119:1014–6.
11. Knol MJ, Cessie S Le, Algra A, Vandenbroucke JP, Groenwold RHH. Overestimation of risk ratios by odds ratios in trials and cohort studies: alternatives to logistic regression. CMAJ 2012;184:895–9.
12. Longhitano S, Coriat P, Agrò F. Postoperative myocardial infarction: pathophysiology, new diagnostic criteria, prevention. Minerva Anestesiol 2006;72:965–83.

13. Manach Y Le, Perel A, Coriat P, Godet G, Bertrand M, Riou B. Early and delayed myocardial infarction after abdominal aortic surgery. Anesthesiology 2005;102:885–91.

14. Martinez EA, Nass CM, Jermyn RM, Rosenbaum SH, Akhtar S, Chan DW, Malkus H, Weiss JL, Fleisher LA. Intermittent Cardiac Troponin-I Screening is an Effective Means of Surveillance for a Perioperative Myocardial Infarction. J Cardiothorac Vasc Anesth 2005;19:577–82.

15. Nagele P, Brown F, Gage BF, Gibson DW, Miller JP, Jaffe AS, Apple FS, Scott MG. High-sensitivity cardiac troponin T in prediction and diagnosis of myocardial infarction and long-term mortality after noncardiac surgery. Am Heart J 2013;166:325–32.

16. Lemos JA de, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, Hashim I, Berry JD, Das SR, Morrow DA, McGuire DK. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA 2010;304:2503–12.

17. Gaggin HK, Szymonifka J, Bhardwaj A, Belcher A, Berardinis B De, Motiwala S, Wang TJ, Januzzi JL. Head-to-head comparison of serial soluble ST2, growth differentiation factor-15, and highly-sensitive troponin T measurements in patients with chronic heart failure. JACC Heart Fail 2014;2:65–72.

18. Burger W, Chemnitius JM, Kneissl GD, Rucker G. Low-dose aspirin for secondary cardiovascular prevention - cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation - review and meta-analysis. J Intern Med 2005;257:399–414.

19. Möllmann H, Nef HM, Hamm CW, Elsässer A. How to manage patients with need for antiplatelet therapy in the setting of (un-)planned surgery. Clin Res Cardiol 2009;98:8–15.

20. Chong C, Lam Q, Ryan J, Sinnappu R, Lim WK. Impact of troponin 1 on long-term mortality after emergency orthopaedic surgery in older patients. Intern Med J 2010;40:751–6.

21. Marston N, Brenes J, Garcia S, Kuskowski M, Adabag S, Santilli S, McFalls EO. Peak postoperative troponin levels outperform preoperative cardiac risk indices as predictors of long-term mortality after vascular surgery Troponins and postoperative outcomes. J Crit Care 2012;27:66–72.

22. Bolliger D, Seeberger MD, Lurati Buse G AL, Christen P, Rupinski B, Gürke L, Filipovic M. A preliminary report on the prognostic significance of preoperative brain natriuretic peptide and postoperative cardiac troponin in patients undergoing major vascular surgery. Anesth Analg 2009;108:1069–75.

23. Chong CP, Lam QT, Ryan JE, Sinnappu RN, Lim WK. Incidence of post-operative troponin I rises and 1-year mortality after emergency orthopaedic surgery in older patients. Age Ageing 2009;38:168–74.

24. Oscarsson A, Fredrikson M, Sörliden M, Anskär S, Gupta A, Swahn E, Eintrei C. Predictors of cardiac events in high-risk patients undergoing emergency surgery. Acta Anaesthesiol Scand 2009;53:986–94.

25. Ausset S, Auroy Y, Lambert E, Vest P, Plotton C, Rigal S, Lenoir B, Benhamou D. Cardiac troponin I release after hip surgery correlates with poor long-term cardiac outcome. Eur J Anaesthesiol 2008;25:158–64.

26. McFalls EO, Ward HB, Moritz TE, Apple FS, Goldman S, Pierpont G, Larsen GC, Hattler B, Shunk K, Littooy F, Santilli S, Rapp J, Thottapurathu L, Krupski W, Reda DJ, Henderson WG. Predictors and outcomes of a perioperative myocardial infarction following elective vascular surgery in patients with documented coronary artery disease: results of the CARP trial. Eur Heart J 2008;29:394–401.

27. Bursi F, Babuin L, Barbieri A, Politi L, Zennaro M, Grimaldi T, Rumolo A, Gargiulo M, Stella A, Modena MG, Jaffe AS. Vascular surgery patients: perioperative and long-term risk according to the ACC/AHA guidelines, the additive role of post-operative troponin elevation. Eur Heart J 2005;26:2448–56.

28. Higham H, Sear JW, Sear YM, Kemp M, Hooper RJL, Foex P. Peri-operative troponin I concentration as a marker of long-term postoperative adverse cardiac outcomes--a study in high-risk surgical patients. Anaesthesia 2004;59:318–23.

29. Kertai MD, Boersma E, Klein J, Urk H Van, Bax JJ, Poldermans D. Long-term prognostic value of asymptomatic cardiac troponin T elevations in patients after major vascular surgery. Eur J Vasc Endovasc Surg 2004;28:59–66.

30. Oscarsson A, Eintrei C, Anskär S, Engdahl O, Fagerström L, Blomqvist P, Fredriksson M, Swahn E. Troponin T-values provide long-term prognosis in elderly patients undergoing non-cardiac surgery. Acta Anaesthesiol Scand 2004;48:1071–9.

31. Landesberg G, Shatz V, Akopnik I, Wolf YG, Mayer M, Berlatzky Y, Weissman C, Mosseri M. Association of Cardiac Troponin, CK-MB, and Postoperative Myocardial Ischemia With Long-Term Survival After Major Vascular Surgery. J Am Coll Cardiol 2003;42:1547–54.

32. Filipovic M, Jeger R, Probst C, Girard T, Pfisterer M, Gürke L, Skarvan K, Seeberger MD. Heart rate variability and cardiac troponin I are incremental and independent predictors of one-year all-cause mortality after major noncardiac surgery in patients at risk of coronary artery disease. J Am Coll Cardiol 2003;42:1767–76.

33. Godet G, Dumerat M, Baillard C, Ayed S Ben, Bernard MA, Bertrand M, Kieffer E, Coriat P. Cardiac troponin I is reliable with immediate but not medium-term cardiac complications after abdominal aortic repair. Acta Anaesthesiol Scand 2000;44:592–7.

34. The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Writing Group. Myocardial Injury after Noncardiac Surgery: A Large, International, Prospective Cohort Study Establishing Diagnostic Criteria, Characteristics, Predictors, and 30-day Outcomes. Anesthesiology 2014;120:564–78.

35. Kristensen SD, Knuuti J, Saraste A, Anker S, Botker HE, Hert S de, Ford I, Gonzalez Juanatey JR, Gorenek B, Heyndrickx GR, Hoeft A, Huber K, Iung B, Kjeldsen KP, Longrois D, Luesher TF, Pierard L, Pocock S, Price S, Roffi M, Sirnes PA, Uva M, Voudris V, Funck-Brentano C. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management. The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesth. Eur J Anaesthesiol 2014;31:517–73.

36. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, Davila-Roman VG, Gerhard-Herman MD, Holly TA, Kane GC, Marine JE, Nelson MT, Spencer CC, Thompson A, Ting HH, Uretsky BF, Wijeysundera DN. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: A report of the American College of Cardiology/American Heart Association task force on practice guidelines. Circulation 2014;130:e278-e333.

37. Landesberg G, Mosseri M, Shatz V, Akopnik I, Bocher M, Mayer M, Anner H, Berlatzky Y, Weissman C. Cardiac troponin after major vascular surgery: the role of perioperative ischemia, preoperative thallium scanning, and coronary revascularization. J Am Coll Cardiol 2004;44:569–75.

38. Cohen MC, Aretz TH. Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. Cardiovasc Pathol 1999;8:133–9.

39. Gualandro DM, Campos CA, Calderaro D, Yu PC, Marques AC, Pastana AF, Lemos PA, Caramelli B. Coronary plaque rupture in patients with myocardial infarction after noncardiac surgery: frequent and dangerous. Atherosclerosis 2012;222:191–5.

40. Hanson I, Kahn J, Dixon S, Goldstein J. Angiographic and clinical characteristics of type 1 versus type 2 perioperative myocardial infarction. Catheter Cardiovasc Interv 2013;82:622–8.

41. Saaby L, Poulsen TS, Diederichsen ACP, Hosbond S, Larsen TB, Schmidt H, Gerke O, Hallas J, Thygesen K, Mickley H. Mortality rate in type 2 myocardial infarction: observations from an unselected hospital cohort. Am J Med 2014;127:295–302.

42. Foucrier A, Rodseth R, Aissaoui M, Ibanes C, Goarin J-P, Landais P, Coriat P, Manach Y Le. The Long-Term Impact of Early Cardiovascular Therapy Intensification for Postoperative Troponin Elevation after Major Vascular Surgery. Anesth Analg 2014;119:1053–63.

43. Chong CP, Gaal WJ van, Ryan JE, Profitis K, Savige J, Lim WK. Does cardiology intervention improve mortality for post-operative troponin elevations after emergency orthopaedic-geriatric surgery? A randomised controlled study. Injury 2012;43:1193–8.

Chapter 4

Kinetics of troponin I in patients with myocardial injury after noncardiac surgery

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Abstract

Background

Myocardial injury after noncardiac surgery, as measured by troponin elevation, is strongly associated with mortality. However, it is unknown in which patients prognosis can be improved. The presence of kinetic changes of troponin may be associated with a worse prognosis and warrant more aggressive management. Therefore, we aimed to study the kinetics of troponin in patients with postoperative myocardial injury, and to determine the added predictive value of kinetic changes of troponin on mortality.

Methods

This cohort study included patients with myocardial injury after noncardiac surgery. Troponin I (TnI) was measured on the first three postoperative days. The primary outcome was all-cause one-year mortality. We studied both absolute and relative TnI changes, and determined the delta TnI that was associated with mortality to distinguish a rise-and-fall TnI pattern from a stable TnI pattern. Next, we determined the added predictive value of a rise-and-fall TnI pattern for mortality.

Results

In total, 634 patients were included. The risk ratio (RR) for mortality increased significantly with an absolute delta TnI of ≥200 ng/L (RR 1.5, 99.4% CI 1.0-2.2, p=0.003). Using this delta TnI to define a rise-and-fall pattern, 459 patients (72%) had a stable TnI pattern and 175 patients (28%) had a rise-and-fall pattern. When added to a model including the highest TnI value and variables from the Revised Cardiac Risk Index, the TnI pattern did not increase the predictive value for mortality.

Conclusions

A postoperative TnI rise-and-fall pattern was associated with one-year mortality, but had no added value in addition to the highest TnI level to predict one-year mortality. Therefore, postoperative TnI kinetics are not useful for further mortality risk stratification in patients with myocardial injury after noncardiac surgery.

Introduction

Postoperative myocardial injury as measured by troponin elevation after noncardiac surgery is strongly associated with mortality.[1–3] Therefore, routine postoperative monitoring of cardiac biomarkers has been recommended to identify patients at risk.[4–6]

Routine troponin I (TnI) measurements were implemented in our hospital as part of our postoperative care protocol, in order to facilitate early identification and subsequent cardiovascular optimization of patients at risk of death. However, a major problem in initiating or optimizing treatment in individual patients is the lack of knowledge of the underlying etiology of myocardial injury in the postoperative phase.[7] When the cause of the injury is often not clear, it is difficult to determine in which patients prognosis can be improved. Consequently, in more than half of the patients the clinical course is awaited without any intervention.[8]unblinded screening with cardiac consultation per protocol was implemented at a tertiary care center. In this study, we evaluated 1-year mortality, causes of death, and consequences of cardiac consultation of this protocol. METHODS: This observational cohort included 3224 patients >/=60 years old undergoing major noncardiac surgery. Troponin I was measured routinely on the first 3 postoperative days. Myocardial injury was defined as troponin I >0.06 mug/L. Regression analysis was used to determine the association between myocardial injury and 1-year mortality. The causes of death, the diagnoses of the cardiologists, and interventions were determined for different levels of troponin elevation. RESULTS: Postoperative myocardial injury was detected in 715 patients (22%

Since the introduction of high sensitivity troponin assays, the number of patients in which elevated troponin is attributable to other conditions than myocardial infarction has increased.[9] Therefore, the pattern of cardiac biomarkers over time has become an important criterion in the diagnosis of myocardial infarction. A pattern with a rise and/or fall of troponin above the 99th percentile of the upper reference limit in the presence of clinical signs and symptoms is considered as evidence of myocardial infarction.[4] In the non-surgical population, absolute troponin changes discriminate well between acute myocardial infarction and other causes of myocardial injury, and have high accuracy in identifying candidates for early coronary angiography.[10] Likewise, the presence of kinetic changes of troponin in the postoperative phase may reflect clinically relevant myocardial ischemia that is associated with a worse prognosis and that warrants more aggressive therapy as compared to troponin elevation without kinetic changes. This may help to identify patients who require follow up and treatment, but evidence for this hypothesis is lacking.

We therefore aimed to study the kinetics of troponin in patients with myocardial injury after noncardiac surgery, and to determine the added predictive value of kinetic changes of troponin on one-year mortality.

Materials and Methods

Patients

This observational cohort study included consecutive patients undergoing noncardiac surgery between January 1st 2011 and December 31st 2012 at the University Medical Center Utrecht, The Netherlands, a 1,000 bed tertiary referral hospital. Patients were eligible if they were aged 60 years or older, were undergoing intermediate to high risk noncardiac surgery under general or spinal anesthesia with an expected postoperative length of hospital stay of at least 24 hours. In these patients, troponin was measured routinely on the first three postoperative days as part of our postoperative care protocol. Patients who had troponin elevation after surgery were included in this study. For patients who underwent surgery more than once, the first surgery was included in the analyses. A reoperation was included as a novel case if this surgery took place at least one year after the first surgery. Patients were excluded if troponin was not measured or measured only once after surgery, or if patients were lost to follow-up within one year after surgery.

The local medical ethics committee waived the need for informed consent, as only routinely collected patient data were used and data were anonymized before analysis (UMC Utrecht Medical Research Ethics Committee, protocol number 11/120-C).

Data collection

All preoperative and postoperative data were obtained from electronic medical and administrative records. Data collected of all patients included patient characteristics, preoperative physical status, comorbidities including factors from the Revised Cardiac Risk Index (RCRI),[11] postoperative TnI measurements and one-year mortality. Emergency surgery was defined as surgery required within 72 hours. High risk surgery was defined as intrathoracic, intra-abdominal or suprainguinal vascular surgery.[11] Ischemic heart disease was defined as a history of myocardial infarction or coronary revascularization. Preoperative renal insufficiency was defined as a preoperative glomerular filtration rate <45 ml/min/1.73m^2. Chronic heart failure was defined as a left ventricular ejection fraction <40%. The municipal personal records database was consulted for mortality data.

Routine Postoperative Troponin Measurements

According to the postoperative care protocol for older surgical patients in our hospital, the occurrence of postoperative myocardial injury was assessed routinely by TnI measurements. TnI was measured daily in the morning on the first three postoperative days. In case of a TnI elevation above the clinical cut-off level (TnI >60 ng/L), the ward physician was notified and a cardiac consult was requested. It was left at the discretion of the ward physician and cardiologist whether follow-up of TnI and further diagnostic

procedures were indicated. Myocardial infarction was diagnosed by the cardiologist according to the third universal definition by judging the height of the TnI level, the presence or absence of a rise and fall in TnI, clinical symptoms, electrocardiography and/or cardiac imaging. In this, a rise and fall in TnI was not defined beforehand.[4]

In the current study, for each patient all postoperative TnI measurements within ten days after surgery were used, including follow-up measurements in addition to the routine TnI measurements. Troponin elevation was defined as a TnI >60 ng/L, which was the lowest value measurable with a 10% coefficient of variation above the 99th percentile of 40 ng/L of the assay used. TnI was analyzed using the third-generation enhanced AccuTnI assay (Beckman Coulter, Brea, California).

Kinetics of troponin

For each patient we first expressed the kinetics of troponin in terms of the absolute and relative change in TnI. The absolute change in TnI was defined as the highest minus the lowest postoperative TnI value. The relative change in TnI was defined as the difference between the highest and the lowest postoperative TnI value, divided by the lowest TnI value.

Subsequently, we categorized patients according to their pattern of TnI changes into two categories (stable pattern and rise-and-fall pattern) as follows. First, we identified potential cut-off values of the highest TnI value and the absolute and relative change in TnI, by grouping patients in deciles, and rounding to the nearest tenths or hundredths. For the highest TnI value, this resulted in the following TnI categories: 70-79 ng/L, 80-89 ng/L, 90-99 ng/L, 100-129 ng/L, 130-169 ng/L, 170-259 ng/L, 260-499 ng/L, 500-1499 ng/L and ≥1500 ng/L. Next, the risk ratio for mortality was calculated for each of these cut-off values. Because nine different cut-off values were tested, Bonferroni correction was used to adjust for multiple comparisons, resulting in a 99.4% confidence interval (p value of 0.05/9=0.006) as level of statistical significance. Based on these results, the change in TnI for which the risk of mortality was increased, was used as a cut-off value to distinguish a stable TnI pattern from TnI patterns with a rise and fall. In assigning each of the patients to either one of the patterns (stable pattern, rise-and-fall) patients with only a rise in TnI or only a fall in TnI were taken together with patients with a rise-and-fall pattern; i.e. these patients were considered to actually have a rise-and-fall pattern where the initial rise or the fall was not measured.

Outcomes

The primary outcome was all-cause mortality within one year after surgery. Postoperative myocardial infarction, defined according to the third universal definition,[4] was included as a secondary outcome.

Statistical analysis

Baseline characteristics were compared between the two different patterns of TnI that we identified. Categorical variables were compared using the Chi-square test and age was compared using the two-sample t-test. The number of TnI measurements was compared between these two groups using the Mann-Whitney-U test.

The highest TnI value and the absolute and relative change in TnI were then compared between patients who were deceased and alive after one year, and between patients with and without postoperative myocardial infarction using the Mann-Whitney-U test. We compared one-year survival between patients with a stable TnI pattern and a rise-and-fall pattern using Kaplan-Meier analysis and the log-rank test.

Cox regression analysis was used to determine the hazard ratio for mortality in patients with a rise-and-fall pattern, as compared to a stable TnI pattern. Multivariable cox regression analysis was used to determine the added predictive value of the TnI pattern on one-year mortality on top of the highest TnI value and RCRI variables. Therefore, we compared the predictive value of a multivariable model including the highest TnI value, RCRI variables and the TnI pattern to a model only including the highest TnI value and RCRI variables using the area under the receiver operating curve (AUROC).

Next, we compared cardiac interventions between the patients with a stable TnI pattern and a rise-and-fall pattern. Furthermore, in the patients with myocardial infarction, we compared one-year mortality between the patients with a stable TnI pattern and a rise-and-fall pattern using the Chi-square test.

Finally, we considered that patients with evident non-cardiac causes of TnI elevation, i.e. patients with sepsis or severe intracranial pathology, may confound the results. Therefore we conducted a sensitivity analysis after exclusion of these patients.

The analysis was performed using SPSS (release 21.0 for Windows). Throughout the analysis a level of significance of 0.05 was used, apart from the aforementioned adaptation of the alpha to 0.006 in the definition of the TnI pattern.

Results

During the study period 4,105 patients were eligible for inclusion, of which 55 (1%) patients were excluded: four patients were transferred to another hospital on the day of surgery, 19 patients died on the day of surgery, hence TnI could not be measured in these patients, and 32 patients were lost to follow up as mortality data could not be obtained from the municipal personal records database. Of the remaining 4,050 patients, TnI was measured after surgery in 3,224 (80%) patients. TnI was elevated in 715 (22%) of these 3,224 patients. From these 715 patients, 66 were excluded because TnI was only measured once, hence the change in TnI could not be calculated. In addition,

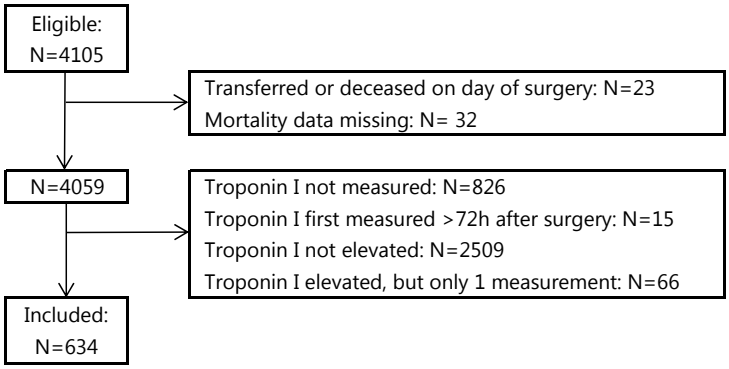

Figure 4.1 *Flow chart of patient inclusion.*

in 15 patients the first elevated TnI was measured on clinical indication at >72h after the start of surgery, and was not part of the postoperative care protocol, and therefore they were excluded. In total, 634 patients were included in the analysis (Figure 4.1).

Figure 4.2 shows the risk ratios (RR) for one-year mortality for several cutoff values. The risk of mortality increased significantly with peak TnI values ≥90 ng/L (RR 1.9, 99.4% CI 1.1-3.1, p=0.001). Furthermore, the risk of mortality increased significantly with an absolute change in TnI of ≥200 ng/L (RR 1.5, 99.4% CI 1.0-2.2, p=0.003), i.e. this was the lowest absolute change at which the risk of mortality was significantly increased. The risk of mortality was not increased for relative changes in TnI. Based on these results, an absolute change in TnI ≥200 ng/L was used as a cutoff level to distinguish a rise-and-fall pattern from a stable pattern.

Of the 634 patients, 459 patients (72%) had a stable TnI pattern, 110 patients (17%) had a rise-and-fall pattern, 26 patients (4%) had a rising pattern, and 39 patients (6%) had a falling pattern. In the further analysis, the patients with a rising pattern or a falling pattern were taken together with the patients with a rise-and-fall pattern. Baseline characteristics, stratified for the different TnI patterns, are given in Table 4.1. Patients with a rise-and-fall pattern more often had diabetes and renal insufficiency, used more cardiovascular medications, and more often underwent vascular surgery and re-operations as compared to patients with a stable TnI pattern. The median number of TnI measurements was 4 (interquartile range (IQR) 3-5) in patients with a rise-and-fall pattern, as compared to 3 measurements (IQR 3-3) in patients with a stable pattern.

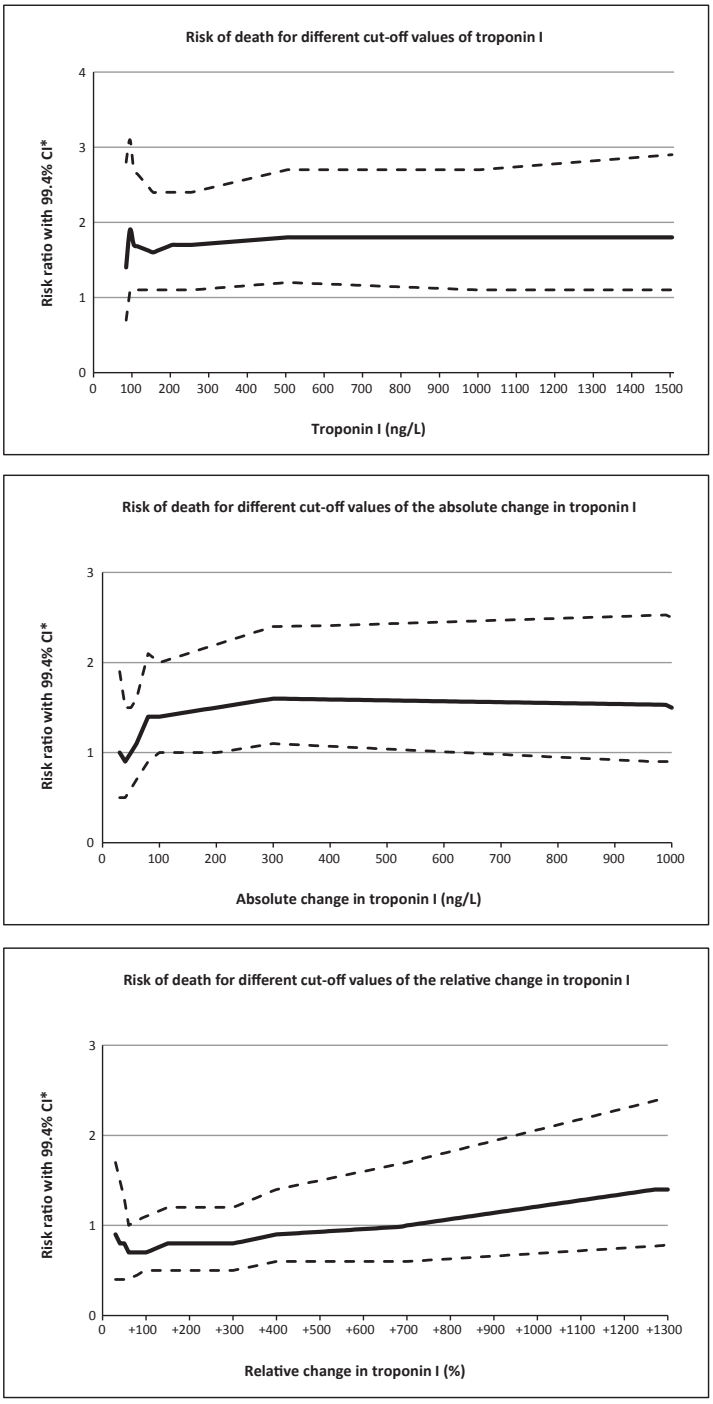

Figure 4.2 *Risk of one-year mortality for different cut-off values of the highest TnI value, the absolute change in TnI, and the relative change in TnI. *Confidence interval*

Table 4.1 *Baseline characteristics, stratified by the pattern of postoperative TnI measurements.*

	Tn stable: ΔTn <200 ng/L N=459		Tn rise-and-fall: ΔTn ≥200 ng/L N=175		p-value
Male	283	(62.0)	98	(56.0)	0.19
Mean age (SD*)	73.0	(8.2)	73.1	(8.2)	0.94
Hypertension	280	(61.0)	114	(65.1)	0.34
Diabetes	84	(18.3)	46	(26.3)	0.03
History of myocardial infarction	61	(13.3)	33	(18.9)	0.08
History of coronary revascularization	84	(18.3)	35	(20.0)	0.62
Chronic heart failure	24	(5.2)	10	(5.7)	0.81
(Paroxysmal) atrial fibrillation	72	(15.7)	23	(13.1)	0.42
Pacemaker and/or ICD†	21	(4.6)	10	(5.7)	0.55
History of cerebrovascular disease	80	(17.4)	39	(22.3)	0.16
Chronic obstructive pulmonary disease	52	(11.3)	18	(10.3)	0.71
Preoperative renal insufficiency	85	(18.5)	50	(28.6)	<0.01
Peripheral vascular disease	66	(14.4)	34	(19.4)	0.12
Chronic medication use					
Beta blockers	177	(38.6)	68	(38.9)	0.95
Angiotensin renin blockers	179	(39.0)	84	(48.0)	0.04
Calcium channel blockers	89	(19.4)	36	(20.6)	0.74
Diuretics	148	(32.2)	57	(32.6)	0.94
Statins	187	(40.7)	89	(50.9)	0.02
Aspirin	159	(34.6)	83	(47.4)	0.03
Warfarins	70	(15.3)	18	(10.3)	0.11
ASA class Δ					
1	36	(7.8)	9	(5.1)	0.51
2	265	(57.7)	98	(56.0)	
≥3	158	(34.4)	68	(38.9)	
General anesthesia	442	(96.3)	170	(97.1)	0.60
High risk surgery	200	(43.6)	83	(47.4)	0.38
Emergency surgery	148	(32.2)	65	(37.1)	0.24
Re-operation within 1 year	99	(21.6	55	(31.4)	0.01
Surgical specialty					
General	162	(35.3)	57	(32.6)	0.16
Neuro	89	(19.4)	28	(16.0)	
Vascular	81	(17.6)	49	(28.0)	
ENT[ǂ] and dental	45	(9.8)	13	(7.4)	
Orthopedic	54	(12.0)	20	(11.4)	
Gynaecology/Urologic	28	(6.1)	8	(4.6)	

Figures are numbers of patients (%), unless indicated otherwise.
**Standard Deviation;†Implantable Cardiovertor Defibrillator; Δ Classification system by the American Society of Anesthesiologists; ǂEar Nose Throat.*

Primary outcome

One-year mortality occurred in 155 (24%) patients. In patients who died, the median highest TnI value was 190 ng/L (IQR 100-660 ng/L), as compared to 120 ng/L in patients who were alive (IQR 80-280 ng/L, p<0.01). The median absolute change in TnI was 110 ng/L (IQR 50 – 460 ng/L) in patients who died within one year, as compared to 71 ng/L (IQR 50 – 180 ng/L) in patients who survived (p=0.02). The median relative change in TnI was +175% in patients who died (IQR +60% – +510%), as compared to +243% in alive patients (IQR +96% – +600%) (p=0.18) (Figure 4.3).

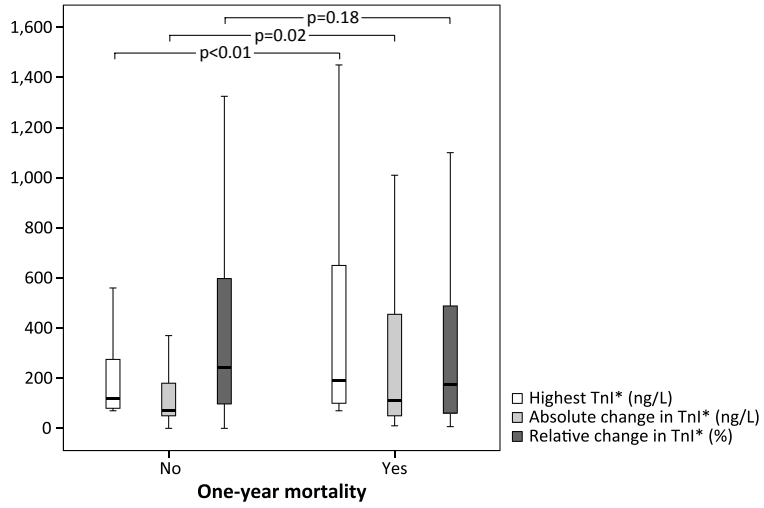

Figure 4.3 *The median highest troponin I value, the median absolute change in troponin I, and the median relative change in troponin I in patients who died within one year and patients who survived. *Troponin I*

One-year survival was better in patients with a stable TnI pattern, as compared to patients with a rise-and-fall or falling TnI pattern (Figure 4.4).

Univariable regression analysis showed that the hazard ratio for mortality was 1.7 (95% CI 1.2-2.3, p<0.01) in patients with a rise-and-fall pattern as compared to patients with a stable TnI pattern. After adjustment for the highest TnI value and the variables from the RCRI, the TnI pattern was not associated with mortality (Table 4.2). Adding the TnI pattern to a model including the highest TnI value and the RCRI variables did not increase the predictive value on mortality: AUROC 0.67 (95% CI 0.62-0.72) versus 0.66 (95% CI 0.61-0.71).

A sensitivity analysis excluding patients with evident non-cardiac causes of TnI elevation, i.e. intracerebral pathology (N=6) or sepsis (N=6) did not alter the results.

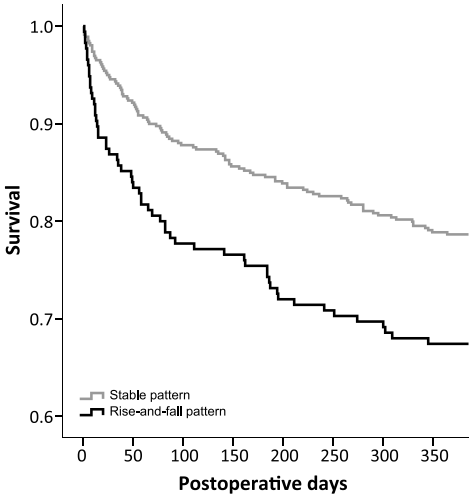

Figure 4.4
Survival curve of patients with different TnI patterns. A stable troponin I pattern was defined as an absolute change in TnI <200 ng/L, and a rise-and-fall pattern was defined as an absolute change in TnI ≥200 ng/L.

Table 4.2 *The hazard ratio of one-year mortality in patients with a rise-and-fall pattern as compared to a stable TnI pattern, adjusted for the highest TnI value and variables from the Revised Cardiac Risk Index.*

	Adjusted analysis		
	*HR**	*95% CI†*	*p-value*
TnI pattern			
Stable (absolute change in TnI <200 ng/L)	*ref*		
Rise-and-fall (absolute change in TnI ≥200 ng/L)	0.5	0.3 – 1.1	0.11
Highest TnI value (ng/L)			
70-79	*ref*		
80-89	0.7	0.3-1.5	0.35
90-99	1.5	0.7-3.5	0.31
100-129	1.4	0.7-2.7	0.31
130-169	1.0	0.5-2.1	0.96
170-259	1.9	1.0-3.7	0.06
260-499	1.9	0.9-4.3	0.10
500-1499	4.1	1.5-10.7	<0.01
≥ 1500	4.3	1.7-11.0	<0.01
Revised Cardiac Risk Index			
High risk surgery	1.0	0.7-1.4	0.89
Ischemic heart disease	0.9	0.6-1.3	0.57
Chronic heart failure	1.1	0.6-2.2	0.70
Cerebrovascular disease	1.1	0.6-1.7	0.84
Preoperative renal insufficiency	2.1	1.5-3.0	<0.01
Insulin use	1.0	0.6-1.7	0.98

**Hazard Ratio; †Confidence Interval*

Secondary outcome

Ninety patients (14%) fulfilled the criteria of myocardial infarction. In those patients, the median highest TnI value was 745 ng/L (IQR 160-6335 ng/L), as compared to 120 ng/L (IQR 80-260 ng/L) in patients without myocardial infarction (p<0.01). The median absolute change in TnI was 525 ng/L (IQR 68 – 4955 ng/L) in patients with myocardial infarction, as compared to 70 ng/L (50 – 160 ng/L) in patients without (p<0.01). The median relative change in TnI was +375% (IQR +67% – +3029%) in patients with myocardial infarction, as compared to +200% (IQR +80% – +450%) in patients without (p<0.01).

Of the 90 patients with postoperative myocardial infarction, 34 patients (38%) had a stable TnI pattern, and 56 (62%) had a rise-and-fall pattern. In these patients with myocardial infarction, mortality within one year occurred in 26 of the 56 patients (46%) with a rise-and-fall pattern, as compared to 9 of the 34 patients (26%) with a stable pattern (p=0.06).

Cardiac interventions in patients with different TnI patterns

A cardiac consultation was performed in 130 (74%) of the 175 patients with a rise-and-fall pattern, as compared to 141 (31%) of the 459 patients with a stable pattern (p<0.01). This was followed by an intervention in 61 patients (35%) as compared to 42 patients (9%) (p<0.01). New medication or a dose increase, including beta-blockers, renin-angiotensin inhibitors, calcium channel blockers, diuretics, statins, aspirin, other

Table 4.3 *Cardiology consultation and cardiac interventions, stratified by the pattern of postoperative TnI measurements.*

	Tn stable: ΔTn <200 ng/L N=459		Tn rise-and-fall: ΔTn ≥200 ng/L N=175		p-value
Cardiology consultation	141	(30.7)	130	(74.3)	<0.01
Any intervention	42	(9.2)	61	(34.9)	<0.01
New prescribed medication or dose increase	37	(8.1)	60	(34.3)	<0.01
Beta blockers	12	(2.6)	37	(21.1)	<0.01
Other antihypertensive drugs*	7	(1.5)	12	(6.9)	<0.01
Statins	5	(1.1)	16	(9.1)	<0.01
Aspirin	10	(2.3)	24	(13.7)	<0.01
Other antiplatelet drugs	0	(0)	14	(8.0)	<0.01
(Low molecular weight) heparin	10	(2.3)	15	(8.6)	<0.01
Other	13	(2.8)	10	(5.7)	0.08
Cardiac monitoring	4	(0.9)	11	(6.3)	<0.01
Coronary angiography	2	(0.4)	12	(6.9)	<0.01
Percutaneous coronary intervention	1	(0.2)	7	(4.0)	<0.01
Coronary artery bypass grafting	0	(0)	1	(0.6)	0.11

Figures are numbers of patients (%).
**including renin angiotensin blockers, calcium channel blockers and diuretics*

antiplatelet drugs, and (low molecular weight) heparin, was prescribed in 60 patients with a rise-and-fall pattern (34%), as compared to 37 patients (8%) with a stable pattern ($p<0.01$). Of the patients with a rise-and-fall pattern, more patients were transferred to the coronary care unit or medium care unit for cardiac monitoring, more patients underwent coronary angiography, and more patients underwent percutaneous coronary intervention (Table 4.3).

Discussion

To help clinicians in interpreting postoperative troponin elevation, we described the kinetic changes of TnI in patients with myocardial injury after noncardiac surgery using troponin values that were routinely measured as part of a clinical protocol. In addition, the added predictive value of kinetic changes in TnI after noncardiac surgery to predict one-year mortality was determined.

Among patients with myocardial injury after surgery, we found that an absolute change in TnI of at least 200 ng/L was associated with mortality. Such a change showing a rise-and-fall pattern was found in 28% of patients. Adding the absolute TnI change to a model including the highest TnI level, did not improve the ability to predict mortality. Relative changes in TnI did not predict mortality.

Limitations

This study has some obvious limitations. First of all, since TnI was not measured before surgery, the results of this study cannot be used to interpret postoperative TnI values in relation to preoperative values. The patients with a stable TnI pattern after surgery may in fact have had a rise-and-fall pattern in relation to a preoperative value, i.e. in those patients the perioperative rise and fall may have been missed because TnI was not measured before surgery. However, this study determined the additional value of TnI kinetics in patients in whom troponin is only measured after surgery, like in our standard postoperative care. In the future, it would be of interest to study postoperative troponin changes in relation to preoperative values. Second, because follow-up of elevated TnI levels was not strictly protocolized, yet was performed at discretion of the attending cardiologist, TnI was not measured every 4-6 hours in all patients. Therefore, a rise-and-fall pattern may have been missed in some patients. Finally, the analysis was not adjusted for treatment interventions that were undertaken in patients with myocardial injury and that may have influenced prognosis. This may have led to an underestimation of the predictive value of TnI kinetics.

Literature

Kinetics of troponin have been well studied and implemented in the diagnosis of myocardial infarction in patients suspected of acute coronary syndrome in a non-perioperative setting. Although a relative change in troponin of >20% is considered to be diagnostic for myocardial infarction in patients after percutaneous coronary intervention or reinfarction,[4] absolute troponin changes are superior to relative changes in discriminating myocardial infarction in patients presenting in the emergency department.[10,12–15]whether rising or falling patterns of high-sensitivity cardiac troponin T (hs-cTnT Absolute TnI changes discriminate well between acute myocardial infarction and cardiac noncoronary artery disease, and are useful in selecting patients who require invasive treatment.[10] To predict outcome however, TnI changes do not improve risk prediction as compared to absolute troponin values and clinical risk factors.[16]

Few studies have evaluated troponin kinetics in the perioperative period. Kavsak and colleagues studied relative changes of postoperative troponin T (TnT) in vascular surgery patients by using two cut-off levels that were based on previous studies in healthy volunteers and patients suspected of acute coronary syndrome.[17] They reported that half of the patients with postoperative troponin elevation had a relative change in TnT >85% as compared to the preoperative TnT level, and one in four patients had a relative TnT change >242%. Gillmann and colleagues studied both absolute and relative changes in patients undergoing vascular surgery, and found that an absolute change in TnT of as small as 6 ng/L, as compared to the preoperative TnT level, was independently associated with major adverse cardiac events, and that adding the TnT absolute change to clinical risk factors improved the predictive accuracy for major adverse cardiac events.[18] These results differ from our study, which may be explained by the fact that they calculated postoperative troponin changes in relation to preoperative troponin levels, while we only studied postoperative troponin values. Furthermore, Gillmann and colleagues reported that absolute TnT changes were superior to relative TnT changes for perioperative risk prediction, which is in concordance with our finding that relative changes were not related to mortality.[18]

Clinical implications

Several studies have shown that myocardial injury after noncardiac surgery as measured by troponin elevation, is an independent predictor of mortality. Yet, because troponin elevation may occur in a variety of conditions and the cause of myocardial injury is often unclear, it is not known in which patients prognosis can be improved. Therefore, improved risk stratification of patients with myocardial injury is warranted. Since kinetic changes of cardiac biomarkers, described as a typical rise and fall, are the cornerstone in the diagnosis of myocardial infarction in the non-perioperative setting, kinetic changes of troponin may be considered important in the further assessment of

prognosis in patients with myocardial injury after surgery. Although we found that postoperative absolute TnI changes of more than 200 ng/L are associated with mortality, these absolute TnI changes had no added value to predict mortality in addition to the highest TnI level. Since absolute changes are larger in patients with high TnI levels, a large absolute change in TnI is inherent to high TnI values, which may explain why TnI changes alone do not have any added predictive value to absolute values. Furthermore, relative changes were not associated with mortality, which may be explained by the fact that relative changes cannot distinguish a patient with low TnI levels, and therefore a relatively good prognosis, from a patient with very high TnI levels and a poor prognosis, e.g. the relative change in TnI from 80 ng/L to 120 ng/L is similar to the relative change in TnI from 2000 ng/L to 3000 (both +50%).

Of note, 38% of the patients with a postoperative myocardial infarction did not show a rise-and-fall in TnI as determined in this study (absolute change >200 ng/L), although a rise-and-fall is required according to the third universal definition of myocardial infarction. This finding highlights an important problem in interpreting the universal definition: since the rise-and-fall that is required to diagnose myocardial infarction is not defined, in fact any change in troponin may be considered a rise-and-fall, hence even patients with very small changes may be diagnosed with myocardial infarction. This issue may be further complicated by the use of high sensitivity troponin assays: it has been shown that when high sensitivity troponin assays are used, the use of troponin changes on top of absolute troponin values improves specificity but reduces sensitivity in patients who are suspected of myocardial infarction in the emergency department.[19] In the perioperative setting, the use of troponin changes as detected by high sensitivity assays are subject to further investigation.

Although only 43% of all patients had cardiology consultation, and interventions were only performed in 24% of patients, this was done more often in patients with a rise-and-fall pattern (in 74% and 35% of patients, respectively). Apparently, cardiologists were more likely to adjudicate a TnI rise-and-fall pattern as a myocardial infarction.

Conclusions

Among patients with myocardial injury after noncardiac surgery, as detected by routine postoperative TnI measurements, kinetics of postoperative TnI showed a rise-and-fall pattern in one third of patients. An absolute change in TnI of more than 200 ng/L was associated with one-year mortality, but had no added predictive value in addition to the highest TnI level. Therefore, we consider TnI kinetics not useful for further stratification of mortality risk in patients with postoperative myocardial injury.

References

1. Levy MM, Heels-Ansdell D, Hiralal R, Bhandari M, Guyatt G, Yusuf S, Cook D: Prognostic Value of Troponin and Creatine Kinase Muscle and Brain Isoenzyme Measurement after Noncardiac Surgery. Anesthesiology 2011; 114:796–806
2. The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators: Association Between Postoperative Troponin Levels and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. JAMA 2012; 307:2295–304
3. Waes JAR van, Nathoe HM, Graaff JC de, Kemperman H, Borst GJ de, Peelen LM, Klei WA van: Myocardial injury after noncardiac surgery and its association with short-term mortality. Circulation 2013; 127:2264–71
4. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand J-P, Menasché P, Ravkilde J, Ohman EM, Antman EM, et al.: Third universal definition of myocardial infarction. Circulation 2012; 126:2020–35
5. Kristensen SD, Knuuti J, Saraste A, Anker S, Botker HE, Hert S de, Ford I, Gonzalez Juanatey JR, Gorenek B, Heyndrickx GR, Hoeft A, Huber K, Iung B, Kjeldsen KP, Longrois D, Luesher TF, Pierard L, Pocock S, Price S, Roffi M, Sirnes PA, Uva M, Voudris V, Funck-Brentano C: 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management. The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesth. Eur. J. Anaesthesiol. 2014; 31:517–73
6. Longo DL, Devereaux PJ, Sessler DI: Cardiac Complications in Patients Undergoing Major Noncardiac Surgery. N. Engl. J. Med. 2015; 373:2258–69
7. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, Davila-Roman VG, Gerhard-Herman MD, Holly TA, Kane GC, Marine JE, Nelson MT, Spencer CC, Thompson A, Ting HH, Uretsky BF, Wijeysundera DN: 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: A report of the American College of Cardiology/American Heart Association task force on practice guidelines. 2014; 130:2246-64
8. Waes JAR van, Grobben RB, Nathoe HM, Kemperman H, Borst GJ de, Peelen LM, Klei WA van: One-Year Mortality, Causes of Death, and Cardiac Interventions in Patients with Postoperative Myocardial Injury. Anesth. Analg. 2016; 123:29–37
9. Hamm CW: Cardiac Troponin Elevations in Patients Without Acute Coronary Syndrome. Circulation 2002; 106:2871–2
10. Haaf P, Drexler B, Reichlin T, Twerenbold R, Reiter M, Meissner J, Schaub N, Stelzig C, Freese M, Heinzelmann A, Meune C, Balmelli C, Freidank H, Winkler K, Denhaerynck K, Hochholzer W, Osswald S, Mueller C: High-sensitivity cardiac troponin in the distinction of acute myocardial infarction from acute cardiac noncoronary artery disease. Circulation 2012; 126:31–40
11. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, Ludwig LE, Pedan A, Goldman L: Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999; 100:1043–9

12. Biener M, Mueller M, Vafaie M, Jaffe AS, Widera C, Katus HA, Giannitsis E: Diagnostic performance of rising, falling, or rising and falling kinetic changes of high-sensitivity cardiac troponin T in an unselected emergency department population. Eur. Hear. journal. Acute Cardiovasc. care 2013; 2:314–22

13. Irfan A, Reichlin T, Twerenbold R, Meister M, Moehring B, Wildi K, Bassetti S, Zellweger C, Gimenez MR, Hoeller R, Murray K, Sou SM, Mueller M, Mosimann T, Reiter M, Haaf P, Ziller R, Freidank H, Osswald S, Mueller C: Early diagnosis of myocardial infarction using absolute and relative changes in cardiac troponin concentrations. Am. J. Med. 2013; 126:781–8.e2

14. Mueller M, Biener M, Vafaie M, Doerr S, Keller T, Blankenberg S, Katus HA, Giannitsis E: Absolute and relative kinetic changes of high-sensitivity cardiac troponin T in acute coronary syndrome and in patients with increased troponin in the absence of acute coronary syndrome. Clin. Chem. 2012; 58:209–18

15. Reichlin T, Irfan A, Twerenbold R, Reiter M, Hochholzer W, Burkhalter H, Bassetti S, Steuer S, Winkler K, Peter F, Meissner J, Haaf P, Potocki M, Drexler B, Osswald S, Mueller C: Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. Circulation 2011; 124:136–45

16. Biener M, Mueller M, Vafaie M, Jaffe AS, Katus HA, Giannitsis E: Prognostic performance of high-sensitivity cardiac troponin T kinetic changes adjusted for elevated admission values and the GRACE score in an unselected emergency department population. Clin. Chim. Acta. 2014; 435:29–35

17. Kavsak PA, Walsh M, Srinathan S, Thorlacius L, Lurati Buse G, Botto F, Pettit S, McQueen MJ, Hill S a, Thomas S, Mrkobrada M, Alonso-Coello P, Berwanger O, Biccard BM, Cembrowski G, Chan MT V, Chow CK, Miguel A de, Garcia M, Graham MM, Jacka MJ, Kueh JH, Li SCH, Lit LCW, Martínez-Brú C, Naidoo P, Nagele P, Pearse RM, Rodseth RN, Sessler DI, et al.: High sensitivity troponin T concentrations in patients undergoing noncardiac surgery: a prospective cohort study. Clin. Biochem. 2011; 44:1021–4

18. Gillmann H-J, Meinders A, Grohennig A, Larmann J, Bünte C, Calmer S, Sahlmann B, Rustum S, Aper T, Lichtinghagen R, Koch A, Teebken OE, Theilmeier G: Perioperative levels and changes of high-sensitivity troponin T are associated with cardiovascular events in vascular surgery patients. Crit. Care Med. 2014; 42:1498–506

19. Aldous SJ, Florkowski CM, Crozier IG, Elliott J, George P, Lainchbury JG, Mackay RJ, Than M: Comparison of high sensitivity and contemporary troponin assays for the early detection of acute myocardial infarction in the emergency department. Ann. Clin. Biochem. 2011; 48:241–8


cTnI
78/54 MMHG
cTnI
90/65 mmHg
type 1 MI
type 2 MI
ischemia
Hb 5.7 mmol/L
78/54 MMHG
HR 96 bpm
type 1 MI
90/65 mmHg
85/40 mmHg
78/54

PART II

DETERMINANTS OF MYOCARDIAL INJURY AFTER NONCARDIAC SURGERY

Chapter 5

Association between intraoperative hypotension and myocardial injury after vascular surgery

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Abstract

Background

Postoperative Out determine the association between IOH and postoperative myocardial injury.

Methods

This cohort study included 890 consecutive patients aged ≥60 years undergoing vascular surgery from two university centers. The occurrence of myocardial injury was assessed by troponin measurements as part of a postoperative care protocol. Intraoperative hypotension was defined by four different thresholds using either relative or absolute values of the mean arterial blood pressure, based on prior studies. Either invasive or noninvasive blood pressure measurements were used. Poisson regression analysis was used to determine the association between IOH and postoperative myocardial injury, adjusted for potential clinical confounders and multiple comparisons.

Results

Depending on the definition used, IOH occurred in 12-81% of the patients. Postoperative myocardial injury occurred in 131 (29%) patients with IOH as defined by a MAP <60 mmHg, as compared to 87 (20%) patients without IOH (p=0.001). After adjustment for potential confounding factors including mean heart rates, a 40% decrease from the pre-induction mean arterial blood pressure with a cumulative duration of more than 30 minutes was associated with postoperative myocardial injury (RR 1.8, 99% CI 1.2-2.6, p<0.001). Shorter cumulative durations (<30 minutes) were not associated with myocardial injury. Postoperative myocardial infarction and death within 30 days occurred in 26 (6%) and 17 (4%) patients with IOH as defined by a MAP <60 mmHg, as compared to 12 (3%) (p= 0.08) and 15 (3%) (p=0.77) patients without IOH, respectively.

Conclusions

In elderly vascular surgery patients, IOH as defined as a 40% decrease from the pre-induction mean arterial blood pressure with a cumulative duration of more than 30 minutes was associated with postoperative myocardial injury.

Introduction

Myocardial infarction after surgery remains one of the leading causes of postoperative complications in the more than 100 million global surgeries annually. Moreover, patients who suffer from (silent) postoperative myocardial injury are at an increased risk of mortality.[1,2] Myocardial injury is detected by elevated cardiac biomarker levels in 12-19% of older patients after intermediate to high risk noncardiac surgery,[1,2] and in up to 27% of patients after vascular surgery.[3–5] The prevention and treatment of myocardial injury may reduce these adverse events. Despite major undertakings, efforts to reduce this important public health issue have so far proved largely unsuccessful. The side effects related to prophylactic suppression of the compensatory sympathetic effects of surgery or the inhibition of platelet function have been shown to outweigh the benefits in several major clinical trials.[6–8] In these trials, perioperative hypotension was reported to be associated with postoperative myocardial infarction. The majority of this hypotension occurs during surgery and represents a potentially modifiable risk factor.[8]

The predominant theory suggests that the etiology of postoperative myocardial injury is due to ischemia.[9,10] Postoperative myocardial ischemia is most commonly seen in patients with diffuse coronary artery disease and predominately the result of an imbalance between myocardial oxygen supply and demand. Hypotension has historically been thought to contribute to this ischemic imbalance by causing a decreased oxygen supply.[11] Intraoperative hypotension has also been implicated in ischemia-reperfusion injury to the heart, brain, and kidneys, and is associated with death.[6,12–16]

Since intraoperative hypotension may be modifiable, it would be imperative to understand if there exists a threshold below which myocardial injury increases. Several definitions of intraoperative hypotension have already been studied, and the association between hypotension and the degree of associated tissue injury varies widely and mostly depends on the definition of hypotension.[17] In the Perioperative Ischemic Evaluation (POISE) trials, hypotension was poorly defined, i.e. a systolic blood pressure <90 mmHg.[6,8] In cohort studies, intraoperative mean blood pressure levels below 50 mmHg and 55 mmHg, and a 40% decrease in mean arterial blood pressure were reported to be associated with myocardial injury.[12,18] The results of these cohort studies must be interpreted cautiously since blood sampling for cardiac biomarkers was only performed in high-risk patients or in those with clinical evidence of myocardial ischemia, which may have led to an unresolved ascertainment bias.[19]

The primary objective of the current investigation was to determine whether intraoperative hypotension, as defined by four different blood pressure thresholds, is associated with the occurrence of postoperative myocardial injury. Vascular surgery patients were the population of interest since they have a high degree of epicardial coronary artery disease, are thought to be less able to tolerate hypotension and are

also known to have increased risk of postoperative myocardial injury. We used intraoperative clinical care data from two university hospitals where blood pressure was measured frequently and selection bias was minimized since biomarkers were assessed routinely after surgery in all patients.

Materials and Methods

Patients

This two-center cohort study included consecutive patients undergoing vascular surgery at the University Health Network Hospital Toronto (UHNT), Canada between January 1, 2010 and December 31, 2011, and at the University Medical Center Utrecht (UMCU), The Netherlands between January 3, 2011, and December 15, 2011. Patients were eligible if they were aged ≥60 years and were having vascular surgery under general anesthesia or a combination of regional and general anesthesia. In patients who underwent surgery more than once, only the first surgery was included in the analyses. A reoperation was included as a novel case if this surgery took place during another hospital admission and at least 30 days after the first surgery. Patients were excluded if intraoperative blood pressure measurements or postoperative troponin measurements were not available. The local ethics committees from both centers waived the need for informed consent (UHNT Research Ethics Board, Toronto, Canada, protocol number 06-0193-AE; and the UMCU Medical Research Ethics Committee, Utrecht, The Netherlands, protocol number 12-425). All data were anonymized before analysis.

Data collection

All preoperative data were obtained from electronic medical records, including patient characteristics, preoperative physical status, comorbidities, type of procedure and postoperative troponin levels. Intraoperative data including blood pressure measurements, heart rate and blood loss were collected from the anesthesia information management systems. In these systems, each minute of heart rate and invasive blood pressure measurements is averaged and then the data are stored. Non-invasive blood pressure measurements are generally stored every 3-5 minutes.

Intraoperative hypotension

In this study we have used four previously defined thresholds for intraoperative hypotension (IOH); two absolute Mean Arterial Pressure (MAP) thresholds (MAP <50 mmHg and MAP <60 mmHg), and two thresholds relative to the pre-induction MAP (a decrease of ≥30% and a decrease of ≥40%).[14,17] The baseline MAP used in calculating the relative change was defined as the mean MAP of all available blood pressure measu-

rements in the operating theatre before induction of anesthesia. The time of induction was calculated using an algorithm that was previously described by Bijker and colleagues.[14] We excluded patients in whom blood pressures before induction of anesthesia were not available in those analyses where IOH was defined as a relative decrease from the pre-induction MAP. When both invasive and non-invasive blood pressure measurements were available, the invasive blood pressure measurements were used. During minutes when no blood pressure measurement was recorded or the measurement was considered to be an artifact, the previous (non-artifact) measurement was used. An episode of IOH with a duration of only one minute (i.e. a single data point) was considered to be a possible artifact and therefore excluded from the analysis.

For each patient the cumulative duration of hypotension was calculated, defined as the total number of minutes that the MAP was below the threshold during the surgical procedure. The number of episodes of IOH was counted, in which an episode was defined as an uninterrupted period of time that the MAP was below the threshold. In order to take the severity of the hypotension into account, the total area under the curve (AUC) of IOH was calculated, defined as the depth below the threshold MAP multiplied by the duration of hypotension.

Outcome

The primary outcome was postoperative myocardial injury, defined as an elevated cardiac troponin I above the 99th percentile with a 10% coefficient of variation within three days after surgery.[11] According to the clinical care protocol in both hospitals, cardiac troponin I was measured routinely after surgery. In the UHNT, troponin was measured immediately after surgery and once daily on the first two postoperative days; measurements were continued to five days after surgery in case of troponin elevation. Troponin was analyzed using the Dade Behring Dimension assay (Siemens Healthcare Diagnostics, Deerfield, USA). In the UMCU, troponin was measured once daily on the first three days after surgery, and follow-up of elevated troponin levels was carried out at discretion of the attending cardiologist. Troponin was analyzed using the enhanced AccuTnI assay (Beckman Coulter, Brea, CA). For each patient, the highest value of all troponin measurements was used in the analysis. Secondary outcomes included the occurrence of postoperative myocardial infarction and all-cause mortality within 30 days. Myocardial infarction was defined according to the universal definition as a troponin value above the clinical cut-off level and symptoms of ischemia, signs of ischemia on the ECG, imaging evidence of new myocardial loss, new wall motion abnormalities or identification of an intracoronary thrombus.[11]

Statistical analysis

Baseline characteristics were compared between patients with and without IOH as defined by a MAP of 60 mmHg. Categorical variables were compared using Chi-square testing and continuous variables were compared using the students t-test or Mann-Whitney test, as appropriate. Data on blood loss were missing in 110 (12%) patients. Data analysis was performed after multiple imputations of these missing data. Five datasets were imputed by the method of fully conditional specification.[20]

We compared the cumulative duration of IOH between patients with and without postoperative myocardial injury using the Chi-square test. Multivariable regression analysis was used to determine the association between the duration of IOH and myocardial injury for each of the four definitions of IOH. We used Poisson regression analysis in order to obtain relative risks.[21] In this, the duration of IOH was categorized into six categories (<1, 2-5, 6-10, 10-20, 20-30 and >30 minutes), because the relationship between IOH and myocardial injury was expected to be nonlinear. We used restricted cubic spline analysis to assess the linearity of this relationship. The association was adjusted for possible confounders in a multivariable model, including age, sex, emergency surgery, preoperative use of beta-blockers, calcium channel blockers, renin-angiotensin system inhibitors and diuretics, intraoperative blood loss, mean intraoperative heart rate, center and the six variables from the revised cardiac risk index, i.e. high risk surgery, history of myocardial infarction, history of cerebrovascular disease, heart failure, diabetes and renal failure.[22] Emergency surgery was defined as surgery required within 72 hours after the indication for surgery was set. Preoperative medication use (beta-blockers, calcium channel blockers and renin-angiotensin system inhibitors) was defined as regular (chronic) use of medication before surgery, irrespective of whether those medications were continued of discontinued on the day of surgery. High risk surgery was defined as intrathoracic, intra-abdominal or suprainguinal vascular surgery. Preoperative renal failure was defined as a preoperative serum creatinine ≥177 micromol/L. Because four different definitions of IOH were tested, Bonferroni correction was used to adjust for multiple comparisons, resulting in a 98.8% confidence interval (p value of 0.05/4 = 0.0125) as level of statistical significance.

We performed sensitivity analyses where the duration of surgery was added to the multivariable model since we considered duration of surgery a potential residual confounder. First, the opportunity to detect IOH is greater in patients with longer durations of surgery. Second, the duration of surgery may also be associated with a higher risk on developing myocardial injury since longer durations of surgery may indicate more complicated procedures.[18] The final sensitivity analyses were conducted to assess the degree of the hypotension. In these analyses the AUC of IOH was substituted in the multivariable model instead of the duration of IOH to determine whether this would alter the results.

The analysis was performed using SPSS (release 20.0 for Windows) and R (release 2.14.1 for Windows).

Results

In total, 1010 vascular surgery patients were eligible for inclusion: 689 patients from the UHNT and 321 patients from the UMCU. Figure 5.1 shows the inclusion of patients. The 104 (10%) patients who were excluded because troponin was not measured, were healthier at baseline compared to the patients in whom troponin was measured. These patients used less beta-blockers preoperatively, were involved in fewer high-risk procedures and had less intraoperative hypotension.

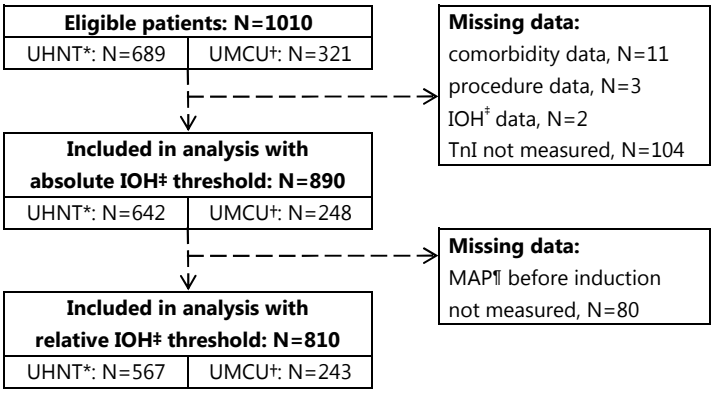


Figure 5.1 *Flow chart of patient inclusion. *University Health Network Toronto; †University Medical Center Utrecht; ‡Intraoperative hypotension*

The remaining 890 (86%) patients were on average 73 years old, two-third underwent high-risk surgery, almost 50% were classified as American Society of Anesthesiologists (ASA) physical status class 4 and about one-third underwent emergency surgery (Table 5.1). In 80 (9%) patients, no pre-induction blood pressure data were available, hence these patients were only included in the analysis where IOH was defined by an absolute threshold (i.e. MAP <50 mmHg and MAP <60 mmHg). Of the 810 patients in whom pre-induction blood pressure data were available, the mean pre-induction MAP was 103 (SD 16) mmHg.

Primary outcome

Postoperative myocardial injury occurred in 131 (29%) patients with IOH as defined by a MAP <60 mmHg, as compared to 87 (20%) patients without IOH (p=0.001) (Table 5.1).

The incidence of IOH was 51% and 12% when using a MAP of 60 mmHg and 50 mmHg to define IOH, and 81% and 52% when IOH was defined as ≥30% and ≥40% decrease from the pre-induction MAP, respectively. IOH as defined by a mean arterial

Table 5.1 *Baseline characteristics, stratified for intraoperative hypotension (IOH), defined as a mean arterial pressure (MAP) < 60mmHg.*

	No IOH* N=440		IOH* N=450		p-value
Center					
UHNT†	297	(67.5)	345	(76.7)	0.002
UMCU‡	143	(32.5)	105	(23.3)	
Male	307	(69.8)	311	(69.1)	0.83
Mean age (SD)	73.4	(7.9)	73.7	(7.8)	0.61
RCRI§ factors					
High risk surgery	273	(62.0)	293	(65.1)	0.34
History of myocardial infarction	72	(16.4)	95	(21.1)	0.07
History of heart failure	28	(6.4)	24	(5.3)	0.51
History of cerebrovascular disease	104	(23.6)	87	(19.3)	0.12
Renal failure (preoperative)	35	(8.0)	36	(8.0)	0.98
Diabetes	54	(12.3)	36	(8.0)	0.04
Peripheral vascular disease	239	(54.3)	277	(61.6)	0.03
Preoperative medication use					
Beta blocker	228	(51.8)	263	(58.4)	0.05
Calcium channel blocker	144	(32.7)	125	(27.8)	0.11
Renin angiotensin system inhibitor	167	(38.0)	174	(38.7)	0.83
Diuretics	129	(29.3)	141	(31.3)	0.56
Statin	257	(58.4)	252	(56.0)	0.47
ASA¶ class					
1	5	(1.1)	2	(0.4)	0.17
2	65	(14.8)	62	(13.8)	
3	169	(38.4)	152	(33.8)	
≥4	201	(45.7)	234	(52.0)	
Emergency surgery	119	(27.0)	146	(32.4)	0.08
Procedure					
Open aortic surgery	13	(3.0)	59	(13.1)	<0.001
(T)EVAR\\	99	(22.5)	115	(25.6)	
Carotid surgery	98	(22.3)	51	(11.3)	
Peripheral bypass surgery	46	(10.5)	87	(19.3)	
Other	184	(41.8)	138	(30.7)	
Mean duration of surgery in minutes (SD)	166	(88)	215	(127)	<0.001
Mean pre-induction MAP** in mmHg (SD)††	106	(16)	100	(16)	<0.001
Mean of average heart rate in beats per minute (SD)	67	(13)	67	(13)	0.81
Median estimated intraoperative blood loss in mL (IQR‡‡) ↑	100	(0-300)	150	(0-500)	0.05
Postoperative myocardial injury	87	(19.8)	131	(29.1)	0.001
Postoperative myocardial infarction	12	(2.7)	26	(5.8)	0.08
Death within 30 days	15	(3.4)	17	(3.8)	0.77

*Figures are numbers of patients (%), unless indicated otherwise. * Intraoperative Hypotension; † University Health Network Toronto; ‡ University medical Center Utrecht; § Revised Cardiac Risk Index; ¶ Physical status classification by the American Society of Anesthesiologists; UMC Utrecht: \\ (Thoracic) Endoscopic Vascular Aneurysm Repair; ** Mean Arterial Pressure; †† N=392 and N=418 respectively, because in 80 patients the pre-induction MAP was not available, hence the relative decrease of MAP could not be calculated; ‡‡ Interquartile range; ↑ N=377 and N=403 respectively, because blood loss data were not available in 110 patients.*

blood pressure <60 mmHg occurred in 54% and 42% of patients from the UHNT and the UMCU, respectively. The incidence of IOH stratified for different categories of the mean intraoperative heart rate is given in Supplemental File Table 5.1. The median cumulative duration of IOH varied between 6 and 49 minutes depending on the used definition and was longest if IOH was defined as ≥30% decrease from the pre-induction MAP. The median number of episodes of IOH varied between 1 and 5, depending on the used definition.

Using a MAP of 60 mmHg or 50 mmHg, IOH occurred in 60% and 17% of patients in whom postoperative myocardial injury occurred, compared to 48% (p=0.001) and 10% of patients (p=0.002) without myocardial injury, respectively. Patients with postoperative myocardial injury had longer durations of IOH compared to patients without postoperative myocardial injury (Table 5.2).

The unadjusted risk of postoperative myocardial injury in patients with IOH was higher compared to patients without IOH for each definition of IOH. Restricted cubic spline analysis showed that this association was not linear (Supplemental File, Figure 5.1). When IOH was defined as ≥40% decrease from the pre-induction MAP, the unadjusted relative risk of myocardial injury was 1.9 (98.8% CI 1.3-2.8, p<0.001) for a cumulative duration of IOH of more than 30 minutes (Table 5.3). Using this definition, IOH with a duration of more than 30 minutes occurred in 60 of 187 (32%) patients with

Table 5.2 *Occurrence and characteristics of intraoperative hypotension (IOH), using four different thresholds of the mean arterial pressure (MAP) to define IOH.*

	No myocardial injury N=672		Myocardial injury N=218		p-value
Number of patients with IOH* (%)					
MAP† <60 mmHg	319	(47.5)	131	(60.1)	0.001
MAP† <50 mmHg	65	(9.7)	38	(17.4)	0.002
≥30% decrease from pre-induction MAP†‡	489	(78.5)	163	(87.2)	0.03
≥40% decrease from pre-induction MAP†‡	312	(50.1)	111	(59.4)	0.08
Median number of episodes of IOH* (IQR§)					
MAP† <60 mmHg	2	(1-4)	3	(1-5)	0.06
MAP† <50 mmHg	1	(1-2)	1	(1-2)	0.23
≥30% decrease from pre-induction MAP†‡	5	(2-9)	4	(2-9)	0.71
≥40% decrease from pre-induction MAP†‡	3	(1-6)	4	(2-7)	0.009
Median duration of IOH* in minutes (IQR§)					
MAP† <60 mmHg	10	(5-27)	18	(7-36)	0.005
MAP† <50 mmHg	5	(3-12)	7	(4-13)	0.24
≥30% decrease from pre-induction MAP†‡	47	(16-113)	66	(13-147)	0.11
≥40% decrease from pre-induction MAP†‡	18	(6-43)	37	(11-77)	<0.001

**Intraoperative Hypotension; †Mean Arterial Pressure; ‡N=623 and N=187 patients without and with myocardial injury, respectively, because in 80 patients the pre-induction MAP was not available, hence the relative decrease of MAP could not be calculated; § Interquartile range.*

postoperative myocardial injury, compared to 107 of 623 (17%) patients without myocardial injury. The baseline MAP of patients with IOH using this definition (118 mmHg, SD13) was higher as compared to patients without IOH (95 mmHg, SD 15) (Figure 5.2).

After adjustment for possible confounding factors and multiple comparisons, IOH with a cumulative duration of >30 minutes was significantly associated with myocardial injury when IOH was defined as a MAP <60 mmHg (RR 1.7, 98.8% CI 1.1-2.6, p=0.004), when IOH was defined as ≥30% decrease from the pre-induction MAP (RR 1.8, 98.8% CI 1.1-3.1, P=0.005), and when IOH was defined as ≥40% decrease in MAP (RR 1.8, 98.8% CI 1.2-2.6, p<0.001) (Tables 5.3 and 5.4).

Table 5.3 *Association between the duration of intraoperative hypotension (IOH), defined as a 40% decrease in mean arterial blood pressure compared to the pre-induction blood pressure, and postoperative myocardial injury.*

	Unadjusted analysis			Adjusted analysis		
	RR*	98.8% CI†	p-value	RR*	98.8% CI†	p-value
Duration of IOH‡ (minutes)						
≤1	*ref*			*ref*		
2-5	1.1	0.6 - 1.8	0.75	1.3	0.7 – 2.2	0.27
6-10	0.6	0.2 - 1.5	0.14	0.8	0.4 – 1.6	0.33
11-20	1.4	0.8 - 2.4	0.14	1.3	0.8 – 2.4	0.21
21-30	1.4	0.7 - 3.0	0.23	0.8	0.4 – 1.7	0.53
>30	1.9	1.3 - 2.8	<0.001	1.8	1.2 – 2.6	<0.001
Female	1.2	0.9 - 1.7	0.19	1.1	0.8 – 1.6	0.40
Age (per 10 years)	1.2	1.0 - 1.5	0.004	1.3	1.1 – 1.5	0.001
Diabetes	1.0	0.6 - 1.7	0.97	0.9	0.5 – 1.6	0.64
History of myocardial infarction	1.9	1.4 - 2.6	<0.001	1.9	1.4 – 2.6	<0.001
History of heart failure	1.7	1.1 - 2.9	0.006	1.3	0.8 – 2.1	0.20
History of cerebrovascular disease	0.7	0.5 - 1.1	0.09	1.0	0.6 – 1.5	0.97
Preoperative renal failure	2.2	1.4 - 3.2	<0.001	1.8	1.1 – 2.7	0.001
Preoperative medication use						
Beta blocker	1.7	1.2 - 2.4	<0.001	1.6	1.2 – 2.3	0.001
Calcium channel blocker	0.9	0.6 - 1.3	0.48	0.9	0.7 – 1.3	0.53
Renin angiotensin system inhibitor	0.8	0.6 - 1.1	0.12	0.8	0.6 – 1.1	0.07
Diuretics	1.5	1.1 – 2.0	0.004	1.3	0.9 – 1.8	0.04
High risk surgery	0.9	0.6 - 1.2	0.36	1.1	0.8 – 1.5	0.60
Emergency surgery	1.9	1.4 - 2.6	<0.001	1.6	1.1 – 2.2	0.001
Mean heart rate (per 10 beats per minute)	1.3	1.2 - 1.4	<0.001	1.3	1.2 – 1.5	0.001
Intraoperative blood loss (mL)						
<500	*ref*			*ref*		
500-1000	1.5	0.9 - 2.4	0.06	1.5	1.0 – 2.4	0.02
1000-2000	2.1	1.3 - 3.4	0.005	1.8	0.9 – 3.6	0.02
>2000	1.6	0.7 - 3.7	0.02	1.4	0.7 – 2.7	0.18
Center: UHNT§	0.8	0.6 - 1.1	0.10	0.6	0.4 – 0.9	0.001

**Relative Risk; †Confidence interval; ‡Intraoperative Hypotension; §University Health Network Toronto.*

Postoperative myocardial injury was also associated with age, a history of myocardial infarction, preoperative renal failure, preoperative beta-blocker use and emergency surgery (Table 5.3). When IOH was defined as a MAP of <50 mmHg, the adjusted relative risk of myocardial injury was 1.5 (98.8% CI 0.4-6.7, p=0.47) for a duration of IOH of more than 30 minutes (Table 5.4). In the light of the significant associations for the other definitions of IOH, we also would expect a significant association when IOH was defined as a MAP of <50 mmHg with a duration of more than 30 minutes, but given its wide confidence interval, this association may not be significant due to the low number of patients with IOH for this definition. IOH defined as ≥30% decrease from the pre-induction MAP and as a MAP <50 mmHg with a duration of 6-10 minutes also appeared to be associated with myocardial injury. However, restricted cubic spline analysis showed that this association only appeared significant as a result of the chosen cut-off points, but that it was not consistent for longer durations of IOH (Table 5.4 and Supplemental File Figure 5.2).

The sensitivity analysis in which the duration of surgery was added to the multivariable model, resulted in a significant association with myocardial injury only when IOH was defined as ≥40% decrease from the pre-induction MAP with a duration of >30 minutes (RR 1.7, 98.8% CI 1.1-2.5, p=0.002) (Supplemental File Table 5.2). When IOH was defined as a MAP of <50 mmHg, a MAP of <60 mmHg or ≥30% decrease from the pre-induction MAP with a duration of >30 minutes, the relative risk of myocardial injury was 1.6 (98.8% CI 0.4-6.0, p=0.38), 1.5 (98.8% CI 0.9-2.3 (p=0.03) and 1.7 (98.8% CI 1.0-2.8, p=0.02), respectively (Supplemental File Table 5.3). This finding supports the significant association between IOH defined as ≥40% decrease from the pre-induction MAP with a duration of >30 minutes that was found in the primary analysis, but attenuates the associations that were found for the other definitions.

The results of the sensitivity analysis in which the AUC of IOH was included in the multivariable model instead of the duration of IOH were comparable to the results of the primary analysis, albeit that the association was significant when IOH was defined as a MAP <50 mmHg (RR 3.4, 98.8% CI 1.3-9.2, p=0.002), when IOH was defined as ≥30% decrease in MAP (RR 1.7, 98.8% CI 1.0-2.8, p=0.007), and when IOH was and as ≥40% decrease in MAP (RR 1.8, 98.8% CI 1.2-2.7, p<0.001), but not when IOH was defined as a MAP <60 mmHg (RR 1.5, 98.8% CI 0.9-2.5, p=0.06) (Supplemental File Tables 5.4-5.5). This result supports the association between IOH as defined as a ≥30% decrease and ≥40% decrease in MAP and myocardial injury that was found in the primary analysis.

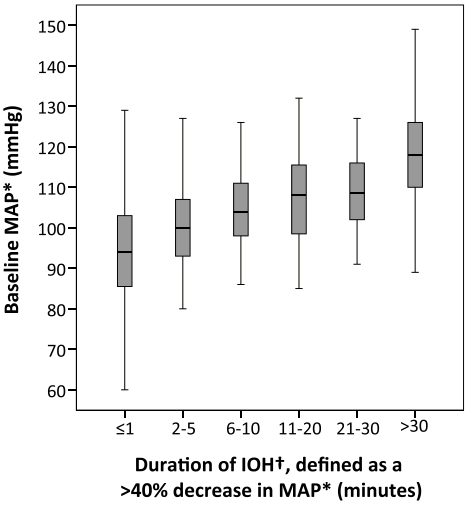


Figure 5.2
*Baseline mean arterial blood pressures for different durations of intraoperative hypotension, defined as a >40% decrease in mean arterial blood pressure. * Mean Arterial Blood Pressure; † Intraoperative Hypotension*

Table 5.4 *Association between the duration of intraoperative hypotension (IOH) and myocardial injury for four different definitions of hypotension. The results are adjusted for age, sex, comorbidities, preoperative medication use, heart rate and intraoperative blood loss.*

Definition of IOH*	Duration of IOH* (minutes)	RR†	98.8% CI‡	p-value
MAP§ < 50 mmHg	≤1	*ref*		
	2-5	1.3	0.8 - 2.2	0.21
	6-10	2.0	1.1 - 3.6	0.003
	11-20	1.0	0.4 - 2.2	0.89
	21-30	2.0	0.8 – 5.1	0.08
	>30	1.5	0.4 – 6.7	0.47
MAP§ < 60 mmHg	≤1	*ref*		
	2-5	1.1	0.7 - 1.7	0.52
	6-10	0.9	0.5 - 1.6	0.58
	11-20	1.5	1.0 - 2.3	0.02
	21-30	1.5	1.0 - 2.5	0.02
	>30	1.7	1.1 – 2.6	0.004
≥30% decrease from pre-induction MAP§	≤1	*ref*		
	2-5	1.7	0.8 – 3.6	0.10
	6-10	2.8	1.6 – 5.1	<0.001
	11-20	1.8	1.0 – 3.5	0.02
	21-30	0.9	0.4 - 2.2	0.81
	>30	1.8	1.1 – 3.1	0.005
≥40% decrease from pre-induction MAP§	≤1	*ref*		
	2-5	1.3	0.7 – 2.2	0.27
	6-10	0.8	0.4 – 1.6	0.33
	11-20	1.3	0.8 – 2.4	0.21
	21-30	0.8	0.4 – 1.7	0.53
	>30	1.8	1.2 – 2.6	<0.001

**Intraoperative Hypotension; †Relative Risk; ‡Confidence interval;*
§Mean arterial pressure.

Secondary outcomes

Postoperative myocardial infarction as defined by the universal definition was diagnosed in 26 (6%) patients with IOH as defined by a MAP <60 mmHg, as compared to 12 (3%) patients without IOH (p=0.08) (Table 5.1).[11] Using this definition of IOH, death within 30 days occurred in 17 (4%) patients with IOH, as compared to 15 (3%) patients without IOH (p=0.77) (Table 5.1).

Discussion

This two-center cohort study in elderly high-risk vascular surgery patients found that a relative decrease in MAP ≥40% from the pre-induction blood pressure is associated with postoperative myocardial injury if the decrease persists for more than 30 cumulative minutes. As an example, this drop in blood pressure is a preoperative pressure of 160/100(120) mmHg falling to 105/55(72) mmHg during anesthesia and sustained below this level for >30 minutes in total. In the present study this degree of blood pressure change occurs in one fifth of the patients. A MAP <60 mmHg and a relative decrease in MAP ≥30% from the pre-induction blood pressure with a duration >30 minutes may also be associated with myocardial injury, but these associations did not remain statistically significant after further adjustment for the duration of surgery, or when the AUC of IOH was studied. Furthermore, we found no statistically significant association between IOH and myocardial injury if the cumulative duration was less than 30 minutes.

We investigated the association between IOH and postoperative myocardial injury by combining data from two hospitals that measure cardiac biomarkers routinely after surgery. One of the strengths of this study is that cardiac troponin was measured as part of a postoperative care protocol, thus increasing generalizability and reducing misclassification or selection bias. Further strengths of our study include the adjustment for more possible confounders than in previous studies. Of note, this analysis was adjusted for preoperative use of cardiovascular medications (beta-blockers, renin angiotensin system inhibitors, calcium channel blockers, diuretics), intraoperative blood loss, heart rate, and also for the duration of surgery in a sensitivity analysis. In addition to the duration of IOH we also assessed the depth of the hypotension by including the AUC of IOH. Although the AUC cannot distinguish between a short period of severe hypotension and a long period of mild hypotension (e.g. 5 mmHg below the MAP threshold for 20 minutes results in the same AUC as 20 mmHg below the MAP threshold for 5 minutes), we included it in a sensitivity analysis as a measure of the severity of IOH.

Several limitations of the study must be addressed. First, factors that may accompany hypotension and may influence the occurrence of myocardial injury, like heart rate variability, pulse pressure variation and hemoglobin level, were not taken into account.

Furthermore, specific triggers of hypotension, e.g. anesthetic overdose or acute severe bleeding, and specific treatments of hypotension like fluid administration and the use of vasopressors and inotropics were not studied. In a retrospective observational study like this, it is challenging to properly model all the factors that influence intraoperative hemodynamics while occurring and being treated simultaneously, and the interactions between these factors. Nevertheless, to fully understand the etiology of hypotension and myocardial injury, these factors should be studied as well. Therefore, although the results of this study indicate that hypotension may be associated with myocardial injury, this should not be interpreted as a definitive answer. Moreover, the obtained relative risks should not be interpreted as absolute figures, but rather as an indication that longer durations of IOH, i.e. longer than approximately 30 minutes, are associated with myocardial injury. Second, although troponin measurements were part of a routine postoperative care protocol in both centers, troponin was not measured in 10% of patients because of non-adherence to the protocol. In addition, some patients did not have troponin measured consecutively on all three postoperative days, hence myocardial injury may have been underestimated. Third, the results were not adjusted for preexisting troponin elevations because troponin was not measured before surgery. This may be an important deficiency since it is now known that troponin is elevated in a variety of patients.[23–27] In addition, this analysis did not adjust for postoperative events, such as sepsis, stroke, acute renal failure and pulmonary embolism which have all been linked to troponin elevations.[10,27–31] Furthermore, the analysis was adjusted for chronic medication use, but did not take into account that certain drugs may have been discontinued before surgery. Fourth, IOH as defined by a MAP of 50 mmHg occurred in only a few patients, which may reflect adequate intraoperative care, but could have resulted in a less stable statistical regression model of myocardial injury. Fifth, we did not measure the association between hypotension and injury in other vital organs in addition to the myocardium, although intraoperative hypotension may cause injury to the brain and kidneys as well.[12,13,32] Our analysis does not consider the possibility that the hypotension may have been refractory to treatment, especially since the hypotension expressed in this study occurred in a fully monitored setting staffed by experienced anesthesiologists. Sixth, the multivariable model shows a significant association between center and myocardial injury, which may indicate important differences between the two centers and may have influenced the results. Finally, like in all retrospective observational analyses, residual confounding may exist.

IOH is thought to lead to diffuse myocardial ischemia through an imbalance between oxygen supply and demand of the myocardium.[11] Recently, the POISE-2 trial showed that hypotension was an independent predictor of myocardial infarction. Although hypotension was defined by a relatively high blood pressure threshold, i.e. a systolic blood pressure <90 mmHg, hypotension occurred less frequent compared to

our study. This may be explained by the healthier study population in POISE-2 as compared to our study population and to differences in definitions of IOH (Supplemental File Table S5.6). Additionally, the duration of hypotension was not taken into account in POISE-2.[8] The association between IOH and postoperative myocardial injury was also studied by Alcock in a smaller cohort of patients. Using a systolic blood pressure <100 mmHg to define IOH, IOH was associated with postoperative myocardial injury, but this association was not adjusted for perioperative beta-blocker use or intraoperative blood loss.[32] Kheterpal reported that high-risk patients experiencing a cardiac adverse event were more likely to experience an episode of a MAP <50 mmHg or a 40% decrease in MAP.[18] Walsh found an association between a MAP <55 mmHg and postoperative myocardial injury in a large cohort of surgical patients.[12] However, both the studies by Walsh and Kheterpal were limited by the fact that myocardial injury was measured selectively and all missing data were assumed to be negative. This problem is illustrated by the reported incidence of the outcome (0.2% and 2.3%, respectively), which was much lower than reported in other studies.[2,33,34] Another study has estimated that this selective monitoring of troponin indeed will underestimate the incidence (>10%) of myocardial injury three-fold.[3] Furthermore, the reported effect measure by Walsh was not adjusted for perioperative use of cardiovascular medications that are also associated with IOH.[6,35,36] Recently, Mascha and colleagues studied the association between intraoperative blood pressure variability and mortality in a large cohort of noncardiac surgery patients.[37] They reported that low MAP variability was associated with 30-day mortality, but that the differences were not clinically important after adjustment for the average MAP. Furthermore, they reported that the cumulative time of MAP less than 50, 55, 60, 70 or 80 mmHg was each associated with higher odds of death.

The occurrence of IOH could be merely a marker of other intraoperative events and comorbidities that are associated with an increased risk of developing postoperative myocardial injury.[10,19] It should be noted that our study was performed in older patients undergoing mainly high-risk vascular surgery, a population where coronary artery disease is common. The influence of IOH on the development of myocardial injury may be more pronounced in the presence of coronary artery disease through an imbalance between myocardial oxygen supply and demand, hence the results from this study are not directly generalizable to a younger and healthier population. Conversely, our results do not imply that durations of IOH of less than 30 minutes are generally safe, since previous studies have shown that shorter durations of hypotension are associated with renal dysfunction.[12,37] In this study, an association between preoperative use of beta-blockers and postoperative myocardial injury was observed, even after adjustment for confounding (Table 5.3). Although this association may well be biased by residual confounding, IOH may be an intermediate factor between beta-blocker therapy and myocardial injury,[38,39] and should be subject to further investigation.

In conclusion, this study shows that a MAP of 40% below the pre-induction MAP with a cumulative duration of more than 30 minutes and irrespective of duration of surgery was associated with the occurrence of postoperative myocardial injury. Importantly, we could not demonstrate an association between IOH durations of less than 30 minutes and myocardial injury. Of note, in interpreting the results of this study, it should be considered that several hemodynamic factors and specific treatments that may accompany hypotension and may influence the occurrence of myocardial injury, were not accounted for in this study.

References

1. Devereaux PJ, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, Leslie K, Purnima R-M, Chrolavicius S, Homer Y, MacDonald C, Avezum A, Lanthier L, Weijiang H, Yusuf S: Characteristics and Short-Term Prognosis of Perioperative Myocardial Infarction in Patients Undergoing Noncardiac Surgery. Ann Intern Med 2011; 154:523–8
2. Waes JAR van, Nathoe HM, Graaff JC de, Kemperman H, Borst GJ de, Peelen LM, Klei WA van: Myocardial injury after noncardiac surgery and its association with short-term mortality. Circulation 2013; 127:2264–71
3. Beattie WS, Karkouti K, Tait G, Steel A, Yip P, McCluskey S, Farkouh M, Wijeysundera DN: Use of clinically based troponin underestimates the cardiac injury in non-cardiac surgery: a single-centre cohort study in 51,701 consecutive patients. Can J Anaesth 2012; 59:1013–22
4. Landesberg G, Shatz V, Akopnik I, Wolf YG, Mayer M, Berlatzky Y, Weissman C, Mosseri M: Association of Cardiac Troponin, CK-MB, and Postoperative Myocardial Ischemia With Long-Term Survival After Major Vascular Surgery. J Am Coll Cardiol 2003; 42:1547–54
5. McFalls EO, Ward HB, Moritz TE, Apple FS, Goldman S, Pierpont G, Larsen GC, Hattler B, Shunk K, Littooy F, Santilli S, Rapp J, Thottapurathu L, Krupski W, Reda DJ, Henderson WG: Predictors and outcomes of a perioperative myocardial infarction following elective vascular surgery in patients with documented coronary artery disease: results of the CARP trial. Eur Heart J 2008; 29:394–401
6. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Málaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P: Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008; 371:1839–47
7. Devereaux PJ, Mrkobrada M, Sessler DI, Leslie K, Alonso-Coello P, Kurz A, Villar JC, Sigamani A, Biccard BM, Meyhoff CS, Parlow JL, Guyatt G, Robinson A, Garg AX, Rodseth RN, Botto F, Lurati Buse G, Xavier D, Chan MT V, Tiboni M, Cook D, Kumar P a, Forget P, Malaga G, Fleischmann E, Amir M, Eikelboom J, Mizera R, Torres D, Wang CY, VanHelder T, Paniagua P, Berwanger O, Srinathan S, Graham M, Pasin L, Le Manach Y, Gao P, Pogue J, Whitlock R, Lamy A, Kearon C, Baigent C, Chow C, Pettit S, Chrolavicius S, Yusuf S: Aspirin in patients undergoing noncardiac surgery. N Engl J Med 2014; 370:1494–503
8. Devereaux PJ, Mrkobrada M, Sessler DI, Leslie K, Alonso-Coello P, Kurz A, Villar JC, Sigamani A, Biccard BM, Meyhoff CS, Parlow JL, Guyatt G, Robinson A, Garg AX, Rodseth RN, Botto F, Lurati Buse G, Xavier D, Chan MT V, Tiboni M, Cook D, Kumar P a, Forget P, Malaga G, Fleischmann E, Amir M, Eikelboom J, Mizera R, Torres D, Wang CY, VanHelder T, Paniagua P, Berwanger O, Srinathan S, Graham M, Pasin L, Le Manach Y, Gao P, Pogue J, Whitlock R, Lamy A, Kearon C, Baigent C, Chow C, Pettit S, Chrolavicius S, Yusuf S: Clonidine in patients undergoing noncardiac surgery. N Engl J Med 2014; 370:1504–13
9. Landesberg G, Mosseri M, Shatz V, Akopnik I, Bocher M, Mayer M, Anner H, Berlatzky Y, Weissman C: Cardiac troponin after major vascular surgery: the role of perioperative ischemia, preoperative thallium scanning, and coronary revascularization. J Am Coll Cardiol 2004; 44:569–75
10. The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Writing Group: Myocardial Injury after Noncardiac Surgery: A Large, International, Prospective Cohort Study Establishing Diagnostic Criteria, Characteristics, Predictors, and 30-day Outcomes. Anesthesiology 2014; 120:564–78

11. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD: the Writing Group on behalf of the ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction: Third universal definition of myocardial infarction. Eur Heart J 2012; 33:2551–67

12. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI: Relationship between Intraoperative Mean Arterial Pressure and Clinical Outcomes after Noncardiac Surgery. Anesthesiology 2013; 119:507–15

13. Bijker JB, Persoon S, Peelen LM, Moons KGM, Kalkman CJ, Kappelle J, Klei WA van: Intraoperative Hypotension and Perioperative Ischemic Stroke after General Surgery. Anesthesiology 2012; 116:658–64

14. Bijker JB, Klei WA van, Vergouwe Y, Eleveld DJ, Wolfswinkel L van, Moons KGM, Kalkman CJ: Intraoperative hypotension and 1-year mortality after noncardiac surgery. Anesthesiology 2009; 111:1217–26

15. Monk TG, Saini V, Weldon BC, Sigl JC: Anesthetic management and one-year mortality after noncardiac surgery. Anesth Analg 2005; 100:4–10

16. Sessler DI, Sigl JC, Kelley SD, Chamoun NG, Manberg PJ, Saager L, Kurz A, Greenwald S: Hospital Stay and Mortality Are Increased in Patients Having a "Triple Low" of Low Blood Pressure, Low Bispectral Index, and Low Minimum Alveolar Concentration of Volatile Anesthesia. Anesthesiology 2012; 116:1195–203

17. Bijker JB, Klei WA van, Kappen TH, Wolfswinkel L van, Moons KGM, Kalkman CJ: Incidence of Intraoperative Hypotension as a Function of the Chosen Definition. Anesthesiology 2007; 107:213–20

18. Kheterpal S, O'Reilly M, Englesbe MJ, Rosenberg AL, Shanks AM, Zhang L, Rothman ED, Campbell DA, Tremper KK: Preoperative and intraoperative predictors of cardiac adverse events after general, vascular, and urological surgery. Anesthesiology 2009; 110:58–66

19. Brady K, Hogue CW: Intraoperative Hypotension and Patient Outcome: Does "One Size Fit All?" Anesthesiology 2013; 119:495–7

20. Buuren S van: Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res 2007; 16:219–42

21. Knol MJ, Cessie S Le, Algra A, Vandenbroucke JP, Groenwold RHH: Overestimation of risk ratios by odds ratios in trials and cohort studies: alternatives to logistic regression. CMAJ 2012; 184:895–9

22. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KKL, Ludwig LE, Pedan A, Goldman L: Derivation and Prospective Validation of a Simple Index for Prediction of Cardiac Risk of Major Noncardiac Surgery. Circulation 1999; 100:1043–9

23. Landesberg G, Jaffe AS, Gilon D, Levin PD, Goodman S, Abu-Baih A, Beeri R, Weissman C, Sprung CL, Landesberg A: Troponin elevation in severe sepsis and septic shock: the role of left ventricular diastolic dysfunction and right ventricular dilatation. Crit Care Med 2014; 42:790–800

24. Nagele P, Brown F, Gage BF, Gibson DW, Miller JP, Jaffe AS, Apple FS, Scott MG: High-sensitivity cardiac troponin T in prediction and diagnosis of myocardial infarction and long-term mortality after noncardiac surgery. Am Heart J 2013; 166:325–32

25. Gaggin HK, Szymonifka J, Bhardwaj A, Belcher A, Berardinis B de, Motiwala S, Wang TJ, Januzzi JL: Head-to-head comparison of serial soluble ST2, growth differentiation factor-15, and highly-sensitive troponin T measurements in patients with chronic heart failure. JACC Heart Fail 2014; 2:65–72

26. Lemos JA de, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, Hashim I, Berry JD, Das SR, Morrow DA, McGuire DK: Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA 2010; 304:2503–12

27. Katerinis I, Nguyen Q-V, Magnin J-L, Descombes E: Cardiac findings in asymptomatic chronic hemodialysis patients with persistently elevated cardiac troponin I levels. Ren Fail 2008; 30:357–62

28. Anders B, Alonso A, Artemis D, Schäfer A, Ebert A, Kablau M, Fluechter S, Findeisen P, Hennerici MG, Fatar M: What does elevated high-sensitive troponin I in stroke patients mean: concomitant acute myocardial infarction or a marker for high-risk patients? Cerebrovasc Dis 2013; 36:211–7

29. Lim W, Qushmaq I, Devereaux PJ, Heels-Ansdell D, Lauzier F, Ismaila AS, Crowther MA, Cook DJ: Elevated cardiac troponin measurements in critically ill patients. Arch Intern Med 2014; 166:2446–54

30. Lankeit M, Friesen D, Aschoff J, Dellas C, Hasenfuss G, Katus H, Konstantinides S, Giannitsis E: Highly sensitive troponin T assay in normotensive patients with acute pulmonary embolism. Eur Heart J 2010; 31:1836–44

31. Beckman JA: Postoperative troponin screening: a cardiac Cassandra? Circulation 2013; 127:2253–6

32. Alcock RF, Kouzios D, Naoum C, Hillis GS, Brieger DB: Perioperative myocardial necrosis in patients at high cardiovascular risk undergoing elective non-cardiac surgery. Heart 2012; 98:792–8

33. Levy MM, Heels-Ansdell D, Hiralal R, Bhandari M, Guyatt G, Yusuf S, Cook D: Prognostic Value of Troponin and Creatine Kinase Muscle and Brain Isoenzyme Measurement after Noncardiac Surgery. Anesthesiology 2011; 114:796–806

34. The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators: Association Between Postoperative Troponin Levels and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. JAMA 2012; 307:2295–304

35. Bertrand M, Godet G, Meersschaert K, Salcedo E, Coriat P: Should the Angiotensin II Antagonists be Discontinued. Anesth Analg 2001; 92:26–30

36. Yu SKH, Tait G, Karkouti K, Wijeysundera D, McCluskey S, Beattie WS: The safety of perioperative esmolol: a systematic review and meta-analysis of randomized controlled trials. Anesth Analg 2011; 112:267–81

37. Mascha EJ, Yang D, Weiss S, Sessler DI: Intraoperative Mean Arterial Pressure Variability and 30-day Mortality in Patients Having Noncardiac Surgery. Anesthesiology 2015; 123:79-91

38. Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT: Renal Dysfunction after Myocardial Revascularization: Risk Factors, Adverse Outcomes, and Hospital Resource Utilization. Ann Intern Med 1998; 128:194–203

39. Ashes C, Judelman S, Wijeysundera D, Tait G, Mazer CD, Hare GMT, Beattie WS: Selective β1-Antagonism with Bisoprolol Is Associated with Fewer Postoperative Strokes than Atenolol or Metoprolol. Anesthesiology 2013; 119:777–87

Supplemental Files

Supplemental File, Table S5.1
Occurrence intraoperative hypotension (IOH) using four different thresholds of the mean arterial pressure (MAP) to define IOH, stratified for different categories of the mean intraoperative heart rate.

	Mean intraoperative heart rate (beats per minute)				
	<60 N=248	60-69 N=296	70-79 N=203	80-89 N=84	>90 N=59
Number of patients with IOH* (%)					
MAP† <60 mmHg	126 (51)	147 (50)	104 (51)	44 (52)	29 (49)
MAP† <50 mmHg	28 (11)	30 (10)	28 (14)	12 (14)	5 (8)
≥30% decrease from pre-induction MAP†‡	192 (83)	221 (82)	149 (81)	57 (70)	33 (70)
≥40% decrease from pre-induction MAP†‡	133 (58)	134 (50)	99 (54)	39 (50)	18 (38)

**Intraoperative Hypotension; †Mean Arterial Pressure; ‡The total number of patients in each category is N=231, N=269, N=185, N=78 and N=47 patients, respectively, because in 80 patients the pre-induction MAP was not available, hence the relative decrease of MAP could not be calculated.*

Supplemental File, Table S5.2

Association between the duration of intraoperative hypotension (IOH) defined as a 40% decrease in mean arterial blood pressure, and myocardial injury, adjusted for age, sex, comorbidities, preoperative medication use, heart rate, intraoperative blood loss and duration of surgery.

	RR[†]	98.8% CI[‡]	p-value
Duration of IOH[§] (minutes)			
≤1	*ref*		
2-5	1.3	0.7 – 2.2	0.27
6-10	0.8	0.4 – 1.6	0.34
11-20	1.3	0.8 – 2.4	0.21
21-30	0.8	0.4 – 1.7	0.46
>30	1.7	1.1 – 2.5	0.002
Female	1.1	0.8 – 1.6	0.34
Age (per year)	1.3	1.1 – 1.5	0.001
Diabetes	0.9	0.5 – 1.5	0.58
History of myocardial infarction	1.8	1.3 – 2.5	<0.001
History of heart failure	1.3	0.8 – 2.1	0.16
History of cerebrovascular disease	1.0	0.7 – 1.6	0.83
Preoperative renal failure	1.7	1.1 – 2.7	<0.01
Preoperative medication use			
Beta blocker	1.6	1.2 – 2.3	<0.001
Calcium channel blocker	0.9	0.6 – 1.3	0.45
Renin angiotensin system inhibitor	0.8	0.6 – 1.1	0.07
Diuretics	1.3	0.9 – 1.8	0.05
High risk surgery	1.0	0.7 – 1.4	0.87
Emergency surgery	1.6	1.1 – 2.2	0.001
Mean heart rate (per 10 beats per minute)	1.3	1.2 – 1.5	<0.001
Intraoperative blood loss			
<500 mL	*ref*		
500-1000 mL	1.5	0.9 – 2.3	0.05
1000-2000 mL	1.5	0.7 – 3.1	0.19
>2000 mL	1.1	0.5 – 2.4	0.72
Center: UHNT[¶]	0.6	0.4 – 0.9	0.001
Duration of surgery (per 10 minutes)	1.01	1.00 – 1.02	0.03

[†] Relative risk; [‡] Confidence interval; [§] Intraoperative hypotension; [¶]University Health Network Toronto.

Supplemental File, Table S5.3

Association between the duration of intraoperative hypotension (IOH) and myocardial injury for four different definitions of hypotension. The results are adjusted for age, sex, comorbidities, preoperative medication use, heart rate, intraoperative blood loss and duration of surgery.

Definition of IOH*	Duration of IOH* (minutes)	RR†	98.8% CI‡	p-value
MAP§ < 50 mmHg	≤1	*ref*		
	2-5	1.3	0.7 – 2.1	0.28
	6-10	2.0	1.2 – 3.6	0.002
	11-20	0.7	0.3 – 2.0	0.41
	21-30	2.4	0.8 – 6.9	0.04
	>30	1.6	0.4 – 6.0	0.38
MAP§ < 60 mmHg	≤1	*ref*		
	2-5	1.1	0.7 – 1.7	0.56
	6-10	0.8	0.5 – 1.5	0.49
	11-20	1.5	1.0 – 2.3	0.01
	21-30	1.4	0.9 – 2.3	0.06
	>30	1.5	0.9 – 2.3	0.03
30% decrease from pre-induction MAP§	≤1	*ref*		
	2-5	1.6	0.8 – 3.6	0.11
	6-10	2.8	1.5 – 5.0	<0.001
	11-20	1.8	0.9 – 3.3	0.03
	21-30	0.9	0.4 – 2.2	0.79
	>30	1.7	1.0 – 2.8	0.02
40% decrease from pre-induction MAP§	≤1	*ref*		
	2-5	1.3	0.7 – 2.2	0.27
	6-10	0.8	0.4 – 1.6	0.34
	11-20	1.3	0.8 – 2.4	0.21
	21-30	0.8	0.4 – 1.7	0.46
	>30	1.7	1.1 – 2.5	0.002

** Intraoperative hypotension; † Relative Risk; ‡ Confidence interval; § Mean arterial pressure.*

Supplemental File, Table S5.4

Association between the severity of intraoperative hypotension (IOH), defined as the area under the curve (duration times depth) below the threshold of a 40% decrease in mean arterial blood pressure, and myocardial injury, adjusted for age, sex, comorbidities, preoperative medication use, heart rate and intraoperative blood loss.

	RR†	98.8% CI‡	p-value
AUC§ of IOH¶ (minutes*mmHg)			
≤10	*ref*		
11-50	1.1	0.7 – 1.9	0.49
51-101	0.7	0.3 – 1.5	0.21
101-200	1.3	0.7 – 2.2	0.25
201-300	1.2	0.5 – 2.8	0.57
>300	1.8	1.2 – 2.7	<0.001
Female	1.1	0.8 – 1.6	0.39
Age (per year)	1.3	1.0 – 1.5	0.002
Diabetes	0.9	0.5 – 1.6	0.62
History of myocardial infarction	1.8	1.3 – 2.5	<0.001
History of heart failure	1.2	0.8 – 2.0	0.27
History of cerebrovascular disease	1.0	0.6 – 1.5	0.85
Preoperative renal failure	1.7	1.1 – 2.6	0.002
Preoperative medication use			
Beta blocker	1.7	1.2 – 2.3	<0.001
Calcium channel blocker	0.9	0.7 – 1.3	0.63
Renin angiotensin system inhibitor	0.8	0.6 – 1.1	0.08
Diuretics	1.3	0.9 – 1.7	0.06
High risk surgery	1.1	0.8 – 1.5	0.52
Emergency surgery	1.5	1.1 – 2.1	0.001
Mean heart rate (per 10 beats per minute)	1.3	1.2 – 1.5	<0.001
Intraoperative blood loss			
<500 mL	*ref*		
500-1000 mL	1.5	0.9 – 2.4	0.03
1000-2000 mL	1.9	1.0 – 3.7	0.01
>2000 mL	1.4	0.7 – 2.7	0.20
Center: UHNT\\	0.6	0.4 – 0.9	<0.001

† Relative risk; ‡ Confidence interval; § Area Under the Curve; ¶ Intraoperative hypotension; \\ University Health Network Toronto.

Supplemental File, Table S5.5

Association between the severity of intraoperative hypotension (IOH), defined as the area under the curve (duration times depth) below the threshold of a 40% decrease in mean arterial blood pressure) for four different definitions of hypotension. The results are adjusted for age, sex, comorbidities, preoperative medication use, heart rate and intraoperative blood loss.

Definition of IOH†	AUC‡ of IOH† (minutes*mmHg)	RR§	98.8% CI¶	p-value
MAP\\ < 50 mmHg	≤10	*ref*		
	11-50	2.0	1.3 – 3.1	<0.001
	51-101	0.9	0.4 – 2.0	0.86
	101-200	1.0	0.2 – 3.9	0.93
	201-300	1.5	0.1 – 18.6	0.68
	>300	3.4	1.3 – 9.2	0.002
MAP\\ < 60 mmHg	≤10	Ref		
	11-50	0.8	0.5 – 1.2	0.20
	51-101	1.0	0.6 – 1.7	0.82
	101-200	1.4	0.9 – 2.2	0.03
	201-300	1.6	1.0 – 2.7	0.02
	>300	1.5	0.9 – 2.5	0.06
30% decrease from pre-induction MAP	≤10	*ref*		
	11-50	2.1	1.2 – 3.7	0.001
	51-101	2.0	1.1 – 3.8	0.005
	101-200	1.0	0.5 – 2.0	0.90
	201-300	1.5	0.6 – 3.3	0.24
	>300	1.7	1.0 – 2.8	0.007
40% decrease from pre-induction MAP	≤10	*ref*		
	11-50	1.1	0.7 – 1.9	0.49
	51-101	0.7	0.3 – 1.5	0.21
	101-200	1.3	0.7 – 2.2	0.25
	201-300	1.2	0.5 – 2.8	0.57
	>300	1.8	1.2 – 2.7	<0.001

† Intraoperative hypotension; ‡ Area Under the Curve; § Relative risk; ¶ Confidence interval; \\ Mean arterial pressure.

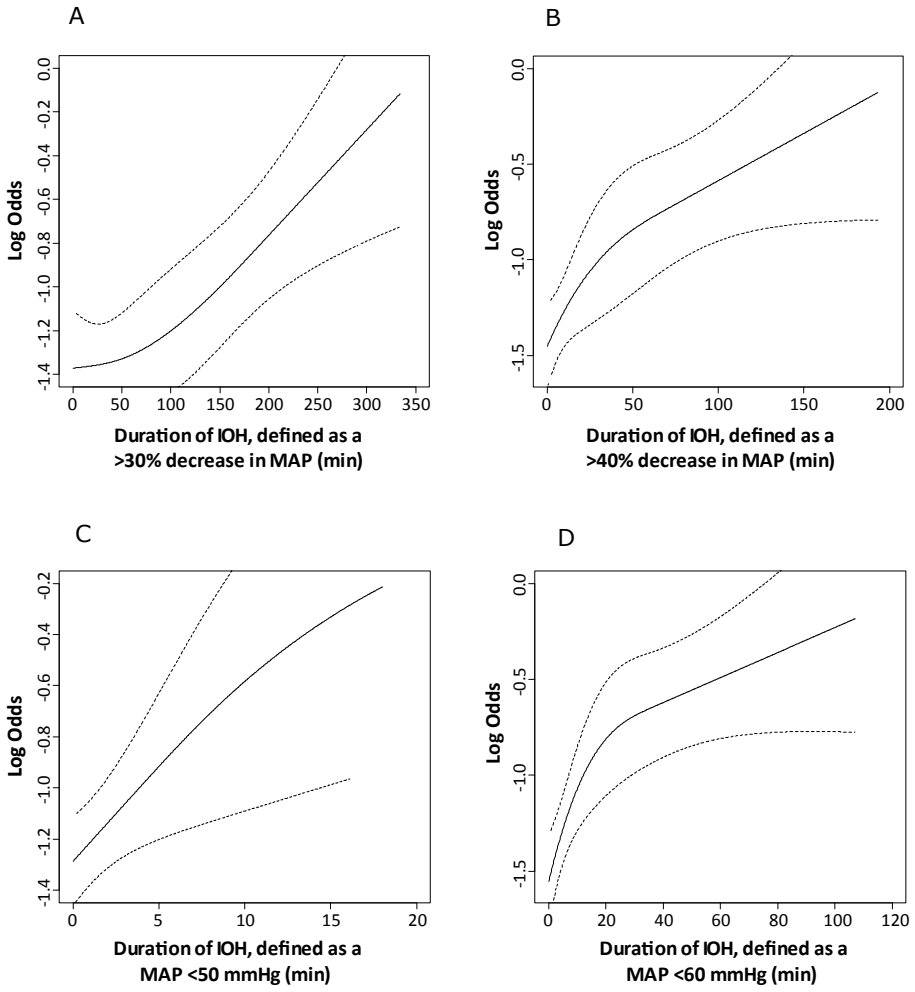
Supplemental File, Table S5.6
Comparison of two hypotension study populations.

	POISE-2 trial*	UHN† Toronto UMC‡ Utrecht	
Mean age (years)	69	73	
Male	53%	70%	
History of coronary artery disease	23%	21%	
History of cerebrovascular disease	5%	20%	
History of chronic heart failure	3%	6%	
Emergency surgery	7%	30%	
Chronic medication use			
Beta-blockers	29%	53%	
Calcium channel blockers	5%	30%	
Renin angiotensin system inhibitors	N.R.§	38%	
Statins	46%	57%	
Myocardial infarction within 30 days	6.4%	4.0%	
30-day mortality	1.3%	3.4%	
Perioperative hypotension (all)	42%	N.R.‡	
Intraoperative hypotension	35%	MAP¶ <60 mmHg:	51%
		MAP¶ <50 mmHg:	12%
		≥30% decrease in MAP¶:	81%
		≥40% decrease in MAP¶:	51%

**Perioperative Ischemic Evaluation 2 trial; †University Health Network Toronto; ‡University Medical Center Utrecht; § Not reported; ¶ Mean arterial pressure.*

Supplemental File, Figure S5.1

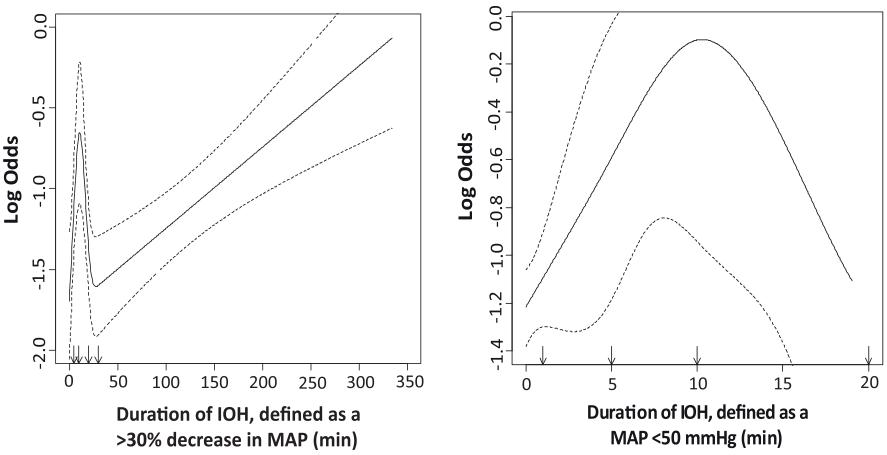
Restricted cubic spline of the association between the duration of intraoperative hypotension (IOH), defined by four different thresholds of the mean arterial pressure (MAP), and postoperative myocardial injury. The log Odds on the Y-axis represents the beta-coefficient of the logistic regression model used in the restricted cubic spline analysis. A) IOH defined as ≥30% decrease in MAP; B) IOH defined as ≥40% decrease in MAP; C) IOH defined as a MAP <60 mmHg; D) IOH defined as a MAP <50 mmHg.



Supplemental File, Figure S5.2

Restricted cubic spline analysis of the association between the duration of intraoperative hypotension (IOH) as defined by a 30% decrease in mean arterial pressure (MAP) or a MAP <50 mmHg, and postoperative myocardial injury, using predefined categories for the duration of hypotension.

The duration of hypotension was analyzed as a categorical variable instead of a continuous variable because the association between hypotension and myocardial injury was expected to be nonlinear. The categories of the duration of hypotension (<1, 2-5, 6-10, 11-20, 21-30 and >30 minutes) were arbitrarily chosen in advance, aiming at more or less equally sized groups for each of the four definitions of hypotension. As is shown in Table 4, there appears to be a significant association between hypotension defined as a ≥30% decrease in MAP and a MAP <50 mmHg with a duration of 6-10 minutes. However, then we would expect that this would be consistent for longer durations of hypotension, i.e. for durations >10 minutes, but that is not the case. We further explored this by studying the restricted cubic splines in which the chosen cut-off points were used to define the knot locations. From these splines, we concluded that the association seen at the 6-10 minute interval was rather due to overfitting by the chosen cut-off points, hence we did not consider this to be a true association.



Chapter 6

Unexpected cardiac CT findings in patients with postoperative myocardial injury

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Submitted.

Abstract

Background

Postoperative myocardial injury (PMI) is a strong predictor of mortality after noncardiac surgery. PMI is believed to be attributable to coronary artery disease (CAD) yet its etiology is largely unclear. We aimed to quantify the prevalence of significant CAD in patients with and without PMI using coronary computed tomography angiography (CCTA).

Methods

Prospective cohort study in patients ≥60 years old without a history of cardiac disease, with and without PMI after intermediate to high-risk noncardiac surgery. PMI was defined as any serum Troponin-I level ≥60 ng/L on the first three postoperative days. Main exclusion criteria were known cardiac disease and post-operative ischemic symptoms or ECG abnormalities. Non-invasive imaging consisted of a postoperative CCTA. Outcomes were CAD defined as >50% coronary stenosis on CCTA, and 30-day mortality.

Results

The analysis included 66 patients. Median troponin levels in the PMI (n= 46) and control group (n = 20) were 150 (IQR 120 – 298) versus 15 (IQR 10 – 31) ng/L ($p<0.01$). CAD was found in 23 patients with PMI (50%) versus 3 without PMI (15%) (RR 3.3, 95%CI 1.1 – 9.8). Remarkably, pulmonary embolism was present in 15 patients with PMI (33%) versus 4 without PMI (20%) (RR 1.6, 95%CI 0.6 – 4.3). In both groups, none of the patients died within 30 days.

Conclusions

In patients without a history of cardiac disease, PMI after noncardiac surgery was associated with CAD. In addition, a clinically silent pulmonary embolism was found in a third of patients with PMI.

Introduction

Annually, over 200 million people undergo major noncardiac surgery worldwide.[1] These procedures are associated with a high risk of mortality and morbidity, which can be attributed to major adverse cardiovascular events (MACE) in up to 50% in high-risk populations.[2-4] Recognition of such events, however, is difficult in the early postoperative phase because of the use of strong analgesics and transiency of ischemic signs on electrocardiography.[5] These difficulties may delay adequate treatment and consecutively influence prognosis.

A promising method to improve early recognition of MACE after surgery is routine postoperative assessment of cardiac troponin, which is a sensitive biomarker with high specificity for the myocardium.[6] Indeed, serum troponin elevations are a strong and independent predictor of 30-day and 12-month mortality.[2, 3] Such postoperative myocardial injury (PMI) is believed to be primarily attributable to an oxygen supply / demand mismatch in the presence of pre-existent coronary artery disease (type II ischemia) or thrombosis on a ruptured atherosclerotic carotid plaque (type I ischemia).[5-8] However, recent trials have shown that platelet aggregation inhibition and suppression of the sympathetic nervous system do not result in a decrease in postoperative MIs and may even be harmful.[9, 10]

In order to enable an improvement of prognosis, it is imperative to understand the etiology of PMI and in particular the role of CAD. The aim of this study was to quantify the prevalence of CAD in patients without a history of cardiac disease, with and without asymptomatic PMI using non-invasive cardiac imaging.

Methods

Patients

This prospective single-center cohort study included patients of 60 years or older who underwent elective intermediate to high-risk noncardiac surgery requiring ≥ 24 hours of hospital admittance in the University Medical Center Utrecht between October 1st 2012 and March 31th, 2015 and whose Troponin-I levels were routinely monitored on the first three postoperative days.[11] Exclusion criteria were prior CAD or myocardial infarction, ST-elevation myocardial infarction, typical angina, non-coronary heart disease (i.e. heart valve disease, cardiomyopathy and/or diastolic heart failure) and contraindications for cardiac CT angiography (CCTA). The local medical ethics committee approved the study protocol and all study subjects provided informed consent (local Medical Research Ethics Committee number 12-017).

Study procedures

All study subjects underwent standardized preoperative anesthesia evaluation including an ECG. Postoperative troponin assessment was performed using a 3rd generation AccuTnI assay (Beckman Coulter, Brea, California).[6] Patients were classified as having PMI if at least one of the troponin measurements exceeded the clinically used threshold of 60 ng/L, which is the lowest value measurable with a 10% coefficient of variation above the 99th percentile of 40 ng/L.[6] Patients without PMI were characterized by a peak troponin below that level. We aimed to include 50 patients with PMI and 20 patients without PMI.

Study procedures consisted of an ECG within 3 days after surgery and a Cardiac CT Angiography (CCTA) during hospital admission. The CCTA was made on a 256-slice CT scanner (Brilliance iCT, Philips Healthcare, Best, The Netherlands) using a prospectively ECG-triggered step-and-shoot mode. Beta-blockade was used – if necessary - to achieve a heart rate of approximately 60 beats per minute. Furthermore, 0.4 mg nitroglycerin spray was administered 3-5 minutes prior to the scan. A non-enhanced scan was performed to calculate the calcium score using the Agatston method.[12] Intravenous contrast fluid (Ultravist 300®) followed by 50 ml of saline flush was subsequently injected into the antecubital vein. Scans were initiated 10 seconds after mean region of interest contrast reached a pre-set threshold of 100 Hounsfield Units. All images were prospectively triggered at 75% of the R–R interval. Scanning parameters included 0.45 mm slice increment, 250 mm field-of-view that included the pulmonary artery, 512x512 matrix, 270 ms gantry rotation-time, tube-voltage and reference tube current were adjusted for patient body-mass index. The degree of stenosis was classified as none (0% stenosis), mild (0 – 25% stenosis), moderate (25 – 50% stenosis) or significant (>50% stenosis) by a radiologist. Furthermore, presence of significant stenosis in either the left main or the proximal left anterior descending artery was examined and also the suggestion of a total occlusion. CCTA images were assessed by an experienced cardiovascular radiologist who was blinded for the troponin values (TL). Follow-up was performed at the cardiology outpatient clinic after 30 days and included an ECG and assessment of adverse cardiovascular events.

Outcomes

The primary study endpoint was CAD, defined as > 50% stenosis in one or more major epicardial vessels on CCTA. The secondary endpoint was 30-day mortality. Incidental findings included pulmonary embolism, which was defined as a sharply delineated pulmonary artery filling defect in at least two consecutive image sections of the CCTA, either located centrally within the vessel or with acute angles at its interface with the vessel wall.[13]

Statistical analysis

The PMI group was compared to the group without PMI using a two-tailed chi-square or Fisher's Exact test for categorical variables, and the *t* test and Mann-Whitney U test for normally distributed and non-normally distributed continuous variables, respectively. Associations between PMI and study endpoints were expressed as unadjusted Relative Risks (RR) with 95% confidence intervals (95%CI). Loss-to-follow-up was defined as withdrawal of consent between the CCTA and the outpatient clinic visit. The analysis was performed using SPSS (release 21.0 for Windows). A value of 0.05 was used as level of significance.

Results

Of the 1205 patients who were screened for study participation (943 with PMI and 262 without PMI), 685 were eligible (Figure 6.1). Within those patients, 322 were unable to provide consent, 106 refused participation and 187 were not included for logistic reasons (e.g. CCTA not available). Four patients were excluded from the analysis because of insufficient imaging quality. Therefore, 66 patients were included in the analysis; 46 with PMI and 20 without. Patients with PMI were significantly older, were more often diabetics and more often used beta-blockers (Table 6.1).

None of the patients underwent additional cardiac tests prior to surgery. The median peak troponin level in the PMI group compared to the group without PMI was 150 (IQR 120 – 298) versus 15 (IQR 10 – 31) ng/L ($p<0.01$). The postoperative ECGs showed new ST depression or T wave inversion in nine patients with PMI (20%) versus four pa-

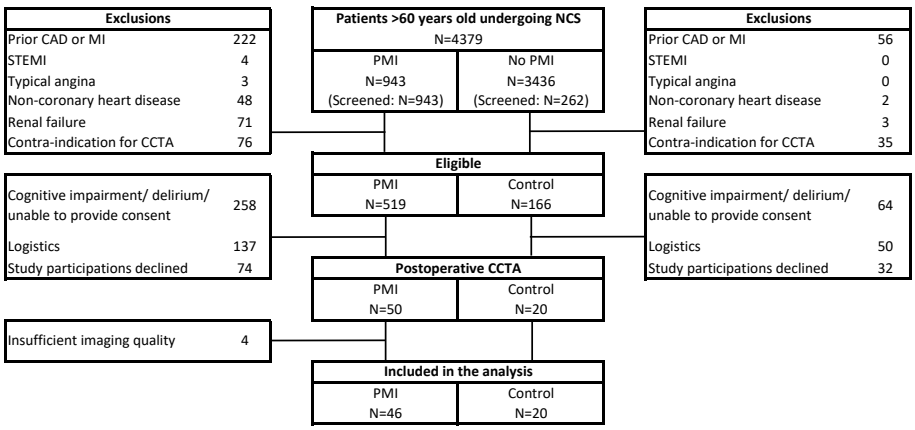


Figure 6.1 *Flow chart of patient inclusion.*

Table 6.1 *Baseline characteristics, stratified for postoperative myocardial injury (PMI).*

	PMI N=46		No PMI N=20		p-value
Mean age (SD)	70	(7)	66	(5)	0.04
Male	25	(54)	13	(65)	0.59
History of myocardial infarction	0	(0)	0	(0)	-
History of coronary intervention	1	(2)	0	(0)	1.00
History of stroke	3	(7)	1	(5)	1.00
Current atrial fibrillation	2	(4)	0	(0)	1.00
Chronic obstructive pulmonary disease	6	(13)	0	(0)	0.17
Renal failure (GFR <30 ml/min/1.73m^2)	0	(0)	0	(0)	-
Cardiovascular risk factors					
Current smoking	9	(20)	2	(10)	0.48
Diabetes mellitus	9	(20)	0	(0)	0.05
Hypertension	27	(59)	8	(40)	0.26
Hypercholesterolemia	14	(31)	4	(20)	0.53
Mean body mass index (SD)	26	(4)	26	(4)	0.74
Medication					
Beta-blocker	13	(28)	1	(5)	0.05
Calcium channel blocker	6	(13)	3	(15)	1.00
ACE-inhibitor	6	(13)	4	(20)	0.48
Other antihypertensive drugs	12	(26)	2	(10)	0.20
Aspirin	8	(17)	3	(15)	1.00
Clopidogrel	3	(7)	0	(0)	0.55
Oral anticoagulation	3	(7)	0	(0)	0.55
Statin	9	(20)	5	(25)	0.75
Insulin	2	(4)	0	(0)	1.00
ASA class					
1 or 2	39	(85)	19	(95)	0.42
3 or 4	7	(15)	1	(5)	
Type of surgery					
Orthopedic	15	(33)	5	(25)	0.33
Vascular	5	(11)	0	(0)	
Neurosurgical	9	(20)	3	(15)	

Figures are numbers of patients (%), unless indicated otherwise. PMI: postoperative myocardial injury; IQR: interquartile range; GFR: glomerular filtration rate; ASA: physical classification system according to the American Society of Anesthesiologists.

Table 6.2 *Outcomes as assessed by coronary computed tomography angiography (CCTA) in patients with and without postoperative myocardial injury (PMI)*

	PMI N= 46	No PMI N=20	Relative Risk (95% CI*)	p-value
Coronary artery disease	23 (50)	3 (15)	3.3 (1.1-9.8)	0.016
Total occlusion	2 (4)	1 (5)		
Median coronary artery calcium score (IQR†)	283 (40–707)	68 (7–289)		0.031
Pulmonary embolism	15 (33)	4 (20)	1.6 (0.6-4.3)	0.46

*Figures are numbers of patients (%), unless indicated otherwise. * Confidence Interval; † Interquartiel range.*

tients without PMI (31%) (p=0.46) and a supraventricular arrhythmia was observed in two (4%) patients versus zero, respectively (p>0.99). Median postoperative hemoglobin levels (g/dL) were 10.9 (IQR 9.7 – 11.9) in patients with PMI versus 10.7 (IQR 9.4 – 12.0) in patients without (p=0.52) and median duration of hospital admittance was 9 days (IQR 7 – 12) versus 9 days (IQR 5 – 11) (p=0.32), respectively. Mortality within 30 days did not occur in both groups.

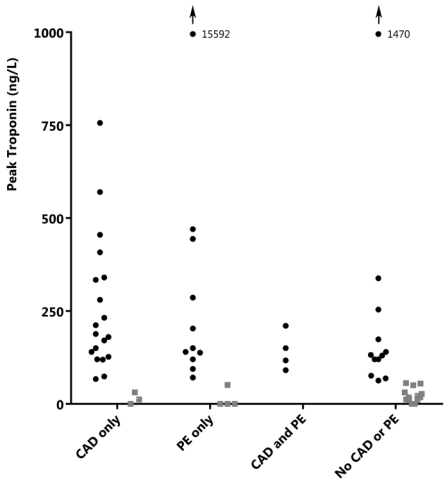
CCTA outcomes

CAD was diagnosed in 23 patients with PMI (50%) versus in three patients without PMI (15%, RR 3.3, 95%CI 1.1 – 9.8) (Table 6.2).

This concerned a total occlusion in two patients (4%) versus one patient (5%), respectively. None of the patients had a left main stenosis. CAD in the proximal LAD was observed in six patients with PMI (13%) versus one patient without PMI (5%). The median coronary artery calcium score was 283 (IQR 40–707) in the PMI group versus 68 (IQR 7–289) in the group without PMI (p=0.031). Incidentally, pulmonary embolism was diagnosed in 15 patients with PMI (33%) versus four patients without PMI (20%) (RR 1.6, 95%CI 0.6 – 4.3). In patients with PMI, the emboli were central, segmental, and subsegmental in four (27%), eight (53%) and three patients (20%), respectively. For patients without PMI, these numbers were zero, two (50%) and two (50%), respectively. Furthermore, pulmonary embolism occurred after orthopedic (8/15), neurosurgical (4/9), head and neck (2/6) and abdominal surgery (1/10) in the PMI group, in comparison to orthopedic (2/5) and abdominal surgery (2/5) in the control group. Median time from surgery to CCTA was 5 days (IQR 4-7) in patients with PMI versus 6 days (IQR 4-7). Median troponin levels for subgroups are shown in Figure 6.2.

Patient management

In 22 of the 26 patients with CAD on CCTA (85%), a cardiac MRI was performed. This MRI showed late gadolinium enhancement in two patients and a perfusion defect in five. In the four patients that did not have a MRI, coronary angiography was performed in two (which confirmed CAD). Coronary revascularization was performed in four patients (i.e. two patients with CAD on coronary angiography and two patients with a perfusion defect on MRI). It was chosen to defer from percutaneous revascularization in three patient with a perfusion defect on MRI because of lack of complaints or if patient was unwilling to undergo the procedure. In the latter group, optimal medical therapy was initiated.18 patients with PMI (39%) were treated with aspirin, beta-blocker, statin and/or antihypertensive drugs, whereas in the group without PMI, 4 patients (20%) were treated as such. Oral anticoagulation was started in 14 (30%) versus 3 patients (15%), respectively.



	PMI group		Control group	
	n =	median (IQR)	n =	median (IQR)
CAD only	19	188 (127 - 340)	3	12 (0 - 31)
PE only	11	150 (120 - 444)	4	10 (0 - 28)
CAD and PE	4	134 (98 - 195)	0	
No CAD or PE	12	131 (87 - 234)	13	18 (10 - 41)

Figure 6.2 *Peak troponin levels for patients with coronary artery disease (CAD) and/or pulmonary embolism (PE), stratified for postoperative myocardial injury (PMI). IQR: interquartile range.*

Discussion

The prognostic relevance of PMI on short and intermediate-term mortality has been established in a variety of surgical populations.[11, 14] Such PMI is believed to be attributable to an oxygen supply and demand mismatch in the presence of stable coronary artery disease, or a coronary plaque rupture which is provoked by perioperative factors such as anemia, tachycardia, hypercoagulability and increased sympathetic tone.[15] Our study suggests that CAD is present in 50% of patients with PMI as measured by troponin elevation, but without a history of cardiac disease. To the best of our knowledge, this is the first study using CCTA in patients with PMI in the postoperative setting.

Studies that assessed the underlying pathophysiologic mechanism of PMI have predominantly focused on symptomatic patients with evident ST segment deviations in whom the prevalence of coronary plaque rupture is relatively high (45%).[8] These patients, however, do not represent the typical patient with PMI, who is generally characterized by absence of clinical symptoms and subtle and/or transient ECG abnormalities.[11] In our study in patients without a history of cardiac disease, silent CAD was present in 50% of the patients with PMI versus 15% in the control group. Based on the combination of relatively minor ECG abnormalities, low troponin levels and a general absence of late enhancement on MRI, it would appear that the vast majority of PMI was caused by demand ischemia rather than an occlusive coronary thrombus. This finding is in line with studies that reported an association between moderate to severe perfusion defects on stress-echocardiography and thallium imaging, and perioperative MI.[16] Fur-

thermore, our results concur with the study by Sheth and colleagues, who performed CCTA prior to noncardiac surgery in 995 patients. In that study, extensive obstructive CAD - defined as ≥50% stenosis in two vessels including the proximal left anterior descending artery, three vessels, or left main - was associated with perioperative MI and cardiac death within 30 days (Hazard Ratio 3.76 (1.12 – 12.62).[17] Interestingly, CAD was absent in 28% of patients who experienced MI or cardiac death, which may indicate that noncardiac pathology plays a larger role in the occurrence of postoperative MI than initially anticipated.

An important finding of our study is the presence of silent pulmonary embolism in 33% of the patients with PMI, of which the majority (80%) was central or segmental. In the patients with PE, minor dyspnea, transient hypotension and atypical thoracic complaints did occur, yet none of them were clinically suspected because these symptoms are common in the postoperative period. It is therefore likely that these embolisms would have been missed without the use of CCTA. Of note, the high incidence of pulmonary embolism in our study is discrepant with registries that reported numbers up to 1%, which can be explained by the predominance of symptomatic pulmonary embolism and lack of modern CT pulmonary angiography use in those studies.[19, 20] Indeed, more recent CTA studies in asymptomatic orthopedic and vascular patients have suggested postoperative embolism rates of 7% and 26%, respectively.[21, 22] PMI in patients with PE could be a result of increased right ventricular pressures or hypoxemia due to a perfusion/ventilation mismatch.[23, 24] Therefore, pulmonary embolism may potentially explain PMI in a part of the patients without obstructive CAD who suffered a postoperative MI.[17] It should also be noted that elevated cardiac markers due to pulmonary embolism are independent predictors of adverse events in the nonsurgical population.[25, 26] One could hypothesize that such an association is also present in the surgical population, which – in part – could explain the association of PMI with mortality.[11]

Multiple observational and intervention studies have been performed in order to improve cardiovascular outcomes after noncardiac surgery yet progress has been slow. For instance, the predictive accuracy of clinical risk stratifying models is generally limited, and adding preoperative imaging either led to underestimation (i.e., in case of perfusion imaging) or overestimation of the cardiac risk (i.e., in case of cardiac CT).[16, 17, 27] Furthermore, preoperative coronary interventions did not improve postoperative mortality, nor did perioperative administration of beta-blockers, aspirin or clonidine.[28-31] In contrast, our study results suggest that postoperative CCTA could be useful for identification and differentiation of silent cardiovascular pathology, which – in turn - could improve patient management. However, CCTA may be challenging to perform in the early postoperative phase. Future studies should focus on the role of CCTA to identify patients with PMI who may benefit from treatment, and on the association of pulmonary embolism with both PMI and (cardiovascular) mortality.[25, 34, 35]

A number of study limitations should be recognized. First, because this study was primarily intended to assess logistic feasibility of CCTA in patients with PMI, a formal sample size calculation was not performed. Moreover, we first aimed to include only patients with PMI to study the prevalence of CAD. However, during the first months of the study, we noticed that PE was frequently found in PMI patients, hence we decided to include a control group as well to determine the prevalence of PE in patients without PMI. This explains the smaller control group as compared to the PMI group. Second, our study was performed in patients without known CAD or prior MI which may limit the generalizability for the entire non-cardiac surgery population. Third, the inclusion rate was low, which was primarily a result of selection of patients without prior CAD, patients who were unable to give informed consent (e.g. due to stroke, sepsis or delirium) and difficult logistics (e.g. transfer to other hospital or unavailability of research-CCTA slots on short notice). Yet, since patients were recruited consecutively, and exclusion percentages and baseline characteristics were similar for both groups, it is unlikely that selection bias will have influenced our results. Finally, some (sub)segmental pulmonary embolisms may have been missed due to the CCTA's limited field of view. This comprised 250 mm and included the pulmonary trunk yet typically did not include the subsegmental branches of especially the superior lobes, which may have led to an underestimation of the incidence of pulmonary embolism.

Conclusions

In patients without a history of cardiac disease, PMI after noncardiac surgery was associated with CAD. In addition, a clinically silent pulmonary embolism was found in a third of patients with PMI.

References

1. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, Gawande AA. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* 2008; 372:139-44.
2. Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, Villar JC, Wang CY, Garutti RI, Jacka MJ, Sigamani A, Srinathan S, Biccard BM, Chow CK, Abraham V, Tiboni M, Pettit S, Szczeklik W, Lurati BG, Botto F, Guyatt G, Heels-Ansdell D, Sessler DI, Thorlund K, Garg AX, Mrkobrada M, Thomas S, Rodseth RN, Pearse RM, Thabane L, McQueen MJ, VanHelder T, Bhandari M, Bosch J, Kurz A, Polanczyk C, Malaga G, Nagele P, Le MY, Leuwer M, Yusuf S. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2012; 307:2295-304.
3. van Waes JA, Nathoe HM, de Graaff JC, Kemperman H, de Borst GJ, Peelen LM, van Klei WA. Myocardial injury after noncardiac surgery and its association with short-term mortality. *Circulation* 2013; 127:2264-71.
4. Noordzij PG, Poldermans D, Schouten O, Bax JJ, Schreiner FA, Boersma E. Postoperative mortality in The Netherlands: a population-based analysis of surgery-specific risk in adults. *Anesthesiology* 2010; 112:1105-15.
5. Landesberg G, Beattie WS, Mosseri M, Jaffe AS, Alpert JS. Perioperative myocardial infarction. *Circulation* 2009; 119:2936-44.
6. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Thygesen K, Alpert JS, White HD, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA, Chaitman BA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S. Third universal definition of myocardial infarction. *Eur Heart J* 2012; 33:2551-67.
7. The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Writing Group. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. *Anesthesiology* 2014;120:564-78.
8. Gualandro DM, Campos CA, Calderaro D, Yu PC, Marques AC, Pastana AF, Lemos PA, Caramelli B. Coronary plaque rupture in patients with myocardial infarction after noncardiac surgery: frequent and dangerous. *Atherosclerosis* 2012; 222:191-5.
9. Devereaux PJ, Mrkobrada M, Sessler DI, Leslie K, Alonso-Coello P, Kurz A, Villar JC, Sigamani A, Biccard BM, Meyhoff CS, Parlow JL, Guyatt G, Robinson A, Garg AX, Rodseth RN, Botto F, Lurati BG, Xavier D, Chan MT, Tiboni M, Cook D, Kumar PA, Forget P, Malaga G, Fleischmann E, Amir M, Eikelboom J, Mizera R, Torres D, Wang CY, VanHelder T, Paniagua P, Berwanger O, Srinathan S, Graham M, Pasin L, Le MY, Gao P, Pogue J, Whitlock R, Lamy A, Kearon C, Baigent C, Chow C, Pettit S, Chrolavicius S, Yusuf S. Aspirin in patients undergoing noncardiac surgery. *N Engl J Med* 2014; 370:1494-503.

10. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Malaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008; 371:1839-47.

11. van Waes JAR, Nathoe HM, de Graaff JC, Kemperman H, de Borst GJ, Peelen LM, van Klei WA. Myocardial injury after noncardiac surgery and its association with short-term mortality. *Circulation* 2013; 127:2264-71.

12. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990; 15:827-32.

13. Stein PD, Goodman LR, Hull RD, Dalen JE, Matta F. Diagnosis and management of isolated subsegmental pulmonary embolism: review and assessment of the options. *Clin Appl Thromb Hemost* 2012; 18:20-6.

14. Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, Villar JC, Wang CY, Garutti RI, Jacka MJ, Sigamani A, Srinathan S, Biccard BM, Chow CK, Abraham V, Tiboni M, Pettit S, Szczeklik W, Lurati BG, Botto F, Guyatt G, Heels-Ansdell D, Sessler DI, Thorlund K, Garg AX, Mrkobrada M, Thomas S, Rodseth RN, Pearse RM, Thabane L, McQueen MJ, Vanhelder T, Bhandari M, Bosch J, Kurz A, Polanczyk C, Malaga G, Nagele P, Le MY, Leuwer M, Yusuf S. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2012; 307:2295-304.

15. Landesberg G, Mosseri M, Shatz V, Akopnik I, Bocher M, Mayer M, Anner H, Berlatzky Y, Weissman C. Cardiac troponin after major vascular surgery: the role of perioperative ischemia, preoperative thallium scanning, and coronary revascularization. *J Am Coll Cardiol* 2004; 44:569-75.

16. Beattie WS, Abdelnaem E, Wijeysundera DN, Buckley DN. A meta-analytic comparison of preoperative stress echocardiography and nuclear scintigraphy imaging. *Anesth Analg* 2006; 102:8-16.

17. Sheth T, Chan M, Butler C, Chow B, Tandon V, Nagele P, Mitha A, Mrkobrada M, Szczeklik W, Faridah Y, Biccard B, Stewart LK, Heels-Ansdell D, Devereaux PJ. Prognostic capabilities of coronary computed tomographic angiography before non-cardiac surgery: prospective cohort study. *BMJ* 2015; 350:h1907.

18. Noordzij PG, van GO, Dijkstra IM, Boerma D, Meinders AJ, Rettig TC, Eefting FD, van LD, van de Garde EM, van Dongen EP. High-sensitive cardiac troponin T measurements in prediction of non-cardiac complications after major abdominal surgery. *Br J Anaesth* 2015; 114:909-18.

19. Mismetti P, Laporte S, Darmon JY, Buchmuller A, Decousus H. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. *Br J Surg* 2001; 88:913-30.

20. Gangireddy C, Rectenwald JR, Upchurch GR, Wakefield TW, Khuri S, Henderson WG, Henke PK. Risk factors and clinical impact of postoperative symptomatic venous thromboembolism. *J Vasc Surg* 2007; 45:335-41.

21. Fujita Y, Nakatsuka H, Namba Y, Mitani S, Yoshitake N, Sugimoto E, Hazama K. The incidence of pulmonary embolism and deep vein thrombosis and their predictive risk factors after lower extremity arthroplasty: a retrospective analysis based on diagnosis using multidetector CT. *J Anesth* 2015; 29:235-41.

22. Kim HJ, Walcott-Sapp S, Adler RS, Pavlov H, Boachie-Adjei O, Westrich GH. Thromboembolic Complications Following Spine Surgery Assessed with Spiral CT Scans: DVT/PE Following Spine Surgery. *HSS J* 2011; 7:37-40.

23. Coma-Canella I, Gamallo C, Martinez OP, Lopez-Sendon J. Acute right ventricular infarction secondary to massive pulmonary embolism. *Eur Heart J* 1988 May;9(5):534-40.

24. Smulders YM. Pathophysiology and treatment of haemodynamic instability in acute pulmonary embolism: the pivotal role of pulmonary vasoconstriction. *Cardiovasc Res* 2000; 48:23-33.

25. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. *Circulation* 2007 ;116:427-33.

26. Lankeit M, Jimenez D, Kostrubiec M, Dellas C, Hasenfuss G, Pruszczyk P, Konstantinides S. Predictive value of the high-sensitivity troponin T assay and the simplified Pulmonary Embolism Severity Index in hemodynamically stable patients with acute pulmonary embolism: a prospective validation study. *Circulation* 2011; 124:2716-24.

27. Ford MK, Beattie WS, Wijeysundera DN. Systematic review: prediction of perioperative cardiac complications and mortality by the revised cardiac risk index. *Ann Intern Med* 2010; 152:26-35.

28. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Malaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet*; 371:1839-47.

29. Devereaux PJ, Mrkobrada M, Sessler DI, Leslie K, Alonso-Coello P, Kurz A, Villar JC, Sigamani A, Biccard BM, Meyhoff CS, Parlow JL, Guyatt G, Robinson A, Garg AX, Rodseth RN, Botto F, Lurati BG, Xavier D, Chan MT, Tiboni M, Cook D, Kumar PA, Forget P, Malaga G, Fleischmann E, Amir M, Eikelboom J, Mizera R, Torres D, Wang CY, Vanhelder T, Paniagua P, Berwanger O, Srinathan S, Graham M, Pasin L, Le MY, Gao P, Pogue J, Whitlock R, Lamy A, Kearon C, Baigent C, Chow C, Pettit S, Chrolavicius S, Yusuf S. Aspirin in patients undergoing noncardiac surgery. *N Engl J Med* 2014 ; 370:1494-503.

30. Zaugg M, Bestmann L, Wacker J, Lucchinetti E, Boltres A, Schulz C, Hersberger M, Kalin G, Furrer L, Hofer C, Blumenthal S, Muller A, Zollinger A, Spahn DR, Borgeat A. Adrenergic receptor genotype but not perioperative bisoprolol therapy may determine cardiovascular outcome in at-risk patients undergoing surgery with spinal block: the Swiss Beta Blocker in Spinal Anesthesia (BBSA) study: a double-blinded, placebo-controlled, multicenter trial with 1-year follow-up. *Anesthesiology* 2007; 107:33-44.

31. McFalls EO, Ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F, Pierpont G, Santilli S, Rapp J, Hattler B, Shunk K, Jaenicke C, Thottapurathu L, Ellis N, Reda DJ, Henderson WG. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med* 2004; 351:2795-804.

32. Sabarudin A, Sun Z, Yusof AK. Coronary CT angiography with single-source and dual-source CT: comparison of image quality and radiation dose between prospective ECG-triggered and retrospective ECG-gated protocols. *Int J Cardiol* 2013; 168:746-53.

33. McCullough PA, Sandberg KR. Epidemiology of contrast-induced nephropathy. *Rev Cardiovasc Med* 2003; 4 Suppl 5:S3-S9.

34. Hakemi EU, Alyousef T, Dang G, Hakmei J, Doukky R. The prognostic value of undetectable highly sensitive cardiac troponin I in patients with acute pulmonary embolism. *Chest* 2015; 147:685-94.

35. Foucrier A, Rodseth R, Aissaoui M, Ibanes C, Goarin JP, Landais P, Coriat P, Le MY. The long-term impact of early cardiovascular therapy intensification for postoperative troponin elevation after major vascular surgery. *Anesth Analg* 2014; 119:1053-63.

cTnI
78/54
MMHG
cTnI
90/65
mmHg
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cTnI
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cTnI
cTnI
cTnI
ischemia
78/54
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cTnI
type 1 MI
cTnI
78/54
90/65
mmHg
cTnI

PART III

SELECTION OF PATIENTS FOR ROUTINE MONITORING OF MYOCARDIAL INJURY AFTER NONCARDIAC SURGERY

Chapter 7

Selection of patients for routine monitoring of myocardial injury after noncardiac surgery

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Submitted.

Abstract

Background

To identify patients at risk for postoperative myocardial infarction early after noncardiac surgery, postoperative monitoring of troponin is advocated.[1,2] However, data on how to select patients for such monitoring are lacking. Therefore, we aimed to identify patients who are at highest risk of postoperative myocardial infarction (POMI) and isolated postoperative troponin elevation (IPTE).

Methods

This observational cohort study included 3,247 patients ≥60 years undergoing intermediate to high risk noncardiac surgery. The primary outcome was POMI. IPTE was a secondary outcome. Classification and regression tree (CART) analysis was used to identify patient groups at high risk of POMI and to calculate the numbers needed to screen (NNS) to identify one patient with POMI. The obtained tree was internally validated by using bootstrapping.

Results

POMI occurred in 102 (3%) and IPTE in 620 (19%) patients. CART analysis divided patients into 10 groups in which the risk of POMI ranged from 0 to 34%. Using a risk of POMI ≥1% to select patients, troponin monitoring would be advocated in patients undergoing emergency surgery, or elective surgery with RCRI class >1 but excluding elective surgery patients aged ≥85 without renal failure. Applying these criteria would result in 2,023 patients eligible for troponin monitoring (95% CI 2017- 2030), which is 62% of the initially included 3,247 unselected patients. The NNS for POMI was 19 patients (95% CI 19-19), and 0.2% of patients with POMI would have been missed.

Conclusions

We used CART analysis to improve selection of patients for postoperative troponin monitoring. Based on our findings, troponin monitoring is advocated in patients undergoing emergency surgery, or elective surgery and RCRI class >1.

Introduction

Adverse cardiac events after noncardiac surgery are an important cause of morbidity and mortality.[3] To identify patients at risk for such events early after surgery, postoperative monitoring of troponin is advocated.[1,2] Several studies have shown that troponin elevation occurs in 8-52% of patients after surgery and that these patients have an increased risk of death.[4–7] Current guidelines recommend to consider postoperative monitoring of troponin in high-risk patients because this could have therapeutic consequences.[8] However, data on how to identify those high-risk patients are sparse. The Revised Cardiac Risk Index (RCRI) and Myocardial Infarction Cardiac Arrest (MICA) calculator derived from the National Surgical Quality Improvement Program (NSQIP) database are well validated risk scores to assess the risk of major cardiac events such as myocardial infarction and cardiac arrest, but are not developed to predict myocardial injury as measured by troponin elevation.[9,10] It is suggested to consider troponin monitoring in patients with RCRI class 3 or higher, in vascular surgery patients with RCRI class 2 or higher and in patients with impaired exercise tolerance;[8] or in patients aged at least 65, or aged at least 45 with a history of coronary artery disease, peripheral vascular disease or cerebral vascular disease.[2] However, none of these criteria are evidence based.

In our hospital, routine troponin I (TnI) measurements were implemented in 2011 as part of the standard postoperative care protocol, followed by cardiology consultation in case of troponin elevation. In absence of established selection criteria for postoperative troponin monitoring, patients were selected based on their age (60 years or older), the surgical risk (intermediate to high), and expected postoperative length of hospital stay (more than 24 hours). As troponin elevation was found in approximately 20% of patients, troponin measurements seemed redundant in a considerable number of patients.[7]

In order to identify patients at highest risk for postoperative troponin elevation, i.e. those who could benefit most from routine postoperative monitoring of troponin, better selection criteria are needed. Therefore, the aim of this study was to identify groups of patients who are at highest risk of postoperative myocardial infarction (POMI) and isolated postoperative troponin elevation (IPTE) after noncardiac surgery.

Materials and Methods

Patients

In this observational cohort study, data were used from a previously described cohort.[7] This cohort included consecutive patients undergoing noncardiac surgery between Ja-

nuary 1st 2011 and December 31st 2012 at the University Medical Center Utrecht, The Netherlands, a 1,000 bed tertiary referral hospital. Patients were eligible if they were aged 60 years or older, were undergoing intermediate to high risk noncardiac surgery under general or spinal anesthesia with an expected postoperative length of hospital stay of at least 24 hours. For patients who underwent surgery more than once, the first surgery was included in the analyses. A reoperation was included as a novel case if this surgery took place at least one year after the first surgery. Patients were excluded if troponin was not measured or measured only once after surgery.

The local medical ethics committee waived the need for informed consent, as only routinely collected patient data were used and data were anonymized before analysis (UMC Utrecht Medical Research Ethics Committee, protocol number 11/120-C).

Outcome

The primary outcome for this study was POMI, defined according to the third universal definition of myocardial infarction.[11] IPTE was included as a secondary outcome and defined as a TnI >60 ng/L without other criteria for POMI being present.

The occurrence of the outcomes was assessed by routine daily TnI measurements on the first three days after surgery, according to the postoperative care protocol for surgical patients over 60 years old in our hospital. TnI was analyzed using a third-generation enhanced AccuTnI assay (Beckman Coulter, Brea, California) with a clinical cut-off of 60 ng/L which is the lowest measurable value with a 10% coefficient of variation above the 99th percentile of 40 ng/L. In case of troponin elevation, a cardiology consultation was ordered. Further diagnostic procedures including an electrocardiogram (ECG) to assess the occurrence of POMI were performed on discretion of the consultant cardiologist.[7]

Data collection

All preoperative and postoperative data were obtained from electronic medical and administrative records. Data collected of all patients included patient characteristics, preoperative physical status, comorbidities, RCRI, postoperative TnI measurements, postoperative ECGs and the occurrence of POMI. The RCRI criteria high risk surgery, history of cerebrovascular disease and preoperative treatment with insulin were defined according to the original RCRI.[9] The other criteria were adapted to be able to obtain the index from the available data: preoperative renal failure was defined as a preoperative glomerular filtration rate <45 ml/min/1.73m^2; ischemic heart disease was defined as previous myocardial infarction and/or coronary revascularization; preoperative heart failure was defined as a left ventricular ejection fraction <40%. Emergency surgery was defined as surgery required within 72 hours after the indication was set.

Statistical analysis

Baseline characteristics were compared between patients without troponin elevation, IPTE, and POMI using the Chi-square test or one-way ANOVA, as appropriate.

Because a postoperative ECG was missing in 41% of patients (see results section for more details), the occurrence of POMI could not be assessed in these patients. Omitting these patients from the analyses and conducting a complete case analysis only, is known to lead to biased effect estimates.[12,13] Alternatively, classifying patients without postoperative ECG as not having POMI, without taking into account any other patient characteristics, would lead to misclassification bias. Therefore, we used multiple imputation to estimate the occurrence of POMI in these patients.[14] Forty datasets were imputed by the method of predictive mean matching with all known patient and procedure characteristics as predictor variables. In order to perform the following analyses, the forty imputed datasets were stacked into one large dataset.

We used Classification and Regression Tree (CART) analysis to identify patient groups at increased risk of POMI and IPTE.[15] In short, this analysis proceeds as follows. The algorithm starts with the entire cohort and subsequently searches for the variable that most optimally separates the patients at high risk from those at low risk. This yields two subgroups, which are in turn also divided into two subgroups which are increasingly homogeneous with respect to the outcome variables. This stepwise procedure continues until no further split can be made, or when a minimum number of patients in a subgroup is reached. Altogether this results in a decision tree with so-called nodes; following a path from the root to the terminal node provides the characteristics of the patients in the terminal node.

In our analyses we used patient- and procedure characteristics to identify groups of patients homogeneous in terms of risk on POMI and IPTE. Predictor variables included age, sex, emergency surgery, physical status classification of the American Society of Anesthesiologists (ASA class), RCRI class, high risk surgery, history of ischemic heart disease, chronic heart failure, preoperative renal failure, (paroxysmal) atrial fibrillation, pacemaker and/or implantable cardioverter defibrillator, history of cerebrovascular disease, peripheral vascular disease, diabetes and chronic obstructive pulmonary disease. POMI and IPTE were included in the analyses as one variable with three possible outcome categories (no troponin elevation, IPTE and POMI), hence we conducted multinomial CART analysis. We used the Gini index to obtain maximum homogeneity, and the minimum classification improvement per node was set at 0.0001. The minimum size for parent and child nodes was set at 36 patients, which equals 5% of the 722 patients with troponin elevation. The maximum number of steps between the first node to one of the terminal nodes was set at 10. No pruning was applied.

After obtaining the tree, the independent variable importance of each variable in the tree was determined by assessing the normalized importance of each variable,

which is defined as the predictive ability of a single variable as compared to the variable with the highest predictive ability in the model. Next, the absolute risk of POMI and IPTE was calculated for the patients in each node in the tree. Furthermore, for each node the number needed to screen (NNS) to identify one patient with POMI was calculated, defined as the total number of patients within the node divided by the number of patients with POMI.

We validated the resulting tree using bootstrapping to obtain confidence intervals of the patient numbers, predicted risks and NNS estimates in each node of the final tree. First, patients were allocated to the nodes of which they were a member in the final tree. As a result, each patient was allocated to one terminal node and the internal nodes on the path toward this terminal node. Subsequently 10,000 sample datasets were created by random sampling with replacement. For each node in each sample dataset, the absolute risk of POMI, the absolute risk of IPTE, and the NNS for POMI was calculated. Next, from the 10,000 samples, for each node we calculated the mean total number of patients, and the mean numbers of patients with POMI and IPTE, the mean risk of POMI and IPTE, and the median NNS for POMI with 95% confidence intervals. This bootstrapping procedure was conducted for each of the 40 imputed datasets separately. Finally, Rubin's rule was applied to pool the estimates from each of the 40 imputed datasets.

The analysis was performed using SPSS (release 21.0 for Windows), and R (release 3.1.1 for Windows) using the mice library for multiple imputation.

Finally, in order to define selection criteria from the resulting tree, a risk of POMI <1% was considered low and was therefore used to exclude patients from troponin monitoring.[8,16]

Results

During the study period 4,099 patients were eligible for inclusion, of which 17 patients (0.4%) were excluded from the analyses; 13 patients died on the day of surgery, and 4 patients were transferred on the day of surgery, hence troponin could not be measured in these patients. Of the remaining 4,082 patients, 835 patients (20%) were excluded because troponin was not measured during the first three postoperative days. Thus, 3,247 patients were included in this study (Table 7.1).

Table 7.1 *Baseline characteristics, stratified for the occurrence of postoperative myocardial infarction (POMI) and isolated postoperative troponin elevation (IPTE).*

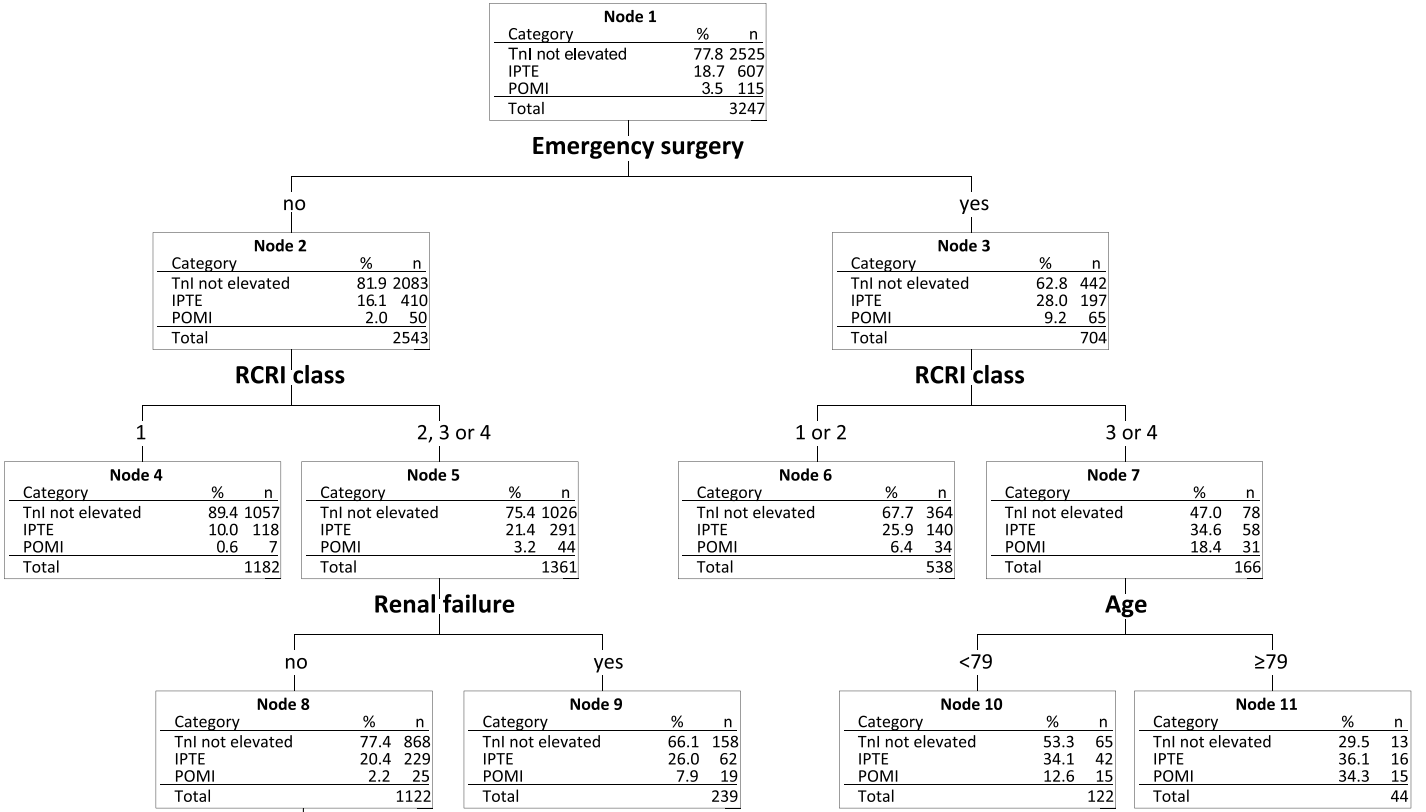
	No TnI* elevation N=2525		IPTE N=620		POMI N=102		p-value
Male	1292	(51.2)	369	(59.5)	58	(56.9)	<0.01
Mean age (SD)	70.4	(7.4)	72.6	(8.1)	74.8	(8.4)	<0.01
Hypertension	1248	(49.4)	365	(58.9)	73	(71.6)	<0.01
Diabetes	406	(16.1)	123	(19.8)	28	(27.5)	<0.01
History of myocardial infarction	195	(7.7)	79	(12.7)	27	(26.5)	<0.01
History of coronary revascularization	251	(9.9)	100	(16.1)	30	(29.4)	<0.01
History of heart failure	56	(2.2)	32	(5.2	7	(6.9)	<0.01
History of atrial fibrillation	263	(10.4)	83	(13.4)	25	(24.5)	<0.01
Pacemaker and/or ICD†	50	(2.0)	32	(5.2)	4	(3.9)	<0.01
History of cerebrovascular disease	361	(14.3)	107	(17.3)	28	(27.5)	<0.01
Preoperative renal failure	224	(8.9)	114	(18.4)	39	(38.2)	<0.01
Peripheral vascular disease	245	(9.7)	93	(15.0)	18	(17.6)	<0.01
COPD‡	233	(9.2)	65	(10.5)	11	(10.8)	0.57
RCRI§ class							
I	1276	(50.5)	197	(31.8)	21	(20.6)	<0.01
II	803	(31.8)	233	(37.6)	26	(25.5)	
III	329	(13.0)	131	(21.1)	29	(28.4)	
IV	117	(4.6)	59	(9.5)	26	(25.5)	
ASA class¶							
1	359	(14.2)	53	(8.5)	5	(4.9)	<0.01
2	1652	(65.4)	365	(58.9)	41	(40.2)	
≥3	514	(20.4)	202	(32.3)	56	(54.9)	
General anesthesia	2349	(93.0)	599	(96.6)	101	(99.0)	<0.01
High risk surgery	728	(28.8)	266	(42.9)	48	(47.1)	<0.01
Emergency surgery	442	(17.5)	205	(33.1)	57	(55.9)	<0.01
Surgical specialty							
General	522	(20.7)	207	(33.4)	35	(34.3)	<0.01
Neuro	638	(25.3)	131	(21.1)	20	(19.6)	
Vascular	366	(14.5)	118	(19.0)	28	(27.5)	
ENT\\ and dental	340	(13.5)	60	(9.7)	5	(4.9)	
Orthopedic	268	(10.6)	68	(11.0)	10	(9.8)	
Gynaecology/Urologic	391	(15.5)	36	(5.8)	4	(3.9)	

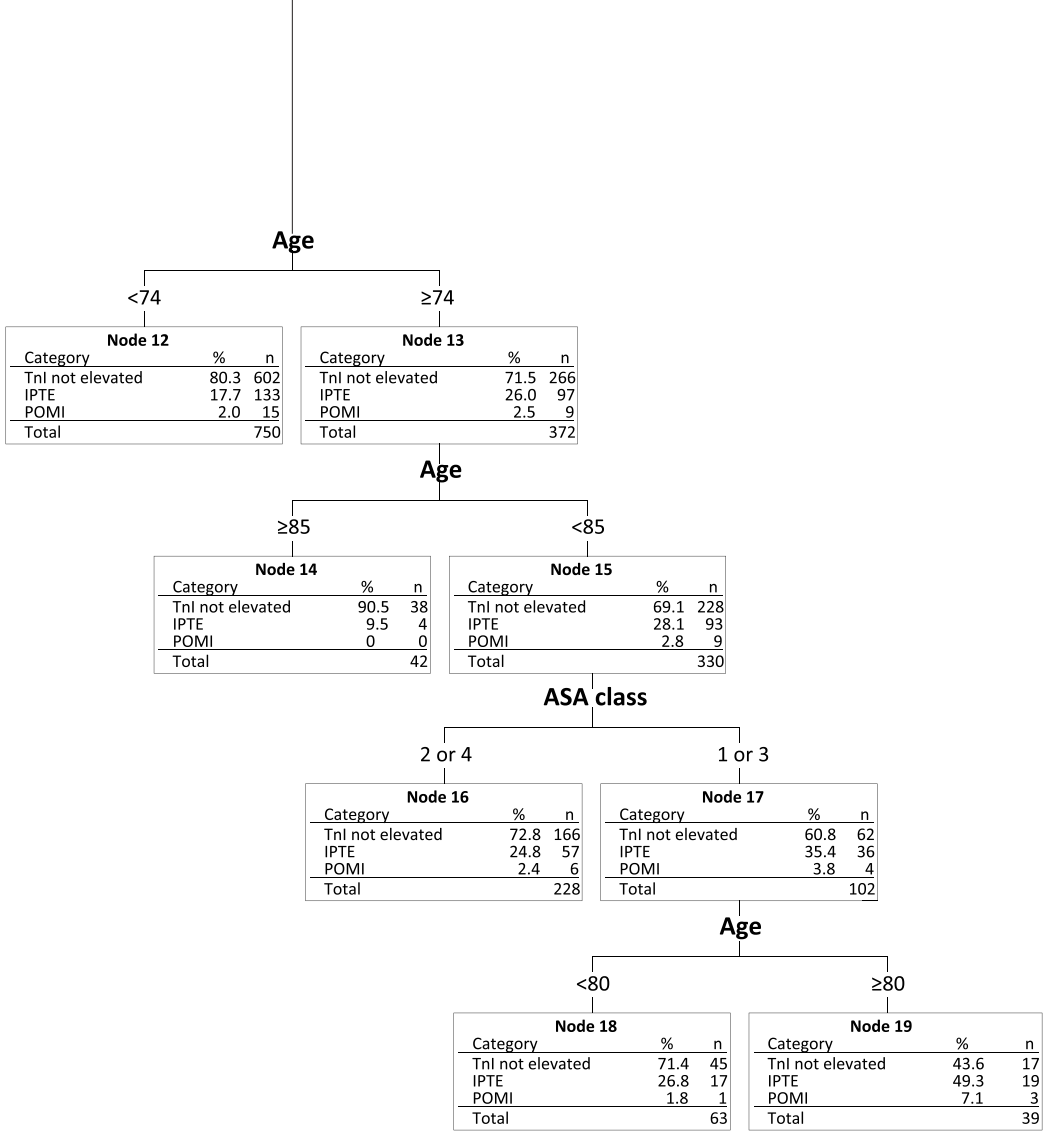
*Figures are numbers of patients (%), unless indicated otherwise. *Troponin I; †Implantable cardioverter defibrillator; ‡Chronic obstructive pulmonary disease; §Revised cardiac risk index; ¶Classification system by the American Society of Anesthesiologists; \\Ear Nose Throat.*

POMI and IPTE

Troponin elevation occurred in 722 patients (22%). To assess the occurrence of POMI, a postoperative ECG was performed in 429 (59%) of these 722 patients, as indicated by the consultant cardiologist. 102 (3%) patients fulfilled the criteria for POMI. In patients without ECG, the median TnI level was lower (90 ng/L, IQR 70-140), as compared to patients with ECG (TnI 200 ng/L, IQR 110-570, p<0.01). After imputation of the missing

Figure 7.1 *Classification tree for the risk of postoperative myocardial infarction and troponin elevation. Predictor variables included age, sex, physical status classification of the American Society of Anesthesiologists (ASA class), Revised Cardiac Risk Index (RCRI class), comorbidities, emergency surgery, and high risk surgery.*




Age
<74
≥74
Node 12
Category % n
TnI not elevated 80.3 602
IPTE 17.7 133
POMI 2.0 15
Total 750
Node 13
Category % n
TnI not elevated 71.5 266
IPTE 26.0 97
POMI 2.5 9
Total 372
Age
≥85
<85
Node 14
Category % n
TnI not elevated 90.5 38
IPTE 9.5 4
POMI 0 0
Total 42
Node 15
Category % n
TnI not elevated 69.1 228
IPTE 28.1 93
POMI 2.8 9
Total 330
ASA class
2 or 4
1 or 3
Node 16
Category % n
TnI not elevated 72.8 166
IPTE 24.8 57
POMI 2.4 6
Total 228
Node 17
Category % n
TnI not elevated 60.8 62
IPTE 35.4 36
POMI 3.8 4
Total 102
Age
<80
≥80
Node 18
Category % n
TnI not elevated 71.4 45
IPTE 26.8 17
POMI 1.8 1
Total 63
Node 19
Category % n
TnI not elevated 43.6 17
IPTE 49.3 19
POMI 7.1 3
Total 39

POMI data, the mean number of patients that were classified as having POMI and IPTE in the 40 imputed datasets was 115 (4%) and 607 patients (19%), respectively.

Classification and regression tree analysis

The resulting tree consisted of 10 terminal nodes (Figure 7.1). The maximum number of steps to reach a terminal node was 7. The first variables that were used to divide patients into groups were emergency surgery and RCRI class. These variables also had the highest normalized variable importance, followed by high risk surgery and age (Figure 7.2). In the different nodes, the absolute risk of POMI ranged from 0 to 34% and was highest among emergency surgery patients with RCRI class >2 and age ≥79 years (node 11) (Figure 7.1). The NNS for POMI ranged from 3 to 181 patients, was lowest (i.e. 3) among emergency surgery patients with RCRI class >2 and age ≥79 years (node 11), and was highest (i.e. 181) among elective surgery patients with RCRI class 1 (node 4) (Table 7.2). The absolute risk of IPTE ranged from 10 to 49%. Table 7.2 depicts the patient numbers and risks with their confidence intervals, as obtained from the boots-trapping procedure.

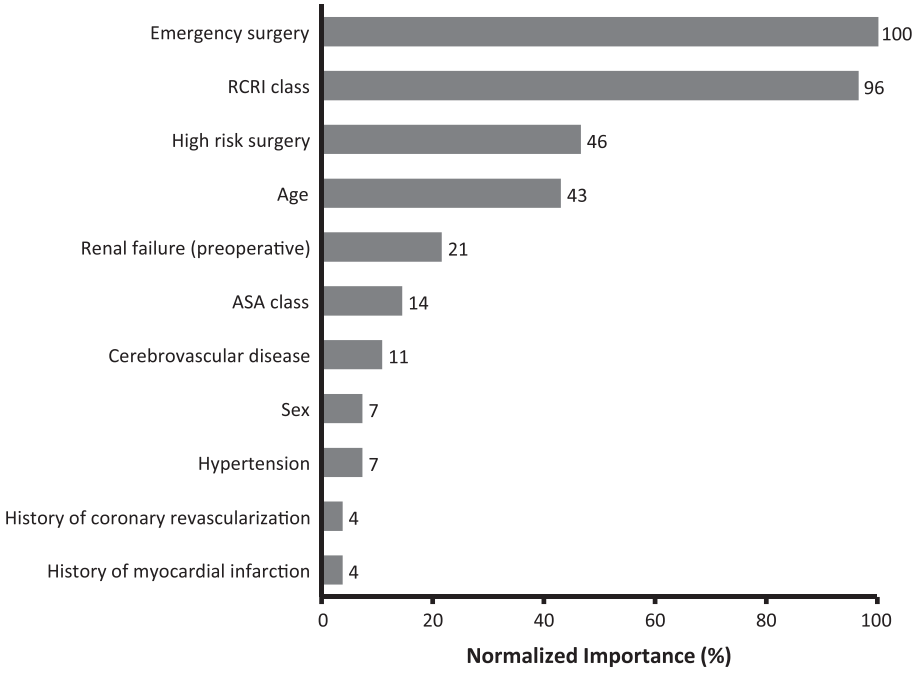


Figure 7.2 *The normalized importance of the predictor variables in the model.RCRI: Revised Cardiac Risk Index; ASA: physical status classification of the American Society of Anesthesiologists; COPD: chronic obstructive pulmonary disease; ICD: implantable cardioverter defibrillator.*

Table 7.2 *One the left side of the table, the numbers of patients with isolated postoperative troponin elevation (IPTE) and postoperative myocardial infarction (POMI), the risk of IPTE and POMI, and the number needed to screen (NNS) to identify one patient with POMI are given for each node in the original tree. The nodes are ordered on the NNS for POMI. On the right side of the table, the numbers and risks with 95% confidence intervals as obtained from bootstrap samples are given. For some nodes, the NNS for POMI was infinite because the number of patients with POMI was zero in the some of the bootstrap samples.*

	ORIGINAL TREE						BOOTSTRAP SAMPLES											
	All patients	IPTE		POMI			All patients		IPTE				POMI					
	N	N	Absolute Risk	N	Absolute Risk	NNS	Mean N	(95% CI)	Mean N	(95% CI)	Mean Risk	(95% CI)	Mean N	(95% CI)	Mean Risk	(95% CI)	NNS	(95% CI)
Node 14	42	4	0.10	0	0	∞	42	(41-43)	4	(4-4)	0.10	(0.09-0.10)	0	(0)	0	(0)	∞	NA
Node 4	1182	118	0.10	7	0.006	181	1182	(1176-1187)	118	(116-120)	0.10	(0.10-0.10)	7	(6-7)	0.006	(0.005-0.006)	∞	NA
Node 18	63	17	0.27	1	0.02	56	63	(62-65)	17	(16-18)	0.27	(0.26-0.28)	1	(1-1)	0.02	(0.014-0.02)	∞	NA
Node 2	2543	410	0.16	50	0.02	51	2543	(2538-2547)	410	(406-414)	0.16	(0.16-0.16)	50	(49-52)	0.02	(0.02-0.02)	52	(50-53)
Node 12	750	133	0.18	15	0.02	49	750	(745-755)	133	(131-135)	0.18	(0.17-0.18)	15	(14-16)	0.02	(0.02-0.02)	54	(50-57)
Node 8	1122	229	0.20	25	0.02	46	1122	(1117-1128)	230	(227-233)	0.20	(0.20-0.21)	25	(24-26)	0.02	(0.02-0.02)	48	(46-50)
Node 16	228	57	0.25	6	0.02	41	228	(225-231)	57	(55-58)	0.25	(0.24-0.25)	6	(5-6)	0.02	(0.02-0.03)	∞	NA
Node 13	372	97	0.26	9	0.03	40	372	(369-376)	97	(95-99)	0.26	(0.26-0.26)	9	(9-10)	0.03	(0.02-0.03)	46	(41-50)
Node 15	330	93	0.28	9	0.03	35	330	(327-334)	93	(91-95)	0.28	(0.28-0.29)	9	(9-10)	0.03	(0.03-0.03)	41	(36-45)
Node 5	1361	291	0.21	44	0.03	31	1361	(1356-1366)	292	(288-295)	0.21	(0.21-0.22)	44	(42-45)	0.03	(0.03-0.03)	32	(31-33)
Node 1	3247	607	0.19	115	0.04	28	3247	(3247-3247)	607	(602-611)	0.19	(0.19-.019)	115	(113-117)	0.04	(0.03-0.04)	28	(28-29)
Node 17	102	36	0.35	4	0.04	26	102	(100-104)	36	(35-37)	0.35	(0.35-0.35)	4	(4-4)	0.04	(0.03-0.04)	∞	NA
Node 6	538	140	0.26	34	0.06	16	538	(534-542)	139	(137-142)	0.26	(0.26-0.26)	34	(33-35)	0.06	(0.06-0.07)	16	(16-17)
Node 19	39	19	0.49	3	0.07	14	39	(38-40)	19	(18-20)	0.49	(0.48-0.51)	3	(2-3)	0.07	(0.06-0.08)	∞	NA
Node 9	239	62	0.26	19	0.08	13	239	(236-241)	62	(60-63)	0.26	(0.25-0.26)	19	(18-20)	0.08	(0.08-0.08)	13	(13-14)
Node 3	704	197	0.28	65	0.09	11	704	(700-709)	197	(194-199)	0.28	(0.28-0.28)	65	(63-66)	0.09	(0.09-0.09)	11	(11-11)
Node 10	122	42	0.34	15	0.13	8	122	(120-124)	42	(40-43)	0.34	(0.33-0.35)	15	(15-16)	0.13	(0.12-0.13)	9	(8-9)
Node 7	166	58	0.35	31	0.18	5	166	(164-169)	57	(56-59)	0.35	(0.34-0.35	31	(29-32)	0.18	(0.18-0.19)	6	(5-6)
Node 11	44	16	0.36	15	0.34	3	44	(43-45)	16	(15-17)	0.36	(0.35-0.37)	15	(14-16)	0.34	(0.33-0.36)	3	(3-3)

Using the tree for patient selection

When using the obtained tree to select patients for troponin monitoring, the number of screened patients and number of patients with missed POMI and IPTE depend on the minimum risk of POMI that is used to include patients. When a risk of POMI ≥1.0% is used to select patients, the patients in terminal node 4 (i.e. those undergoing elective surgery and classified as RCRI 1) and node 14 (i.e. those undergoing elective surgery with RCRI class >1 and age ≥85, but without renal failure) would be excluded from routine postoperative troponin monitoring (Figure 7.1). Selected patients among patients ≥60 years undergoing noncardiac surgery would include emergency surgery patients (node 3) and elective surgery patients with RCRI class >1 (node 5), but excluding elective surgery patients aged ≥85 without renal failure (node 14). In that case, 2,023 (95% CI 2,017- 2,030) patients would be eligible for monitoring. These 2,023 patients comprise 62% of the initially included 3,247 unselected patients. The overall NNS to detect one patient with POMI would be 19 (95% CI 19-19). The number of patients with missed POMI and IPTE would be 7 patients (95% CI 6-7) and 122 patients (95% CI 120-124), respectively.

Discussion

Postoperative troponin monitoring is advocated in patients at high risk of POMI undergoing noncardiac surgery. However, selection criteria for such monitoring are currently based on consensus rather than clinical evidence. Therefore, we used the CART method to identify groups of patients with the highest risk of POMI in whom routine postoperative troponin monitoring could provide most benefit. Among patients ≥60 years undergoing intermediate to high risk noncardiac surgery, we found that emergency surgery and the combination of elective surgery and RCRI class >1, excluding the combination of elective surgery and no renal failure and age ≥85, were factors that corresponded with the highest risk of POMI. Postoperative troponin monitoring may be applied in these patients to facilitate early identification of POMI. If these criteria would be applied, the NNS to identify one patient with POMI would be 19 patients and 38% (1,224/3,247) of the patients ≥60 years undergoing intermediate to high risk noncardiac surgery would not be included in routine troponin monitoring at the cost of 0.2% (7/3,247) of patients experiencing POMI who would be missed.

Literature

The Revised Cardiac Risk Index is currently the most widely used index to estimate the perioperative cardiac risk, and therefore was included as a predictor variable in our study.[9] It was derived from a cohort of 4,315 patients aged ≥50 undergoing noncardiac

surgery by using routine CK-MB measurements and ECGs after surgery to assess the occurrence of the outcome. High risk surgery, ischemic heart disease, heart failure, cerebrovascular disease, serum creatinine >2.0 mg/dL and insulin use were identified as independent predictors of POMI and other major cardiac complications.

Several other studies determined single predictors of adverse cardiac events by using routine measurements of cardiac biomarkers.[10,17–20] A multicenter prospective database, the American College of Surgeons' 2007 National Surgical Quality Improvement Program (NSQIP) database including 211,410 patients, identified type of surgery, dependent functional status, abnormal creatinine, ASA class, and increasing age as cardiac risk factors, and were incorporated in the Myocardial Infarction and Cardiac Arrest (MICA) risk calculator.[10] The Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) study included 13,948 patients in a prospective cohort. The authors reported that age ≥75, male sex, atrial fibrillation, diabetes, hypertension, congestive heart failure, coronary artery disease, peripheral vascular disease, stroke, impaired glomerular filtration rate and urgent/emergent surgery were independent predictors of troponin elevation.[17] Furthermore, RCRI>2, preoperative insulin use and ankle-branch index ≤0.9 were reported to predict cardiac complications.[18–20] In contrast to our study, all these studies determined predictors and risk calculators that are very suitable for assessing the absolute risk in individual patients, but that are less useful in selecting groups of high risk patients.

Limitations

Several limitations must be addressed. First, as our results are obtained from a single center, the external validity should be assessed by applying the proposed selection criteria to other cohorts. Second, because troponin was only measured on the first three days after surgery, POMI and IPTE that may have occurred after the third postoperative day were missed. However, previous research has shown that troponin elevation occurs primarily within the first three postoperative days.[17,21–23] Third, because troponin was not measured in 835 patients (20%), selection bias may have been present. As compared to patients with troponin measurements, these patients underwent more emergency surgery, less high risk surgery, and had more often RCRI class 1 as compared to patients with troponin measurements. Applying the tree to these patients, 345 patients (41%) would be in node 4 or 14 and would therefore be excluded from troponin monitoring. Fourth, a postoperative ECG was performed in only 59% of patients with troponin elevation. As a consequence, POMI may have been missed in the patients without ECG and the occurrence of POMI may be underestimated. Because ECGs were performed only if clinically indicated by the consultant cardiologist, it may not have been performed in particular in patients with a low suspicion of POMI. This is supported by our finding that the troponin level in patients without ECG was lower as

compared to patients with ECG. However, we considered classifying patients without postoperative ECG as having IPTE not appropriate, and we used multiple imputation to estimate the occurrence of POMI in these patients. Fifth, since this study included patients ≥60 years, the results of this study do not apply to younger patients.

Clinical implications

Although the etiology of postoperative troponin elevation is largely unclear and it is often unknown whether and how the prognosis in patients with such troponin elevation can be improved,[7,24] troponin monitoring after noncardiac surgery in high risk patients is currently advocated by experts and in the 2014 ESC/ESA guidelines on non-cardiac surgery.[2,8,25]

When the selection criteria from the 2014 ESC/ESA guidelines on non-cardiac surgery are applied to our cohort, i.e. RCRI class ≥3 or RCRI class ≥2 in vascular surgery patients, 863 patients would fulfill the criteria for troponin monitoring.[8] Fifty-nine (1.8%) of the 3,247 patients would be diagnosed with POMI, the NNS for POMI would be 15 and in 43 patients (1.3%) POMI would be missed. It should be noted that an impaired exercise tolerance, which is another selection criterion according to this guideline, was not taken into account in this calculation because data on exercise tolerance were not available in our study. In comparison, when the criteria as determined in this study are applied to select patients for troponin monitoring, the NNS of POMI would be 19 and in 7 patients (0.2%) POMI would be missed. Hence, according to the criteria as determined in our study less POMI will be missed as compared to the criteria from the ESC/ESA guidelines, and less patients need to be screened as compared to when a simple age criterion is used, like in the VISION study and our own previous studies.[5–7,17]

It is important to note that we used a risk of POMI <1.0% as a criterion to exclude patients from troponin monitoring, as this risk is considered low by two guidelines.[8,16] However, a risk of POMI of 1.0% within three days after surgery could be considered high, and worth routine troponin monitoring.

Of note, the number of patients with a combination of elective surgery with RCRI class >1 and age ≥85 but without renal failure, that would be excluded from troponin monitoring based on a risk of POMI <1.0%, was small (node 14; N=42, i.e. 1% of the study population). Therefore, we recommend not to exclude these patients from troponin monitoring, as this would simplify the selection criteria, but would not influence the NNS for POMI.

Because we aimed at preoperative selection of patients, perioperative and postoperative factors were not studied. However, in selecting patients for troponin monitoring, factors that may be associated with POMI and IPTE such as hypotension, ST seg-

ment changes, tachycardia and anemia could also be taken into account.[3,26–31] Hence, apart from the proposed selection criteria, patients in whom such factors occur may be selected for troponin monitoring as well.

Still, an important problem with respect to postoperative troponin monitoring is the unresolved relevance of troponin elevation in absence of POMI. We know that it is an excellent predictor of a poor outcome, but we do not know whether we can improve prognosis and from what intervention patients could benefit. It is therefore understandable that the current guidelines on perioperative management do not concur in this respect. As compared to the 2014 ESC/ESA guidelines on non-cardiac surgery,[8] the 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery is more hesitant by stating that the usefulness of routine postoperative troponin monitoring in unselected patients without signs or symptoms suggestive of myocardial ischemia or myocardial infarction is uncertain in absence of established risks and benefits of a defined management strategy.[16] As long as this is not elucidated, the advantages of routine troponin monitoring are limited. Further research regarding the etiology of myocardial injury and possible interventions is therefore essential.

Conclusions

In this study we identified patients who are at highest risk for POMI using CART analysis, in order to define selection criteria for routine postoperative troponin monitoring. Based on our findings, routine troponin monitoring could be considered in patients undergoing emergency surgery, or elective surgery with RCRI class >1.

References

1. Longo DL, Devereaux PJ, Sessler DI: Cardiac Complications in Patients Undergoing Major Noncardiac Surgery. N. Engl. J. Med. 2015; 373:2258–69
2. Mauermann E, Puelacher C, Lurati Buse G: Myocardial injury after noncardiac surgery. Curr. Opin. Anaesthesiol. 2016; 29:403–12
3. Landesberg G, Beattie WS, Mosseri M, Jaffe AS, Alpert JS: Perioperative myocardial infarction. Circulation 2009; 119:2936–44
4. Levy MM, Heels-Ansdell D, Hiralal R, Bhandari M, Guyatt G, Yusuf S, Cook D: Prognostic Value of Troponin and Creatine Kinase Muscle and Brain Isoenzyme Measurement after Noncardiac Surgery. Anesthesiology 2011; 114:796–806
5. The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators: Association Between Postoperative Troponin Levels and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. JAMA 2012; 307:2295–304
6. Waes JAR van, Nathoe HM, Graaff JC de, Kemperman H, Borst GJ de, Peelen LM, Klei WA van: Myocardial injury after noncardiac surgery and its association with short-term mortality. Circulation 2013; 127:2264–71
7. Waes JAR van, Grobben RB, Nathoe HM, Kemperman H, Borst GJ de, Peelen LM, Klei WA van: One-Year Mortality, Causes of Death, and Cardiac Interventions in Patients with Postoperative Myocardial Injury. Anesth. Analg. 2016; 123(1):29-37
8. Kristensen SD, Knuuti J, Saraste A, Anker S, Botker HE, Hert S de, Ford I, Gonzalez Juanatey JR, Gorenek B, Heyndrickx GR, Hoeft A, Huber K, Iung B, Kjeldsen KP, Longrois D, Luesher TF, Pierard L, Pocock S, Price S, Roffi M, Sirnes PA, Uva M, Voudris V, Funck-Brentano C: 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management. The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesth. Eur. J. Anaesthesiol. 2014; 31:517–73
9. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk C a, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, Ludwig LE, Pedan a, Goldman L: Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999; 100:1043–9
10. Gupta PK, Gupta H, Sundaram A, Kaushik M, Fang X, Miller WJ, Esterbrooks DJ, Hunter CB, Pipinos II, Johanning JM, Lynch TG, Forse RA, Mohiuddin SM, Mooss AN: Development and validation of a risk calculator for prediction of cardiac risk after surgery. Circulation 2011; 124:381–7
11. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus H a, Lindahl B, Morrow D a, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox K a, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand J-P, Menasché P, Ravkilde J, Ohman EM, Antman EM, et al.: Third universal definition of myocardial infarction. Circulation 2012; 126:2020–35
12. Donders ART, Heijden GJMG van der, Stijnen T, Moons KGM: Review: A gentle introduction to imputation of missing values. J. Clin. Epidemiol. 2006; 59:1087–91
13. Groenwold RHH, Donders ART, Roes KCB, Harrell FE, Moons KGM: Dealing with missing outcome data in randomized trials and observational studies. Am. J. Epidemiol. 2012; 175:210–7

14. Buuren S van, Groothuis-Oudshoorn K: Mice: multivariate imputation by chained equations in R. J Stat Softw 2011; 45: 1-67

15. Breiman L, Friedman J, Stone C, Olshen R: Classification and Regression Trees. Belmont, CA, Wadsworth International Group, 1984

16. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, Davila-Roman VG, Gerhard-Herman MD, Holly TA, Kane GC, Marine JE, Nelson MT, Spencer CC, Thompson A, Ting HH, Uretsky BF, Wijeysundera DN: 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: A report of the American College of Cardiology/American Heart Association task force on practice guidelines. Circulation 2014; 130:2246-2264

17. The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Writing Group: Myocardial Injury after Noncardiac Surgery: A Large, International, Prospective Cohort Study Establishing Diagnostic Criteria, Characteristics, Predictors, and 30-day Outcomes. Anesthesiology 2014; 120:564–78

18. Carmo GA, Calderaro D, Gualandro DM, Pastana AF, Yu PC, Marques AC, Caramelli B: The Ankle-Brachial Index is Associated With Cardiovascular Complications After Noncardiac Surgery. Angiology 2016; 67:187–92

19. Conti D, Ballo P, Boccalini R, Sarti A: Predictors of early postoperative troponin increase after noncardiac surgery: a pilot study in a real-world population admitted to the recovery room. Br. J. Anaesth. 2015; 115:945–6

20. Sousa G, Lopes A, Reis P, Carvalho V, Santos A, Abelha FJ: Major Cardiac Events After Non-cardiac Surgery. World J. Surg. 2016; 40:1802-8

21. Martinez EA, Nass CM, Jermyn RM, Rosenbaum SH, Akhtar S, Chan DW, Malkus H, Weiss JL, Fleisher LA: Intermittent Cardiac Troponin-I Screening is an Effective Means of Surveillance for a Perioperative Myocardial Infarction. J. Cardiothorac. Vasc. Anesth. 2005; 19:577–82

22. Manach Y Le, Perel A, Coriat P, Godet G, Bertrand M, Riou B: Early and delayed myocardial infarction after abdominal aortic surgery. Anesthesiology 2005; 102:885–91

23. Nagele P, Rao LK, Penta M, Kallogjeri D, Spitznagel EL, Cavallone LF, Nussenbaum B, Piccirillo JF: Postoperative myocardial injury after major head and neck cancer surgery 2011; 33:1085–91

24. Landesberg G, London MJ: The Enigma of Postoperative Troponin Elevation. Anesth. Analg. 2016; 123:5-7

25. Khan J, Alonso-Coello P, Devereaux PJ: Myocardial injury after noncardiac surgery. Curr. Opin. Cardiol. 2014; 29:307–11

26. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI: Relationship between Intraoperative Mean Arterial Pressure and Clinical Outcomes after Noncardiac Surgery. Anesthesiology 2013; 119:507–15

27. Waes JAR van, Klei WA van, Wijeysundera DN, Wolfswinkel L van, Lindsay TF, Beattie WS: The association between intraoperative hypotension and myocardial injury after vascular surgery. Anesthesiology 2016; 124:35–44

28. Landesberg G, Mosseri M, Zahger D, Wolf Y, Perouansky M, Anner H, Drenger B, Hasin Y, Berlatzky Y, Weissman C: Myocardial infarction after vascular surgery: the role of prolonged stress-induced, ST depression-type ischemia. J. Am. Coll. Cardiol. 2001; 37:1839–45

29. Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, Katus HA, Newby LK, Ravkilde J, Chaitman B, Clemmensen PM, Dellborg M, Hod H, Porela P, Underwood R, Bax JJ, Beller G a, Bonow R, Wall EE Van der, Bassand J-P, Wijns W, Ferguson TB, Steg PG, Uretsky BF, Williams DO, Armstrong PW, Antman EM, Fox K a, Hamm CW, Ohman EM, et al.: Universal definition of myocardial infarction. Circulation 2007; 116:2634–53

30. Martinez EA, Kim LJ, Faraday N, Rosenfeld B, Bass EB, Perler BA, Williams GM, Dorman T, Pronovost PJ: Sensitivity of routine intensive care unit surveillance for detecting myocardial ischemia. Crit. Care Med. 2003; 31:2302–8

31. Maile MD, Engoren MC, Tremper KK, Tremper TT, Jewell ES, Kheterpal S: Variability of Automated Intraoperative ST Segment Values Predicts Postoperative Troponin Elevation. Anesth. Analg. 2015; 122:608–15


cTnI
78/54
MMHG
90/65
mmHg
type 1 MI
type 2 MI
ischemia
Hb 5.7 mmol/l
HR 96 bpm
85/40
mmHg
type 1 MI
78/54
MMHG
90/65
mmHg

PART VI

DISCUSSION AND SUMMARY

Chapter 8

General Discussion

The effects of routine postoperative troponin monitoring

At the start of this thesis project in 2010, there was growing evidence that patients suffering from postoperative myocardial injury as measured by troponin elevation had a worse prognosis in terms of survival as compared to patients without myocardial injury. Although it was not studied whether cardiac interventions would be beneficial and prognosis could be improved in these patients, several experts recommended to monitor troponin routinely after surgery in high risk patients.[1–5] Therefore, in January 2011 routine postoperative troponin monitoring was implemented in our hospital in patients above 60 years of age undergoing intermediate to high risk surgery. At that time, we aimed to study the effect of routine postoperative troponin monitoring and subsequent cardiology consultation on patient outcomes, i.e. the occurrence of cardiovascular events and mortality within one year after surgery. It was expected that patients with asymptomatic myocardial infarction would be identified and would be treated according to existing guidelines.[6,7] However, after two years of monitoring, it appeared that an intervention in order to improve prognosis was only carried out in a minority of patients (**Chapter 3**). Of course, with hardly any intervention being applied, no effect of monitoring on patient outcomes could be expected, as monitoring by itself is not going to change the patient's outcome. Therefore, from that moment onwards we focused on evaluating the effect of monitoring on cardiac interventions, and more importantly, on explanations for a lack of interventions.

At first, we aimed to confirm the prognostic value of troponin on mortality in a clinical setting. Until then, this was only evaluated in a research setting,[5,8] and it is known that research findings may not be directly translated into clinical practice.[9] The results of our study confirmed that myocardial injury measured by troponin elevation in a clinical setting was a strong and independent predictor of short- and long-term mortality (**Chapters 2 and 3**), and routine postoperative troponin monitoring was able to identify patients with myocardial injury, who are at risk of myocardial infarction and death, early after surgery. Among patients with myocardial injury, further risk stratification would be useful to identify patients with the highest risk of mortality. As the risk of mortality increased with increasing levels of troponin (**Chapters 2 and 3)**,[8] the height of the troponin level may be used as a predictor of poor outcome. Furthermore, we found that POMI was more frequently diagnosed, and that more interventions were undertaken, in patients with a marked rise and/or fall of troponin, as compared to patients with stable troponin levels, suggesting that clinicians considered an intervention to be more beneficial or more required in patients with a troponin rise and fall pattern. Although a rise and fall pattern was associated with mortality, it had no additional value in defining prognosis on top of the height of the troponin level (**Chapter 4**).

Lack of cardiac interventions

Cardiology consultation was performed in only 41% of patients with myocardial injury in our study. Moreover, a cardiac intervention in order to improve prognosis was performed in only 16% of patients with myocardial injury (**Chapter 3**). We had expected these numbers to be much higher when routine monitoring was introduced in 2011. In a recent study also only 50% of patients with myocardial injury received cardiology consultation.[10] Foucrier and colleagues retrospectively compared patients with myocardial injury who received intensified medical treatment to patients who did not and reported that 65% of patients received additional medication.[11] Patients without intervention had a hazard ratio of 2.8 on one-year mortality as compared to patients with medical intervention. However, this finding was not adjusted for the indications or contra-indications for treatments, hence no firm conclusion can be drawn from this study. Chong and colleagues performed a randomized controlled trial in 70 patients with myocardial injury, in which patients were allocated to intensified cardiac monitoring versus standard care.[12] New medication was prescribed in 83% of patients in the intervention group, and in-hospital POMI was found in 17% of patients, as compared to 3% of patients in our study. This difference may be explained by the fact that the study included patients at higher risk of myocardial injury (age above 80, emergency orthopedic surgery), ECGs were performed daily, clinical signs and symptoms were assessed daily, all patients had cardiology consultation, and all patients underwent cardiac monitoring. This implies that, even with routine troponin monitoring as performed in our study, POMI may still be missed if subsequent intensive cardiac monitoring is not applied. Moreover, even in patients who fulfill the criteria of MI as detected by troponin elevation and ischemic ECG changes, POMI was diagnosed in only 10-33% of patients (**Chapter 3**).[10] This finding shows that clinicians are hesitant in diagnosing MI in the perioperative setting. And when POMI is not diagnosed, it may not be optimally treated.

The overall lack of interventions in patients with myocardial injury may be explained by the lack of knowledge of the underlying cause of postoperative myocardial injury, by difficulties in identifying treatable causes of such injury in individual patients, and by lacking treatment options for POMI.

Underlying cause of myocardial injury

The most important problem is the lack of knowledge of the underlying cause of postoperative myocardial injury. If the cause of myocardial injury is not known, it is conceivable that clinicians do not know how to treat and prevent further injury (**Chapter 3**). This is supported by the experience from the only randomized controlled trial that

was performed up to date, as the authors state that "cardiology care was difficult to implement when the cause of troponin elevation was not clear".[12]

POMI is believed to be caused mainly by an imbalance between myocardial oxygen supply and demand (type 2 MI). This is based on the finding that POMI is strongly associated with prolonged, ST depression-type ischemia.[13–15] Many perioperative factors contribute to type 2 ischemia, as the perioperative period is associated with neuroendocrine, metabolic, and immunological changes, referred to as the surgical stress response. This stress response results in increased sympathetic activity and elevated serum concentrations of catecholamines which may lead to in cardiovascular instability.[16,17] Intraoperative hypotension is one of the perioperative factors that may contribute to an imbalance between myocardial oxygen supply and demand, leading to type 2 MI. The finding that hypotension may be associated with myocardial injury (**Chapter 5**),[18–22] supports the belief that POMI is a type 2 MI. However, none of these studies answered the question whether hypotension actually caused the myocardial injury, or whether it was merely a risk factor or an accompanying factor of the true cause.

However, not all evidence points towards supply/demand mismatch as being the major explanation for POMI. The results from some autopsy studies in patients with POMI suggested that POMI was caused by plaque rupture, i.e. type 1 MI, in about half of the patients.[23,24] But, because these studies only included patients who died of POMI, this may not be generalizable to patients who survive POMI. In the latter patients, POMI may be less severe and therefore not lead to mortality because of another underlying cause. Angiography in patients who survived POMI showed plaque rupture in 45-59%.[25,26] However, more patients had symptomatic POMI as compared to other studies (41-48% versus 3-16%) (**Chapters 2 and 3**).[27] Since patients with type 1 MI more often have typical symptoms of MI,[28] the occurrence of type 1 MI may have been higher in these studies than in groups of patients with mainly asymptomatic POMI. Another study in patients with POMI showed a coronary thrombus on angiography in 63% of patients, indicating type 1 MI.[29] However, two third of the included patients had ST-elevation MI, which is much more frequent than was reported in other studies (**Chapters 2 and 3**),[13,15,27] and which is associated with type 1 MI.[30] Taken altogether, although these studies may not be generalizable to patients with asymptomatic POMI, they raise the question whether POMI indeed is mainly caused by type 2 MI, or whether other factors play a role.

Recently, obstructive coronary artery disease was found in 46% of patients who underwent coronary angiography because of postoperative myocardial injury.[31] Using preoperative cardiac computed tomography angiography (CCTA), 72% of the patients with POMI had obstructive coronary artery disease, defined as ≥50% stenosis.[32] Furthermore, obstructive coronary artery disease was present on CCTA in 50% of the patients with asymptomatic myocardial injury, but without a known history of coronary

artery disease or other heart disease (**Chapter 6**). These results imply that coronary artery disease indeed plays a major role in the etiology of POMI. However, these studies did not elucidate whether the myocardial injury in the presence of CAD was caused by coronary thrombosis, by an oxygen supply-demand mismatch, or by a non-ischemic cause. Moreover, it is suggested that coronary thrombosis, designated as type 1 MI, may not necessarily be the cause of MI but the result of type 2 MI, because tachycardia in the presence of a coronary artery stenosis could lead to a decrease in coronary blood flow by shortening of the diastolic time period and by vasoconstriction secondary to ischemia, which may result in thrombosis.[13]

Concerning non-ischemic causes of myocardial injury, several factors may play a role in the perioperative phase, e.g. heart failure, renal failure, myocarditis, arrhythmias, pulmonary embolism, cardiac contusion, stress cardiomyopathy, and sepsis.[33–35] In many patients undergoing noncardiac surgery one or more of these factors is present postoperatively (**Chapter 3**).

Identifying causes of myocardial injury in individual patients

One of the remaining crucial questions is how to identify the cause of myocardial injury in individual patients. And even more important, how to find treatable causes or conditions in which current treatment can be further optimized. Given all the possible causes of myocardial injury as described above, it is likely not treatable in every patient. The cause of the injury may have yet been resolved by the time the myocardial injury is detected, e.g. in a patient with intraoperative hypotension and anemia due to massive (unexpected) blood loss. Next, it may be the result of chronic disease in a patient who is already optimally treated, e.g. in a patient with renal failure or heart failure. Moreover, it may be the direct effect of severe disease, e.g. in a patient with stress cardiomyopathy due to intracranial bleeding or in a patient with severe sepsis (**Chapter 3**),[30,35] in which the underlying disease must be primarily treated and not the myocardial injury itself.

In finding the cause of the myocardial injury in individual patients, it would be useful to know when the injury occurs. Was it already present before surgery, or did it occur during or after surgery? It is hypothesized that the injury occurs mainly during emergence from anesthesia and during the first postoperative hours, when factors that contribute to ischemia are most present (**Chapter 2**).[13,36] By using routine troponin measurements as in this study, i.e. the first measurement in the morning of the first postoperative day, the delay in detecting ischemia is at least about 12 hours. In order to prevent further myocardial injury as early as possible, troponin measurements earlier after surgery may be useful, e.g. on the day of surgery. Furthermore, chronic myocardial injury should be distinguished from acute myocardial injury. Patients with chronic causes of troponin elevation, e.g. chronic renal failure

and chronic heart failure, may have slightly elevated but stable levels of troponin. Therefore it would be useful to measure troponin before surgery in order to detect a rise and/or fall and distinguish chronic from acute myocardial injury. However, the use of troponin kinetics is limited because the definition of a rise and fall has not yet been established (**Chapter 4**).[30] Concerning ECG monitoring, ischemia may go undetected on a single ECG or repeated ECGs because ECG changes are often transient.[13] In order to detect ischemic changes, monitoring with a continuous 12-leads ECG should be applied,[37] but its use in clinical practice is limited because ECG lead placement may interfere with the surgical field and because artefacts may occur due to diathermia during surgery or movements in awake patients.

After surgery, several imaging techniques may be used to identify treatable causes. Using CCTA, pulmonary embolism was found incidentally in a considerable number of patients with myocardial injury. Increased right ventricular pressures and hypoxemia that may occur in pulmonary embolism may explain the myocardial injury in these patients. However, pulmonary embolism was also frequently found in patients without myocardial injury, and because of a limited sample size it cannot be concluded that pulmonary embolism is found more frequently in patients with myocardial injury (**Chapter 6**). Nonetheless, CCTA may be useful to find other causes of myocardial injury such as pulmonary embolism and to guide treatment, but this has not yet been investigated. In non-perioperative MI, coronary angiography is the diagnostic tool of choice to distinguish type 1 from type 2 MI, and to treat obstructive coronary artery disease at the same time. However, since treatment possibilities in patients with POMI are limited because anticoagulation drugs are often contra-indicated in the early postoperative phase, this is often not performed. This is illustrated in the study by Chong and colleagues, where none of the patients with myocardial infarction underwent angiography.[12]

Treatment options

Taking into account that the exact cause of the postoperative myocardial injury in individual patients is often not known, what interventions may be considered beneficial?

Preoperative prevention of myocardial injury by pharmacological suppression of the surgical stress response has not yet been proven beneficial. In several randomized controlled trials studying the effect of perioperative beta-blockade, including the POISE-1 trial, treatment with beta-blockade resulted in a decreased risk of POMI, but an increased risk of stroke, mortality, hypotension, and bradycardia.[38,39] However, questions are being raised whether this was caused by the type of beta-blockers and the timing and dosage that were used. It is proposed that an earlier start of beta-blocker therapy with more selective drugs and optimal dosage may be beneficial.[40] In the POISE-2 trial, the effects of aspirin and clonidine were studied.[22,41] Neither aspirin

nor clonidine reduced the risk of myocardial infarction or mortality, but increased the risk of adverse outcomes including major bleeding, hypotension and nonfatal cardiac arrest. Perioperative administration of nitrates was not found to prevent POMI, but the evidence was considered insufficient to draw firm conclusions.[42] Perioperative statin therapy was studied in some small randomized controlled trials, that showed no effect on the occurrence of POMI or mortality.[17] However, a recent large cohort study showed that patients who already used statins before surgery had a lower risk of myocardial injury and cardiovascular mortality, but not myocardial infarction.[43] The effect of preoperative coronary revascularization has not been proven to be beneficial in patients with significant coronary artery disease in the CARP trial.[44] However, in another more recent trial in asymptomatic patients without a history of coronary artery disease, coronary revascularization reduced the incidence of POMI.[45]

Intraoperative measures to prevent myocardial injury include liberal blood transfusion and optimization of hemodynamics. A liberal transfusion strategy to maintain the hemoglobin level above 10 g/dL (= 6.2 mmol/L) may reduce the risk of myocardial infarction, but the quality of this evidence is considered low.[46] Moreover, such a transfusion strategy did not reduce all-cause and cardiovascular mortality.[47] Intra- and postoperative hemodynamic therapy consisting of fluid and inotropes guided by cardiac output was shown to have no effect on the incidence of myocardial injury.[48]

As described earlier in this chapter, the effect of postoperative treatment with cardiovascular medication may improve prognosis, but has not yet been proven to be beneficial.[11,12] POMI should be treated according to the guidelines for the treatment of non-perioperative MI, by antiplatelet and anticoagulant drugs, nitrates, beta-blockade, ACE-inhibitors and statins.[49,50] However, except for statins, this treatment regimen is often contra-indicated in the early postoperative phase because of hypotension, anemia and bleeding risks.[17,49] Moreover, as the evidence of current guidelines for the treatment of type 2 MI in the non-perioperative phase is being questioned,[51] it is understandable that treatment options in POMI, which is probably mainly type 2 MI, are not well established. The effect of postoperative coronary revascularization was not studied. In patients who underwent coronary angiography because of myocardial injury, 26% and 7% of patients had an indication and were suitable for PCI or CABG,[31] indicating that a considerable number of patients might benefit from revascularization. However, in 22% of these patients serious bleeding complications occurred, which was associated with increased mortality, indicating that revascularization procedures are seriously limited because of the bleeding risk due to antiplatelet and anticoagulation therapy.

In conclusion, given the many factors that may contribute to the occurrence of myocardial injury and infarction, it seems obvious that not a single treatment, but rather a treatment regimen consisting of several components would be beneficial. Therefore, suggested interventions in literature include treatment with aspirin and statins

when type 1 MI is suspected, followed by coronary angiography, and when type 2 MI is suspected, treatment with statins and optimization of the oxygen supply and demand balance by correcting hypotension, tachycardia and other factors that contribute to an oxygen imbalance, followed by outpatient ischemia workup.[52] Importantly, in studying the effect of such interventions on prognosis, it is essential to carefully consider the expected effect. The only randomized controlled trial that evaluated the effect of improved cardiology care expected a decrease in all-cause one-year mortality of 20% (from 35 to 15%), which is likely too large, as most patients with myocardial injury die of malignancy and other non-cardiac causes (**Chapter 3**).[10] Hence, all-cause mortality may not be an adequate outcome measure in this context. If cardiac interventions are beneficial, it would rather have an effect on cardiovascular events and functional capacity by preventing a decline of cardiac function during the time a patient survives after surgery. Therefore, besides cardiovascular outcomes, quality of life, functional capacity or disability-free survival may be more suitable outcome measures.

Selection of patients for monitoring

As described above, postoperative myocardial injury is associated with poor outcome and may indicate myocardial infarction. Defining the cause of myocardial injury in individual patients is difficult however, and treatment options are limited. Therefore, as long as the effect of monitoring on prognosis is not established, it seems prudent to limit monitoring to patients with the highest risk of POMI who may benefit most from treatment, in order to prevent patient harm and to save financial costs. Although troponin monitoring is indeed recommended only in high risk patients, there is no consensus on how to select patients at high risk. Risk indices including the RCRI may be useful, but these indices were not developed for predicting postoperative myocardial injury. Some experts recommend to apply troponin monitoring to patients above 45 years of age undergoing major surgery,[27,52] whereas others suggest that when using these selection criteria, monitoring in patients within the lowest risk stratum will have a low yield.[53] However, when stricter selection criteria are used, as proposed by the guidelines on noncardiac surgery from the European Society of Cardiology and European Society of Anaesthesiology, i.e. RCRI class ≥3 or RCRI class ≥2 in vascular surgery patients,[37] less patients will undergo monitoring, but a considerable number of patients with POMI will be missed (**Chapter 7**), hence these criteria may be too strict. When the criteria as proposed in **Chapter 7** are applied, only patients with a risk of POMI >1% who may benefit most from treatment, will be screened. However, these criteria need external validation before they are applied. Moreover, once intervention strategies are proven to be beneficial, it should be evaluated which patients may benefit from treatment, and new selection criteria should be developed.

Future role of troponin monitoring

Troponin monitoring after noncardiac surgery has been proven to be a simple and feasible way to identify patients at risk for POMI and mortality (**Chapters 2 and 3**). Although a beneficial effect of monitoring has not been shown yet, it is reasonable to think that the risk of POMI and mortality may be altered in at least some patients. However, because interventions may also harm, the etiology of myocardial injury must first be elucidated and more importantly, targeted treatment must have been proven beneficial, before routine postoperative troponin monitoring is widely implemented in clinical care.

Postoperative troponin monitoring may be regarded to as screening. On the one hand, it may be considered as screening for POMI in order to improve the postoperative outcome as part of perioperative care. On the other hand, as CAD was found in 50% of asymptomatic patients with myocardial injury but no history of CAD (**Chapter 6**), it may be considered a more general screening method to detect CAD in selected patients in order to prevent future cardiac events, irrespective of surgery. Although the importance of prevention of cardiovascular disease is highlighted, routine assessment of circulating biomarkers is not recommended as a general screening method for risk stratification in current guidelines.[54] However, as surgery evokes a physical stress response that may be considered a cardiac stress test,[16] surgery may offer a good opportunity to detect and subsequently treat coronary artery disease in a selected population. In terms of numbers needed to screen (NNS), screening with postoperative troponin monitoring cannot yet be compared to other types of screening, as the NNS of a certain screening program is defined as the number of people that need to be screened for a given duration to prevent one death or adverse event,[55] and troponin monitoring has not yet been proven to positively influence these patient outcomes. The number needed to screen to identify one patient with POMI was found to be 31 (**Chapter 7**). As compared to the number of patients that is diagnosed with a certain disease by population screening programs, this number is small.[56–58] However, population screening requires that there is scientific evidence of screening program effectiveness, and that the overall benefits of screening outweigh the harm,[59] both of which postoperative troponin monitoring does not yet fulfill, and which is currently one of the most challenging problems in the field of perioperative care.

Concerning the implementation of troponin monitoring, it must be taken into account that the number of patients that received cardiology consultation and cardiac interventions was small when postoperative initiation of diagnostic procedures and treatment was completely left up to the discretion of the attending clinician (**Chapter 3**). A strictly defined diagnostic strategy may reduce the number of patients in whom POMI is missed, and consequently may increase the number of interventions. Such a

diagnostic strategy may include preoperative troponin measurement, more frequent postoperative troponin measurements, closer postoperative monitoring by repeated ECGs and telemetry, and postoperative cardiac imaging.[12] As perioperative factors like tachycardia, anemia and hypotension may play a major role in the etiology of myocardial infarction, and myocardial injury may often be due to non-ischemic causes such as pulmonary embolism, the initial management of patients with myocardial injury may be a task that is most suitable for the anesthesiologist, who has the skills and experience to deal with such perioperative factors. Obviously, in case POMI or another cardiac condition is suspected that may require treatment, a cardiologist needs to be involved to define further management. Furthermore, because the surgical stress response that may provoke myocardial injury and infarction, occurs in both the intraoperative phase as well as the postoperative phase, the close intraoperative monitoring and hemodynamic optimization as provided by the anesthesiologist should ideally be continued in the postoperative phase. Therefore, the problem of postoperative myocardial injury provides an excellent opportunity for anesthesiologists to extend their knowledge and skills to the postoperative period.

Conclusions and directions for future research

In conclusion, this thesis has presented the results from studies that evaluated troponin monitoring after noncardiac surgery. Routine troponin monitoring identifies patients with an increased risk of POMI and death, and may therefore be a promising method to detect and treat myocardial injury early after surgery. However, it has yet little effect on interventions to prevent further myocardial injury and death, as in most patients the cause of the myocardial injury is not clear and treatment options are not well established. Therefore, future research should determine whether patients may benefit from routine troponin monitoring. As long as this is not elucidated, it should not be broadly implemented in clinical care.

From here, future research aims should include the following:

1. To elucidate the etiology of myocardial injury, in order to quantify the proportion of patients that suffer from myocardial injury caused by ischemia and other causes, and to find substrates for treatment;
2. To elucidate the etiology of POMI (type 1 or type 2) in individual patients, in order to define targeted treatment;
3. To redefine diagnostic criteria for POMI, including the definition of a biomarker rise and/or fall;
4. To evaluate diagnostic techniques to identify patients who may benefit from treatment, including noninvasive cardiac imaging and coronary angiography;

5. To define targeted treatment options in individual patients, and to evaluate treatment by using adequate outcome measures such as disability free survival;
6. To define whether troponin monitoring could be useful as a tool for selective population screening.

References

1. Oscarsson A, Eintrei C, Anskär S, Engdahl O, Fagerström L, Blomqvist P, Fredriksson M, Swahn E: Troponin T-values provide long-term prognosis in elderly patients undergoing non-cardiac surgery. Acta Anaesthesiol. Scand. 2004; 48:1071–9
2. Kim LJ, Martinez EA, Faraday N, Dorman T, Fleisher LA, Perler BA, Williams GM, Chan D, Pronovost PJ: Cardiac Troponin I Predicts Short-Term Mortality in Vascular Surgery Patients. Circulation 2002; 106:2366–71
3. Devereaux PJ, Goldman L, Yusuf S, Gilbert K, Leslie K, Guyatt GH: Surveillance and prevention of major perioperative ischemic cardiac events in patients undergoing noncardiac surgery: a review. CMAJ 2005; 173:779–88
4. Martinez EA, Nass CM, Jermyn RM, Rosenbaum SH, Akhtar S, Chan DW, Malkus H, Weiss JL, Fleisher LA: Intermittent Cardiac Troponin-I Screening is an Effective Means of Surveillance for a Perioperative Myocardial Infarction. J. Cardiothorac. Vasc. Anesth. 2005; 19:577–82
5. Levy MM, Heels-Ansdell D, Hiralal R, Bhandari M, Guyatt G, Yusuf S, Cook D: Prognostic Value of Troponin and Creatine Kinase Muscle and Brain Isoenzyme Measurement after Noncardiac Surgery. Anesthesiology 2011; 114:796–806
6. Kushner FG, Hand M, Smith SC, King SB, Anderson JL, Antman EM, Bailey SR, Bates ER, Blankenship JC, Casey DE, Green LA, Hochman JS, Jacobs AK, Krumholz HM, Morrison DA, Ornato JP, Pearle DL, Peterson ED, Sloan MA, Whitlow PL, Williams DO: 2009 focused updates: ACC/AHA guidelines for the management of patients with st-elevation myocardial infarction (Updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (Updating the 2005 Guideline and 2007 Focused Update): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2009; 120:2271–306
7. Wright RS, Anderson JL, Adams CD, Bridges CR, Casey DE, Ettinger SM, Fesmire FM, Ganiats TG, Jneid H, Lincoff AM, Peterson ED, Philippides GJ, Theroux P, Wenger NK, Zidar JP, Jacobs AK: 2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/ Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011; 123:2022–60
8. The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators: Association Between Postoperative Troponin Levels and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. JAMA 2012; 307:2295–304
9. Kristensen N, Nymann C, Konradsen H: Implementing research results in clinical practice- the experiences of healthcare professionals. BMC Health Serv. Res. 2016; 16:48
10. Gorgun E, Lan BY, Aydinli HH, Reed GW, Menon V, Sessler DI, Stocchi L, Remzi FH: Troponin Elevation After Colorectal Surgery. Ann. Surg. 2016; 264:605-11
11. Foucrier A, Rodseth R, Aissaoui M, Ibanes C, Goarin J-P, Landais P, Coriat P, Manach Y Le: The Long-Term Impact of Early Cardiovascular Therapy Intensification for Postoperative Troponin Elevation after Major Vascular Surgery. Anesth. Analg. 2014; 119:1053–63
12. Chong CP, Gaal WJ van, Ryan JE, Profitis K, Savige J, Lim WK: Does cardiology intervention improve mortality for post-operative troponin elevations after emergency orthopaedic-geriatric surgery? A randomised controlled study. Injury 2012; 43:1193–8

13. Landesberg G, Mosseri M, Zahger D, Wolf Y, Perouansky M, Anner H, Drenger B, Hasin Y, Berlatzky Y, Weissman C: Myocardial infarction after vascular surgery: the role of prolonged stress-induced, ST depression-type ischemia. J. Am. Coll. Cardiol. 2001; 37:1839–45

14. Landesberg G, Beattie WS, Mosseri M, Jaffe AS, Alpert JS: Perioperative myocardial infarction. Circulation 2009; 119:2936–44

15. Martinez EA, Kim LJ, Faraday N, Rosenfeld B, Bass EB, Perler BA, Williams GM, Dorman T, Pronovost PJ: Sensitivity of routine intensive care unit surveillance for detecting myocardial ischemia. Crit. Care Med. 2003; 31:2302–8

16. Desborough JP: The stress response to trauma and surgery. Br. J. Anaesth. 2000; 85:109–17

17. Priebe HJ: Pharmacological modification of the perioperative stress response in noncardiac surgery. Best Pract. Res. Clin. Anaesthesiol. 2016; 30:171–89

18. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI: Relationship between Intraoperative Mean Arterial Pressure and Clinical Outcomes after Noncardiac Surgery. Anesthesiology 2013; 119:507–15

19. Kheterpal S, O'Reilly M, Englesbe MJ, Rosenberg AL, Shanks AM, Zhang L, Rothman ED, Campbell DA, Tremper KK: Preoperative and intraoperative predictors of cardiac adverse events after general, vascular, and urological surgery. Anesthesiology 2009; 110:58–66

20. Sessler DI, Sigl JC, Kelley SD, Chamoun NG, Manberg PJ, Saager L, Kurz A, Greenwald S: Hospital Stay and Mortality Are Increased in Patients Having a "Triple Low" of Low Blood Pressure, Low Bispectral Index, and Low Minimum Alveolar Concentration of Volatile Anesthesia. Anesthesiology 2012; 116:1195–203

21. Alcock RF, Kouzios D, Naoum C, Hillis GS, Brieger DB: Perioperative myocardial necrosis in patients at high cardiovascular risk undergoing elective non-cardiac surgery. Heart 2012; 98:792–8

22. Devereaux PJ, Sessler DI, Leslie K, Kurz A, Mrkobrada M, Alonso-Coello P, Villar JC, Sigamani A, Biccard BM, Meyhoff CS, Parlow JL, Guyatt G, Robinson A, Garg AX, Rodseth RN, Botto F, Lurati Buse G, Xavier D, Chan MT V, Tiboni M, Cook D, Kumar PA, Forget P, Malaga G, Fleischmann E, Amir M, Eikelboom J, Mizera R, Torres D, Wang CY, et al.: Clonidine in patients undergoing noncardiac surgery. N. Engl. J. Med. 2014; 370:1504–13

23. Dawood MM, Gutpa DK, Southern J, Walia A, Atkinson JB, Eagle KA: Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. Int. J. Cardiol. 1996; 57:37–44

24. Cohen MC, Aretz TH: Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. Cardiovasc. Pathol. 1999; 8:133–9

25. Gualandro DM, Campos CA, Calderaro D, Yu PC, Marques AC, Pastana AF, Lemos PA, Caramelli B: Coronary plaque rupture in patients with myocardial infarction after noncardiac surgery: frequent and dangerous. Atherosclerosis 2012; 222:191–5

26. Hanson I, Kahn J, Dixon S, Goldstein J: Angiographic and clinical characteristics of type 1 versus type 2 perioperative myocardial infarction. Catheter. Cardiovasc. Interv. 2013; 82:622–8

27. The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Writing Group: Myocardial Injury after Noncardiac Surgery: A Large, International, Prospective Cohort Study Establishing Diagnostic Criteria, Characteristics, Predictors, and 30-day Outcomes. Anesthesiology 2014; 120:564–78

28. Lippi G, Sanchis-Gomar F, Cervellin G: Chest pain, dyspnea and other symptoms in patients with type 1 and 2 myocardial infarction. A literature review. Int. J. Cardiol. 2016; 215:20–2

29. Berger PB, Bellot V, Bell MR, Horlocker TT, Rihal CS, Hallett JW, Dalzell C, Melby SJ, Charnoff NE, Holmes DR: An Immediate Invasive Strategy for the Treatment of Acute Myocardial Infarction Early After Noncardiac Surgery. Am. J. Cardiol. 2001; 87:1100–2

30. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand J-P, Menasché P, Ravkilde J, Ohman EM, Antman EM, et al.: Third universal definition of myocardial infarction. Circulation 2012; 126:2020–35

31. Parashar A, Agarwal S, Krishnaswamy A, Sud K, Poddar KL, Bassi M, Ellis S, Tuzcu EM, Menon V, Kapadia SR: Percutaneous Intervention for Myocardial Infarction After Noncardiac Surgery. J. Am. Coll. Cardiol. 2016; 68:329–38

32. Sheth T, Chan M, Butler C, Chow B, Tandon V, Nagele P, Mitha A, Mrkobrada M, Szczeklik W, Faridah Y, Biccard B, Stewart LK, Heels-Ansdell D, Devereaux PJ: Prognostic capabilities of coronary computed tomographic angiography before non-cardiac surgery: prospective cohort study. BMJ 2015; 350:h1907

33. Jaffe AS, Ravkilde J, Roberts R, Naslund U, Apple FS, Galvani M, Katus H: It's Time for a Change to a Troponin Standard. Circulation 2000; 102:1216–20

34. Roongsritong C, Warraich I, Bradley C: Common causes of troponin elevations in the absence of acute myocardial infarction: Incidence and clinical significance. Chest 2004; 125:1877–84

35. Jeremias A, Gibson CM: Review Narrative Review : Alternative Causes for Elevated Cardiac Troponin. Ann. Intern. Med. 2008:1024–30

36. Manach Y Le, Perel A, Coriat P, Godet G, Bertrand M, Riou B: Early and delayed myocardial infarction after abdominal aortic surgery. Anesthesiology 2005; 102:885–91

37. Kristensen SD, Knuuti J, Saraste A, Anker S, Botker HE, Hert S de, Ford I, Gonzalez Juanatey JR, Gorenek B, Heyndrickx GR, Hoeft A, Huber K, Iung B, Kjeldsen KP, Longrois D, Luesher TF, Pierard L, Pocock S, Price S, Roffi M, Sirnes PA, Uva M, Voudris V, Funck-Brentano C: 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management. The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesth. Eur. J. Anaesthesiol. 2014; 31:517–73

38. Wijeysundera DN, Duncan D, Nkonde-Price C, Virani SS, Washam JB, Fleischmann KE, Fleisher LA: Perioperative Beta Blockade in Noncardiac Surgery: A Systematic Review for the 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J. Am. Coll. Cardiol. 2014; 64:2406–25

39. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Málaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P: Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008; 371:1839–47

40. Wijeysundera DN, Beattie WS, Wijeysundera HC, Yun L, Austin PC, Ko DT: Duration of Preoperative β-Blockade and Outcomes After Major Elective Noncardiac Surgery. Can. J. Cardiol. 2014; 30:217–23

41. Devereaux PJ, Mrkobrada M, Sessler DI, Leslie K, Alonso-Coello P, Kurz A, Villar JC, Sigamani A, Biccard BM, Meyhoff CS, Parlow JL, Guyatt G, Robinson A, Garg AX, Rodseth RN, Botto F, Lurati Buse G, Xavier D, Chan MT V, Tiboni M, Cook D, Kumar PA, Forget P, Malaga G, Fleischmann E, Amir M, Eikelboom J, Mizera R, Torres D, Wang CY, et al.: Aspirin in patients undergoing noncardiac surgery. N. Engl. J. Med. 2014; 370:1494–503

42. Zhao N, Xu J, Singh B, Yu X, Wu T, Huang Y: Nitrates for the prevention of cardiac morbidity and mortality in patients undergoing non-cardiac surgery. Cochrane database Syst. Rev. 2016; 8:CD010726

43. Berwanger O, Manach Y Le, Suzumura EA, Biccard B, Srinathan SK, Szczeklik W, Espirito Santo JA, Santucci E, Cavalcanti AB, Archbold RA, Devereaux PJ: Association between pre-operative statin use and major cardiovascular complications among patients undergoing non-cardiac surgery: the VISION study. Eur. Heart J. 2016; 37:177–85

44. McFalls EO, Ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F, Pierpont G, Santilli S, Rapp J, Hattler B, Shunk K, Jaenicke C, Thottapurathu L, Ellis N, Reda DJ, Henderson WG: Coronary-Artery Revascularization before Elective Major Vascular Surgery. N. Engl. J. Med. 2004; 351:2795–804

45. Illuminati G, Schneider F, Greco C, Mangieri E, Schiariti M, Tanzilli G, Barillà F, Paravati V, Pizzardi G, Calio' F, Miraldi F, MacRina F, Totaro M, Greco E, Mazzesi G, Tritapepe L, Toscano M, Vietri F, Meyer N, Ricco JB: Long-term results of a randomized controlled trial analyzing the role of systematic pre-operative coronary angiography before elective carotid endarterectomy in patients with asymptomatic coronary artery disease. Eur. J. Vasc. Endovasc. Surg. 2015; 49:366–74

46. Brunskill SJ, Millette SL, Shokoohi A, Pulford EC, Doree C, Murphy MF, Stanworth S: Red blood cell transfusion for people undergoing hip fracture surgery. Cochrane Database Syst Rev 2015; 4:Cd009699

47. Carson JL, Sieber F, Cook DR, Hoover DR, Noveck H, Chaitman BR, Fleisher L, Beaupre L, Macaulay W, Rhoads GG, Paris B, Zagorin A, Sanders DW, Zakriya KJ, Magaziner J: Liberal versus restrictive blood transfusion strategy: 3-year survival and cause of death results from the FOCUS randomised controlled trial. Lancet 2015; 385:1183–9

48. Gillies MA, Shah AS V, Mullenheim J, Tricklebank S, Owen T, Antonelli J, Strachan F, Mills NL, Pearse RM: Perioperative myocardial injury in patients receiving cardiac output-guided haemodynamic therapy: a substudy of the OPTIMISE Trial. Br. J. Anaesth. 2015:1–7

49. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, Lemos J a. De, Ettinger SM, Fang JC, Fesmire FM, Franklin B a., Granger CB, Krumholz HM, Linderbaum J a., Morrow D a., Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX: 2013 ACCF/AHA guideline for the management of st-elevation myocardial infarction: A report of the American college of cardiology foundation/american heart association task force on practice guidelines. J. Am. Coll. Cardiol. 2013; 61

50. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ: 2014 AHA/ACC guideline for the management of patients with Non-ST-Elevation acute coronary syndromes: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J. Am. Coll. Cardiol. 2014; 64:e139–228

51. Saaby L, Poulsen TS, Diederichsen ACP, Hosbond S, Larsen TB, Schmidt H, Gerke O, Hallas J, Thygesen K, Mickley H: Mortality rate in type 2 myocardial infarction: observations from an unselected hospital cohort. Am. J. Med. 2014; 127:295–302

52. Mauermann E, Puelacher C, Lurati Buse G: Myocardial injury after noncardiac surgery. Curr. Opin. Anaesthesiol. 2016; 29:403–12

53. Beattie WS, Karkouti K, Tait G, Steel A, Yip P, McCluskey S, Farkouh M, Wijeysundera DN: Use of clinically based troponin underestimates the cardiac injury in non-cardiac surgery: a single-centre cohort study in 51,701 consecutive patients. Can. J. Anaesth. 2012; 59:1013–22

54. Piepoli F, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney M, Corra U, Cosyns B, Deaton C, I Graham I, Hall MS, Hoobs FDR, Lochen M, Lollgen H, Marquez-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, Worp HB van der, Dis I van, Verschuren WMM: 2016 European guidelines on cardiovascular disease prevention in clinical practice. Eur. Heart J. 2016; 37:2315–81

55. Rembold CM: Number needed to screen: development of a statistic for disease screening. BMJ 1998; 317:307–12

56. Australian Institute of Health and Welfare 2016: Cervical screening in Australia 2013-2014. Cancer Ser. no. 97. Cat. no. CAN 95. Canberra AIHW.

57. Australian Institute of Health and Welfare 2015: BreastScreen Australia monitoring report 2012–2013. Cancer Ser. no. 95. Cat. no. CAN 93. Canberra AIHW.

58. Screening and Immunisations Team: Breast Screening Programme, England 2014-2015. Health and Social Care Information Centre 2016

59. Andermann A, Blancquaert I, Beauchamp S, Déry V: Revisiting Wilson and Jungner in the genomic age: A review of screening criteria over the past 40 years. Bull. World Health Organ. 2008; 86:317–9

Chapter 9

Addendum

Summary

Postoperative myocardial infarction (POMI) is an important complication after noncardiac surgery, that is associated with increased risk of mortality. The course of POMI is however mainly silent and therefore POMI is often not recognized. In order to improve prognosis, routine postoperative monitoring with cardiac biomarkers is recommended to identify patients at risk for POMI early after surgery. Routine troponin monitoring in patients above 60 years of age after intermediate to high risk noncardiac surgery was implemented in the University Medical Center Utrecht in 2011. In this thesis, we have evaluated the effect of such routine troponin monitoring, we explored determinants of myocardial injury (troponin elevation), and also determined patient selection criteria for monitoring.

In **Part I** the effect of routine postoperative troponin monitoring was evaluated. In **Chapter 2,** we studied the association between postoperative myocardial injury and short-term mortality in 1,617 patients after intermediate to high risk noncardiac surgery. Myocardial injury as measured by troponin elevation occurred in 19% of the patients. We found that myocardial injury was a strong predictor of mortality. Patients with myocardial injury had a 2.4-4.2 times increased risk of mortality within 30 days after surgery as compared to patients without myocardial injury, and this risk was dependent on the level of troponin elevation, but independent of preoperative factors known to be associated with postoperative death. In **Chapter 3,** we first determined the association between myocardial injury and long-term mortality in 3,224 patients. Patients with myocardial injury had a 1.4-2.2 times increased risk of mortality within one year after surgery. The one-year mortality rate was 40% in patients with major troponin elevations. However, most patients died of malignancies, and only 5% of patients were reported to have died of cardiac causes. Second, we determined the suspected cause of the myocardial injury as proposed by the attending cardiologist, and assessed the occurrence of POMI. In one third of patients the myocardial injury was considered to be due to predisposing cardiac conditions, including tachyarrhythmia and pre-existent coronary artery disease, in another one third it was considered to be due to perioperative triggers including anemia, hypotension and tachycardia, or to a combination of both. In the remaining patients it was not clear what may have caused the myocardial injury. Although POMI was diagnosed real time in less than 1% of the patients, we found in retrospect that 3% of patients fulfilled the criteria for POMI according to the universal definition of myocardial infarction. Thus, despite troponin monitoring, POMI was still missed in a considerable number of patients. Finally, we determined interventions that were undertaken by the consulting cardiologist, and found that an intervention was carried out in only 16% of patients with myocardial injury. This lack of interventions may be explained by the lack of knowledge of the un-

derlying cause of postoperative myocardial injury, by difficulties in identifying treatable causes of such injury in individual patients, and by lacking treatment options for POMI. **Chapter 4** describes the additional prognostic value of postoperative troponin kinetics on mortality in patients with myocardial injury. An absolute change in troponin of 200 ng/L was significantly associated with mortality (Relative Risk 1.5), but such a rise-and-fall pattern had no additional prognostic value to predict mortality on top of the highest troponin value that was measured. Relative troponin changes were not related to mortality. Therefore, postoperative TnI kinetics are not considered useful for further mortality risk stratification in patients with myocardial injury after noncardiac surgery.

In **Part II** determinants of myocardial injury were explored. In **Chapter 5,** we studied the association between intraoperative hypotension and postoperative myocardial injury in 890 patients from the University Health Network Toronto and the University Medical Center Utrecht undergoing vascular surgery. We used four different absolute and relative thresholds to define hypotension: a mean arterial pressure (MAP) <50 mmHg, a MAP <60 mmHg, a MAP decrease >30% as compared to the preoperative blood pressure, and a MAP decrease >40%. After adjustment for potential confounders we found that an intraoperative decrease in mean arterial blood pressure of >40% as compared to the preoperative blood pressure, with a duration of more than 30 minutes, may be associated with myocardial injury. Less severe hypotension and shorter durations of hypotension were not associated with myocardial injury. The pilot study described in **Chapter 6** estimated the prevalence of coronary artery disease in 70 patients with and without myocardial injury after surgery who did not have a history of coronary artery disease by using cardiac computed tomography angiography. We found that coronary artery disease was more prevalent in patients with myocardial injury, as compared to control patients without myocardial injury (50% versus 15%, Relative Risk 3.3). This indicates that coronary artery disease may play an important role in the etiology of myocardial injury, although this study did not elucidate the exact cause in individual patients. Incidentally, we found pulmonary emboli in 33% of the patients with myocardial injury, versus 20% of patients without myocardial injury. Pulmonary emboli may play a role in the etiology of myocardial injury, but because this difference was not statically significant this cannot be concluded from this study.

From the studies described above it may be concluded that defining the cause of myocardial injury in individual patients is difficult and that treatment options are limited. Therefore, as long as the effect of monitoring on prognosis is not established, it seems prudent to limit monitoring to patients with the highest risk of POMI who may benefit most from treatment, in order to prevent patient harm and to save financial costs. Therefore, in **Part III, Chapter 7,** we determined patient groups at highest risk of POMI, in order to define selection criteria for routine troponin monitoring. Among 3,247 patients above 60 years of age undergoing intermediate to high risk surgery,

we found that emergency surgery patients, or elective surgery patients with a Revised Cardiac Risk Index >1 had the highest risk of POMI (>1%), hence these patients may be selected for routine troponin monitoring.

In summary, this thesis has presented the results from studies that evaluated troponin monitoring after noncardiac surgery. Routine troponin monitoring strongly identifies patients with an increased risk of POMI and death. However, it has yet little effect on interventions to prevent POMI and death, as in most patients the cause of the myocardial injury is not clear and treatment options are not well established. Therefore, future research should determine whether patients may benefit from routine troponin monitoring. As long as this is not elucidated, it should not be broadly implemented in clinical care.

Samenvatting in het Nederlands

Ieder jaar ondergaan wereldwijd miljoenen patiënten een operatie. Een belangrijke complicatie van een operatie is een hartinfarct. Een operatie brengt in het lichaam een uitgebreide stressreactie op gang, waardoor in de hartspier een tekort aan zuurstof kan ontstaan. Als gevolg van dit zuurstoftekort kan een hartinfarct optreden. Verschillende factoren spelen hierbij een rol, zoals ontstekingsreacties, pijn, een snelle hartslag, een (te) lage of juist hoge bloeddruk, acute bloedarmoede door bloedverlies, en een verhoogde neiging van het bloed om te stollen. Het hartinfarct treedt met name op bij oudere patiënten die een grote operatie ondergaan, zoals een buik- of heupoperatie. Soms ontstaat het tijdens een operatie, maar meestal in de eerste uren tot dagen daarna. Door het gebruik van narcosemiddelen en pijnstillers bemerken patiënten meestal geen specifieke klachten zoals pijn op de borst. Daardoor wordt een postoperatief hartinfarct vaak gemist, en dus niet behandeld. Een belangrijk gegeven is dat patiënten bij wie een dergelijk 'stil' hartinfarct optreedt, een slechte prognose hebben: zij hebben een sterk verhoogd risico om binnen afzienbare tijd te overlijden. Om het 'stille' hartinfarct bij deze patiënten toch vast te kunnen stellen en zo nodig te kunnen behandelen, wordt in de medische literatuur gesuggereerd dat patiënten na een operatie gecontroleerd zouden moeten worden op schade aan de hartspier. Zulke schade kan worden vastgesteld door het meten van de stof troponine in het bloed. Troponine is een eiwit dat vrijkomt uit beschadigde hartspiercellen.

In 2011 werd in het Universitair Medisch Centrum Utrecht een nieuw zorgpad geïmplementeerd, waarbij het troponine bij patiënten van 60 jaar of ouder op de eerste drie dagen na een grote niet-cardiale operatie (d.w.z. een operatie buiten het hart) gecontroleerd wordt. Een verhoogd troponine duidt op schade aan de hartspier, maar dit hoeft niet het gevolg te zijn van een hartinfarct. De schade kan namelijk ook ontstaan door andere problemen, zoals hartfalen, nierfalen of een ernstige infectie. De hartspierschade kan ook niet in alle gevallen worden behandeld. Daarom wordt bij patiënten bij wie schade aan de hartspier is geconstateerd, verder gekeken naar de oorzaak van de schade en hoe die zou kunnen worden behandeld om verdere schade te voorkomen.

De **hypothese** van dit proefschrift was dat een 'stil' hartinfarct na een operatie vroegtijdig zou kunnen worden opgespoord door routinematige controle van het troponine na grotere operaties bij oudere patiënten, en dat behandeling verdere schade zou kunnen voorkomen en een gunstig effect zou hebben op de prognose. In dit proefschrift werd het effect van deze 'postoperatieve troponine monitoring' op de klinische zorg geëvalueerd, werden mogelijke oorzaken van postoperatieve hartschade onderzocht, en werd vastgesteld welke patiënten voor deze monitoring zouden kunnen worden geselecteerd.

Deel I beschrijft het effect van routinematige troponine monitoring op de klinische zorg. In **Hoofdstuk 2** werd de relatie tussen het optreden van hartspierschade en overlijden onderzocht bij 1617 patiënten die een grote operatie ondergingen. Hartspierschade, vastgesteld d.m.v. troponine metingen, werd gevonden bij 19% van de patiënten. Deze hartspierschade was een zeer sterke voorspeller van overlijden: patiënten met hartspierschade hadden een twee- tot viermaal verhoogd risico om te overlijden binnen 30 dagen na de operatie, afhankelijk van de hoogte van het troponine. In **Hoofdstuk 3** werd de relatie tussen hartspierschade en overlijden op langere termijn bepaald bij 3224 patiënten. Patienten met hartspierschade hadden een tweemaal verhoogd risico om binnen een jaar na de operatie te overlijden. Bij patiënten met een sterk verhoogd troponine was dit risico 40%. Echter, de meeste patiënten overleden aan kanker, en slechts 5% van de patiënten bleek te zijn overleden aan een hartprobleem. Vervolgens werd bepaald wat de meest waarschijnlijke oorzaak was van de postoperatieve hartspierschade. Bij één derde deel van de patiënten werd gedacht aan een hartprobleem, zoals een ritmestoornis of verkalking van de kransslagaders. Bij een ander derde deel van de patiënten werd gedacht aan factoren die optreden rondom operaties, zoals acute bloedarmoede, een te snelle hartslag of een lage bloeddruk, of aan een combinatie hiervan. Bij de overige patiënten was de oorzaak van de hartspierschade niet duidelijk. Een postoperatief hartinfarct werd door de in de kliniek geconsulteerde cardioloog vastgesteld bij minder dan 1% van de patiënten. Echter, door het achteraf terugkijken en opnieuw beoordelen van hartfilmpjes bleek dat 3% van de patiënten aan de criteria van een hartinfarct voldeed. Dus, ondanks postoperatieve troponine monitoring werd het postoperatieve hartinfarct alsnog gemist in een behoorlijk aantal patiënten. Tenslotte werd onderzocht welke actie of behandeling door de cardioloog was ondernomen in geval van een verhoogd troponine. Bij slechts 16% van de patiënten met hartspierschade was een behandeling ingezet. Dit kan worden verklaard doordat er onvoldoende bekend is over de oorzaak van hartspierschade rondom operaties, en doordat het vaak niet mogelijk is om de precieze oorzaak vast te stellen. Daarnaast zijn er in de periode na een operatie weinig behandelopties: bijvoorbeeld bloedverdunners kunnen vaak niet worden gegeven vanwege het risico op ontstaan van bloedingen in het operatiegebied. In **Hoofdstuk 4** werd onderzocht of het risico op overlijden bij patiënten met schade aan de hartspier beter kan worden ingeschat aan de hand van het verloop van de hoogte van de postoperatieve troponinewaarden. De hypothese was dat een plotselinge sterke stijging en daling van de troponinewaarden een slechtere prognose voorspelt dan stabiel verhoogde troponinewaarden. Het bleek dat een absolute stijging van het troponine van 200 ng/L geassocieerd was met een verhoogd risico op overlijden. Echter, een dergelijke stijging en daling in het troponine had geen toegevoegde voorspellende waarde t.o.v. de troponinewaarde zelf. Een relatieve stijging van het troponine was niet geassocieerd met overlijden. Daarom blijkt

het beloop van troponinewaarden niet bruikbaar voor het inschatten van het risico op overlijden bij patiënten met postoperatieve hartspierschade.

In **Deel 2** van dit proefschrift werden mogelijke oorzaken van hartspierschade bestudeerd. In **Hoofdstuk 5** werd de relatie tussen het optreden van een lage bloeddruk tijdens de operatie en hartspierschade onderzocht bij 890 patiënten die een vaatchirurgische ingreep ondergingen. Omdat bij patiënten die onder narcose zijn niet bekend is bij welke bloeddruk er sprake is van een te lage bloeddruk, werden vier verschillende absolute en relatieve bloeddrukgrenzen bestudeerd: een gemiddelde bloeddruk <50 mmHg, een gemiddelde bloeddruk <60 mmHg, een relatieve daling van >30% t.o.v. de bloeddruk voor het begin van de narcose, en een relatieve daling van >40%. Het bleek dat een relatieve daling van >40% gedurende minstens 30 minuten mogelijk geassocieerd was met het optreden van hartspierschade. Kortere periodes van een dergelijk lage bloeddruk, of minder lage bloeddrukken waren niet geassocieerd met hartspierschade. **Hoofdstuk 6** beschrijft een studie naar kransslagaderverkalking bij patiënten met postoperatieve hartspierschade. D.m.v. een CT-scan van het hart werd bij 50 patienten met hartspierschade en bij 20 patiënten zonder hartspierschade vastgesteld of er sprake was van kransslagaderverkalking. Verkalkte kransslagaderen werden vaker gevonden bij patiënten met hartspierschade (50%) dan bij patiënten zonder hartspierschade (15%). Dit suggereert dat kransslagaderverkalking een belangrijke rol speelt bij het optreden van hartspierschade, hoewel de exacte oorzaak van de schade niet kon worden achterhaald in deze studie. Per toeval werd bij 33% van de patiënten met hartspierschade een longembolie gevonden en bij 20% van de patiënten zonder hartspierschade, zonder dat deze patiënten daar klachten van hadden. Longembolieën zouden dus een rol kunnen spelen bij het ontstaan van hartspierschade, maar dat kon in deze studie niet met zekerheid worden vastgesteld vanwege het geringe aantal patiënten.

Uit bovenstaande onderzoeken kan worden geconcludeerd dat het vaststellen van de precieze oorzaak van postoperatieve hartspierschade bij individuele patiënten moeilijk is en dat behandelopties beperkt zijn. Zolang niet duidelijk is of het monitoren van troponine een gunstig effect heeft op de prognose zou het routinematig monitoren van troponine op zijn minst beperkt moeten worden tot de patiënten met het hoogste risico op een postoperatief hartinfarct. Deze patienten zouden namelijk het meeste baat kunnen hebben bij monitoring. Daarnaast kan op deze manier schade door complicaties van onnodig ingezette behandelingen, zoals bloedingen, worden voorkomen en kunnen onnodige kosten worden vermeden. Daarom werd in **Deel III**, **Hoofdstuk 7**, onderzocht welke groepen patiënten het hoogste risico hebben op een hartinfarct. Op basis van de resultaten zouden patiëntgroepen kunnen worden geselecteerd die in aanmerking komen voor troponine monitoring. In een groep van 3247 patiënten bleek dat patiënten die een spoedoperatie ondergingen, of patiënten die een geplande operatie ondergingen én een *Revised Cardiac Risk Index* >1 hadden (dit

is een veelgebruikte index waarmee het risico op hartproblemen rondom een operatie kan worden ingeschat) het grootste risico hadden op het optreden van een hartinfarct (>1%). Deze patiënten zouden dus geselecteerd kunnen worden voor troponine monitoring.

Samengevat beschrijft dit proefschrift de resultaten van enkele studies over routinematige troponine monitoring na niet-cardiale operaties. Patiënten met een verhoogd risico op een hartinfarct en overlijden na een operatie kunnen vroegtijdig worden geïdentificeerd d.m.v. troponine monitoring. Echter, omdat de oorzaak van de hartspierschade bij veel patiënten niet bekend is en de mogelijkheden tot behandeling beperkt zijn, volgt er vaak geen behandeling. Daarom zou toekomstig onderzoek moeten uitwijzen of én hoe patiënten baat zouden kunnen hebben bij troponine monitoring. Zolang dit niet bekend is, zou troponine monitoring niet routinematig moeten worden uitgevoerd na niet-cardiale operaties.

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About the author

Judith Anne Rolanda van Waes was born on March 13th 1982 in Doetinchem, The Netherlands. She gradruated from pre-university secondary school (Gymnasium, Rijksscholengemeenschap Lingecollege, Tiel) in 2001. After that, she started her medical training at the University of Utrecht and obtained her Medical Doctor degree in 2008. Subsequently, she started as a resident in Anesthesiology at the University Medical Center Utrecht under supervision of prof. dr. J.T.A. Knape and prof. dr. R.H. Hoff. She combined her residency with research on postoperative monitoring of cardiac complications under supervision of prof. dr. W.A. van Klei, dr. L.M. Peelen and dr. H.M. Nathoe. She obtained her Master of Science degree in Clinical Epidemiology at the University of Utrecht in 2013. In 2016 she finished her specialty training in Anesthesiology.

Currently, Judith works as an anesthesiologist at the University Medical Center Utrecht. She and her partner Jan-Erik Boersma have two daughters: Aafke and Hilde.

List of publications

- **van Waes JAR**, de Graaff JC, Egberts ACG, van Klei WA. Medication discontinuity errors in the perioperative period. *Acta Anaesthesiol Scand.* 2010; 54:1185-91.
- Kool NP, **van Waes JAR**, Bijker JB, van Wolfswinkel L, van Klei WA. Artifacts in research data obtained from anesthesia information management systems. *Can J Anaesth.* 2012;59:833-41.
- **van Waes JAR**, Nathoe HM, de Graaff JC, Kemperman H, de Borst GJ, Peelen LM, van Klei WA; Cardiac Health After Surgery (CHASE) Investigators. Myocardial injury after noncardiac surgery and its association with short-term mortality. *Circulation.* 2013;127:2264-71.
- van Klei WA, Grobbee DE, Grobben RB, **van Waes JAR**, Nathoe HM. Detection and management of asymptomatic myocardial injury after noncardiac surgery. *Eur J Prev Cardiol.* 2013;20:918-21.
- Grobben RB, **van Waes JAR**, van Klei WA, Nathoe HM. Asymptomatic myocardial infarction after non-cardiac surgery; importance of routine testing of troponin concentration. *Ned Tijdschr Geneeskd*. 2013;157:A5915. (in Dutch)
- **van Waes JAR**, van Klei WA, Wijeysundera DN, van Wolfswinkel L, Lindsay TF, Beattie WS. Association between intraoperative hypotension and myocardial injury after vascular surgery. *Anesthesiology.* 2016;124:35-44.
- Grobben RB, Vrijenhoek JE, Nathoe HM, Den Ruijter HM, **van Waes JAR**, Peelen LM, van Klei WA, de Borst GJ. Clinical relevance of cardiac troponin assessment in patients undergoing carotid endarterectomy. *Eur J Vasc Endovasc Surg.* 2016;51:473-80.
- **van Waes JAR**, Grobben RB, Nathoe HM, Kemperman H, de Borst GJ, Peelen LM, van Klei WA; Cardiac Health After Surgery (CHASE) Investigators. One-year mortality, causes of death, and cardiac interventions in patients with postoperative myocardial injury. *Anesth Analg.* 2016;123:29-37.
- **van Waes JAR**, Peelen LM, Kemperman H, Grobben RB, Nathoe HM, van Klei WA. Kinetics of troponin I in patients with myocardial injury after noncardiac surgery. *Clin Chem Lab Med.* 2016 (ePub ahead of print)
- van Klei WA, **van Waes JAR**, Pasma W, Kappen TH, van Wolfswinkel L, Peelen LM, Kalkman CJ. Relationship between preoperative evaluation blood pressure and preinduction blood pressure: a cohort study in patients undergoing general anesthesia. *Anesth Analg.* 2017; 124:431-437.