MYOCARDIAL INJURY AFTER NONCARDIAC SURGERY

PREDICTION, DETECTION, AND MANAGEMENT OF MYOCARDIAL INJURY AFTER NONCARDIAC SURGERY

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LAY ABSTRACT

Damage to the heart muscle occurring after a noncardiac surgery, called myocardial injury after noncardiac surgery (MINS), occurs frequently and negatively impacts patient's short- and long-term health and survival. Most patients who suffer a MINS do not present symptoms suggestive of heart problems. Blood tests obtained after surgery measuring troponins, a marker of heart damage, is necessary to detect which patients are having MINS. Different troponin tests are available, including a test called high-sensitivity troponin I, for which there is limited information on how to diagnose MINS using this test. How to predict who is at higher risk of MINS and how to treat patients who suffered a MINS are also areas that need further research. This thesis presents studies that inform on these knowledge gaps.

ABSTRACT

Myocardial injury after noncardiac surgery (MINS) is common in patients undergoing inpatient noncardiac surgery and has been shown to adversely impact short- and long-term patient prognosis. Most MINS events are asymptomatic and systematic troponin measurement early after surgery is of paramount importance to detect these events. The largest study to determine thresholds and prognostic importance of MINS used troponin T and high-sensitivity troponin T. There is limited information on how to diagnose MINS using high-sensitivity troponin I (hsTnI). How to predict who is at higher risk of MINS and would benefit the most from troponin monitoring, and how to manage patients who suffer a MINS are also areas that need further research. This thesis presents studies that inform on these knowledge gaps. Chapter 2 describes the result of a large prospective cohort of patients undergoing noncardiac surgery which determined the utility of preoperative N-Terminal pro-B type Natriuretic Peptide to predict 30-day MINS and vascular death, in addition to clinical evaluation. Chapter 3 uses data collected as part of a large prospective cohort with a nested biobank to determine thresholds of hsTnI that can predict major cardiovascular events in patients who underwent noncardiac surgery and be used to diagnosis MINS using hsTnI. Chapter 4 details the methods of an international, multicentre, randomized placebo-controlled trial (MANAGE Trial) determining the impact of dabigatran, a blood thinner, and using a partial factorial design, of omeprazole, a gastric acid reducing drug, on the occurrence of major vascular and upper gastrointestinal events in patients who suffered a MINS and are followed for up to 2 years. Chapter 5 presents the results of the omeprazole component of the MANAGE Trial. Chapter 6 discusses the key findings of the thesis and future research directions.

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LIST OF ABBREVIATIONS

ACC/AHA	American College of Cardiology/American Heart Association
ACEi	Angiotensin-Converting Enzyme Inhibitor
aHR	Adjusted Hazard Ratio
ARB	Angiotensin II Receptor Blocker
ASA	Acetylsalicylic Acid
BNP	Brain Natriuretic Peptide
CABG	Coronary Artery Bypass Grafting
CAD	Canadian Dollars
CCS	Canadian Cardiovascular Society
CCSC	Canadian Cardiovascular Society Class
CI	Confidence Interval
CK-MB	Creatinine Kinase-MB
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies Trial
COGENT	Clopidogrel and the Optimization of Gastrointestinal Events Trial
CRF	Case Report Form
CRLB	Clinical Research Laboratory and Biobank
CT	Computed Tomography
DMC	Data Monitoring Committee
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
eCrCl	Estimated Creatinine Clearance
eGFR	Estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
Hb	Hemoglobin
HR	Hazard Ratio
hsTnI	High-sensitivity Troponin I
hsTnT	High-sensitivity Troponin T
ICU	Intensive Care Unit
INR	International Normalization Ratio
IQR	Interquartile Range
LBBB	Left Bundle Branch Block
MACE	Major Adverse Cardiac Events
MANAGE	Management Of Myocardial Injury After Noncardiac Surgery Trial
MI	Myocardial Infarction
MINS	Myocardial Injury After Noncardiac Surgery
MRI	Magnetic Resonance Imaging
NARI	Net Absolute Reclassification Improvement
NIHSS	National Institutes of Health Stroke Scale
NRI	Net Reclassification Index
NSAID	nonsteroidal anti-inflammatory drug
NT-proBNP	N-terminal pro-B-type Natriuretic Peptide
OPTIMISE	OPtimisation of Peri-operaTive CardIovascular Management to Improve Surgical outcomE Trial

OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
PE	Pulmonary Embolism
PEP	Pulmonary Embolism Prevention Trial
POISE	Perioperative Ischemic Evaluation Study
PHRI	Population Health Research Institute
RCRI	Revised Cardiac Risk Index
RCI	Randomized Controlled Trial
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy Trial
ROC	Receiver Operator Curve
RR	Relative Risk
SD	Standard Deviation
TnI	Troponin I
TnT	Troponin T
TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis
URL	Upper Reference Limit
VISION	Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Study

DECLARATION OF ACADEMIC ACHIEVEMENT

Chapter 1 and Chapter 6: Emmanuelle Duceppe wrote the chapters in their entirety.

Chapter 2: Emmanuelle Duceppe (first author) contributed to the study's and statistical analysis plan design, data collection, data analysis, outcome adjudication process, biomarker analysis coordination, and interpretation of the results. She wrote the first draft of the statistical analysis plan and first draft of the manuscript, provided critical revisions, drafted, and approved the final version of the manuscript, and submitted for publication in a peer-reviewed journal. She drafted the responses to comments following peer review.

Chapter 3: Emmanuelle Duceppe (first author) contributed to the study's and statistical analysis plan design, data collection, data analysis, outcome adjudication process, biomarker analysis coordination, and interpretation of the results. She wrote the first draft of the statistical analysis plan and the manuscript.

Chapter 4 and Chapter 5: Emmanuelle Duceppe (first author) was the MANAGE trial's project officer, member of the steering committee, and site investigator. As the project officer of the MANAGE Trial, she was involved in the day-to-day management of the trial for 3 years. She was actively involved in the central organization and running of the trial and participated in patient's recruitment. She performed site initiations, research personnel training, site monitoring, and data quality and completeness evaluations. She wrote the first draft of the statistical analysis plan. She wrote the first draft of the methods paper (**Chapter 4**), provided critical revisions, and approved the final version of the manuscript. She submitted the manuscript for publication in a peer-reviewed journal and drafted the responses to comments following peer review. She wrote the first draft of the omeprazole trial paper (**Chapter 5**).

The contributorship of co-authors is detailed at the end of each chapter.

CHAPTER 1

INTRODUCTION

CHAPTER 1 – INTRODUCTION

1.1 Background

Almost everyone undergoes surgery during their lifetime. In fact, in Western countries it is estimated that individuals undergo an average of seven procedures during their lifespan.[1] Some of these interventions may be minor interventions but some patients will undergo complex procedures, including surgeries to improve function (e.g., total hip or knee replacement, spine surgery for spinal stenosis), to relieve symptoms (e.g., colectomy for inflammatory bowel disease, peripheral arterial bypass for claudication), or to prolong longevity (e.g., cancer surgery, aortic aneurysm repair). These major surgeries in adults will often require at least an overnight stay in hospital. There are several reasons to keep patients in an acute care facility after surgery rather than sending them home to recover. These include pain control and regaining mobility and independence; additionally, one of the main reasons is to monitor patients for postoperative complications that are at highest risk of occurrence in the first few days following surgery.

Most adults who underwent surgery fare well but, unfortunately, a substantial proportion suffer postoperative complications, some resulting in death. In adults undergoing noncardiac surgery with overnight stay in hospital (i.e., inpatient surgery), one in 60 patients dies within 30 days after surgery.[2] Myocardial injury, infarction, and bleeding are one of the leading complications contributing to postoperative death in this population.[2]

1.2 Myocardial injury after noncardiac surgery: incidence and prognostic importance

Several studies have demonstrated the prognostic importance of troponin elevation after noncardiac surgery on short- and long-term outcomes.[2-4] In a systematic review and individual patient-data meta-analysis of observational studies published in 2011, Levy et al. summarized the results of 14 studies (n=3318 patients), including various types of noncardiac surgery, and found

a 6-fold increase in all-cause mortality at 12 months in patients with elevated troponin after surgery.[3] Another systematic review and meta-analysis (2011) including only patients who underwent vascular surgery (9 studies; 1873 patients) showed a 5-fold increase in the risk of 30-day mortality in patients with postoperative troponin elevation that did not fulfill the criteria for myocardial infarction (MI).[5]

The Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study was an international prospective cohort of patients 45 years of age or older who underwent inpatient noncardiac surgery at 28 centres in 14 countries.[2] Patients had troponin levels measured 6 to 12 hours after surgery and on postoperative days 1, 2, and 3 and were followed for 30 days. The first part of VISION included 15,133 patients enrolled between 2007 and 2011 who had troponin T (TnT) levels (i.e., 4th generation TnT) measured for the first few days after surgery.[6] The second part of VISION measured high-sensitivity (hsTnT) levels (i.e., 5th generation TnT) in 21,842 participants and completed enrollment in 2013.[7] The VISION study identified peak postoperative TnT and hsTnT thresholds that significantly impacted patient's 30-day prognosis.[7,8] Patients with a peak postoperative TnT or hsTnT measurements above the empirically identified thresholds, that were believed to be due to an ischemic etiology, were associated with a significant increase in 30-day mortality compared to patients without troponin elevation.

Hence, the VISION study introduced the term "myocardial injury after noncardiac surgery" (MINS), defined as "*myocardial injury caused by ischemia (that may or may not result in necrosis), has prognostic relevance, and occurs during or within 30 days after noncardiac surgery*."[8] The MINS definition includes postoperative troponin elevations and events meeting the definition of MI. In the VISION cohort, the 30-day mortality rate was 6.0 % (95%

confidence interval [CI] 5.4%–6.7%) in patients with MINS, compared to 1.2% (95% CI 1.0%-1.3%) in patients without MINS (adjusted hazard ratio [aHR]2.2, 95% CI 1.9–2.6). The proportion of deaths attributable to MINS in the population was 15.9% (attributable fraction).[2]

Another major finding of the VISION study was that most MINS were asymptomatic.[7,8] Thus, systematic measurement of troponin values in the first postoperative days is the only way to ensure that the majority of these prognostically important events are detected. This was also observed in a study by Puelacher et al. (2018) which enrolled 2018 patients who underwent 2546 inpatient noncardiac surgeries and were ≥65 years of age, or ≥45 years with history of coronary artery disease, peripheral artery disease, or stroke.[4] Patients had hsTnT measured on postoperative day 1 and day 2, and troponin elevation was defined as a delta change ≥14 ng/L in hsTnT. Eighty-two percent of patients who had a hsTnT measurement did not experience ischemic symptoms. Postoperative troponin elevation was associated with 30-day (aHR 2.7, 95% CI 1.5-4.8) and 1-year (aHR 1.6, 95% CI 1.2-2.2) increase in mortality.

A more recent systematic review (2019) summarized the studies that looked at the association between troponin elevations and postoperative outcomes after noncardiac surgery and found similar association with adverse outcomes.[9] Several studies included in the review used hsTnT, TnT, and conventional troponin I (TnI), but no study reported on high-sensitivity troponin I (hsTnI).

1.3 Detecting MINS using high-sensitivity troponin I

Myocardial injury is detected and confirmed by elevated troponin levels. TnT and TnI are two of the three subunits of troponin which regulate cardiac muscle contraction that can be measured by blood tests. Both types of troponin do not occur in smooth muscles.[10] TnI is found exclusively in the cardiac muscle. TnT is present in small amounts in skeletal muscles but found

in much higher concentration in the heart. Several processes can induce myocardial injury, which lead to cardiomyocytes cell membrane's disruption and release of intracellular content, including troponins, into extracellular space and into the bloodstream in larger amounts than regular cell turnover.

Immunoassay techniques to reliably detect increased troponin levels in the blood were developed in the 1990s and became increasingly available in clinical settings in the 2000s. TnT and TnI are biomarkers highly *specific* to cardiac muscles, but analytic *sensitivity* was also required to ensure early detection of ongoing myocardial injury, particularly in the context of acute MI for which the tests were initially designed. A newer generation of high-sensitivity assays were developed and are gaining popularity worldwide. As the name implies, high-sensitivity troponin assays have been shown to have higher sensitivity to detect acute MI, especially in patients with low and moderate pre-test probability[11], and allow for earlier rule-out of MI than conventional assays.[12]

Many different troponin assays are available for clinical use, but analytical methods differ between manufacturers. Only one TnT/hsTnT assay is available (Roche Diagnostics) and utilizes two cardiac specific antibodies directed to part of the TnT molecules.[13] Contrarily, there are several TnI and hsTnI assays available using mono- or polyclonal antibodies against different parts of the TnI subunit, resulting in tests of varying sensitivities and reference ranges.[13] MI diagnostic thresholds therefore vary between hsTnT and various types of TnI and hsTnI. hsTnI assays are being used increasingly in various clinical settings and thresholds to define MINS have not been described.

1.4 Predicting who is at higher risk of suffering MINS

Systematic troponin monitoring for the first 48-72 hours after inpatient noncardiac surgery is recommended in at-risk patients as per Canadian guidelines.[14] Cost-consequence analyses have determined that the incremental cost to avoid missing a MINS event by performing systematic troponin T monitoring after inpatient noncardiac surgery in unselected patients aged ≥45 years is $1650 CAD.[15] Implementation of troponin monitoring strategies targeted at high-risk patients would facilitate reducing this cost, given tools are available to effectively discriminate which patients are higher risk of MINS and other cardiovascular events. The Canadian Cardiovascular Society (CCS) perioperative guidelines recommend measuring troponin daily for 48-72 hours after inpatient noncardiac surgery in adults aged 65 years or older, patients with a Revised Cardiac Risk Index (RCRI) score ≥1[16], or aged 45-64 years with significant cardiovascular disease. The CCS guidelines also recommended using natriuretic peptides to further risk stratify patients and determine eligibility for postoperative troponin monitoring.

Natriuretic peptides include brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP). BNP is a hormone secreted by the cardiomyocytes alongside the N-terminal part of the prohormone of BNP, NT-proBNP. BNP and NT-proBNP have been shown to improve preoperative cardiac risk prediction in addition to a clinical evaluation score (i.e., RCRI). In a systematic review, Rodseth et al. obtained individual-patient data from 10 studies (1560 patients) who had NT-proBNP measured before noncardiac surgery and found that a BNP threshold of 92 ng/L and NT-proBNP threshold of 300 ng/L improved risk discrimination in addition to RCRI to predict 30-day nonfatal MI and death.[17] Patients with natriuretic peptides above and below the thresholds had a 30-day incidence of MI and death of 21.8% and 4.9%, respectively. The largest cohort included in the meta-analysis enrolled 400 patients and studies

mainly included patients undergoing mostly thoracic, major vascular, and urgent/emergent orthopedic surgery.

These promising findings warranted external validation in a large representative cohort of mixed noncardiac surgeries. Further, the large difference in incidence between patients above and below the BNP/NT-proBNP thresholds suggested that there may be more than one significant threshold that could improve risk discrimination.

1.5 Management of MINS

Ultimately, the goal of detecting MINS is to implement interventions that can reduce and treat cardiac complications and improve patient prognosis. The large POISE, POISE-2, and the ongoing POISE-3 trials (ClinicalTrials.gov Identifier: NCT03505723) have assessed potential perioperative interventions to *prevent* major cardiac complications and mortality at 30 days after noncardiac surgery.[18-20] There was no randomized controlled trial on the management of patients who suffered a MINS; only observational data informed the management of these patients.[21,22] Given the magnitude of the problem, trials on MINS were needed.

The mechanisms underlying MINS remain unclear. Laboratory, autopsy, imaging, and clinical evidence suggest that coronary artery thrombosis may be one of the main pathophysiological mechanisms.[23-26] In the non-operative setting, antithrombotic therapy is a key part of the short- and long-term management of patients who suffer an acute MI, to prevent recurrent cardiac events and mortality.[27,28] Warfarin in addition to aspirin has been shown to reduce the composite of death, non-fatal MI, and non-fatal stroke, but increased the risk of major bleeding compared to aspirin alone in patients recovering from an acute MI.[29] In patients with stable coronary disease, low-dose rivaroxaban combined with aspirin has also been shown to

reduce long-term cardiovascular events, but increased major bleeding.[30] Oral anticoagulants could be beneficial and are a promising therapy in patients who have MINS.

The drawback of anticoagulation therapy, however, is bleeding, particularly when added to aspirin. Data from perioperative trials on antithrombotic therapy have shown that gastrointestinal bleeding is one the main sites of bleeding after surgery.[19] Postoperative bleeding can also increase the risk of MINS and long-term mortality.[18,19,22] Therefore, studying an anticoagulation drug in combination with a gastroprotective agent was of interest in patients with MINS.

1.6 Topics addressed in this thesis

This thesis details a research program focusing on MINS and the following chapters present prospective studies on the prediction, detection, and management of MINS. Designs used to achieve our objectives include a prospective cohort, a prospective biobank cohort, and a randomized controlled trial. The chapters also present innovative research methodological approaches, including a modified minimal p-value approach to determine optimal cutpoints for a continuous variable predicting a dichotomous outcome, a modification of the net reclassification index to determine improvement in discrimination using absolute numbers of events and relative change in risk, and a partial 2x2 factorial design embedded in a randomized controlled trial. We also discuss strategies to address challenges in recruitment and sample size requirement during the conduct of a randomized controlled trial.

Chapter 2 presents the findings of an international, prospective nested cohort study in patients 45 years or older undergoing inpatient noncardiac surgery which determined the association and incremental predictive value of preoperative NT-proBNP in addition to clinical evaluation to identify patients at risk of postoperative MINS and vascular death at 30 days.

Chapter 3 presents the result of an international, prospective, nested biobank cohort study in patients 45 years or older who underwent inpatient noncardiac surgery and were followed for 30 days to determine the association between peak postoperative hsTnI within the first 3 days postoperatively and the occurrence of major cardiac events and mortality. Prognostically important thresholds to define MINS using hsTnI were identified.

Chapter 4 details the rationale and design of a large, international, randomized, placebo-controlled trial – the MANAGE Trial - of adults who suffered a MINS to determine if dabigatran can prevent major vascular complications and omeprazole can prevent upper gastrointestinal complications, in patients followed for up to 2 years.

Chapter 5 presents the results of the omeprazole component of the MANAGE Trial.

Chapter 6 discusses the key findings in the thesis, limitations, and the future directions of research in the field of MINS.

Author's contribution: Emmanuelle Duceppe is the sole author of this chapter; this chapter is not published.

REFERENCES – CHAPTER 1

1. Gawande A. Two Hundred Years of Surgery. New England Journal of Medicine 2012;366:1716-23.

2. Association between complications and death within 30 days after noncardiac surgery. Cmaj 2019;191:E830-e7.

3. Levy M, Heels-Ansdell D, Hiralal R, et al. 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.

4. Puelacher C, Lurati Buse G, Seeberger D, et al. Perioperative Myocardial Injury After Noncardiac Surgery: Incidence, Mortality, and Characterization. Circulation 2018;137:1221-32.

5. Redfern G, Rodseth RN, Biccard BM. Outcomes in vascular surgical patients with isolated postoperative troponin leak: a meta-analysis. Anaesthesia 2011;66:604-10.

6. Devereaux PJ, Chan MT, Alonso-Coello P, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. Jama 2012;307:2295-304.

7. Devereaux PJ, Biccard BM, Sigamani A, et al. Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. Jama 2017;317:1642-51.

8. Botto F, Alonso-Coello P, Chan MT, et al. 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.

9. Smilowitz NR, Redel-Traub G, Hausvater A, et al. Myocardial Injury After Noncardiac Surgery: A Systematic Review and Meta-Analysis. Cardiology in Review 2019;27:267-73.

10. Troponin. 2020. (Accessed June 3, 2020, at https://www.ncbi.nlm.nih.gov/books/NBK507805/.)

11. Freund Y, Chenevier-Gobeaux C, Bonnet P, et al. High-sensitivity versus conventional troponin in the emergency department for the diagnosis of acute myocardial infarction. Critical Care 2011;15:R147.

12. Aldous SJ, Richards M, Cullen L, Troughton R, Than M. Diagnostic and prognostic utility of early measurement with high-sensitivity troponin T assay in patients presenting with chest pain. Cmaj 2012;184:E260-8.

13. Maynard SJ, Menown IBA, Adgey AAJ. Troponin T or troponin I as cardiac markers in ischaemic heart disease. Heart 2000;83:371.

14. Duceppe E, Parlow J, MacDonald P, et al. Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery. Can J Cardiol 2017;33:17-32.

15. Buse GL, Manns B, Lamy A, et al. Troponin T monitoring to detect myocardial injury after noncardiac surgery: a cost-consequence analysis. Can J Surg 2018;61:185-94.

16. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999;100:1043-9.

17. Rodseth RN, Biccard BM, Le Manach Y, et al. The prognostic value of pre-operative and post-operative B-type natriuretic peptides in patients undergoing noncardiac surgery: B-type natriuretic peptide and N-terminal fragment of pro-B-type natriuretic peptide: a systematic review and individual patient data meta-analysis. J Am Coll Cardiol 2014;63:170-80.

18. Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008;371:1839-47.

19. Devereaux PJ, Mrkobrada M, Sessler DI, et al. Aspirin in patients undergoing noncardiac surgery. N Engl J Med 2014;370:1494-503.

20. Devereaux PJ, Sessler DI, Leslie K, et al. Clonidine in patients undergoing noncardiac surgery. N Engl J Med 2014;370:1504-13.

21. Foucrier A, Rodseth R, Aissaoui M, et al. The long-term impact of early cardiovascular therapy intensification for postoperative troponin elevation after major vascular surgery. Anesthesia and analgesia 2014;119:1053-63.

22. Devereaux PJ, Xavier D, Pogue J, et al. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. Ann Intern Med 2011;154:523-8.

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. Ellis SG, Hertzer NR, Young JR, Brener S. Angiographic correlates of cardiac death and myocardial infarction complicating major nonthoracic vascular surgery. Am J Cardiol 1996;77:1126-8.

26. Priebe HJ. Triggers of perioperative myocardial ischaemia and infarction. Br J Anaesth 2004;93:9-20.

27. Roffi M, Patrono C, Collet J-P, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). European heart journal 2016;37:267-315.

28. Amsterdam EA, Wenger NK, Brindis RG, et al. 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 2014;64:e139-e228.

29. Andreotti F, Testa L, Biondi-Zoccai GG, Crea F. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25,307 patients. Eur Heart J 2006;27:519-26.

30. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med 2017;377:1319-30.

CHAPTER 2

PREOPERATIVE NT-PROBNP AND CARDIOVASCULAR EVENTS AFTER NON-CARDIAC SURGERY: A COHORT STUDY

CHAPTER 2 - Preoperative NT-proBNP and cardiovascular events after non-cardiac surgery: A cohort study

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ABSTRACT

Background: Preliminary data suggest preoperative N-terminal pro-B-type natriuretic peptide (NT-proBNP) may improve risk prediction in patients undergoing non-cardiac surgery.

Objectives: Determine whether preoperative NT-proBNP has additional predictive value beyond a clinical risk score for the composite of vascular mortality and myocardial injury after non-cardiac surgery (MINS) within 30 days after surgery.

Design: Prospective cohort study.

Setting: 16 hospitals in 9 countries.

Patients: 10,402 patients ≥45 years of age, undergoing in-patient non-cardiac surgery.

Measurements: All patients had NT-proBNP measured before surgery and troponin T measurements daily for up to 3 days after surgery.

Results: Multivariable analyses demonstrated that compared to preoperative NT-proBNP <100 pg/mL (the reference group), values of ≥100 to <200 pg/mL , ≥200 to <1500 pg/mL, and ≥1500 pg/mL were associated with adjusted hazard ratio of 2.27 (95% CI 1.90-2.70), 3.63 (95% CI 3.13-4.21), and 5.82 (95% CI 4.81-7.05), and corresponding incidences of the primary outcome in 12.3% (226/1843), 20.8% (542/2608), and 37.5% (223/595), respectively. Adding NT-proBNP thresholds to clinical stratification (i.e., the Revised Cardiac Risk Index [RCRI]) resulted in a net absolute reclassification improvement of 258 patients in 1000 patients. Preoperative NT-proBNP values were also significantly associated with 30-day all-cause mortality, <100 pg/mL incidence 0.3%, ≥100 to <200 pg/mL 0.7%, ≥200 to <1500 pg/mL 1.4%; and ≥1500 pg/mL 4.0%.

Limitations: External validation, of the identified NT-proBNP thresholds in other cohorts, would reinforce confidence in our findings.

Conclusions: We confirmed that preoperative NT-proBNP is strongly associated with vascular mortality and MINS within 30 days following non-cardiac surgery and improves cardiac risk prediction, in addition to the RCRI.

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INTRODUCTION

Myocardial injury after non-cardiac surgery (MINS) represents the most common major vascular complication after surgery and is associated with perioperative mortality[1-3]. Accurate preoperative cardiovascular risk prediction is important to facilitate informed decision-making regarding the appropriateness of non-cardiac surgery and to guide management decisions. Several guidelines recommend using the Revised Cardiac Risk Index (RCRI) for perioperative cardiac risk prediction[4-7]. Although easy to use, the RCRI's accuracy in predicting major perioperative cardiovascular complications is limited[8,9].

Preliminary evidence suggests that N-terminal pro-B-type natriuretic peptide (NT-proBNP) measurement may improve perioperative cardiovascular risk prediction[10,11]. The Vascular Events in Non-cardiac Surgery Patients Cohort Evaluation (VISION) Study enrolled adults who underwent in-patient non-cardiac surgery[1,2]. We undertook a planned sub-study that included patients with a prospectively collected preoperative NT-proBNP measurement. Our objective was to determine whether preoperative NT-proBNP had additional predictive value beyond the RCRI for the composite of vascular mortality and MINS within 30 days after surgery.

METHODS

In this nested sub-study within the VISION Study (ClinicalTrials.gov NCT005121090), an international, prospective, cohort study, we included patients ≥45 years of age who underwent in-patient non-cardiac surgery, with regional and/or general anesthesia, and consented to participate in the VISION NT-proBNP sub-study. Patients were excluded if they were previously enrolled in VISION. Between August 2007 and October 2013, 18,920 patients from 16 centres in 9 countries were enrolled in the VISION Study, of which 10,402 patients were

enrolled in this NT-proBNP sub-study (**eAppendix 1**). Ethics/institutional review board at each centre approved the study protocol before patient enrollment began.

Study Procedures

The methods for the VISION Study have been described elsewhere[1,2]. Research personnel interviewed and examined patients and reviewed charts at enrollment to obtain baseline variables (e.g., comorbidities and RCRI variables). The RCRI was calculated after study completion at the statistical analysis stage, and study personnel were unaware of this calculation. The RCRI score includes the following variables (worth 1 point each): history of ischemic heart disease, congestive heart failure, cerebrovascular disease, undergoing high-risk surgery (i.e., intraperitoneal, intrathoracic, suprainguinal vascular), preoperative insulin use, and preoperative creatinine >177 μmol/L (2 mg/dL).

All patients had blood drawn preoperatively with samples refrigerated within 2 hours after collection. Five centres measured NT-proBNP locally, of which, 1 performed NT-proBNP measurements in real time. The other 4 sites batched their samples before running the assays locally, at the same time. Samples collected at the other 11 centres were centrifuged, frozen, and shipped to the Clinical Research Laboratory and Biobank (CRLB) in Hamilton (Ontario, Canada). Later these samples were thawed and NT-proBNP measurements were subsequently undertaken, at the same time[12]. Each laboratory performed their own quality control as part of their standard operating procedures with NT-proBNP results generated with Roche immunoassay analyzers in line with laboratory recommendations[13]. Healthcare providers and study personnel were blinded to NT-proBNP measurements. Patients had troponin T (TnT) or high-sensitivity troponin T (hsTnT) (Roche Diagnostics) measured 6 to 12 hours after surgery and on

postoperative day 1, 2, and 3. Patients with postoperative TnT elevation above the 99th percentile were evaluated for ischemic signs or symptoms and had an electrocardiogram. Sites were encouraged to perform electrocardiograms for several days following a troponin elevation.

Research staff contacted patients 30 days after surgery to determine whether any outcome had occurred. If an outcome was reported, relevant documentation was obtained and sent to the study coordination centre (Population Health Research Institute, Hamilton, Canada). Data were entered in case report forms and submitted and stored in a secure, online, data management system (iDatafax).

Outcomes

The primary outcome was a composite of vascular mortality and MINS at 30 days. MINS includes myocardial infarction (MI) and ischaemic myocardial injury that does not satisfy the definition of MI[3,14]. **eAppendix 2** reports the secondary outcomes and the outcome definitions. Blinded outcome adjudicators evaluated outcomes, and their decisions were used in all statistical analyses.

Statistical Analyses

A statistical analysis plan was prespecified before analyses was undertaken and is available (**eAppendix 13**). A priori, we planned a sample size of 10,000 patients. We expected 1000 patients would have a primary event and this would provide >55 events per variable explored in our multivariable analyses (i.e., we could explore NT-proBNP thresholds up to and >4000 pg/ml based on the increments outlined in our iterative process to identify prognostically important NT-proBNP thresholds), which would ensure a stable model[15].

We assessed the association between preoperative NT-proBNP and the primary outcome based on categorizing NT-proBNP at iterative thresholds to objectively identify optimal categories (**eAppendix 3**)[2,16]. Cox proportional hazard models were undertaken in which the dependent variable was vascular mortality or MINS and the independent variables were the RCRI score and preoperative NT-proBNP values. Patients with missing data for the RCRI calculation were assumed not to have the RCRI risk factor and were included in the analyses. Missing data mainly related to a missing preoperative serum creatinine. Patients with a missing preoperative serum creatinine were younger, had fewer medical comorbidities, and more commonly underwent low-risk surgery compared to patients who were known not have a preoperative serum creatinine >177 μmol/L (2 mg/dL).

We compared model performance for the multivariable model including RCRI, with and without the NT-proBNP thresholds, using the c-statistic corrected for optimism and a bias-corrected calibration curve using 1000 bootstrapped samples[17]. We subsequently determined the association between the NT-proBNP thresholds and the secondary outcomes. We assessed the utility of using the NT-proBNP thresholds for risk prediction in addition to the RCRI score by calculating the Net Absolute Reclassification Improvement (NARI)[18]. The NARI were calculated using pre-determined risk categories (i.e., <5, 5-15%, >15-30%, >30%) for vascular mortality or MINS and also using a relative change of 25% of predicted risk, as a minimally important change (**eAppendix 4**).

We undertook post-hoc sensitivity analyses assessing the association between preoperative NT-proBNP and the 30-day composite of vascular mortality and MINS. We first undertook a complete-case sensitivity analysis, excluding patients with any missing RCRI data. We also performed a sensitivity analysis using a split sample derivation-validation. Since a validation

cohort with >100 primary events was large enough to avoid overfitting (i.e., a validation cohort based on approximately 10% of the overall cohort), this allowed us to have a derivation cohort based on approximately 90% of the overall cohort, to maximize statistical power to identify NT-proBNP thresholds through iterative Cox proportional hazards models. We performed one analysis split by calendar time and the second using randomly selected centres.

A two-sided p-value <0.050 was used to determine statistical significance unless stated otherwise. Statistical analyses were performed using Statistical Analysis Software (SAS Institute Inc., version 9.4) and R (The R Project for Statistical Computing, version 3.4.0). We followed the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement in preparing this manuscript[19].

Role of the Funding Source

The overall VISION Study was funded by >70 grants and funding sources. Roche Diagnostics provided the NT-proBNP assays and some funding. The Australian and New Zealand College of Anaesthetists Project Grant (grant 13/008) also provided funding for this study. No funding entity had a role in data collection, statistical analysis, manuscript writing or decision to publish.

RESULTS

Of 18,920 patients enrolled in VISION during the NT-proBNP sub-study's enrollment period, 10,402 patients were included in the NT-proBNP sub-study and the current analyses (**eAppendix 5**). Approximatively 40% of patients came from centres in North America, 30% from Asia-Pacific, and 20% from Europe (**eAppendix 1**). The mean age was 65 years (standard

deviation 11.1) and 50.0% were male (**Table 1**). Patients had a history of diabetes (20.2%), coronary artery disease (14.7%), congestive heart failure (3.3%), peripheral vascular disease (7.7%), and a cerebral vascular event (6.9%). The most common surgeries were major orthopedic (25.3%), major general (17.9%), and major urology/gynecology (13.8%). A third of the patients (33.3%) underwent low-risk surgeries, and 4.4% of surgeries were urgent or emergent.

The primary composite outcome of vascular mortality (54 events, 0.5%) and MINS (1237 events, 11.9%) occurred in 1269 patients (12.2%) within 30 days following surgery. Characteristics of patients with and without the composite primary outcome are presented in **eAppendix 6**. Our Cox proportional hazards models demonstrated that compared to the reference group (i.e., NT-proBNP <100 pg/mL), NT-proBNP measurements of ≥100 to <200 pg/mL were associated with an adjusted hazard ratio (aHR) of vascular mortality or MINS of 2.27 (95% CI 1.90-2.70) and an incidence of 12.3% (226/1843); ≥200 to <1500 pg/mL an aHR of 3.63 (95% CI 3.13-4.21) and an incidence of 20.8% (542/2608); and ≥1500 pg/mL an aHR of 5.82 (95% CI 4.81-7.05) and an incidence of 37.5% (223/595 (**Table 2**). **Figure 1** shows the cumulative risk of the primary outcome at 30 days according to NT-proBNP thresholds. The incidence of 30-day vascular mortality or MINS for patients with RCRI scores of 0, 1, 2, and ≥3 was 7.4% (439/5899), 14.1% (449/3180), 24.7% (239/967), and 39.9% (142/356), respectively. The optimism-corrected c-statistic to predict the primary outcome based on the RCRI score was 0.65 (95% CI 0.64-0.67) and increased to 0.73 (95% CI 0.72-0.74) when the NT-proBNP thresholds were included. The calibration curve did not show any important miscalibration (**eAppendix 7**).

The NT-proBNP thresholds also independently predicted all of the secondary outcomes (**Table 2**). The addition of the NT-proBNP thresholds improved model discrimination to predict the composite of all-cause mortality and MI (optimism-corrected c-statistic for RCRI 0.66 [95% CI, 0.66-0.71] and RCRI plus NT-proBNP thresholds 0.75 [95% CI, 0.73-0.78]). **eAppendix 8** reports the incidence of primary and secondary outcomes in the subset of patients who underwent elective surgery; these results were similar to the overall cohort. **Table 3** reports the reclassification tables of patients who had – and, separately, who did not have – the primary composite outcome, according to their predicted risk using RCRI and RCRI plus NT-proBNP thresholds. The percentage reclassification showed an improvement in risk prediction (i.e., patients were classified in more appropriate risk categories) when NT-proBNP values were included for patients with and without events (i.e., 21.4% and 26.4%, respectively). This resulted in a NARI of 258 per 1000 patients (25.8%). The risk reclassification improvement calculated using a 25% relative change in predicted probabilities showed a NARI of 321 per 1000 patients (32.1%).

eAppendix 9 reports the results from the post-hoc split sample sensitivity analyses. In the derivation cohort split by time (n=9391), we identified the same NT-proBNP thresholds (i.e., 100, 200, and 1500 pg/mL) with similar adjusted hazard ratios for the primary outcome, as the ones identified using the overall cohort. In the derivation cohort split by centres (n=9331), we found similar thresholds (100, 300 and 2000 pg/mL). For both analyses, we assessed the independent association between the primary outcome and the NT-proBNP thresholds and found similar associations as seen in our main analysis. We assessed the model performance and demonstrated similar discrimination between the whole, derivation, and validation cohorts in the

analyses split by time (i.e., c-statistic 0.73, 0.73, 0.71, respectively) and split by centres (i.e., c-statistic 0.73, 0.74, 0.69, respectively).

We performed a sensitivity analysis to compare the results of centres that measured NT-proBNP in their local laboratories to centres who shipped samples to the CRLB for measurement. We did not find a meaningful difference in the associations between NT-proBNP thresholds and the primary outcome (see **eAppendix 10**), across these 2 cohorts of centres. A complete-case sensitivity analysis excluding patients with missing RCRI data (n= 463) identified the same statistically significant NT-proBNP thresholds (i.e., 100, 200 and 1500 pg/mL) with no meaningful difference in hazard ratios (**eAppendix 11**). A post-hoc analysis demonstrated that the addition of RCRI to NT-proBNP thresholds also improved risk discrimination for the primary outcome; c-statistic 0.70 for NT-proBNP thresholds alone and 0.73 for the combined RCRI and NT-proBNP model.

DISCUSSION

In this prospective cohort study of 10,402 patients undergoing in-patient non-cardiac surgery, we found that preoperative NT-proBNP concentrations were independently associated with the occurrence of vascular mortality or MINS at 30 days after surgery. Preoperative NT-proBNP thresholds substantially improved discrimination of patients (c-statistic increase from 0.66 to 0.75) and perioperative risk stratification (25.8% improved risk reclassification) in addition to the RCRI. The preoperative NT-proBNP thresholds also predicted the risk of the secondary outcomes. Notably, healthcare providers were blinded to the NT-proBNP measurements, and therefore could not act on the results and potentially alter the relationship between NT-proBNP and our primary and secondary outcomes.

In an individual patient-data meta-analysis by Rodseth et al. including 1560 patients from 10 cohort studies that measured NT-proBNP before non-cardiac surgery, a NT-proBNP value of ≥300 pg/mL was independently associated with the composite of perioperative all-cause mortality or nonfatal MI, in a model that included the RCRI[11]. In a recent, multicentre, prospective cohort study, 1347 patients had preoperative NT-proBNP measurement before undergoing major non-cardiac surgery[20]. NT-proBNP concentrations showed significant independent associations and risk reclassification improvement for death or MINS at 30 days. They did not, however, use or establish NT-proBNP thresholds. Most studies that have evaluated the prognostic capabilities of preoperative NT-proBNP have used a predetermined or dichotomized NT-proBNP threshold[11,21,22]. Our prospective cohort had a much larger sample size, allowing for greater statistical power to identify multiple NT-proBNP thresholds and demonstrated improved risk prediction when added to the RCRI.

The incidence of all-cause mortality or MI, 4.3% in our cohort was lower than reported by Rodseth and colleagues[11]. Our cohort included 4.4% urgent/emergent surgeries and 6.3% vascular surgeries, compared to 22.7% and 28.8%, respectively, in Rodseth et al. In the overall VISION Study compared to this sub-cohort, the incidence of MINS was 13.0% versus 11.3%, all-cause mortality 1.8% versus 0.8%, and vascular mortality 0.9% versus 0.5%, respectively[1,2]. The lower incidence of these complications in this NT-proBNP cohort compared to the overall VISION cohort may be explained by the lower incidence of urgent/emergent surgeries 4.4% versus 10.5%, respectively[1,2].

The required preoperative blood sample drawn for NT-proBNP prevented enrolment of some patients undergoing urgent/emergent surgery. This may not represent a limitation of the current study; the utility for preoperative risk stratification may be greatest in the context of

elective surgeries. Urgent/emergent surgeries are generally performed for organ- or life-threatening conditions and avoiding delays generally outweigh concerns for preoperative cardiac risk stratification. In our cohort, the incidence of 30-day major cardiac outcomes in patients undergoing elective surgery was very similar to the overall VISION cohort, confirming that the results can be used to inform cardiac risk for elective cases.

Several national guidelines have proposed the use of NT-proBNP for preoperative risk stratification. The 2014 European Society of Cardiology (ESC) perioperative guideline noted that NT-proBNP/ B-Type natriuretic peptide (BNP) measurements may be considered for cardiac risk stratification in patients at higher risk but failed to provide a definition of higher risk and an NT-proBNP threshold[5]. The 2017 Canadian Cardiovascular Society (CCS) perioperative guidelines recommended to measure NT-proBNP/BNP in patients with a baseline risk >5% and a NT-proBNP threshold ≥300 pg/mL, based on the study by Rodseth and colleagues[7]. Our analyses found a threshold of ≥200 pg/mL was associated with a risk >5%. The differences in threshold are likely due to greater statistical power in our study.

The RCRI is the most validated model for preoperative cardiac risk stratification. Many perioperative guidelines recommending using the RCRI to predict perioperative cardiovascular risk[5,7,23]; however, studies have demonstrated the RCRI only has moderate discrimination[8]. Our results confirm the findings from previous studies that NT-proBNP can improve patient's cardiac risk reclassification in addition to the RCRI, which is important for several reasons. It is an ethical requirement to accurately inform patients about their risk in order to facilitate optimally inform decisions regarding the appropriateness of surgery[24].

Accurate risk estimation can also impact preoperative management. It can guide choices of surgical and anesthetic approaches (e.g., outpatient versus in-patient surgery, open versus

laparoscopic/endovascular, general versus regional anesthesia), decisions to perform further preoperative evaluation (e.g., cardiology consultation), and intensity of postoperative surveillance (e.g., troponin monitoring, telemetry, postoperative joint surgical and medical follow-up).

Assessment of troponins 48-72 hours after major non-cardiac surgery in at-risk patients is recommended by the CCS and ESC perioperative guidelines[5,7]. The 2014 American College of Cardiology/American Heart Association (ACC/AHA) perioperative guidelines mentioned uncertainty regarding postoperative troponin screening in high risk patients in the absence of a defined management strategy[23]. Since the 2014 ACC/AHA guidelines, large non-cardiac cohort studies have confirmed the utility of systematic troponin monitoring after surgery to detect MINS[2,25,26], and new evidence regarding treatment options for MINS have been published (e.g., an international randomized controlled trial of 1754 patients demonstrating the benefits of dabigatran in patients with MINS)[27].

Our study has demonstrated that NT-proBNP can help identify patients who are at higher risk of postoperative cardiac events and may benefit the most from perioperative troponin monitoring. The CCS guidelines suggested troponin monitoring in patients with a baseline risk of death or MI ≥5%[7]. In our cohort, patients with a NT-proBNP <200 pg/mL had a ≤3.0% risk of death or MI, whereas patients with an NT-proBNP 200-<1500 pg/ml had a 7.9% risk of death or MI. Therefore, clinicians could use NT-proBNP to inform decision making about ordering postoperative troponin measurements, with potential cost savings in avoiding such measurements in low risk patients, and to guide management of patients at higher risk of MINS.

Our primary outcome was vascular mortality or MINS. Some physicians may not recognize the prognostic relevance of MINS because most patients are asymptomatic; however,

large prospective cohort studies have demonstrated the prognostic relevance of MINS.[28] To put the prognosis of MINS into perspective, consider the control group outcomes in COMPASS (a large international trial that included patients with known coronary or peripheral arterial disease)[29] and MANAGE (a large international trial that included patients with MINS)[27]. Although COMPASS had substantially longer follow-up than MANAGE (i.e., mean of 23 months versus 16 months, respectively), MANAGE patients compared to the COMPASS control patients had a >3-fold and >2-fold higher risk of vascular mortality and MI, respectively.

Our study has limitations. Although we confirmed the independent association reported previously between preoperative NT-proBNP and major cardiac events and mortality after non-cardiac surgery[11], we identified new prognostically important NT-proBNP thresholds. These thresholds were derived from our entire cohort and have not undergone external validation in a separate cohort study. We did, however, perform two split sample sensitivity analyses (one by calendar time and one by random centre selection) to determine if the results would have differed. In the derivation cohort split by time, we identified the same significant thresholds and similar adjusted hazard ratios as the ones identified using the entire cohort (**eAppendix 9**). In the derivation cohort split by centres, we found similar thresholds. Both validation cohorts found similar independent association between NT-proBNP thresholds adjusted for RCRI and our primary outcome with comparable model performance.

We did not measure BNP and cannot inform its optimal thresholds for preoperative cardiac risk stratification. Although BNP and NT-proBNP reflect the same cardiac hormonal activity (the prehormone proBNP is cleaved into equal proportions of BNP and NT-proBNP), there is no conversion factor for the comparison between BNP and NT-proBNP values[30].

Informing the optimal BNP thresholds in non-cardiac surgery will require further investigation; however, this may be challenging due to instability and shorter half-life of the BNP analyte[12].

Although the RCRI is one of the most validated models for preoperative cardiac risk stratification, it was not designed to predict vascular death and MINS. We systematically monitored troponin measurements only until day 3 after surgery. Therefore, after day 3, we may have missed additional MINS events in patients who did not experience an ischemic symptom. Optimal use of the RCRI with NT-proBNP measurement will require an online calculator in which clinicians can enter RCRI variables and NT-proBNP and receive an output of patients' risk of major adverse events.

CONCLUSION

We demonstrated that preoperative NT-proBNP levels are strongly associated with major cardiac events and mortality in patients undergoing in-hospital non-cardiac surgery. NT-proBNP significantly improved discrimination among patients who did and did not suffer the primary outcome. Clinicians may consider using preoperative NT-proBNP to improve preoperative cardiac risk stratification in patients undergoing in-hospital non-cardiac surgery.

REFERENCES – CHAPTER 2

1. Devereaux PJ, Chan MT, Alonso-Coello P, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. Jama 2012;307:2295-304.

2. Devereaux PJ, Biccard BM, Sigamani A, et al. Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. Jama 2017;317:1642-51.

3. Devereaux PJ, Szczeklik W. Myocardial injury after non-cardiac surgery: diagnosis and management. European heart journal 2019.

4. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999;100:1043-9.

5. Kristensen SD, Knuuti J, Saraste A, et al. 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 Anaesthesiology (ESA). European journal of anaesthesiology 2014;31:517-73.

6. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;130:2215-45.

7. Duceppe E, Parlow J, MacDonald P, et al. Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery. The Canadian journal of cardiology 2017;33:17-32.

8. Ford MK, Beattie WS, Wijeysundera DN. Systematic review: prediction of perioperative cardiac complications and mortality by the revised cardiac risk index. Annals of internal medicine 2010;152:26-35.

9. Fronczek J, Polok K, Devereaux PJ, et al. External validation of the Revised Cardiac Risk Index and National Surgical Quality Improvement Program Myocardial Infarction and Cardiac Arrest calculator in noncardiac vascular surgery. British journal of anaesthesia 2019;123:421-9.

10. Park SJ, Choi JH, Cho SJ, et al. Comparison of transthoracic echocardiography with N-terminal pro-brain natriuretic Peptide as a tool for risk stratification of patients undergoing major noncardiac surgery. Korean circulation journal 2011;41:505-11.

11. Rodseth RN, Biccard BM, Le Manach Y, et al. The prognostic value of pre-operative and post-operative B-type natriuretic peptides in patients undergoing noncardiac surgery: B-type natriuretic peptide and N-terminal fragment of pro-B-type natriuretic peptide: a systematic review and individual patient data meta-analysis. Journal of the American College of Cardiology 2014;63:170-80.

12. Kavsak PA, Beattie J, Ma J. Effect of Storage Temperature for B-Type Natriuretic Peptide Concentrations for Primary Healthcare Populations. Clinical chemistry 2019;65:811-2.

13. Kavsak PA, Lam CSP, Saenger AK, et al. Educational Recommendations on Selected Analytical and Clinical Aspects of Natriuretic Peptides with a Focus on Heart Failure: A Report from the IFCC Committee on Clinical Applications of Cardiac Bio-Markers. Clinical chemistry 2019;65:1221-7.

14. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation 2012;126:2020-35.

15. Babyak MA. What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. Psychosomatic medicine 2004;66:411-21.

16. Mazumdar M, Smith A, Bacik J. Methods for categorizing a prognostic variable in a multivariable setting. Statistics in medicine 2003;22:559-71.

17. Smith GC, Seaman SR, Wood AM, Royston P, White IR. Correcting for optimistic prediction in small data sets. American journal of epidemiology 2014;180:318-24.

18. Sheth T, Chan M, Butler C, et al. Prognostic capabilities of coronary computed tomographic angiography before non-cardiac surgery: prospective cohort study. BMJ (Clinical research ed) 2015;350:h1907.

19. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. Annals of internal medicine 2015;162:55-63.

20. Wijeysundera DN, Pearse RM, Shulman MA, et al. Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study. Lancet (London, England) 2018;391:2631-40.

21. Vetrugno L, Langiano N, Gisonni R, et al. Prediction of early postoperative major cardiac events after elective orthopedic surgery: the role of B-type natriuretic peptide, the revised cardiac risk index, and ASA class. BMC anesthesiology 2014;14:20.

22. Weber M, Luchner A, Seeberger M, et al. Incremental value of high-sensitive troponin T in addition to the revised cardiac index for peri-operative risk stratification in non-cardiac surgery. European heart journal 2013;34:853-62.

23. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. Developed in collaboration with the American College of Surgeons, American Society of Anesthesiologists, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Vascular Medicine Endorsed by the Society of Hospital Medicine. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 2015;22:162-215.

24. Devereaux PJ, Sessler DI. Cardiac Complications in Patients Undergoing Major Noncardiac Surgery. The New England journal of medicine 2015;373:2258-69.

25. Puelacher C, Lurati Buse G, Seeberger D, et al. Perioperative Myocardial Injury After Noncardiac Surgery: Incidence, Mortality, and Characterization. Circulation 2018;137:1221-32.

26. Beattie WS, Karkouti K, Tait G, et al. Use of clinically based troponin underestimates the cardiac injury in non-cardiac surgery: a single-centre cohort study in 51,701 consecutive patients. Canadian journal of anaesthesia = Journal canadien d'anesthesie 2012;59:1013-22.

27. Devereaux PJ, Duceppe E, Guyatt G, et al. Dabigatran in patients with myocardial injury after non-cardiac surgery (MANAGE): an international, randomised, placebo-controlled trial. Lancet (London, England) 2018;391:2325-34.

28. Spence J, VISION Investigators ea. Frequency, timing, and causes of 30-day mortality after noncardiac surgery: Impact of cardiovascular complications. ESC Late Breaking Trial 2018.

29. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. The New England journal of medicine 2017;377:1319-30.

30. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. Heart (British Cardiac Society) 2006;92:843-9.

Table 1. Baseline characteristics

	All patients n=10,402	Preoperative NT-proBNP (pg/mL)			
		<100 n=5356	100 to <200 n=1843	200 to <1500 n=2608	≥1500 n=595
Age (years), n (%)					
45-64	5426 (52.2)	3707 (69.2)	767 (41.6)	793 (30.4)	159 (26.7)
65-74	2857 (27.5)	1270 (23.7)	632 (34.3)	805 (30.9)	150 (25.2)
≥75	2119 (20.4)	379 (7.1)	444 (24.1)	1010 (38.7)	286 (48.1)
Males, n (%)	5204 (50.0)	2777 (51.8)	812 (44.1)	1277 (49.0)	338 (56.8)
Diabetes, n (%)[†]	2103 (20.2)	932 (17.4)	348 (18.9)	616 (23.6)	207 (34.8)
Hypertension, n (%)[‡]	5552 (53.4)	2348 (43.8)	1028 (55.8)	1707 (65.5)	469 (79.0)
Congestive heart failure, n (%)[§]	346 (3.3)	36 (0.7)	25 (1.4)	145 (5.6)	140 (23.6)
Coronary artery disease, n (%)[‖]	1527 (14.7)	374 (7.0)	261 (14.2)	652 (25.0)	240 (40.4)
Peripheral vascular disease, n (%)	796 (7.7)	211 (3.9)	128 (6.9)	316 (12.1)	141 (23.7)
Cerebrovascular disease, n (%)	717 (6.9)	203 (3.8)	112 (6.1)	284 (10.9)	118 (19.8)
Preoperative eGFR, n (%)[¶]					
<30 or on dialysis	308 (3.1)	26 (0.5)	24 (1.4)	107 (4.2)	151 (25.7)
30 to <45	483 (4.9)	78 (1.5)	67 (3.8)	254 (10.0)	84 (14.3)
45 to <60	1084 (10.9)	325 (6.4)	242 (13.7)	438 (17.3)	79 (13.4)
≥60	8075 (81.2)	4623 (91.5)	1439 (81.2)	1739 (68.5)	274 (46.6)
Cancer (active cancer or metastatic disease), n (%)	2765 (26.6)	1342 (25.1)	501 (27.2)	766 (29.4)	156 (26.2)

Surgery, n (%)					
Major vascular	654 (6.3)	203 (3.8)	120 (6.5)	250 (9.6)	81 (13.6)
Major general	1859 (17.9)	922 (17.2)	356 (19.3)	479 (18.4)	102 (17.1)
Major thoracic	277 (2.7)	152 (2.8)	46 (2.5)	71 (2.7)	8 (1.3)
Major uro/gynecology	1440 (13.8)	777 (14.5)	242 (13.1)	351 (13.5)	70 (11.8)
Major orthopedic	2632 (25.3)	1239 (23.1)	536 (29.1)	711 (27.3)	146 (24.5)
Major neurosurgery	524 (5.0)	271 (5.1)	100 (5.4)	131 (5.0)	22 (3.7)
Low risk surgeries	3467 (33.3)	2049 (38.3)	539 (29.2)	702 (26.9)	177 (29.7)
Urgent/emergent surgery, n (%)	455 (4.4)	159 (3.0)	63 (3.4)	168 (6.4)	65 (10.9)
RCRI score, n (%)					
0	5899 (56.7)	3553 (66.3)	1053 (57.1)	1159 (44.4)	134 (22.5)
1	3180 (30.6)	1484 (27.7)	584 (31.7)	926 (35.5)	186 (31.3)
2	967 (9.3)	270 (5.0)	167 (9.1)	387 (14.8)	143 (24.0)
≥3	356 (3.4)	49 (0.9)	39 (2.1)	136 (5.2)	132 (22.2)

†4 missing patient data. ‡2 missing patient data.
§9 missing patient data. ‖5 missing patient data.
¶ mL/min per 1.73 m^2; 452 missing patient data
Abbreviations: eGFR, estimated glomerular filtration rate; IQR, interquartile range; MINS, myocardial injury after non-cardiac surgery; RCRI, Revised Cardiac Risk Index.

Table 2. Incidence of 30-day outcomes according to preoperative NT-proBNP values

		Preoperative NT-proBNP (pg/mL)			
	All n=10,402	<100 n=5356	100 to <200 n=1843	200 to <1500 n=2608	≥1500 n=595
Composite of vascular mortality or MINS					
No. events (incidence; 95% CI)*	1269 (12.2; 11.6-12.8)	278 (5.2; 4.6-5.8)	226 (12.3; 10.8-13.8)	542 (20.8; 19.2-22.3)	223 (37.5; 33.5-41.3)
aHR (95% CI)	-	1.00	2.27 (1.90-2.70)	3.63 (3.13-4.21)	5.82 (4.81-7.05)
Composite of all-cause mortality or MI					
No. events (incidence; 95% CI)*	446 (4.3; 3.9-4.7)	92 (1.7; 1.4-2.1)	55 (3.0; 2.2-3.8)	205 (7.9; 6.8-8.9)	94 (15.8; 12.8-18.7)
aHR (95% CI)	-	1.00	1.57 (1.12-2.19)	3.64 (2.83-4.69)	5.35 (3.91-7.34)
MINS					
No. events (incidence; 95% CI)*	1237 (11.9; 11.3-12.5)	272 (5.1; 4.5-5.7)	223 (12.1; 10.6-13.6)	529 (20.3; 18.7-21.8)	213 (35.8; 31.9-39.6)
aHR (95% CI)	-	1.00	2.29 (1.91-2.73)	3.62 (3.12-4.21)	5.70 (4.69-6.92)
MI					
No. events (incidence; 95% CI)*	378 (3.6; 3.3-4.0)	82 (1.5; 1.2-1.9)	46 (2.5; 1.8-3.2)	175 (6.7; 5.7-7.7)	75 (12.6; 9.9-15.3)

aHR (95% CI)	-	1.00	1.47 (1.02-2.10)	3.46 (2.64-4.53)	4.68 (3.32-6.60)
All-cause mortality					
No. events (incidence; 95% CI)*	88 (0.8; 6.9-10.4)	14 (0.3; 0.1-0.4)	13 (0.7; 0.4-1.1)	37 (1.4; 1.0-1.9)	24 (4.0; 2.4-5.6)
aHR (95% CI)	-	1.00	2.41 (1.13-5.14)	4.12 (2.20-7.73)	8.40 (4.10-17.23)
Vascular mortality					
No. events (incidence; 95% CI)*	54 (0.5; 0.4-0.7)	11 (0.2; 0.1-0.4)	8 (0.4; 0.2-0.9)	18 (0.7; 0.4-1.1)	17 (2.9; 1.8-4.5)
aHR (95% CI)	-	1.00	1.84 (0.74-4.59)	2.41 (1.11-5.21)	6.75 (2.90-15.70)

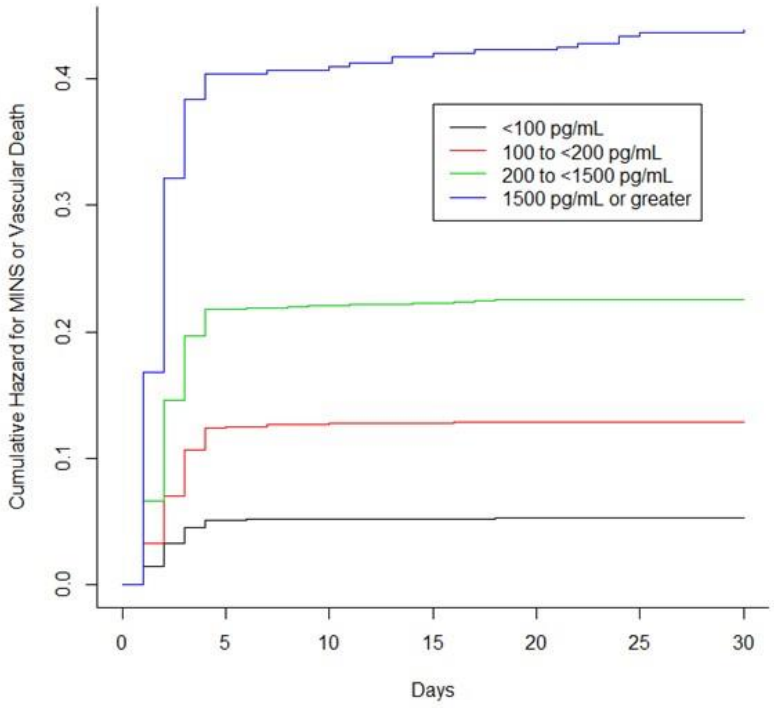
Results based on multivariable Cox regression model including RCRI score (i.e., 0, 1, 2, and ≥3) and NT-proBNP categories.
*30-day cumulative incidences calculated from the Kaplan-Meier estimates of survival with 95% CI.
Abbreviations: aHR, adjusted Hazard Ratio; CI, confidence interval; MINS, myocardial injury after non-cardiac surgery; MI, myocardial infarction

Table 3. Risk classification improvement using NT-proBNP thresholds*

Patients with Events (n=1269)					
	RCRI only				Percentage reclassification
RCRI and NT-proBNP	<5%	5 to 15%	>15 to 30%	>30%	
<5%	0	133	0	0	
5 to 15%	0	460	34	8	
>15 to 30%	0	229	40	13	21.4%
>30%	0	66	165	121	
Patients without Events (n=9133)					
	RCRI only				Percentage reclassification
RCRI and NT-proBNP	<5%	5 to 15%	>15 to 30%	>30%	
<5%	0	3420	0	0	
5 to 15%	0	3820	236	41	
>15 to 30%	0	831	127	26	26.4%
>30%	0	120	365	147	
Category-based Net Reclassification					
Net Absolute Reclassification Index	258 per 1000 patients				

*NARI is calculated with the following formula: (proportion reclassification for patients with events X event rate) + (proportion reclassification for patients without events X (1 – event rate). The total is multiplied by a 1000 to get the overall NARI.
Abbreviations: MINS, myocardial injury after non-cardiac surgery; NARI, Net Absolute Reclassification Index; RCRI, Revised Cardiac Risk Index.

Figure 1. Kaplan–Meier curve of 30-day risk for MINS or vascular death, by NT-proBNP threshold.



No. at risk							
<100 pg/mL	5356	5073	5065	5063	5060	5059	5057
100 to <200 pg/mL	1843	1621	1614	1612	1610	1610	1608
200 to <1500 pg/mL	2608	2080	2068	2063	2054	2050	2048
1500 pg/mL and greater	595	384	381	377	374	369	368

MINS = myocardial injury after noncardiac surgery; NT-proBNP =*N*-terminal pro–B-type natriuretic peptide.

SUPPLEMENTAL MATERIAL

Supplement

eAppendix 1. Continent from which patients were enrolled

	n=10,402 n (%)
North America (7 centres)	4336 (41.7)
South America (1 centre)	856 (8.2)
Europe (4 centres)	1937 (18.6)
Asia-Pacific (3 centres)	3053 (29.4)
Africa (1 centre)	220 (2.1)

eAppendix 2. Primary and secondary outcomes and diagnostic criteria

Primary outcome: composite of vascular mortality or myocardial injury after noncardiac surgery (MINS).

MINS was defined as a troponin elevation believed to be due to an ischemic etiology and occurring within 30 days following a non-cardiac surgery. A postoperative Troponin T (TnT) ≥ 0.03 ng/mL(31), high-sensitivity TnT (hsTnT) ≥20 ng/L with a change ≥5 ng/L, or hsTnT ≥ 65 ng/L(2) in a patients without evidence of a non-ischemic etiology of troponin elevation (e.g., pulmonary embolism, sepsis, chronic elevation) within 30 days after non-cardiac surgery. For non-TnT MINS events, the first value considered abnormal by the lab or the 99th percentile reported by the manufacturer was used to determine a troponin elevation.

Vascular mortality was defined as any death with a vascular cause and includes death following a MI, cardiac arrest, stroke, cardiac revascularization procedure (i.e., percutaneous coronary intervention or coronary artery bypass graft surgery), pulmonary embolus, hemorrhage, or due to an unknown cause.

Secondary outcomess:

1. Composite of myocardial infarction and all-cause mortality; where myocardial infarction (MI) was defined using the Third Universal Definition of Myocardial Infarction(14)
2. MI
3. MINS
4. Vascular mortality
5. All-cause mortality

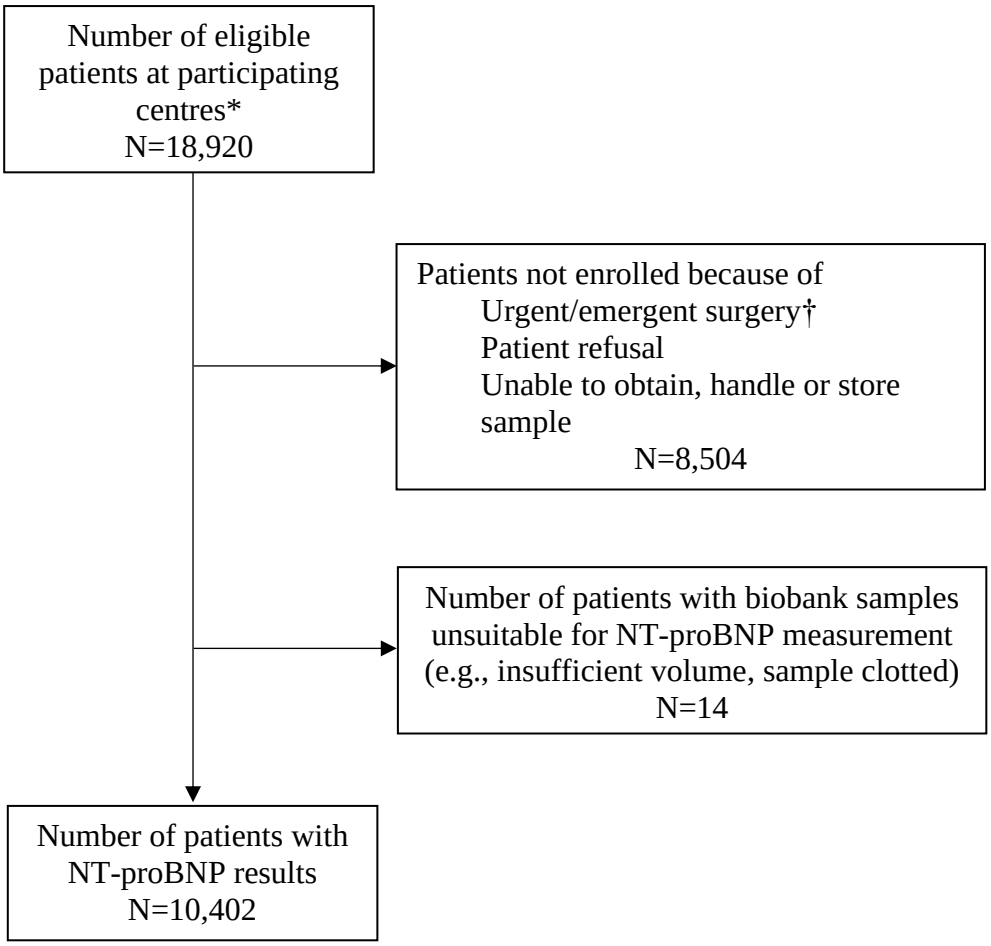
eAppendix 3. Statistical analyses to determine NT-proBNP thresholds

We explored the association between preoperative NT-proBNP and the 30-day composite of vascular mortality and myocardial injury after non-cardiac surgery (MINS) by undertaking a Cox proportional hazard model that included the Revised Cardiac Risk Index (RCRI) score (i.e., the most validated perioperative cardiac risk prediction score and recommended by national guidelines)(7-9) and preoperative NT-proBNP as an independent variable. The RCRI score includes the following risk factors worth 1 point each: history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, undergoing high-risk surgery (i.e., intraperitoneal, intrathoracic, suprainguinal vascular), preoperative insulin use, and preoperative creatinine >176 μmol/L (2 mg/dL). We first incorporated preoperative NT-proBNP as a continuous variable in the model to avoid the loss of statistical power and inflation of type-1 error that can be observed when determining the association between an outcome and a continuous variable that has been categorized before entering in the model(32-34). We then undertook a multivariable Cox proportional hazard model including the RCRI score, and used our modification of the approach to find an optimal cutpoint proposed by Mazumdar(16, 35) to look for preoperative NT-proBNP thresholds that corresponded to an important change in the risk of vascular mortality and MINS. We first used a scatter plot of the primary outcome incidence according to increments of preoperative NT-proBNP to explore for obvious prognostic thresholds and to evaluate the type of relationship between the two (e.g., linear, J-shaped)(35). The approach proposed by Mazumdar is an iterative process that allows to identify a single statistically optimal threshold of a predictor of interest (in this case preoperative NT-proBNP), for which the Cox regression model yields the smallest p-value from a chi-squared test based on the log-likelihood of the multivariable model with and without the predictor of interest. Our modification of this approach allowed us to look for more than one threshold. We explored NT-proBNP thresholds by increments of 100 between 100 and 1000, and increments of 500 for NT-proBNP >1000 up to 4000. We also used a p-value ≤0.010 to consider a threshold significant to adjust the p-value and account for multiple testing. If a threshold had an outcome incidence ≥5% in the higher risk category(7), we considered the threshold an important prognostic NT-proBNP value. We looked for additional thresholds until we no longer found significant model improvement on the log-likelihood ratio test (p>0.010).

eAppendix 4. Net Absolute Reclassification Improvement detailed analysis

We calculated the Net Absolute Reclassification Improvement (NARI) based on pre-determined risk categories of <5%, 5 to <15%, 15% to <30%, and ≥30%. Better risk classification was defined as shifting to a higher category for patients who experienced an event and shifting to a lower risk category for patients who did not experience an event. Worse risk classification was defined as the opposite. The proportion reclassification for patients with events was calculated using the following formula: (patients who moved up in risk category – patients who moved down in risk category) / total number of patients with events. The proportion reclassification for patients without events was calculated using the following formula: (patients who moved down a risk category – patients who moved up a risk category) / total number of patients without an event. The NARI was then calculated by multiplying the proportion reclassification for patients with events by the event rate and multiplying the proportion reclassification for patients without events by (1 - event rate), and then summing the two results. The total is then multiplied by 1000. The NARI can be interpreted as the number of patients with improved risk classification in a sample of 1000. Contrary to the conventional net reclassification index (NRI), the NARI takes into account the event rate in determining if adding a new predictor improves overall risk reclassification. This avoids misleading results in situations where the proportions of risk reclassification are discordant among patients who have events and patients who do not have events (i.e., one shows better and the other worse reclassification) or when the proportion reclassification is very large in patients with events, but the event rate is very low, resulting in an overestimation of overall risk reclassification in absolute number of patients.

eAppendix 5. Patient flow diagram



* Patients were enrolled between August 2007 and October 2013 at 16 participating centres. Patients were considered eligible if they met all the VISION Study eligibility criteria and were enrolled in the main VISION Study during the recruitment period for the NT-proBNP Study at one of the participating centres.
† The required blood sample drawn for NT-proBNP before undergoing surgery prevented enrolment of some patients undergoing urgent/emergent surgery.

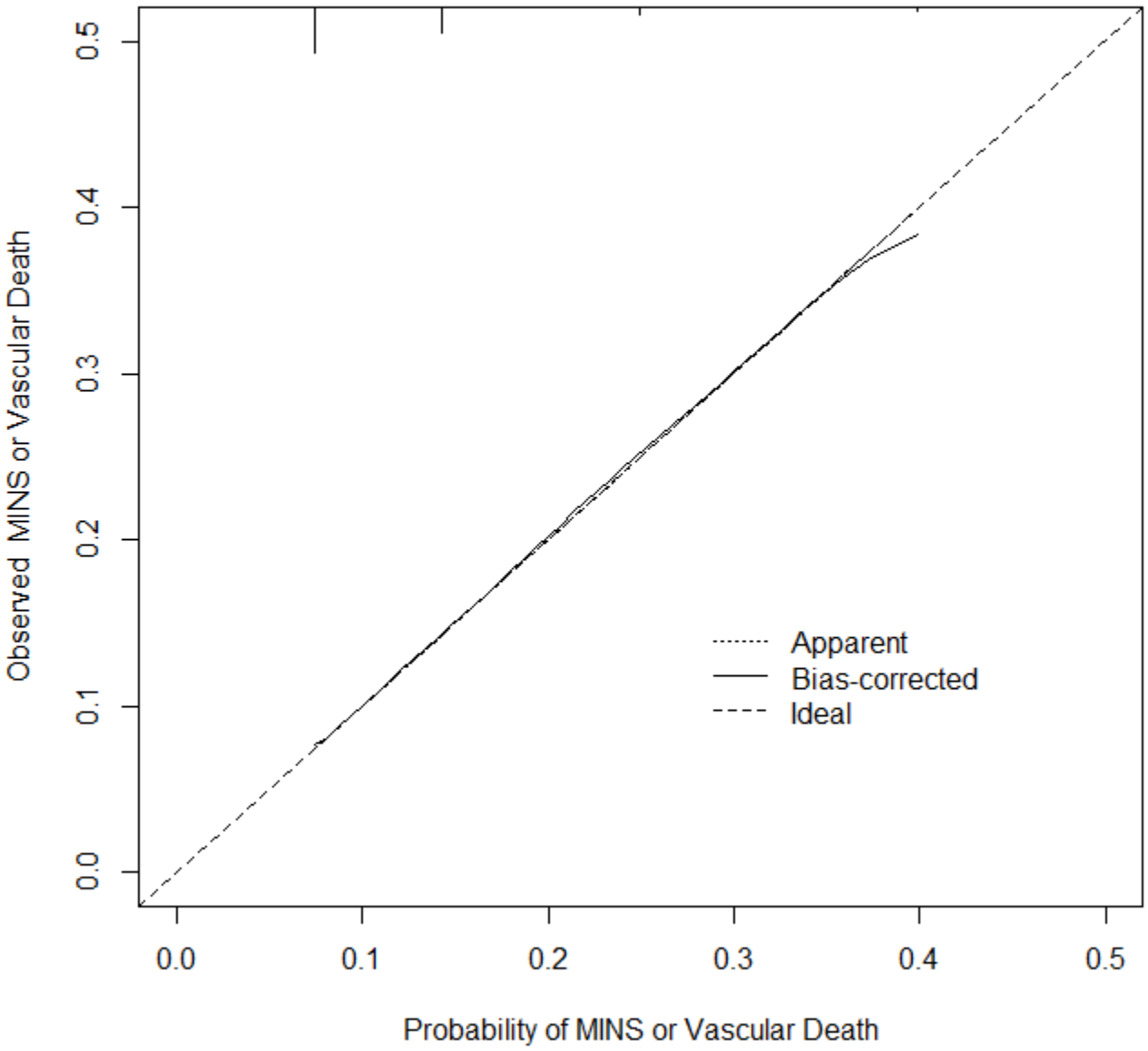
eAppendix 6. Characteristics of patients who had and did not have a primary outcome (i.e., vascular death or MINS) at 30 days

	All patients n=10402	Patients who did not have a primary outcome n=9133	Patients who had a primary outcome n=1269
Age, n (%)			
45-64 years old	5426 (52.2)	5074 (55.6)	352 (27.7)
65-74 years old	2857 (27.5)	2485 (27.2)	372 (29.3)
≥75 years old	2119 (20.4)	1574 (17.2)	545 (42.9)
Males, n (%)	5204 (50.0)	4464 (48.9)	740 (58.3)
Diabetes, n (%)[†]	2103 (20.2)	1726 (18.9)	377 (29.7)
Hypertension, n (%)[‡]	5552 (53.4)	4643 (50.8)	909 (71.7)
Congestive heart failure, n (%)[§]	346 (3.3)	221 (2.4)	125 (9.9)
Coronary artery disease, n (%)[‖]	1527 (14.7)	1155 (12.7)	372 (29.3)
Peripheral vascular disease, n (%)	796 (7.7)	565 (6.2)	231 (18.2)
Cerebrovascular disease, n (%)	717 (6.9)	553 (6.1)	164 (12.9)
Cancer (active cancer or metastatic disease), n (%)	2765 (26.6)	2411 (26.4)	354 (27.9)
Preoperative eGFR, n (%)[¶]			
<30 or on dialysis	308 (3.1)	175 (2.0)	133 (10.7)
30 to <45	483 (4.9)	340 (3.9)	143 (11.5)
45 to <60	1084 (10.9)	865 (9.9)	219 (17.7)
≥60	8075 (81.2)	7330 (84.2)	745 (60.1)

Surgery, n (%)			
Major vascular	654 (6.3)	479 (5.2)	175 (13.8)
Major general	1859 (17.9)	1632 (17.9)	227 (17.9)
Major thoracic	277 (2.7)	221 (2.4)	56 (4.4)
Major urology/gynecology	1440 (13.8)	1289 (14.1)	151 (11.9)
Major orthopedic	2632 (25.3)	2218 (24.3)	414 (32.6)
Major neurosurgery	524 (5.0)	463 (5.1)	61 (4.8)
Low-risk surgeries	3467 (33.3)	3237 (35.4)	230 (18.1)
Urgent/emergent surgery, n (%)	455 (4.4)	382 (4.2)	73 (5.8)
Preoperative NT-proBNP, median (Q1-Q3)	94.7 (39.9-264.7)	83.7 (36.4-216.5)	296.0 (120.1-904.1)
RCRI score, n (%)			
0	5899 (56.7)	5460 (59.8)	439 (34.6)
1	3180 (30.6)	2731 (29.9)	449 (35.4)
2	967 (9.3)	728 (8.0)	239 (18.8)
≥3	356 (3.4)	214 (2.3)	142 (11.2)

†4 missing patient data. ‡2 missing patient data.
§9 missing patient data. ‖5 missing patient data.
¶ mL/min per 1.73 m^2; 452 missing patient data
Abbreviations: eGFR, estimated glomerular filtration rate; IQR, interquartile range; MINS, myocardial injury after non-cardiac surgery; Primary outcome, vascular death or MINS; RCRI, Revised Cardiac Risk Index.

eAppendix 7. Calibration curve for the multivariable model including the Revised Cardiac Risk Index and NT-proBNP thresholds to predict vascular mortality or MINS



Abbreviations: MINS, myocardial injury after noncardiac surgery.

eAppendix 8. 30-day incidence of outcomes according to preoperative NT-proBNP thresholds in patients who underwent elective surgeries only (excluding urgent or emergent surgery)

	Preoperative NT-proBNP (pg/mL)			
n=9947	<100 n=5197 n (%)	100 to <200 n=1780 n (%)	200 to <1500 n=2440 n (%)	≥1500 n=530 n (%)
Vascular mortality or MINS	273 (5.3)	217 (12.2)	511 (20.9)	195 (36.8)
All-cause mortality or MI	91 (1.8)	53 (3.0)	194 (8.0)	81 (15.3)
MINS	267 (5.1)	214 (12.0)	500 (20.5)	189 (35.7)
MI	81 (1.6)	45 (2.5)	168 (6.9)	68 (12.8)
Vascular mortality	11 (0.2)	7 (0.4)	16 (0.7)	11 (2.1)
All-cause mortality	14 (0.3)	12 (0.7)	33 (1.4)	18 (3.4)

Abbreviations: MINS, myocardial injury after noncardiac surgery; MI, myocardial infarction.

eAppendix 9. Validation of the NT-proBNP thresholds in split sample analysis by time and centres

		Preoperative NT-proBNP (pg/mL)		
	Number of events (%)	100 to <200 aHR (95% CI)	200 to <1500 aHR (95% CI)	≥1500 aHR (95% CI)
Whole cohort	1269/10,402 (12.2)	2.27 (1.90-2.70)	3.63 (3.13-4.21)	5.82 (4.81-7.05)
Derivation split by time	1159/9391 (12.3)	2.40 (2.00-2.89)	3.69 (3.16-4.32)	6.17 (5.05-7.53)
Validation split by time	110/1011 (10.9)	1.32 (0.72-2.43)	3.20 (2.02-5.07)	3.67 (1.86-7.23)
Derivation split by centres	1137/9331 (12.2)	2.32 (1.94-2.78)	4.02 (3.44-4.70)	6.89 (5.59-8.49)
Validation split by centres	132/1071 (12.3)	1.75 (0.82-3.74)	2.19 (1.24-3.86)	3.96 (2.14-7.31)

Cox proportional hazard model including NT-proBNP thresholds and RCRI with MINS and vascular death as the outcome and NT-proBNP <100 as the comparator.
Abbreviations: aHR, adjusted Hazard Ratio; CI, confidence intervals.

eAppendix 10. Sensitivity analysis comparing results from centres that measured NT-proBNP locally to the centres that shipped their samples to Hamilton for measurement of NT-proBNP

NT-proBNP (pg/ml)	11 sites NT-proBNP measured in Hamilton 829 events in 6279 patients Hazard Ratio (95% CI)	5 sites NT-proBNP measured locally 440 events in 4123 patients Hazard Ratio (95% CI)
<100	1.00	1.00
100 to <200	2.38 (1.94-2.92)	1.83 (1.29-2.59)
200 to <1500	4.08 (3.41-4.88)	3.06 (2.36-3.98)
≥1500	6.28 (4.82-8.19)	5.90 (4.40-7.93)

Abbreviations: CI, confidence intervals.

eAppendix 11. Complete case sensitivity analysis

	No. events/No. patients	Preoperative NT-proBNP (pg/mL) aHR (95% CI)			
		<100	100 to <200	200 to <1500	≥1500
Composite of MINS or vascular mortality					
Complete case*	1233/9939	1.00	2.21 (1.85-2.65)	3.56 (3.07-4.14)	5.80 (4.78-7.03)
Whole cohort	1269/10,402	1.00	2.27 (1.90-2.70)	3.63 (3.13-4.21)	5.82 (4.81-7.05)
Composite of MI or mortality					
Complete case*	443/9939	1.00	1.56 (1.11-2.20)	3.68 (2.85-4.76)	5.35 (3.89-7.37)
Whole cohort	446/10,402	1.00	1.57 (1.12-2.19)	3.64 (2.83-4.69)	5.35 (3.91-7.34)
MI					
Complete case*	367/9939	1.00	1.49 (1.03-2.16)	3.50 (2.66-4.61)	4.67 (3.29-6.63)
Whole cohort	378/10,402	1.00	1.47 (1.02-2.10)	3.46 (2.64-4.53)	4.68 (3.32-6.60)
All-cause mortality					
Complete case*	86/9939	1.00	2.20 (1.01-4.76)	3.95 (2.10-7.43)	8.19 (3.99-16.81)
Whole cohort	88/10,402	1.00	2.41 (1.13-5.14)	4.12 (2.20-7.73)	8.40 (4.10-17.23)

* Cox regression model including RCRI and NT-proBNP thresholds only in patients with complete data for RCRI calculation (i.e., excluding the 463 patients with missing data for RCRI calculation).
aHR, adjusted hazard ratio; CI, confidence interval; MI, myocardial infarction; MINS, myocardial injury after noncardiac surgery.

eAppendix 12. Statistical Analysis Plan

Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Study

Preoperative N-terminal pro-B-type natriuretic peptide

Statistical Analysis Plan

March 27, 2018

1.0 INTRODUCTION

The serum postoperative troponin elevation is independently associated with 30-day postoperative mortality. Myocardial Injury after Noncardiac Surgery (MINS) was introduced to focus attention on the prognostic relevance of ischemic troponin elevations after noncardiac surgery(31). In the Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study (clinicaltrials.gov, identifier NCT00512109), which included >15,000 patients who underwent noncardiac surgery, MINS was independently associated with a 3 to 4 fold excess 30-day mortality(31). These findings have recently been replicated in an analysis of the high sensitivity troponin T (hsTnT)(2).

There is encouraging individual patient data suggesting that both preoperative and postoperative B-type natriuretic peptide evaluation has clinical utility(36) in significantly improving upon clinical risk stratification to predict postoperative major adverse cardiac events, defined as a composite of death and nonfatal myocardial infarction (MI)(11, 37-39). As a result of this evidence, preoperative B-type risk stratification has been recommended in the 2016 guidelines published by the Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery(7).

The clinical utility of B-type natriuretic peptide risk stratification is unknown for MINS. Further, thresholds of NT-proBNP associated with a change in 30-day prognostic have only been studied in smaller cohorts(11). We also propose to identify optimal cut points of preoperative NT-proBNP to predict a composite of MINS and vascular mortality in a large cohort of patients who underwent in-hospital noncardiac surgery.

2.0 STUDY OBJECTIVES

Among patients undergoing noncardiac surgery, we will utilize preoperative NT-proBNP measurement to:

1. determine the association between preoperative NT-proBNP and 30-day risk of the composite of MINS and vascular mortality;
2. determine preoperative NT-proBNP optimal thresholds to predict 30-day risk of the composite of MINS and vascular mortality;
3. determine the relationship between preoperative NT-proBNP and, separately, identified preoperative NT-proBNP optimal thresholds and the risk of 30-day MI and all-cause mortality as per the Universal Definition;(14)
4. determine the relationship between preoperative NT-proBNP and, separately, identified preoperative NT-proBNP optimal thresholds and the risk of 30-day MI;
5. determine the relationship between preoperative NT-proBNP and, separately, identified preoperative NT-proBNP optimal thresholds and the risk of 30-day all-cause mortality;
6. describe the characteristics of patients with and without the composite of MINS and vascular death, and according to the preoperative NT-proBNP thresholds identified;
7. determine the incremental predictive value of preoperative NT-proBNP thresholds in addition to established clinical risk score (i.e., Revised Cardiac Risk Index) to predict the composite of MINS and vascular mortality;
8. determine the incidence of the composite of MINS and vascular death in patients with and without NT-proBNP elevation according to the preoperative risk factors defined by the CCS Preoperative Guidelines.(4)

3.0 STATISTICAL AND ANALYTICAL METHODS

3.1 Analysis population

This analysis will include all the patients in the VISION study who had preoperative NT-proBNP measurement done as part of the VISION NT-proBNP Study. We will report how many patients were excluded from the analyses and the corresponding reasons (i.e. NT-proBNP not measured before surgery). We will also report the number of patients who did not have a postoperative troponin T (TnT) or high sensitivity troponin T (hsTnT) measured; these patients will be included in the analyses and considered to not have suffered a MINS.

3.2 Outcomes

MINS will be defined according to the VISION adjudicated MINS cases for the publications which defined MINS(2, 31). MI will be defined according to the Third Universal Definition of MI(14). Vascular death is defined as any death with a vascular cause and includes those deaths following a MI, cardiac arrest, stroke, cardiac revascularization procedure (i.e., percutaneous coronary intervention or coronary artery bypass graft surgery), pulmonary embolus, hemorrhage, or deaths due to an unknown cause. MINS and MI were adjudicated by clinicians with expertise in perioperative cardiovascular complications. We will analyze data generated by the VISION Adjudication Committee.

3.2 Statistical analysis

We will report how many patients sustained: i) the composite of MINS or vascular death, ii) the composite of MI or all-cause death, iii) MINS, iv) MI, v) vascular mortality, and vi) all-cause mortality up to 30 days following surgery. We will report how many patients either died before 30 days or completed the 30-day follow-up. We will censor patients at the time of their last assessment if they did not complete the 30-day follow-up. For all tests, we will report p-values to 3 decimal places with p-values less than 0.001 reported as $p<0.001$. We will use alpha = 0.05 level of significance, unless otherwise specified.

3.2.1 First objective: "Determine the association between preoperative NT-proBNP and the risk of 30-day MINS and vascular mortality"

We will first explore the association between preoperative NT-proBNP and 30-day risk of the composite of MINS and vascular mortality using preoperative NT-proBNP as a continuous variable. This is to avoid the loss of statistical power and inflation of the type I error that can be observed when determining the association between an outcome and continuous variable that has been categorized(32-34). We will undertake a Cox Proportional Hazards Model where the dependent variable will be a composite of MINS and vascular mortality at 30 days. Independent variables will include the Revised Cardiac Risk Index. We will then incorporate preoperative NT-proBNP (continuous variable) to the model. We will report the adjusted hazard ratio (HR) with corresponding 95% confidence interval (CI) and p-value.

If a statistically significant association is not found, we will explore the possibility of the lack of significant association being related to non-linearity of association between NT-proBNP and the outcome. We will look at the distribution of outcome probability by plotting pre-operative NT-proBNP values by increment of 100 up to 4000 against the incidence of event for each NT-proBNP category. If the plot suggests a non-linear relationship, we will explore the association between preoperative NT-proBNP and the composite of MINS and vascular mortality using a different statistical model appropriate for non-linear relationships (i.e., multiple fractional polynomial model).

3.2.2 Second objective: "Determine preoperative NT-proBNP optimal thresholds to predict 30-day risk of the composite of MINS and vascular mortality"

We will undertake a Cox Proportional Hazards Model where the dependent variable will be the composite of MINS and vascular mortality at 30 days. Independent variables will include the Revised Cardiac Risk Index score(4) (i.e., the most validated perioperative risk index and recommended by many guideline committees(5-7)). We will then use our modification to the approach by Mazumdar(35) to look for preoperative NT-proBNP thresholds that corresponds to important change in the risk of MINS and vascular death. We will refer to such important values as deflection points. Our modification of the Mazumdar approach will identify statistically optimal deflection points as the NT-proBNP for which the Cox regression model yields the smallest p-value from a chi-squared test based on the log likelihood of the multivariable model including NT-proBNP and the log likelihood of the multivariable model without NT-proBNP. We will look at the following thresholds: 100 to 1000 by increments of 100 and from 1000 to 4000 by increment of 500. If the optimal deflection point has an outcome incidence ≥5% in the higher risk category (based on the CCS perioperative guideline recommended risk threshold(7)) we will use that optimal deflection point as an important prognostic NT-proBNP value threshold. If the first optimal deflection point does not meet these criteria, we will look for the second optimal threshold (and following ones if required) until we find a deflection point meeting these criteria.

We will explore the possibility of a second deflection point, by introducing a 3-group categorical variable for NT-proBNP risk and again applying the modified Mazumdar approach. We will do this by looking simultaneously for the best 2 thresholds. Again, we will only consider a second threshold as important if there is at least a 5% risk-incidence increase between the first and second threshold. We will compare these models using the likelihood ratio test. If the 3-category model is an improvement over the 2-category model ($p \leq 0.01$), we will look for the best-fitting 4-category model. We will repeat this process until we no longer find significant model improvement ($p > 0.01$).

3.2.3 Third objective: "Determine the relationship between preoperative NT-proBNP and, separately, identified preoperative NT-proBNP optimal thresholds, and the risk of 30-day MI and all-cause death;

We will first determine the association between preoperative NT-proBNP and the composite of MI and all-cause death. We will perform a Cox regression model which will include Revised Cardiac Risk Index score. We will add the NT-proBNP as a continuous variable, entered as a linear association. The dependent variable will be 30-day MI or all-cause death. We will report the HR corresponding standard error, 95% confidence intervals and associated p-values.

We will then use the preoperative NT-proBNP thresholds identified in the previous objective to predict MI according to the Third Universal Definition of MI and all-cause death. We will perform a Cox regression model, which will include only the NT-proBNP thresholds and the Revised Cardiac Risk Index score. The dependent variable will be 30-day MI or all-cause death. We will report the HR corresponding 95% confidence intervals and associated p-values.

We will assess the model performance by means of calibration and discrimination statistics. We will evaluate calibration through a calibration curve, and discrimination through the C-statistic and C-statistic corrected for optimism.

3.2.4 Forth objective: "Determine the relationship between preoperative NT-proBNP and, separately, identified preoperative NT-proBNP optimal cutpoints, and the risk of 30-day MI"

We will first determine the association between preoperative NT-proBNP and MI. We will perform a Cox regression model which will include Revised Cardiac Risk Index score. We will add the NT-proBNP as a continuous variable, entered as a linear association. The dependent variable will be 30-day MI. We will report the HR corresponding 95% confidence intervals and associated p-values.

We will then use the preoperative NT-proBNP thresholds identified in the previous objective to predict MI. We will perform a Cox regression model which will include only the NT-proBNP thresholds and the Revised Cardiac Risk Index. The dependent variable will be 30-day MI. We will report the HR corresponding 95% confidence intervals and associated p-values.

We will assess the model performance by means of calibration and discrimination statistics. We will evaluate calibration through a calibration curve, and discrimination through the C-statistic and C-statistic corrected for optimism.

3.2.5 Fifth objective: "Determine the relationship between preoperative NT-proBNP and, separately, identified preoperative NT-proBNP optimal cutpoints, and the risk of 30-day all-cause mortality"

We will first determine the association between preoperative NT-proBNP and all-cause mortality. We will perform a Cox regression model which will include Revised Cardiac Risk Index score. We will add the NT-proBNP as a continuous variable, entered as a linear association. The dependent variable will be 30-day all-cause mortality. We will report the HR corresponding 95% confidence intervals and associated p-values.

We will then use the preoperative NT-proBNP thresholds identified in the previous objective to predict all-cause mortality. We will perform a Cox regression model which will include only the NT-proBNP thresholds and the Revised Cardiac Risk Index. The dependent variable will be 30-day all-cause mortality. We will report the HR corresponding 95% confidence intervals and associated p-values.

We will assess the model performance by means of calibration and discrimination statistics. We will evaluate calibration through a calibration curve, and discrimination through the C-statistic and C-statistic corrected for optimism.

3.2.5 Sixth objective: "Describe the characteristics of patients with and without MINS or vascular death, and according to the preoperative NT-proBNP thresholds identified."

We will describe the baseline and surgical characteristics of patients with and without nonfatal MINS and vascular death (Table 1). Proportions across the groups will be compared using a chi-square test or Fisher's exact. Normally distributed continuous variables across the groups will be compared using the student's t-test. Non-normally distributed continuous variables across the groups will be compared using the Mann-Whitney U test. We will report p-values for each comparison.

We will describe the baseline and surgical characteristics of patients according to the NT-proBNP thresholds found (Table 2). Proportions across the groups will be compared using a chi-square test or Fisher's exact. Normally distributed continuous variables across the groups will be compared using the student's t-test (if one threshold found) or ANOVA test (if more than one threshold found). Non-normally distributed continuous variables across the groups will be

compared using the Mann-Whitney U test (if one threshold found) or Kruskal-Wallis test (if more than one threshold found). We will report p-values for each comparison.

Regarding outcomes, proportion of 30-day nonfatal MINS and vascular death, MI, and all-cause mortality of patients for each category of NT-proBNP thresholds will be reported (see Table 3).

3.2.6 Seventh objective: "Determine the incremental predictive value of preoperative NT-proBNP thresholds in addition to established clinical risk score (i.e., Revised Cardiac Risk Index) to predict MINS and vascular mortality"

We will use the identified optimal NT-proBNP thresholds to predict MINS and vascular mortality and compare the predictive performance of NT-proBNP in addition to the Revised Cardiac Risk Index (RCRI).

We will first perform a Cox Regression model with the RCRI only to predict MINS and vascular mortality. We will assess the model performance by means of calibration and discrimination statistics. We will evaluate calibration through a calibration curve, and discrimination through the C-statistic. We will also calculate the C-statistic corrected for optimism (17).

We will perform a second model that will include the RCRI and preoperative NT-proBNP thresholds to predict MINS and vascular mortality. We will calculate the c-statistic and c-statistic corrected for optimism for the second model. We will plot a calibration curve on the same graph as the RCRI only model.

We will calculate a Weighted Net Reclassification Index (NRI) and Net Absolute Reclassification Index (NARI) using the following risk categories: <5, 5-15%, >15-30%, >30%. We will present the number and proportion of patients reclassified in a reclassification table for patients with events and patients without events separately. We will calculate the Weighted NRI by first, multiplying the proportion reclassification for patients with events to the outcome incidence, the multiplying the proportion reclassification for patients without event to (1 – the outcome incidence). We will then sum the two to obtain the Weighted NRI, which will be reported in percentage.

For the NARI, we will report the absolute number of patients of a sample of 1000 patients that were reclassified when adding NT-proBNP in addition to the RCRI. We will present a Reclassification table for patients with events and separately without events.

We will also calculate a NARI using a relative chance in risk of 25% to determine risk reclassification. Better risk classification will be defined as shifting to a higher category (≥25% relative increase in risk prediction) for patients who experienced an event and shifting to a lower risk category (≥25% relative decrease in risk prediction) for patients who did not experience an event. Worse risk classification was defined as the opposite. The NARI using relative change will then calculated using the same method as described above for the category-based NARI.

We will then calculate a Weighted NRI using confidence bands based on a minimally important absolute difference of 5%. We will calculate for patients without events the difference between the predicted probabilities from the second model (RCRI + NT-proBNP) and the first model (RCRI only). To calculate the NRI using confidence bands, we will calculate for patients with events, the difference between the predicted probabilities between the two models. For patients with predicted probability ≤30% in the first model, any change ≥ +5% of predicted probability will be counted as a "1" for appropriate reclassification; any change ≤ -5% of predicted probability will be counter as a "1" for inappropriate reclassification. For patients with predicted probability >30% is the first model, any change ≥ +10% of predicted probability will

be counted as a "1" for appropriate reclassification; any change ≤ -10% of predicted probability will be counter as a "1" for inappropriate reclassification. We will then calculate the reclassification for patient with events using the following formula: number of appropriate reclassification in events/total patients with events – number of inappropriate reclassification in events/total patients with events.

We will then calculate the reclassification for patients without events. We will calculate for patients without events the difference between the two predicted models. For patients with predicted probabilities ≤30%, any change ≤ -5% of predicted probability will be counted as a "1" for appropriate reclassification; any change ≥ +5% of predicted probability will be counter as a "1" for inappropriate reclassification. For patients with predicted probabilities >30%, any change ≤ -10% of predicted probability will be counted as a "1" for appropriate reclassification; any change ≥ +10% of predicted probability will be counter as a "1" for inappropriate reclassification. We will then calculate the reclassification for patient without events using the following formula: number of appropriate reclassification without events/total patients without events – number of inappropriate reclassification without events/total patients without events.

We will present a 2 x 2 Reclassification table. We will report the proportion reclassification for patients with and without events. The Weighted NRI and NARI using confidence bands will be calculated in the same manner as described above. We will calculate the 95% CI for the NRI and corresponding NARI.

3.2.7 Eight objective: "Determine the incidence of MINS and vascular death in patients with and without NT-proBNP elevation according to the preoperative risk factors defined by the CCS Preoperative Guidelines."

The 2016 Canadian Cardiovascular Society Perioperative Guidelines identify a subgroup of patients at higher preoperative risk for which preoperative NT-proBNP measurement is recommended. The risk factors are: age ≥ 65 years, RCRI score ≥ 1, age 45-64 years and significant cardiovascular disease (i.e., significant cardiovascular disease includes known history of coronary artery disease, cerebral vascular disease, peripheral artery disease, congestive heart failure, severe pulmonary hypertension or a severe obstructive intracardiac abnormality [e.g., severe aortic stenosis, severe mitral stenosis, or severe hypertrophic obstructive cardiomyopathy].

We will report the proportion of MINS and vascular death according to NT-proBNP thresholds in patients in the following subgroups:

- age ≥ 65 years vs age <65 years;
- age 45 – 64 years with at least one of the following characteristics: history of peripheral artery disease or severe aortic stenosis vs age 45-64 years without these characteristics;
- RCRI score ≥ 1 vs RCRI score 0;
- patients meeting any of the following criteria: 1) age ≥ 65 years, 2) age 45 – 64 years with at least one of the following characteristics: history of peripheral artery disease or severe aortic stenosis, or 3) RCRI score ≥ 1 vs patients not meeting any of these criteria.
-

3.3 Subgroup analysis

We will determine the incidence of the composite of MINS and vascular death, composite of MI and all-cause death, MINS, MI, vascular death and all-cause death in the subgroup of patients who underwent elective surgery only (excluding urgent/emergent surgery).

SUPPLEMENTAL REFERENCES

31. Botto F, Alonso-Coello P, Chan MT, Villar JC, Xavier D, Srinathan S, et al. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. Anesthesiology. 2014;120(3):564-78.
32. Austin PC, Brunner LJ**.** Inflation of the type I error rate when a continuous confounding variable is categorized in logistic regression analyses. Stat Med. 2004;23(7):1159-78.
33. Barnwell-Menard JL, Li Q, Cohen AA**.** Effects of categorization method, regression type, and variable distribution on the inflation of Type-I error rate when categorizing a confounding variable. Stat Med. 2015;34(6):936-49.
34. Royston P, Altman DG, Sauerbrei W**.** Dichotomizing continuous predictors in multiple regression: a bad idea. Stat Med. 2006;25(1):127-41.
35. Mazumdar M, Glassman JR**.** Categorizing a prognostic variable: review of methods, code for easy implementation and applications to decision-making about cancer treatments. Stat Med. 2000;19(1):113-32.
36. Hlatky MA, Greenland P, Arnett DK, Ballantyne CM, Criqui MH, Elkind MS, et al. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. Circulation. 2009;119(17):2408-16.
37. Rodseth RN, Lurati Buse GA, Bolliger D, Burkhart CS, Cuthbertson BH, Gibson SC, et al. The predictive ability of pre-operative B-type natriuretic peptide in vascular patients for major adverse cardiac events: an individual patient data meta-analysis. J Am Coll Cardiol. 2011;58(5):522-9.
38. Biccard BM, Lurati Buse GA, Burkhart C, Cuthbertson BH, Filipovic M, Gibson SC, et al. The influence of clinical risk factors on pre-operative B-type natriuretic peptide risk stratification of vascular surgical patients. Anaesthesia. 2012;67(1):55-9.
39. Rodseth RN, Biccard BM, Chu R, Lurati Buse GA, Thabane L, Bakhai A, et al. Postoperative B-type natriuretic peptide for prediction of major cardiac events in patients undergoing noncardiac surgery: systematic review and individual patient meta-analysis. Anesthesiology. 2013;119(2):270-83.

CO-AUTHORS' CONTRIBUTORSHIP – CHAPTER 2

Emmanuelle Duceppe's contribution is detailed in the Declaration of Academic Achievement.

The contributorship of other authors is detailed in the table below.

Authors' contributorship						
	Conception and Design	Data Acquisition	Analysis and Interpretation of Data	Drafting Manuscript	Critical Manuscript Revision	Approval of Final Manuscript
AP		X			X	X
MTVC	X	X			X	X
OB	X	X			X	X
GA		X			X	X
PAK	X		X		X	X
RR	X	X			X	X
BB	X	X			X	X
CKC		X			X	X
FKB			X		X	X
GG	X		X		X	X
RP		X			X	X
DIS	X	X			X	X
DHA	X		X		X	X
AK		X			X	X
CYW		X			X	X
WS	X	X			X	X
SS	X	X			X	X
AXG	X	X			X	X
SP	X		X		X	X
ENS		X			X	X
JLJ			X		X	X
MM			X		X	X
GLB		X			X	X
NLM					X	X
LZ		X			X	X
RS		X			X	X
GP			X		X	X
MW	X		X		X	X
RW	X				X	X
AL	X				X	X
SH		X			X	X
LT			X		X	X
SY	X		X		X	X
PJD	X	X	X		X	X

CHAPTER 3

ASSOCIATION BETWEEN HIGH-SENSITIVITY TROPONIN I AND MAJOR CARDIAC COMPLICATIONS AFTER NONCARDIAC SURGERY

Chapter 3 - Association between high-sensitivity troponin I and major cardiac complications after noncardiac surgery

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ABSTRACT

Background: Myocardial injury after noncardiac surgery (MINS) is common and associated with short- and long-term recurrent major vascular events. Diagnostic criteria for MINS using high-sensitivity troponin I (hsTnI) are unknown.

Objectives: The purpose of this study was to determine the prognostically important thresholds of hsTnI associated with major cardiac events at 30 days after noncardiac surgery.

Methods: We performed a prospective cohort study of adults undergoing in-patient noncardiac surgery who had postoperative serum samples collected up to postoperative day 3 and tested for hsTnI. We determined peak postoperative hsTnI thresholds independently associated with the occurrence of major cardiac events and death at 30 days (i.e., composite of all-cause mortality, and non-fatal myocardial infarction after 3 days postoperative, cardiac arrest, and congestive heart failure).

Results: Of 3947 included patients, 66 (1.7%) experienced major cardiac events at 30 days. Peak hsTnI values and associated incidence of major cardiac events and death were as follows: <60 ng/L, 1.0% (95% confidence interval [CI], 0.7-1.3); 60 ng/L to <700 ng/L, 8.6% (95% CI 5.6-13.0); and ≥700 ng/L, 27.3% (95% CI 16.4-41.9. Compared to peak hsTnI <60 ng/L, adjusted hazard ratios (aHR) hsTnI were 7.54 (95% CI% 4.27-13.32) for values of 60 ng/L to <700 ng/L and 26.87 (95% CI 13.27-54.41) for values ≥700 ng/L.

Conclusion: HsTnI elevation within the first 3 days after noncardiac surgery independently predicts major cardiac events and death at 30 days. A postoperative hsTnI ≥60 ng/L, with or without clinical signs or symptoms of myocardial ischemia, was associated with a >7-fold increase in the risk of subsequent major cardiac events and mortality at 30 days.

INTRODUCTION

In 2014, researchers defined Myocardial injury after noncardiac surgery (MINS) as myocardial injury that may or may not result in myocardial necrosis, is due to myocardial ischemia (i.e., secondary to supply-demand mismatch or thrombosis), has prognostic relevance, and occurs during or within 30 days after non-cardiac surgery.[1] MINS is common after in-hospital noncardiac surgery and significantly impacts short- and long-term prognosis.[2,3] Most MINS events are asymptomatic and require systematic cardiac troponin monitoring for detection in at-risk patients.[2,4]

The Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) study has demonstrated a strong association between troponin T (TnT) and high sensitivity troponin T (hsTnT) elevation and mortality after in-hospital noncardiac surgery.[1,2] Prognostically important thresholds for TnT and hsTnT have established diagnostic criteria for myocardial injury after noncardiac surgery (MINS).

Many centres worldwide use high-sensitivity troponin I (hsTnI). Informing the definition of MINS using hsTnI assay requires determining the association between hsTnI levels and major cardiac events and mortality after noncardiac surgery. We therefore addressed the association between hsTnI and major cardiac events while identifying thresholds that clinicians can use to identify important MINS events believed to be due to an ischemic etiology that impact patient prognosis at 30 days.

METHODS

We undertook an international, nested, prospective cohort study within the VISION study[2,5] and the VISION Biobank study. The methods for the VISION study have been described elsewhere.[2,5] The VISION Biobank was a VISION substudy that enrolled patients

from 8 centres in 3 countries (Canada, United Kingdom, and Hong Kong) who had preoperative and postoperative serum samples collected up to postoperative day 3, or discharge, and stored for biomarker analysis.

For this hsTnI sub-study, eligible patients were 45 years or older, underwent noncardiac surgery with at least one overnight stay after surgery, under regional or general anesthesia, and provided written consent to participate in VISION and the VISION Biobank studies. Patients also had at least one postoperative serum sample available in the VISION Biobank for hsTnI measurement.

Study personnel followed patients throughout their hospital stay, reviewed their charts, and collected baseline and surgical characteristics, medication, and outcomes. Patients discharged from hospital were contacted at 30 days to determine if outcomes had occurred. If patients or their next of kin reported an outcome, research personnel obtained the source documents, which were anonymized and sent to the VISION project office (McMaster University and Population Health Research Institute, Hamilton, Canada).

Patients had TnT or hsTnT (Roche Diagnostics, Mannheim, Germany) measured 6-12 hours after surgery and on the first 3 postoperative days as part of the main VISION study. TnT/hsTnT assays measured prospectively were available to clinicians who were encouraged to perform daily electrocardiograms (ECG) in patients with troponin elevations.

High-sensitivity Troponin I measurement

Patients participating in the VISION Biobank study had serum samples collected preoperatively and for the first 3 postoperative days, or up to discharge, whichever occurred first. Serum blood samples were centrifuged, divided in aliquots, refrigerated, and shipped to the

Clinical Research Laboratory and Biobank (Hamilton, ON, Canada) where they were stored in liquid nitrogen at -180°C for future testing. HsTnI assays (Abbott Laboratories, Abbott Park, IL, USA) were measured on thawed preoperative and postoperative samples on the Architect STAT platform.

Outcome

The primary outcome, the occurrence of a major cardiac events and death constituted a composite of all-cause mortality, non-fatal myocardial infarction after 3 days post-surgery, cardiac arrest, and congestive heart failure. Appendix 1 provides outcome definitions. To ensure a distinction between MINS occurring within the first 3 days detected using the hsTnI and subsequent myocardial infarctions we included only myocardial infarction after postoperative day 3.

As part of the main VISION studies, all troponin TnT/hsTnT elevation above the 99th percentile were adjudicated by clinicians with expertise in perioperative medicine to determine if there was a non-ischemic etiology (e.g., sepsis, rapid atrial fibrillation, pulmonary embolism, chronic troponin elevation) for the troponin elevation and if the patient's event met the definition for myocardial infarction (i.e., troponin elevation with including ischemic signs or symptoms). Because the hsTnIs were measured on stored biobank samples that were collected at the same time points at which the TnT/hsTnT were measured, we used the adjudication decision from the main VISION study for all patients who had both a TnT/hsTnT elevation and hsTnI elevation in the first 3 postoperative days. Patients who had a hsTnI elevation above the 99th percentile (26 ng/L) but did not have a concomitant TnT/hsTnT elevation in the main VISION study underwent adjudication using available source documents.

Statistical methods

All statistical analyses were performed according to a prespecified statistical analysis plan. We undertook a Cox proportional hazard model to determine the association between peak hsTnI measurements within the first 3 postoperative days and the primary composite outcome of major cardiac events and death within 30 days. The model included independent predictors of 30-day mortality identified in previous VISION analyses[2,5] (i.e., age, peripheral arterial disease, chronic obstructive pulmonary disease, urgent or emergent surgery, active cancer, and general surgery). Patients were excluded from these analyses if they experienced a primary outcome event before or on the day of the first hsTnI measurement or if they were missing data on a baseline clinical variable included in the multivariable model. Only hsTnI measurement prior to a primary outcome occurrence were considered in the peak postoperative hsTnI analyses.

For the primary analysis, we performed iterative Cox proportional hazards models to identify hsTnI thresholds associated with the primary outcome. The iterative process – a modification of the optimal cut-point approach described by Mazumdar[6] - facilitates identification of statistically significant optimal troponin thresholds, which correspond to important changes in the risk of the primary outcome. We explored the following hsTnI thresholds: from 5 to 100 ng/L by increments of 5 ng/L (except used 26 ng/L instead of 25 ng/L), 100 to 200 ng/L by increments of 10 ng/L, and 200 to 1000 ng/L by increments of 100 ng/L. A threshold was considered important if it had a corresponding adjusted hazard ratio (aHR) ≥ 3, a baseline incidence of primary outcome $\geq 3\%$, and p-value <0.01.[2] These requirements for a threshold to be considered significant were used in other VISION studies with a similar design[1,2] and were determined by feedback from international perioperative researchers.[2]

For patients with peak postoperative hsTnI values less than the lowest significant postoperative threshold determined in the primary analysis, we explored if a change in hsTnI from preoperative to postoperative values predicted major cardiovascular complications. Finally, once important hsTnI thresholds were identified, we explored if the presence of ischemic symptoms or ECG changes impacted the association between hsTnI thresholds and 30-day major cardiac events and death. For these analyses, patients were excluded if they had a postoperative troponin elevation adjudicated believed to be due to a non-ischemic etiology. In these analyses, patients with a preoperative hsTnI value greater than or equal to the peak postoperative hsTnI were counted as not having a postoperative troponin elevation.

RESULTS

Table 1 presents the baseline and surgical characteristics of the 3953 patients who had postoperative samples available for hsTnI measurement. Half (50.2%; 1986/3953) of the participants were 65 years or older, 50.5% (1996/3953) were female, 13.8% (544/3953) had a past history of coronary artery disease, 17.5% (691/3953) diabetes, 4.9% (195/3953) peripheral arterial disease, and 3.4% (134/3953) a prior stroke. The most common surgeries were major orthopedic surgery (1428/3953; 36.1%), low risk surgeries (798/3953; 20.2%), and general surgery (677/3953; 17.1%). The incidence of the composite of major cardiac events and death at 30 days was 1.7% (66/3953); 10 patients had a myocardial infarction between days 4 and 30, 3 non-fatal cardiac arrest, 28 congestive heart failure, and 25 deaths.

The multivariable iterative Cox models identified two significant hsTnI thresholds: peak postoperative hsTnI values of <60 ng/L, 60 ng/L to <700 ng/L and ≥700 ng/L were associated with an incidence of major cardiac events and death of 1.0% (95% confidence interval [CI]),

8.6% (95% CI 5.6-13.0), and 27.3% (95% CI 16.4-41.9), respectively. Compared to patients with peak hsTnI <60 ng/L (reference group), hsTnI values 60 ng/L to <700 ng/L and ≥700 ng/L were associated with aHR of 7.54 (95% CI 4.27-13.32) and 26.87 (95% CI 13.27-54.41), respectively (Table 2). In patients with peak postoperative hsTnI <60 ng/L, a delta change of 5 ng/L was the best cut point identified that yielded an increase in risk, but it was below our prespecified HR of 3 (HR=1.22). Further, adding a 5 ng/L change from preoperative to postoperative hsTnI did not show model improvement in predicting 30-day major cardiac events and death in addition to postoperative thresholds only (p=0.63 on likelihood ratio test).

Of patients with a postoperative peak hsTnI ≥60 ng/L 15.2% experienced symptoms of cardiac ischemia (Appendix 2). Patients with a postoperative peak hsTnI ≥60 ng/L and no clinical features of ischemia (i.e., ischemic signs or symptoms, ECG changes, and/or cardiac imaging suggestive of new or presumed new ischemia) had a 6.1% incidence of the primary outcome, compared to 1.0% in patients with peak postoperative hsTnI <60 ng/L (aHR 5.60, 95% CI 2.67-11.72). Relative to patients with neither feature, patients with peak hsTnI ≥60 ng/L and clinical features of ischemia had a 16.1% incidence of 30-day major cardiac events and death (aHR 15.52, 95% CI 7.73-27.25) (Table 3).

Based on these results, we chose a peak postoperative hsTnI ≥60 ng/L in patients without evidence of non-ischemia etiology for troponin elevation, with or without clinical features of ischemia, as our diagnostic criteria for MINS. In the multivariable model, patients with MINS had an aHR of 8.99 (95% CI 5.30-15.26; p<0.001) of major cardiac events or death at 30 days (Table 2). Patients with MINS had a mortality rate at 30 days of 4.2%; those without MINS of 0.4% (unadjusted odds ratio 10.65, 95% CI 4.73-23.96) (Appendix 3).

DISCUSSION

Postoperative peak hsTnI levels measured in the first 3 days after noncardiac surgery proved independently association with the 30-day occurrence of major cardiac events and death. Postoperative hsTnI levels ≥60 ng/L to <700 ng/L were associated with a 7-fold increase in the hazard of major cardiac events and death, and levels ≥700 ng/L with a 25-fold increase. A peak postoperative hsTnI ≥60 ng/L in patients without evidence of non-ischemia etiology for troponin elevation, with or without clinical features of ischemia, was independently associated with the primary outcome. Therefore, we propose diagnostic criteria for MINS of a peak postoperative hsTnI ≥60 ng/L in patients without evidence of non-ischemia etiology for troponin elevation, with or without clinical features of ischemia. Consistent with previous VISION studies[1,5], most (84.8%) patients with MINS were asymptomatic.

Studies using TnT, TnI, and hsTnT have consistently demonstrated the prognostic importance of early postoperative troponin elevation after noncardiac surgery.[2,3,5,7,8] The VISION studies have, in large representative cohorts of patients undergoing noncardiac surgery, confirmed the independent association between TnT[1,5] and hsTnT[2] and 30-day mortality, and identified thresholds to define MINS using these biomarkers.

Although TnT and troponin I (TnI) are two subunits of troponin found in cardiomyocytes that are released at the same time when myocardial injury occurs, their levels cannot be directly correlated when measured by immunoassays. Analytical methods used to measure troponin levels differ between manufacturers. Troponin immunoassays utilize various cardiac specific mono- or polyclonal antibodies against different parts of the TnT or TnI subunit, resulting in tests of varying sensitivities and reference ranges.[9] For this reason, each assay must undergo testing to determine thresholds for use in the clinical setting.

Our study is the largest cohort to evaluate hsTnI developed by Abbott Laboratories in noncardiac surgery patients. Yang et al.[10] measured hsTnI levels (Abbott Laboratories) for 3 days postoperatively in 175 patients, 45 years or older, admitted to a surgical intensive care unit (ICU) to determine the association with 30-day major adverse cardiac events (MACE) (i.e., composite of death, non-fatal cardiac arrest, myocardial infarction, and acute decompensated heart failure). They used receiver operating characteristic (ROC) curves in a multivariable model combining peak postoperative hsTnI adjusted for the Revised Cardiac Risk Index[11] to determine hsTnI optimal cutpoint (dichotomized). The ROC curve analyses found a hsTnI value of 53.0 ng/L as the optimal cut-off for prediction of 30-day MACE. The two cutpoints (53.0 and 60 ng/L) proved remarkably close.

A substudy of the OPTIMISE trial[12], which randomized patients to intraoperative hemodynamic therapy or standard of care, also measured postoperative hsTnI (Abbott Diagnostics) at 24h and 72h in 288 high-risk patients age 50 years or older undergoing major gastrointestinal surgery.[13] High risk was defined as age ≥65 years, non-elective surgery, acute or chronic renal impairment, diabetes mellitus, or presence of a risk factor for cardiac or respiratory disease. In the standard of care group, 47.6% of patients had a postoperative hsTnI elevation above the manufacturer's 99th percentile (26 ng/L). In multivariable analysis, they did not find an association between peak hsTnI concentration with the composite outcome of death or MACE at 30 days (odds ratio 1.09, 95% CI, 0.90–1.31).[13] Investigators failed to undertake an analysis to identify prognostically significant thresholds were undertaken.

Study limitations

Our study's limitations include limited statistical power to detect important thresholds due to a low primary outcome event rate. In the overall VISION study, the incidence of 30-day

mortality was 1.8% compared to 0.6% in our sub-study.[14] The lower event rate may be explained by the biobank design that required patients to have preoperative samples collected, limiting the enrolled of urgent and emergent surgeries; some patients likely went to the operating room before research staff could obtain informed consent for participation. Urgent and emergent surgeries are associated with higher mortality than elective surgeries.[2] Our biobank study included 3.7% urgent or emergent surgeries compared to 10.5% in the overall VISION cohort.[14]

The incidence of MINS was also lower in our study (6.1%) compared to the hsTnT VISION study (17.9%).[2] This may be due to limitations in statistical power rather than a true lower MINS incidence. The hsTnT VISION (21,819 patients; 310 events) identified five significant thresholds (hsTnT 5 ng/L, 14 ng/L, 20 ng/L, 65 ng/L, and 1000 ng/L) using the same iterative methods, whereas in our cohort (3953 patients; 66 events) we identified two thresholds (hsTnI 60 ng/L and 700 ng/L). The incidence of MINS in patients who had hsTnT levels above one of the two higher hsTnT thresholds (i.e., 65 ng/L and 1000 ng/L) was 5.3%, similar to our 6.1% MINS incidence using hsTnI. This suggests that there may be prognostically significant hsTnI thresholds below 60 ng/L that were not identified in our iterative analysis due to limited statistical power.

Another limitation was that, since they were measured on biobank samples after follow-up was completed, clinicians were not aware of the hsTnI results. Since ECGs were not mandated in every patient but only in patients with nT/hsTnT elevation, it is possible that some patients had a hsTnI elevation without TnT/hsTnT elevation and did not have an ECG ordered. Moreover, some ischemic clinical features may have been missed. Only 14 patients with hsTnI elevation above the 99th percentile, however, did not have any other source documents available for adjudication.

CONCLUSION

MINS is common and associated with poor prognosis. As the majority are asymptomatic and would otherwise likely go undetected, detection of MINS in at-risk patients requires systematic troponin monitoring in the first days following surgery. Many centres worldwide have moved to high-sensitivity assays, including hsTnI. In patient who underwent in-hospital noncardiac surgery, a postoperative hsTnI ≥60 ng/L, with or without clinical signs or symptoms of myocardial ischemia is associated with a 10% incidence and 9-fold increased risk of subsequent major cardiac events and mortality at 30 days. Clinicians should consider using this threshold to define MINS when using Abbott hsTnI.

REFERENCES – CHAPTER 3

1. Botto F, Alonso-Coello P, Chan MT, et al. 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.

2. Devereaux PJ, Biccard BM, Sigamani A, et al. Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. Jama 2017;317:1642-51.

3. Puelacher C, Lurati Buse G, Seeberger D, et al. Perioperative Myocardial Injury After Noncardiac Surgery: Incidence, Mortality, and Characterization. Circulation 2018;137:1221-32.

4. Duceppe E, Parlow J, MacDonald P, et al. Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery. The Canadian journal of cardiology 2017;33:17-32.

5. Devereaux PJ, Chan MT, Alonso-Coello P, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. Jama 2012;307:2295-304.

6. Mazumdar M, Smith A, Bacik J. Methods for categorizing a prognostic variable in a multivariable setting. Statistics in medicine 2003;22:559-71.

7. Levy M, Heels-Ansdell D, Hiralal R, et al. 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.

8. Smilowitz NR, Redel-Traub G, Hausvater A, et al. Myocardial Injury After Noncardiac Surgery: A Systematic Review and Meta-Analysis. Cardiol Rev 2019;27:267-73.

9. Maynard SJ, Menown IBA, Adgey AAJ. Troponin T or troponin I as cardiac markers in ischaemic heart disease. Heart (British Cardiac Society) 2000;83:371.

10. Hyun Suk Y, M.D, Mina H, et al. Prognostic Role of High-sensitivity Cardiac Troponin I and Soluble Suppression of Tumorigenicity-2 in Surgical Intensive Care Unit Patients Undergoing Non-cardiac Surgery. Ann Lab Med 2018;38:204-11.

11. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999;100:1043-9.

12. Pearse RM, Harrison DA, MacDonald N, et al. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. Jama 2014;311:2181-90.

13. Gillies MA, Shah AS, Mullenheim J, et al. Perioperative myocardial injury in patients receiving cardiac output-guided haemodynamic therapy: a substudy of the OPTIMISE Trial. British journal of anaesthesia 2015;115:227-33.

14. Association between complications and death within 30 days after noncardiac surgery. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2019;191:E830-e7.

Table 1 – Baseline characteristics and type of surgery for all participants, and participants with and without MINS

	All N= 3953	**No MINS N=3710**	**MINS N=243**	**p-value***
Age, y				<0.001
45-64	1967 (49.8)	1890 (50.9)	77 (31.7)	
65-74	1197 (30.3)	1126 (30.4)	71 (29.2)	
≥75	789 (20.0)	694 (18.7)	95 (39.1)	
Women	1996 (50.5)	1882 (50.7)	114 (46.9)	0.261
History of				
Diabetes†	691 (17.5)	633 (17.1)	58 (23.9)	0.009
Hypertension‡	2106 (53.3)	1937 (52.2)	169 (69.5)	<0.001
Congestive heart failure‡	90 (2.3)	81 (2.2)	9 (3.7)	0.121
Coronary artery disease†	544 (13.8)	472 (12.7)	72 (29.6)	<0.001
Previous coronary revascularization§	231 (5.8)	198 (5.3)	33 (13.6)	<0.001
Peripheral artery disease	195 (4.9)	175 (4.7)	20 (8.2)	0.021
Stroke	134 (3.4)	119 (3.2)	15 (6.2)	0.025
Chronic obstructive pulmonary disease	326 (8.2)	301 (8.1)	25 (10.3)	0.229
Active cancer	1106 (28.0)	1020 (27.5)	86 (35.4)	0.010
Pre-operative estimated glomerular filtration rate, mL/mi/1.73m^2 ¶				<0.001
<30 or on dialysis at baseline	78 (2.0)	69 (1.9)	9 (3.8)	
30-44	184 (4.8)	153 (4.3)	31 (13.1)	
45-59	430 (11.3)	392 (11.0)	38 (16.1)	
≥ 60	3121 (81.9)	2963 (82.8)	158 (66.9)	
Type of surgery**				
Vascular	171 (4.3)	152 (4.1)	19 (7.8)	0.013
General	677 (17.1)	628 (16.9)	49 (20.2)	0.189
Thoracic	180 (4.6)	160 (4.3)	20 (8.2)	0.010
Major urology or gynecology	519 (13.1)	486 (13.1)	33 (13.6)	0.844

Major orthopedic Major neurosurgery Low risk surgery	1428 (36.1) 223 (5.6) 798 (20.2)	1342 (36.2) 206 (5.6) 776 (20.9)	86 (35.4) 17 (7.0) 22 (9.1)	0.836 0.317 <0.001
Urgent or emergent surgery	148 (3.7)	139 (3.7)	9 (3.7)	1.000

Abbreviations: MINS = myocardial injury after noncardiac surgery
* Students' t-test for continuous variables, Fisher's Exact test for binary variables, and chi-squared test for categorical variables with more than 2 categories, for comparison between patients with and without MINS. † 3 missing. ‡ 2 missing. § 4 missing. ¶ 140 missing. ** Some patients had more than one type of surgery.

Table 2. Peak postoperative hsTnI thresholds associated with 30-day major cardiac events and death and thresholds to define MINS

hsTnI Thresholds (ng/L)	Number of Participants N (%)	Number of participants with the primary outcome No (%)	Adjusted Hazard Ratio (95% CI)
Thresholds			
<60	3682 (93.3)	35 (1.0)	1.00 (reference)
60 to <700	221 (5.6)	19 (8.6)	7.54 (4.27-13.32)
≥700	44 (1.1)	12 (27.3)	26.87 (13.27-54.41)
MINS threshold			
<60	3688 (93.9)	37 (1.0)	1.00 (reference)
≥60	240 (6.1)	24 (10.0)	8.99 (5.30-15.26)

Abbreviations: CI = confidence interval; hsTnI = high-sensitivity troponin I; MINS = myocardial injury after noncardiac surgery.

A total of 3947 patients with at least one postoperative Abbott hsTnI were included in this analysis. Patients with the primary outcome on day of surgery were excluded from this analysis. The Cox proportional hazards model included the following additional variables: age, history of peripheral vascular disease, history of chronic obstructive pulmonary disease, urgent or emergent surgery, active cancer, and general surgery. Postoperative hsTnI measurements during the first 3 postoperative days were assessed in these analyses.

Table 3. Ischemic clinical features of participants with and without MINS

	Incidence of Predictors N (%)	Primary Outcome N (%)	Adjusted Hazard Ratio (95% CI)
Postoperative non-elevated hsTnI	3688 (93.9)	37 (1.0)	1.00 (reference)
Postoperative elevated hsTnI with no ischemic clinical features	147 (3.7)	9 (6.1)	5.60 (2.67-11.72)
Postoperative elevated hsTnI with ischemic clinical features	93 (2.4)	15 (16.1)	14.52 (7.73-27.25)

Abbreviations: CI = confidence interval; ECG = electrocardiogram; hsTnI = high-sensitivity troponin I; MINS = myocardial injury after noncardiac surgery.
Postoperative elevated hsTnI was defined as hsTnI ≥60 ng/L. Clinical features of ischemic include ischemic symptoms, ECG changes, and/or cardiac imaging suggestive of new or presumed new ischemia. If postoperative electrocardiogram not done, we have assumed no electrocardiogram changes. The Cox proportional hazards model included the following additional variables: age, history of peripheral vascular disease, history of chronic obstructive pulmonary disease, urgent or emergent surgery, active cancer, and general surgery.

SUPPLEMENTAL MATERIAL

Appendix 1. Outcome definitions

Outcome	Definition
All-cause mortality	Death from any cause
Congestive heart failure	The definition of congestive heart failure required at least one of the following clinical signs (i.e., an elevated jugular venous pressure, respiratory rales/crackles, crepitations, or presence of S3) and at least one of the following radiographic findings (i.e., vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema).
Nonfatal cardiac arrest	Nonfatal cardiac arrest is defined as successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy, or cardiac defibrillation.
Myocardial infarction	The diagnosis of myocardial infarction requires any one of the following criterion: 1. Detection of a rise or fall of a cardiac biomarker (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following: A. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema); B. development of pathologic Q waves present in any two contiguous leads that are ≥ 30 milliseconds; C. new or presumed ECG changes indicative of ischemia (i.e., ST segment elevation [≥ 2 mm in leads V1, V2, or V3 OR ≥ 1 mm in the other leads], ST segment depression [≥ 1 mm], or symmetric inversion of T waves ≥ 1 mm) in at least two contiguous leads; D. new LBBB; or E. new cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging F. identification of intracoronary thrombus on angiography or autopsy 2. Cardiac death, with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

3. Percutaneous coronary intervention (PCI) related myocardial infarction is defined by elevation of a troponin value (>5 x 99th percentile URL) in patients with a normal baseline troponin value (≤99th percentile URL) or a rise of a troponin measurement >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia or (ii) new ischemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

4. Stent thrombosis associated with myocardial infarction when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one of value above the 99th percentile URL.

5. Coronary artery bypass grafting (CABG) related myocardial infarction is defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with a normal baseline troponin value (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

6. For patients who are believed to have suffered a myocardial infarction within 28 days of a MINS event or within 28 days of a prior myocardial infarction, the following criterion for myocardial infarction is required: Detection of a rise or fall of a cardiac biomarker (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) and 20% higher than the last troponin measurement related to the preceding event together with evidence of myocardial ischemia with at least one of the following:
A. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema);
B. development of pathologic Q waves present in any two contiguous leads that are > 30 milliseconds;
C. new or presumed new ECG changes indicative of ischemia (i.e., ST segment elevation [> 2 mm in leads V1, V2, or V3 OR > 1 mm in the other leads], ST segment depression [> 1 mm], or symmetric inversion of T waves > 1 mm) in at least two contiguous leads;
D. new LBBB; or
E. new cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging
F. identification of intracoronary thrombus on angiography or autopsy

Appendix 2. Clinical features of patients with MINS

	Prevalence of feature N=243
Ischemic symptoms	
chest discomfort	18 (7.4)
neck/jaw/arm discomfort	0 (0.0)
dyspnea	13 (5.3)
pulmonary edema	18 (7.4)
any of the above	37 (15.2)
New Q waves	5 (2.1)
ST elevation	4 (1.6)
ST depression	33 (13.6)
T wave inversion	49 (20.2)
New LBBB	0 (0.0)
New wall motion abnormality on echocardiogram	2 (0.8)
Presumed new wall motion abnormality on echocardiogram	23 (9.5)
New fixed deficit on nuclear imaging	1 (0.4)
Presumed new fixed deficit on nuclear imaging	3 (1.2)
Any of the above	95 (39.1)

hsTnI = high sensitivity troponin I; LBBB = Left bundle branch block; MINS = myocardial injury after noncardiac surgery.

Appendix 3. Association between MINS and components of the primary outcome

	Patients without MINS N=3688	**Patients with MINS N=240**	
	N (%)	**N (%)**	**Unadjusted OR (95% CI), versus no MINS**
Myocardial infarction after 3 days postoperative	9 (0.2)	1 (0.4)	1.71 (0.22-13.56)
Nonfatal cardiac arrest	1 (0.03)	2 (0.8)	-
Congestive heart failure	14 (0.4)	14 (5.8)	16.26 (7.66-34.51)
All-cause death	15 (0.4)	10 (4.2)	10.65 (4.73-23.96)

Abbreviations: CI = confidence interval; MINS = myocardial injury after noncardiac surgery; OR = odds ratio.

CO-AUTHORS' CONTRIBUTION – CHAPTER 3

Emmanuelle Duceppe's contribution is detailed in the Declaration of Academic Achievement.

The contributorship of other authors is detailed in the table below.

Co-authors' contributorship						
	Conception and Design	Data Acquisition	Analysis and Interpretation of Data	Drafting Manuscript	Critical Manuscript Revision*	Approval of Final Manuscript*
FKB	X	X	X			
MT		X				
RP		X				
MTVC		X				
SS		X				
PAK	X		X			
DS		X				
AXG		X				
DIS	X	X	X			
RS		X				
SP	X	X	X			
JV		X				
MW	X					
LT	X					
GG	X					
PJD	X	X	X			

* The co-authors have reviewed the abstract for submission to an international conference, but not the manuscript yet. The manuscript will be sent to all authors for critical revision and final approval prior to submission to a peer-reviewed journal.

CHAPTER 4

DESIGN OF A RANDOMIZED PLACEBO-CONTROLLED TRIAL TO ASSESS DABIGATRAN AND OMEPRAZOLE IN PATIENTS SUFFERING MYOCARDIAL INJURY AFTER NONCARDIAC SURGERY

CHAPTER 4 - Design of a randomized placebo-controlled trial to assess dabigatran and omeprazole in patients suffering myocardial injury after noncardiac surgery

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ABTRACT

Background: Worldwide approximately 200 million adults undergo major surgery annually, of whom 8 million are estimated to suffer a myocardial injury after noncardiac surgery (MINS). There is currently no trial data informing the management of MINS. Antithrombotic agents such as direct oral anticoagulants may prevent major vascular complications in patients with MINS.

Methods: The Management of myocardial injury After NoncArdiac surGEry (MANAGE) Trial is a large international blinded randomized controlled trial (RCT) of dabigatran versus placebo in patients who suffered MINS. We used a partial factorial design to also determine the impact of omeprazole versus placebo in reducing upper gastrointestinal bleeding and complications. Both study drugs were initiated in eligible patients within 35 days of suffering MINS and continued for a maximum of 2 years. The primary outcome is a composite of major vascular complications for the dabigatran trial and a composite of upper gastrointestinal complications for the omeprazole trial. We present the rationale and design of the trial and baseline characteristics of enrolled patients.

Results: The trial randomized 1754 patients between January 2013 and July 2017. Patients' mean age was 69.9 years, 51.1% were male, 14.3% had a history of peripheral artery disease, 6.6% had a history of stroke or transient ischemic attack, 12.9% had a prior myocardial infarction, and 26.0% had diabetes. The diagnosis of MINS was based on an isolated ischemic troponin elevation in 80.4% of participants.

Conclusions: MANAGE is the first RCT to evaluate a potential treatment of patients who suffered MINS.

Registration: Clinicaltrials.gov NCT01661101

INTRODUCTION

Myocardial injury represents the leading cause of death after major noncardiac surgery.[1,2] Annually, approximately 8% of the 200 million adults undergoing major surgery will suffer a myocardial injury globally.[3,4] Large international clinical studies have demonstrated that myocardial injury after noncardiac surgery (MINS) is independently associated with 30-day (adjusted hazard ratio [HR]>2.5)[1,2] and 1-year all-cause mortality (adjusted HR >1.5) (Table S1 in Supplemental Material).[5,6] The mechanisms underlying MINS remain unclear; however, there is laboratory, autopsy, imaging, and clinical evidence suggesting that coronary artery thrombosis may be one of the main pathophysiological mechanisms.[7-10]

Only observational studies currently inform the management of MINS.[11,12] Dabigatran, an oral direct thrombin inhibitor that has been tested in the perioperative setting for the prevention of venous thromboembolism, has potential to benefit patients who have MINS. Bleeding is the major limitation of anticoagulation therapy and the gastrointestinal system is a common site of bleeding after surgery.[13] Moreover, bleeding after noncardiac surgery has been shown to independently increase the risk of MINS and long-term mortality.[12-14] We hypothesize that, in patients who suffered MINS, dabigatran will reduce the occurrence of major vascular complications, and separately, omeprazole will reduce the occurrence of major upper gastrointestinal complications.

METHODS

Trial Design

The MANAGE Trial is an international randomized controlled trial (RCT) which enrolled 1754 patients who suffered MINS. Patients were randomized to dabigatran or matching

placebo and, using a partial factorial design for eligible patients, to omeprazole or matching placebo within 35 days of MINS. Patients, healthcare providers, investigators, data collectors, and outcome adjudicators were blinded to treatment allocation.

Trial Population

All adults ≥45 years of age who underwent in-hospital noncardiac surgery and had MINS were considered for eligibility. Patients met the criteria for MINS if, after undergoing noncardiac surgery, they either (1) had an elevated troponin or CK-MB with ischemic signs or symptoms, ischemic electrocardiographic changes, or new or presumed new abnormality on cardiac imaging (i.e., MINS that also met the Universal Definition of Myocardial Infarction[15]); or (2) had an isolated elevated troponin measurement without alternative explanation (e.g., pulmonary embolism) to ischemic myocardial injury (Table 1). Thresholds defining a perioperative troponin elevation are detailed in the Supplemental Material in Appendix 1. Other inclusion and exclusion criteria are reported in Table 1 and Table 2. Eligible patients were approached for informed consent as long as they could be randomized within 35 days of having MINS. Patients not receiving treatment with a proton pump inhibitor and not meeting any exclusion criteria specific to the omeprazole factorial component were also approached for informed consent and participation in the omeprazole trial.

Patient recruitment

Participating centres received approval from their National Regulatory Authorities and Research Ethics Committee/Institutional Review Board before patient recruitment was initiated. The trial recruited patients from 84 centres in 19 countries. Research personnel screened postoperative patients on surgical floors and in critical care units to identify eligible patients. Centres used multiple sources to identify patients, including screening of operative room lists

and asking anesthesia, surgery, and medicine services to notify the study personnel regarding all patients with MINS. Centres were encouraged to measure routine postoperative troponin measurements in adults undergoing noncardiac surgery, as per international guideline recommendation.[15-17] Research personnel approached all potentially eligible patients to obtain written informed consent.

Randomization

Randomization occurred as soon as an eligible patient provided written informed consent. Research personnel randomized patients through a 24-hour computerized randomization internet system, which ensured allocation concealment. Random allocation was performed using block randomization, stratified by centre; study personnel were blinded to the block size. We randomized patients 1:1 to dabigatran or placebo and, using a partial factorial design, 1:1 to omeprazole or placebo. Both randomizations occurred at the same time. Figure 1 summarizes the trial randomization flow diagram.

Trial Drug Administration

Dabigatran 110 mg orally twice daily or matching placebo was taken by all participants. Participants enrolled in the omeprazole factorial also took omeprazole 20 mg orally daily or corresponding placebo. Study drugs were resupplied to patients every 6 months and continued until completion of the trial follow-up. Patients took the study drugs for a minimum of 4 months and a maximum of 2 years.

Monitoring for and Approach to Potential Problems

Dabigatran is primarily excreted via the kidneys and is therefore contraindicated in patients with severe renal impairment. To ensure patient safety, creatinine was measured in all patients at 1 month, 6 months, 12 months, 18 months, and 24 months of follow-up. The

Cockroft-Gault formula was used to calculate the estimated creatinine clearance (eCrCl) at each time point; if the eCrCl at any stage during follow-up fell <30 ml/min, the dabigatran/placebo study drug was held. Measures were taken as clinically indicated to improve renal function, at the discretion of the local medical team. If the eCrCl improved (i.e., ≥30 ml/min) within 30 days, the patient was allowed to restart the dabigatran/placebo study drug. If the eCrCl remained <30 ml/min for >30 days, patients remained off dabigatran/placebo study drug permanently. Approaches to other issues such as bleeding, initiation of anticoagulation therapy, and requirement of another surgery occurring during the trial are detailed in the Supplemental Material in Appendix 2.

Other Management at the Discretion of the Attending Physician

All management was left to the discretion of the treating physician, including cardiovascular medications. We recommended that all patients with MINS take low-dose acetylsalicylic acid (ASA) and a statin.[11,12] Due to the increased risk of bleeding associated with dual antiplatelet therapy in combination with dabigatran[18], physicians were cautioned regarding initiating a thienopyridine (i.e., clopidogrel, ticlopidine, prasugrel) or ticagrelor in combination with ASA in patients taking dabigatran/placebo study drug. If an indication for dual antiplatelet therapy arose, the decision resided with the treating physician to continue or withhold the dabigatran/placebo study drug.

Patients participating in the omeprazole trial were instructed to interrupt their omeprazole/placebo study drug if they started taking clopidogrel due to potential interaction between omeprazole and clopidogrel; these patients were only allowed to resume their omeprazole/placebo study drug if they subsequently stopped taking clopidogrel.

Participant Follow-up

Participants were followed for a maximum of 2 years, with the last participant randomized followed for 4 months. Participants randomized while in hospital were followed throughout their hospital stay. Participants were contacted 1 week after randomization or hospital discharge (whichever occurred later) to ensure medication compliance. Participants were seen in follow-up at 1 month after randomization and subsequently every 6 months until completion of study follow-up. During office visits, study personnel (1) checked the participants' vital signs and weight, measured the participants' serum creatinine and calculated the eCrCl; (2) recorded concomitant medication and study drug compliance; and (3) assessed the occurrence of efficacy and safety outcomes and adverse events. Interim telephone follow-up visits occurred at 3, 9, 15, and 21 months between office visits to assess for the occurrence of efficacy and safety outcomes, adverse events and study drug compliance. All participants were followed for outcome occurrence until the trial was completed, even if study drug was discontinued.

Data Management

Study personnel at participating centres captured data on Case Report Forms (CRFs) and submitted centrally through a secure computerized database (i.e., iDataFax) via the internet. Patients were identified using a unique numeric code and all patient data was anonymized to ensure patient confidentiality. Data validity checks were preprogrammed in the database and were monitored by data management assistants from the Project Office through multi-level data validation of CRFs.

Trial Outcomes

Dabigatran trial

The primary efficacy outcome for the dabigatran trial is the occurrence of a major vascular complications (i.e., a composite of vascular mortality and any of the following nonfatal events: myocardial infarction, non-hemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic venous thromboembolism [i.e., symptomatic pulmonary embolism or symptomatic proximal deep venous thrombosis]). The primary safety outcome is a composite of life-threatening, major, and critical organ bleeding (i.e., intracranial, intraocular, intraspinal, pericardial, retroperitoneal). Secondary efficacy and safety outcomes for the dabigatran trial are listed in Appendix 3.

Omeprazole trial

The primary efficacy outcome for the omeprazole trial is the occurrence of a major upper gastrointestinal complications (i.e., a composite of overt gastroduodenal bleeding, overt upper gastrointestinal bleeding of unknown origin, or upper gastrointestinal perforation). Secondary outcomes are listed in Appendix 3. The safety outcomes are Clostridium difficile-associated diarrhea, diarrhea, community-acquired pneumonia, and fracture.

Appendix 4 provides definitions for all outcomes.

Outcome Adjudication

Physicians with expertise in the perioperative outcomes, who are blinded to treatment allocation, are adjudicating the trial's outcomes. A list of adjudicated outcomes can be found in Appendix 3. Adjudicator's decisions will be used for the all statistical analyses.

STATISTICAL CONSIDERATIONS

Sample Size

The trial initially planned to recruit 3200 patients followed for a mean of 12 months, with a primary efficacy composite outcome of vascular mortality, nonfatal myocardial infarction, nonfatal stroke, nonfatal peripheral arterial thrombosis, and nonfatal symptomatic pulmonary embolism. Recruitment was slower than anticipated, due to delays in regulatory approvals and some hospitals not being able to implement routine troponin measurement following noncardiac surgery. Funding for the trial was curtailed because of the slowness in recruitment, which allowed only for enrolment of 1750 patients. We also broadened the primary outcome to include major arterial and venous vascular events based on the results of the recent COMPASS trial with rivaroxaban in patients with stable vascular disease.[19,20] These changes were made without knowledge of the trial's unblinded results.

We assumed a control event rate of 20% and that dabigatran would result in a HR of 0.65 for the primary efficacy outcome (i.e., composite of vascular mortality, nonfatal myocardial infarction, nonfatal non-hemorrhagic stroke, nonfatal peripheral arterial thrombosis, nonfatal amputation, and nonfatal symptomatic venous thromboembolism), which would provide 90% power (2-sided $\alpha = 0.05$). Even considering control event rates of 18% and 15%, we would still have a power of 87% and 80% to detect a difference, respectively. Our sample size calculation also took into account that up to 15% patients in the dabigatran arm would discontinue their dabigatran and up to 3% of participants in the control group would start an anticoagulant during the trial.

We expected that a third of patients in the dabigatran trial would be eligible for the omeprazole trial. We therefore anticipated to include 600 patients in the omeprazole partial factorial component of the MANAGE Trial. Based on our VISION Study[21] cohort data (unpublished data), we anticipated a 1-year incidence of major upper gastrointestinal

complications (i.e., a composite of overt gastroduodenal bleeding, overt upper gastrointestinal bleeding of unknown origin, or upper gastrointestinal perforation) of 10%. Assuming a HR of 0.30 with omeprazole, as demonstrated in the COGENT Trial[22], for reduction of the primary efficacy outcome of major gastrointestinal complications, a 15% omeprazole discontinuation rate in the omeprazole group and a 15% starting rate of a proton pump inhibitor in the control group, we estimated 81% power to detect a difference (2-sided $\alpha = 0.05$).

Data Analysis

Patients will be analyzed in the treatment group they were allocated to, according to the intention-to-treat principle. Patients allocated to the dabigatran study drug will be compared to patients allocated to placebo dabigatran, and patients allocated to omeprazole study drug will be compared to patients allocated to placebo omeprazole.

Main Analysis

Time to the first occurrence of any one of the components of the primary composite outcome will be presented using the Kaplan-Meier estimator. Occurrence rate of the primary composite outcome will be compared between groups using the log-rank test. We will use Cox-proportional hazard models to estimate the effect of dabigatran, and omeprazole separately, on the HR between groups for the primary and secondary outcomes. We will also undertake a Cox proportional hazard model for both study drugs separately, with stratification according to whether patients received the other study drug. We will calculate 95% confidence intervals (CI) for the HRs and associated p-values. Statistically significant difference will be claimed if the 2-sided p-value is less than α 0.05. Any patients lost to follow-up will be censored at the time they were lost to follow-up.

For the dabigatran primary outcome analysis, we will explore if any of the following baseline variables are significant predictors of overall primary outcome rate using Cox proportional hazards models: (1) MINS criteria A (myocardial infarction) or B (isolated ischemic troponin elevation); (2) recent high-risk coronary artery disease; (3) history of stroke; (4) history of pulmonary embolism; and (5) history of diabetes. If any of these variables is shown to be a significant predictor of the primary outcome and has a HR >2.0, it will be included as a covariate in the final Cox proportional hazards model. We will evaluate for the possibility of synergism or antagonism between the two study drugs by formally testing the interaction term in a Cox model.

Each individual secondary and safety outcome will be analyzed using the same approach outlined for the primary outcome. For all non-fatal secondary outcomes, we will also perform competing-risk analyses.

Subgroup Analyses

The following subgroup analyses will be performed: (1) randomization within 5 days after suffering MINS and while in hospital, versus randomization >5 days after suffering MINS or after hospital discharge; we hypothesized a larger treatment effect in patients who were randomized within 5 days after suffering MINS and while they were still in-hospital, (2) MINS diagnosis criteria A (i.e. elevated cardiac biomarker meeting the Universal Definition of Myocardial Infarction[15]) versus criteria B (i.e. MINS diagnosis based upon an isolated ischemic troponin elevation without an alternative diagnosis); we hypothesized a larger treatment effect in patients who met criteria A, (3) history of peripheral vascular disease versus no history of peripheral vascular disease; we hypothesized a larger treatment effect in patients with a history of peripheral vascular disease, (4) patients on dual antiplatelet therapy at the time of

randomization; we hypothesized a smaller treatment effect in patients treated with dual antiplatelet therapy.

For all subgroup analyses, we will use Cox proportional hazards models for the primary composite outcome (i.e., major vascular complication), and we will incorporate terms for dabigatran treatment, omeprazole treatment, subgroup of interest, and a study drug by subgroup interaction term. We will infer a subgroup effect if the interaction term of treatment and subgroup is statistically significant at a 2-sided p-value less than α 0.05. The power for the subgroup analyses is, however, attenuated by the reduction in our sample size.

Interim Analyses

Three interim efficacy analyses based on the primary outcome were planned when 25%, 50% and 75% of the patients had been followed on average for 1 year. The Data Monitoring Committee (DMC) employed the modified Haybittle-Peto rule of 4 standard deviations (SDs) for the first and second interim analyses ($\alpha = 0.0001$) and 3 SDs for the third interim analysis ($\alpha = 0.00047$).[23,24] These predefined boundaries had to be exceeded in at least 2 consecutive analyses, 3 or more months apart for a finding of 1 or both active treatments to be considered significant. Given the infrequent interim analyses and their extremely low α levels, the α level for the final analysis will remain at the conventional $\alpha = 0.05$.

The DMC monitored for adverse effects of dabigatran on life-threatening or major bleeding, or omeprazole on major vascular complications. A 3 SDs excess in the first half and a 2.6 SDs excess in the second half of the trial in these analyses would have prompted deliberations about stopping for harm. The first interim analyses was performed when 25% of the patients were enrolled based on the initial 3200 patients sample size. The second (i.e., 50% followed for 1 year) and third (i.e., 75% patients followed for 1 year) interim analyses were performed as planned, but the percentages of patients were calculated using the revised 1750 patients sample size. The DMC did not recommend interruption of the trial following any of the interim analyses. The DMC had members with expertise in clinical trials, perioperative medicine, and biostatistics and were independent from the sponsor and competing interests.

TRIAL ORGANIZATION AND FUNDING

The MANAGE Trial is coordinated by the Population Health Research Institute (Hamilton, ON, Canada) which was primarily responsible for the organization of the trial, development of the random allocation list, central randomization, study database, ensuring data quality, ensuring site monitoring, coordination of the trial centres, conducting the trial, and data analyses. The trial structure also includes the following: Project Office Operations Committee, Project Office, National Leaders and National Coordinators, International Operations Committee, Steering Committee, Event Adjudication Committee, and Data Monitoring Committee. Appendix 5 lists the different trial groups and members.

The MANAGE Trial is an investigator-initiated trial. The academic not-for-profit Population Health Research Institute is the study Sponsor. The Population Health Research Institute obtained a grant from Boehringer Ingelheim to fund the MANAGE Trial and Boehringer Ingelheim provided the Population Health Research Institute with the dabigatran and matching placebo for all the MANAGE patients. The Population Health Research Institute obtained omeprazole and matching placebo from Liconsa. This trial is also supported by a Canadian Institutes of Health Research Foundation Grant.

CURRENT STATUS OF THE TRIAL

The MANAGE Trial recruited 1754 patients over 84 centres in 19 countries between January 2013 and July 2017; 556 participants were also enrolled in the omeprazole trial. Full list of countries, recruiting centres and site investigators are reported in Appendix 6. Table 3 presents baseline characteristics and type of surgery of the patients enrolled in the trial.

At enrollment, patients' mean age was 69.9 years (SD 10.5), 51.1% were male, 12.9% had a prior myocardial infarction, 14.3% had a history of peripheral artery disease, 6.6% had a history of stroke or transient ischemic attack, and 26.0% had diabetes. MINS criteria was met by having an isolated elevated troponin measurement without an alternative non-ischemic explanation in 80.4% of enrolled patients, and 19.6% had cardiac biomarker elevations with signs, symptoms or electrocardiography or cardiac imaging evidence of myocardial ischemia. Among included patients, 75.1% underwent elective surgery and 24.9% underwent urgent/emergent surgery before suffering their MINS and the three most frequent types of surgery were orthopedic, general and vascular surgery in 38.2%, 28.1% and 13.5% of patients, respectively.

DISCUSSION

Worldwide, 200 million adults undergo major surgery and 8% of these patients suffer MINS every year.[1,25] MINS is not only frequent but is also associated with poor short- and long-term prognosis.[1,5,6] Despite the magnitude of this problem, the current evidence to guide clinician's management of MINS is limited to observational studies.[11,12] There is promising evidence suggesting that an anticoagulant both in the acute and long-term setting may prevent major vascular complications in patients who have had MINS. Further, gastrointestinal bleeding is also associated with perioperative morbidity and a proton pump inhibitor could reduce the occurrence of major upper gastrointestinal complications in patients who suffered a MINS.

Dabigatran is an oral direct thrombin inhibitor which prevents thrombus formation by inhibiting conversion of fibrinogen to fibrin. Unlike warfarin, dabigatran does not require routine laboratory monitoring, does not interact with food and has very few drug interactions.

Warfarin has been shown to reduce myocardial infarction in the non-operative setting. In a meta-analysis of 10 trials including 7836 patients who suffered an acute coronary syndrome, warfarin (target international normalization ratio [INR] 2-3) and ASA, compared to ASA alone, was associated with a reduced risk of the composite of all-cause mortality, nonfatal myocardial infarction, and nonfatal thromboembolic stroke in the subsequent years after initiating therapy (851 events; odds ratio [OR], 0.73; 95% CI, 0.63-0.84).[26] However, the combination of warfarin and ASA also demonstrated an increased risk of major bleeding (146 events; OR, 2.32; 95% CI, 1.63-3.29) compared to ASA alone.[26] The RE-LY Trial randomized 18,113 patients with atrial fibrillation to dabigatran 150 mg BID, dabigatran 110 mg BID, or warfarin (target INR 2-3).[27] Dabigatran 110 mg BID – the dose used in the MANAGE Trial - was non-inferior to warfarin for the prevention of stroke or systemic embolism (relative risk [RR], 0.91; 95% CI, 0.74-1.11).[27] Patients randomized to dabigatran 110 mg BID compared to patients randomized to warfarin had a lower risk of major bleeding (RR, 0.80; 95% CI, 0.69-0.93), a lower risk of life-threatening bleeding (RR, 0.68; 95% CI, 0.55-0.83), a lower risk of intracranial bleeding (RR, 0.31; 95% CI, 0.20-0.47), and a similar risk of major gastrointestinal bleeding (RR, 1.10; 95% CI, 0.86-1.41).[27] In the perioperative setting, four blinded RCTs have assessed the impact of dabigatran compared to alternative anticoagulants for the postoperative prevention of venous thromboembolism.[28-31] In these trials, two different doses of dabigatran were evaluated in patients who had major orthopedic surgery (i.e., dabigatran 220 mg once daily [n=3,749 patients] and dabigatran 150 mg once daily [n=2,759 patients]). The result of these trials consistently showed no difference in the incidence of major postoperative bleeding between dabigatran 220 mg once daily compared to enoxaparin 40 mg subcutaneously once daily initiated 1 to 4 hours after orthopedic surgery. The event rate for major bleeding in patients taking dabigatran was 2.0% or less in all four trials.

The favorable risk-benefit ratio of dabigatran compared to warfarin therapy in a large international trial and the demonstrated safety of dabigatran in postoperative venous thromboembolism prophylaxis trials provides the rationale for selecting dabigatran as the anticoagulant to evaluate in the setting of MINS. Further, the availability of an antidote (i.e., idarucizumab) that can be used to rapidly reverse the anticoagulant effect of dabigatran in the case of bleeding also makes it a compelling option compared to other direct oral anticoagulants.

Several large trials have evaluated interventions in an attempt to prevent major perioperative vascular complications.[13,14,32,33] MANAGE differs from these prior trials in that it targets the management of the most common major perioperative vascular complication (i.e., MINS, a high-risk population) attempting to prevent subsequent major vascular complications. The MANAGE Trial is a large international randomized placebo-controlled trial of dabigatran, and separately omeprazole using a partial factorial design, evaluating the effect on major vascular complications and major upper gastrointestinal complications, respectively, in patients who suffered MINS and are followed for an average of 1 year. As the first randomized trial in patients with MINS, the MANAGE Trial will offer the first high-quality evidence to guide management of this common, high-risk condition.

FUNDING: Population Health Research Institute (PHRI) has obtained a grant from Boehringer Ingelheim to fund the MANAGE Trial and Boehringer Ingelheim has provided the PHRI with the dabigatran and matching placebo. PHRI obtained omeprazole and matching placebo from Liconsa. This trial is also supported in part by a Canadian Institutes of Health Research Foundation Grant held by Dr. PJ Devereaux.

REFERENCES – CHAPTER 4

1. Devereaux PJ, Biccard BM, Sigamani A, et al. Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. Jama 2017;317:1642-51.

2. Botto F, Alonso-Coello P, Chan MT, et al. 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.

3. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet (London, England) 2008;372:139-44.

4. Devereaux PJ, Sessler DI. Cardiac Complications in Patients Undergoing Major Noncardiac Surgery. The New England journal of medicine 2015;373:2258-69.

5. Puelacher C, Lurati Buse G, Seeberger D, et al. Perioperative Myocardial Injury After Noncardiac Surgery: Incidence, Mortality, and Characterization. Circulation 2017.

6. Levy M, Heels-Ansdell D, Hiralal R, et al. 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.

7. Dawood MM, Gutpa DK, Southern J, Walia A, Atkinson JB, Eagle KA. Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. International journal of cardiology 1996;57:37-44.

8. Cohen MC, Aretz TH. Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology 1999;8:133-9.

9. Ellis SG, Hertzer NR, Young JR, Brener S. Angiographic correlates of cardiac death and myocardial infarction complicating major nonthoracic vascular surgery. The American journal of cardiology 1996;77:1126-8.

10. Priebe HJ. Triggers of perioperative myocardial ischaemia and infarction. British journal of anaesthesia 2004;93:9-20.

11. Foucrier A, Rodseth R, Aissaoui M, et al. The long-term impact of early cardiovascular therapy intensification for postoperative troponin elevation after major vascular surgery. Anesthesia and analgesia 2014;119:1053-63.

12. Devereaux PJ, Xavier D, Pogue J, et al. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. Annals of internal medicine 2011;154:523-8.

13. Devereaux PJ, Mrkobrada M, Sessler DI, et al. Aspirin in patients undergoing noncardiac surgery. The New England journal of medicine 2014;370:1494-503.

14. Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet (London, England) 2008;371:1839-47.

15. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation 2012;126:2020-35.

16. Kristensen SD, Knuuti J, Saraste A, et al. 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 Anaesthesiology (ESA). European journal of anaesthesiology 2014;31:517-73.

17. Duceppe E, Parlow J, MacDonald P, et al. Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery. The Canadian journal of cardiology 2017;33:17-32.

18. Oldgren J, Budaj A, Granger CB, et al. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. European heart journal 2011;32:2781-9.

19. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. The New England journal of medicine 2017;377:1319-30.

20. Anand SS, Bosch J, Eikelboom JW, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet (London, England) 2017.

21. Devereaux PJ, Chan MT, Alonso-Coello P, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. Jama 2012;307:2295-304.

22. Wallentin L, Wilcox RG, Weaver WD, et al. Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomised controlled trial. Lancet (London, England) 2003;362:789-97.

23. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. The British journal of radiology 1971;44:793-7.

24. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. British journal of cancer 1976;34:585-612.

25. Weiser TG, Haynes AB, Molina G, et al. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. Lancet (London, England) 2015;385 Suppl 2:S11.

26. Andreotti F, Testa L, Biondi-Zoccai GG, Crea F. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25,307 patients. European heart journal 2006;27:519-26.

27. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. The New England journal of medicine 2009;361:1139-51.

28. Eriksson BI, Dahl OE, Rosencher N, et al. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. Journal of thrombosis and haemostasis : JTH 2007;5:2178-85.

29. Eriksson BI, Dahl OE, Rosencher N, et al. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. Lancet (London, England) 2007;370:949-56.

30. Ginsberg JS, Davidson BL, Comp PC, et al. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. The Journal of arthroplasty 2009;24:1-9.

31. Eriksson BI, Dahl OE, Huo MH, et al. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II*). A randomised, double-blind, non-inferiority trial. Thrombosis and haemostasis 2011;105:721-9.

32. Devereaux PJ, Sessler DI, Leslie K, et al. Clonidine in patients undergoing noncardiac surgery. The New England journal of medicine 2014;370:1504-13.

33. Myles PS, Leslie K, Chan MT, et al. The safety of addition of nitrous oxide to general anaesthesia in at-risk patients having major non-cardiac surgery (ENIGMA-II): a randomised, single-blind trial. Lancet (London, England) 2014;384:1446-54.

Table 1. Inclusion criteria of the MANAGE Trial

Patients were eligible if they:
1. had undergone noncardiac surgery
2. were ≥45 years of age
3. had suffered MINS based upon fulfilling one of the following criteria: A. Elevated troponin or CK-MB measurement with one or more of the following defining features i. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema); ii. development of pathologic Q waves present in any two contiguous leads that are ≥30 milliseconds; iii. electrocardiogram (ECG) changes indicative of ischemia (i.e., ST segment elevation [≥2 mm in leads V_1, V_2, or V_3 OR ≥1 mm in the other leads], ST segment depression [≥1 mm], OR symmetric inversion of T waves ≥1 mm) in at least two contiguous leads; iv. new LBBB; or v. new or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging; OR B. Elevated troponin measurement after surgery with no alternative explanation (e.g., pulmonary embolism, sepsis) to myocardial injury; AND
4. provided written informed consent to participate within 35 days of suffering their MINS.

LBBB = Left bundle branch block; MINS = Myocardial injury after noncardiac surgery.

Table 2. Exclusion criteria of the MANAGE Trial

Patients were excluded if they met any of the following criteria:
1. hypersensitivity or known allergy to dabigatran;
2. history of intracranial, intraocular, or spinal bleeding;
3. hemorrhagic disorder or bleeding diathesis
4. known hepatic impairment or liver disease expected to have an impact on survival;
5. condition that required therapeutic dose anticoagulation (e.g., prosthetic heart valve, venous thromboembolism, atrial fibrillation);
6. using or planned to initiate rifampicin, cyclosporine, itraconazole, tacrolimus, ketoconazole, or dronedarone;
7. women who were pregnant, breastfeeding, or of childbearing potential who refused to use a medically acceptable form of contraception throughout the study;
8. investigator considered the patient unreliable regarding requirement for study follow-up or study drug compliance; OR
9. previously enrolled in the MANAGE Trial.
Patients were also excluded if any of the following criteria persisted beyond 35 days of their suffering MINS:
1. the attending surgeon believed it was not safe to initiate therapeutic dose anticoagulation therapy;
2. the attending physician believed ASA, intermittent pneumatic compression, or elastic stockings were not sufficient for venous thromboembolism prophylaxis and that the patient required a prophylactic-dose anticoagulant;
3. the patient had an indwelling epidural or spinal catheter that could not be removed, or the first dose of dabigatran would occur within 4 hours of epidural catheter removal;
4. estimated glomerular filtration rate was <35 ml/min, as estimated by calculated creatinine clearance; OR
5. the patient was awaiting cardiac catheterization beyond 35 days after their suffering MINS.
Exclusion Criteria Specific to Patients in the Omeprazole Factorial Component of the Trial
We excluded patients meeting any of the following criteria:
1. hypersensitivity or known allergy to omeprazole;
2. requirement for a proton pump inhibitor, an H2-receptor antagonist, sucralfate, atazanavir, clopidogrel, or misoprostol;
3. esophageal or gastric variceal disease; OR
4. patient declined participation in the omeprazole arm of MANAGE.

ASA = acetylsalicylic acid; MINS = Myocardial injury after noncardiac surgery.

Table 3. Baseline characteristics prior to randomization (n=1754)

Age (years) - mean (SD)	69.9 (10.5)
Male sex - n (%)	896 (51.1)
Baseline medical history prior to randomization - n (%)	
Prior myocardial infarction	226 (12.9)
Current or prior history of peripheral arterial disease	251 (14.3)
History of stroke or transient ischemic attack	115 (6.6)
History of congestive heart failure	60 (3.4)
Diabetes treated with insulin or an oral hypoglycemic agent	456 (26.0)
Hypertension	1172 (66.8)
High cholesterol/on cholesterol lowering medication <1 month	993 (56.6)
Prior tobacco use	800 (45.6)
Chronic obstructive pulmonary disease	187 (10.7)
Recent/active cancer within last 6 months	220 (12.5)
Previous venous thromboembolism (DVT/PE)	42 (2.4)
History of Atrial fibrillation	51 (2.9)
Urgency surgery rating - n (%)	
Elective surgery	1318 (75.1)
Urgent/emergent surgery	436 (24.9)
Type of surgery prior to MINS event - n (%)	
Orthopedic	670 (38.2)
General	493 (28.1)
Vascular	236 (13.5)
Carotid	16 (0.9)
Thoracic	84 (4.8)
Spinal	56 (3.2)
Urological or gynecological	160 (9.1)
Low risk surgery	75 (4.3)
Recruitment by Region – n (%)	
North America	765 (43.6)
South America	94 (5.4)
Europe, Australia, Africa	627 (35.7)
Asia	268 (15.3)

DVT = deep vein thrombosis; PE = pulmonary embolism; SD = standard deviation.

SUPPLEMENTAL MATERIAL

Supplemental Table S1. Observational studies addressing the prognostic importance of myocardial injury after noncardiac surgery

Study	Type of study	Sample size	Population	Type of troponin	Follow-up	Findings
Devereaux 2017[7]	Prospective cohort	21,842 patients	Mixed noncardiac	hsTnT	30 day	30-day mortality: aHR 23.63 (95% CI, 10.32-54.09) for hsTnT 20-64 ng/L
Puelacher 2017[58]	Prospective cohort	2018 patients	Mixed noncardiac surgery	hsTnT	12 months	30-day mortality aHR 2.7 (95% CI, 1.5-4.8) 1-year mortality aHR 1.6 (95% CI, 1.2-2.2)
Reed 2017[72]	Retrospective cohort	12,882 patients	Vascular surgery	TnT	5 years	5-year mortality aHR 1.57 (95% CI, 1.07-2.31) for TnT 0.01-0.29 ng/mL
Botto 2014[8]	Prospective cohort	15,065 patients	Mixed noncardiac	TnT	30 day	30-day mortality: aOR 3.90 (95% CI 2.90-5.27) MINS Population Attributable Risk for Mortality = 34.0%
Van Waes 2013[73]	Prospective cohort	2232 patients	Mixed noncardiac surgery	TnI	30 day	30-day mortality aRR 2.4 (95% CI, 1.3-4.2) for TnI 0.07-0.59 ug/L
Redfern 2011[5]	Systematic review of observational studies	1873 patients (9 studies)	Vascular surgery	TnI and TnT	30 day	30-day mortality: OR 5.03 (95% CI, 2.88-8.79) I^2=*24.7%*
Levy 2011[3]	Systematic review of observational studies	3318 patients (14 studies)	Mixed noncardiac surgeries	TnI and TnT	12 months	12-month mortality: aOR 6.7 (95% CI, 4.1-10.9) I^2= *0%*

aHR = adjusted hazard ratio; aRR = adjusted relative risk; aOR = adjusted odds ratio; CI = confidence interval; hsTnT = high-sensitivity troponin T; MINS = myocardial injury after noncardiac surgery; OR = odds ratio; TnI = troponin I; TnT = troponin T.

APPENDIX 1: Thresholds defining a perioperative troponin elevation

Participating centres used various troponin assays, both non-high sensitive and high sensitive troponin T and I. The threshold for each troponin varied according to the type of troponin and to the centre. Whenever a large prospective cohort study had established a perioperative troponin threshold independently associated with mortality, sites were instructed to use that threshold[7,8]. If centres used a different troponin, we instructed these sites to follow their site's local laboratory threshold if the local site had undertaken internal validation work establishing the troponin threshold. Otherwise, we instructed sites to use either the 99th percentile or the 10% coefficient of variation, depending on the troponin assay and available literature. When literature was lacking on a specific troponin, we consulted with a biochemist expert in cardiac biomarkers to determine the troponin threshold based on manufacturer information.

APPENDIX 2: Approaches to potential issues Other than renal function

Bleeding was managed at the discretion of the attending physician, with the recommendation that dabigatran/placebo study drug be held in the context of severe or life-threatening bleeding. At trial initiation, the antidote to counteract the activity of dabigatran was not available; thus study personnel recommended centres treat bleeding according to local practice. During the trial's recruitment period, idarucizumab (Praxbind) was approved in several countries to reverse dabigatran's activity. Following the dabigatran antidote's approval and availability at centres, it could be used according to local practice in patients with bleeding to rapidly reverse the anticoagulating effect of dabigatran.
If a patient required another elective surgery, we recommended to hold dabigatran/placebo study drug for at least 24 to 48 hours and 3 to 5 days before surgery in patients with eCrCl ≥50 ml/min and <50 ml/min, respectively. In case of urgent or emergent surgery, it was suggested to weigh the risk of delaying surgery versus the potential bleeding risk; the decision regarding delaying surgery and using anticoagulant reversal agent was left at the discretion of the treating physician. For patients who required therapeutic anticoagulation during the course of the trial (e.g. patient with myocardial infarction), we recommended to start anticoagulation at least 12 hours after the last dose of dabigatran/placebo study drug or when the aPTT was <1.5 times the upper limit of normal.

APPENDIX 3: Outcomes and adjudication

Secondary individual efficacy outcomes for dabigatran trial: vascular mortality, all-cause mortality, myocardial infarction, cardiac revascularization procedure, non-hemorrhagic stroke, peripheral arterial thrombosis, amputation, symptomatic venous thromboembolism (i.e., symptomatic pulmonary embolism or symptomatic proximal deep venous thrombosis), and rehospitalization for vascular reasons.
Secondary individual safety outcomes for dabigatran trial: life-threatening bleeding, major bleeding, critical organ bleeding, intracranial bleeding, hemorrhagic stroke, significant lower gastrointestinal bleeding, non-significant lower gastrointestinal bleeding, minor bleeding, fracture, and dyspepsia.
Secondary efficacy outcomes for omeprazole trial: 1) upper gastrointestinal complication (i.e., composite of overt gastroduodenal bleeding, overt upper gastrointestinal bleeding of unknown

origin, symptomatic gastroduodenal ulcer, gastrointestinal pain with underlying multiple gastroduodenal erosions, or upper gastrointestinal perforation), 2) major vascular complication (i.e., a composite of vascular mortality, nonfatal myocardial infarction, nonfatal non-hemorrhagic stroke, nonfatal peripheral arterial thrombosis, nonfatal amputation, and nonfatal symptomatic venous thromboembolism [i.e., symptomatic pulmonary embolism or symptomatic proximal deep venous thrombosis]), 3) each of the following individual secondary outcomes: overt gastroduodenal bleeding, overt esophageal bleeding, overt upper gastrointestinal bleeding of unknown origin, symptomatic gastroduodenal ulcer, gastrointestinal pain with underlying multiple gastroduodenal erosions, upper gastrointestinal perforation, bleeding of assumed occult gastrointestinal origin with a documented drop in hemoglobin of ≥3.0 g/dL, dyspepsia, and mortality.

Adjudicated outcomes: death (vascular versus non-vascular), myocardial infarction, hemorrhagic and non-hemorrhagic stroke, peripheral arterial thrombosis, symptomatic pulmonary embolism, symptomatic deep venous thrombosis, life-threatening bleeding, major bleeding, minor bleeding, intracranial bleeding, significant lower gastrointestinal bleeding, overt gastroduodenal bleeding, overt upper gastrointestinal bleeding of unknown origin, symptomatic gastroduodenal ulcer, gastrointestinal pain with underlying multiple gastroduodenal erosions, or upper gastrointestinal perforation.

APPENDIX 4: Outcome definitions

Outcome	Definition
Subclassification of Death	Vascular death is defined as any death with a vascular cause and includes those deaths following a MI, cardiac arrest, stroke, cardiac revascularization procedure (i.e., PCI or CABG), PE, hemorrhage, or deaths due to an unknown cause. Non-vascular death is defined as any death due to a clearly documented non-vascular cause (e.g. trauma, infection, malignancy).
Myocardial Infarction	The diagnosis of MI requires any one of the following criterion: 1. Detection of a rise or fall of a cardiac biomarker (preferably troponin) with at least one value above the 99th percentile of the URL together with evidence of myocardial ischemia with at least one of the following: A. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema); B. development of pathologic Q waves present in any two contiguous leads that are ≥30 milliseconds; C. new or presumed ECG changes indicative of ischemia (i.e., ST segment elevation [≥2 mm in leads V_1, V_2, or V_3 OR ≥1 mm in the other leads], ST segment depression [≥1 mm], or symmetric inversion of T waves ≥1 mm) in at least two contiguous leads; D. new LBBB; or

	E. new cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging F. identification of intracoronary thrombus on angiography or autopsy 2. Cardiac death, with symptoms suggestive of myocardial ischemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased. 3. PCI related MI is defined by elevation of a troponin value (>5 x 99th percentile URL) in patients with a normal baseline troponin value (≤99th percentile URL) or a rise of a troponin measurement >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required. 4. Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one of value above the 99th percentile URL. 5. CABG related MI is defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with a normal baseline troponin value (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. 6. For patients who are believed to have suffered a MI within 28 days of the index MINS event or within 28 days of a prior MI, the following criterion for MI is required: Detection of a rise or fall of a cardiac biomarker (preferably troponin) with at least one value above the 99th percentile of the URL and 20% higher than the last troponin measurement related to the preceding event together with evidence of myocardial ischemia with at least one of the following: A. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema); B. development of pathologic Q waves present in any two contiguous leads that are ≥30 milliseconds; C. new or presumed new ECG changes indicative of ischemia (i.e., ST segment elevation [≥2 mm in leads V_1, V_2, or V_3 OR ≥1 mm in the other leads], ST segment

	depression [≥1 mm], or symmetric inversion of T waves ≥1 mm) in at least two contiguous leads; D. new LBBB; or E. new cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging F. identification of intracoronary thrombus on angiography or autopsy
Cardiac Revascularization Procedure	Cardiac revascularization procedures include PCI and CABG surgery.
Stroke	Stroke is defined as a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting more than 24 hours or leading to death. Stroke will be sub-classified into hemorrhagic and non-hemorrhagic stroke. Non-hemorrhagic stroke will sub-classified into ischemic, ischemic with secondary transformation, or stroke of uncertain classification. Hemorrhagic stroke will be sub-classified into primary intracerebral hemorrhage and primary subarachnoid hemorrhage. 1. Ischemic stroke: focal brain infarction caused by an arterial (or rarely venous) obstruction and as documented by CT/MRI that is normal or shows an infarct in the clinically expected area. 2. Secondary hemorrhagic transformation of ischemic stroke: hemorrhagic transformation of ischemic stroke may be symptomatic or asymptomatic. A. Symptomatic transformation of ischemic stroke is defined as a hematoma occupying 30% or more of the infarcted tissue associated with a significant neurologic deterioration (consistent with a decrease of 4 points in the NIHSS) compared to immediately before the worsening and an absence of an alternative explanation for deterioration. B. Asymptomatic transformation of ischemic stroke is defined as a hemorrhagic transformation not meeting the criteria for symptomatic transformation. 3. Undetermined stroke: definite stroke that does not meet the criteria for ischemic or hemorrhagic stroke because CT scan or MRI are not done and there are no autopsy data. Rarely it cannot be determined with confidence whether the stroke was ischemic vs. hemorrhagic, even after review of CT/MRI images (e.g., primary intracerebral hemorrhage

	vs. severe hemorrhagic transformation); these stroke events will be classified as undetermined. 4. Hemorrhagic stroke: hemorrhagic stroke requires neuroimaging or autopsy confirmation and includes two subcategories: primary intracerebral hemorrhage (intraparenchymal or intraventricular) and primary subarachnoid hemorrhage. Intracranial bleeding caused by head trauma, bleeding associated with tumors, hemorrhagic transformation of ischemic stroke and subdural/epidural hematomas are not considered as hemorrhagic strokes (but these will be counted separately as critical organ bleeding). Microbleeds are not considered intracranial hemorrhage. A. Primary intracerebral hemorrhage: These are symptomatic hemorrhagic strokes with CT/MRI or autopsy evidence of bleeding into the substance of the brain or ventricular spaces. Large or superficial intracerebral hemorrhages often are associated with minor amounts of subarachnoid hemorrhage, but these should be classified as intracerebral hemorrhages. Does not include secondary hemorrhage into cerebral infarct (i.e. hemorrhagic transformation which is defined separately), or intracerebral bleeding (i.e. contusions) due to trauma, or microbleeds detected by MRI. B. Primary subarachnoid hemorrhage: Typical clinical syndrome of sudden onset headache, with or without focal signs (subarachnoid hemorrhage may not have focal deficits), and CT or cerebrospinal fluid evidence of bleeding primarily into the subarachnoid space. Subarachnoid bleeding due to ruptured intracranial aneurysms and vascular malformation are counted as hemorrhagic strokes, but traumatic subarachnoid hemorrhage is not (but will be counted as critical organ bleeding).
Symptomatic Pulmonary Embolism	The diagnosis of symptomatic PE requires symptoms (e.g., dyspnea, pleuritic chest pain) and any one of the following: 1. A high probability ventilation/perfusion lung scan, 2. An intraluminal filling defect of segmental or larger artery on a helical CT scan, 3. An intraluminal filling defect on pulmonary angiography, or 4. A positive diagnostic test for DVT (e.g., positive compression ultrasound) and one of the following: A. non-diagnostic (i.e., low or intermediate probability) ventilation/perfusion lung scan, or

	B. non-diagnostic (i.e., subsegmental defects or technically inadequate study) helical CT scan
Symptomatic Proximal Deep Venous Thromboembolism of the Leg or Arm	The diagnosis of symptomatic proximal DVT requires: 1. Symptoms (e.g., leg pain). 2. Thrombosis involving the popliteal vein or more proximal veins for leg DVT and axillary or more proximal veins for arm DVT, 3. Evidence of vein thrombosis by any one of the following: A. A persistent intraluminal filling defect on contrast venography, B. Noncompressibility of one or more venous segments on B mode compression ultrasonography, or C. A clearly defined intraluminal filling defect on contrast enhanced CT
Amputation	Amputation is defined as an amputation procedure, or auto amputation subsequent to the initial surgery.
Peripheral Arterial Thrombosis	We will consider a peripheral arterial thrombosis to have occurred where there is clear evidence of abrupt occlusion of a peripheral artery (i.e., not a stroke, MI, or PE) consistent with either an acute local thrombotic event or a peripheral arterial embolism. To fulfill this definition we require at least one of the following objective findings of peripheral arterial thrombosis: 1. Surgical report indicating evidence of arterial thrombosis/ peripheral arterial embolism, 2. Pathological specimen demonstrating arterial thrombosis/ peripheral arterial embolism, 3. Imaging evidence consistent with arterial thrombosis/ peripheral arterial embolism, or 4. Autopsy reports documenting arterial thrombosis/ peripheral arterial embolism
Re-Hospitalization for Vascular Reasons	Re-hospitalization for vascular reasons is defined as re-hospitalization for MI, cardiac arrest, stroke, congestive heart failure, ischemic symptoms with ST or T wave changes on an ECG, cardiac arrhythmia, cardiac revascularization procedure, amputation, peripheral arterial thrombosis, DVT, PE, any vascular surgery, or bleeding.
Life-Threatening Bleeding	Life-threatening bleeding is bleeding that is fatal, or leads to: significant hypotension that requires inotrope or vasopressor therapy, urgent (within 24 hours) surgery (other than superficial vascular repair), or intracranial hemorrhage.

Major Bleeding	Major bleeding is defined as bleeding that is not specified under "life-threatening bleeding" above, and results in a drop in Hb ≥4.0 g/dL; the patient receiving a transfusion of ≥3 units of red blood cells within a 24 hour period; leads to one of the following interventions (i.e., embolization, superficial vascular repair, nasal packing); OR is intraspinal, intramuscular with compartment syndrome, retroperitoneal, pericardial, or intraocular (confirmed clinically or on imaging).
Critical Organ Bleeding	Bleeding that is intracranial, intraocular, intraspinal, pericardial, or retroperitoneal.
Minor Bleeding	Minor bleeding is any bleeding that does not fulfill the criteria for "life-threatening bleeding", "critical organ bleeding" or "major bleeding" as specified above.
Dyspepsia	Dyspepsia is a symptom reported by a patient in one or more of the following ways: 1. Indigestion (a pain or discomfort in the upper abdomen), 2. Heartburn (a burning feeling behind the breastbone), 3. Regurgitation (an acid taste coming up into the mouth from the stomach), or 4. Nausea (a feeling of sickness without being sick).
Overt Gastroduodenal Bleeding	The definition of overt gastroduodenal bleeding requires confirmation of bleeding, from a gastroduodenal lesion, by upper endoscopy or radiography.
Overt Esophageal Bleeding	The definition of overt esophageal bleeding requires confirmation of bleeding, from the esophagus, by upper endoscopy or radiography.
Overt Upper Gastrointestinal Bleeding of Unknown Origin	The definition of overt upper gastrointestinal bleeding of unknown origin requires confirmed of the bleeding by upper endoscopy or radiography without localization of the culprit lesion and a drop in Hb ≥3.0 g/dL.
Symptomatic Gastroduodenal Ulcer	The definition of symptomatic gastroduodenal ulcer requires confirmation of the ulcer on endoscopy or radiography and persistent pain of presumed gastrointestinal origin with a duration ≥3 days.

Gastrointestinal Pain with Underlying Multiple Gastroduodenal Erosions	The definition of gastrointestinal pain with underlying multiple gastroduodenal erosions requires confirmation of ≥5 gastroduodenal erosions on endoscopy and persistent pain of presumed gastrointestinal origin with a duration ≥3 days.
Upper Gastrointestinal Perforation	To fulfill the definition of upper gastrointestinal perforation a patient requires radiographic or surgical evidence of upper gastrointestinal perforation.
Bleeding Of Assumed Occult Gastrointestinal Origin with a Documented Drop in Hemoglobin of ≥3.0 g/dL	This diagnosis requires a documented drop in Hb of ≥3.0 g/dL and the investigator believes the bleed was due to an occult gastrointestinal source.
Significant Lower Gastrointestinal Bleeding	Hematochezia or melena (if the latter is used no cause of bleeding should be found on upper gastrointestinal endoscopy) WITH evidence of hemodynamic instability requiring fluid resuscitation AND/OR evidence of blood loss (>2.0g/dL Hb drop or need for blood transfusion).
Non-significant Lower Gastrointestinal Bleeding	Hematochezia or melena (if the latter is used no cause of bleeding should be found on upper gastrointestinal endoscopy) WITHOUT evidence of hemodynamic instability OR evidence of blood loss (>2.0g/dL Hb drop or need for blood transfusion).
Clostridium Difficile Associated Diarrhea	This outcome requires laboratory documentation of Clostridium-difficile and diarrhea.
Diarrhea	This outcome is defined by new onset >3 loose bowel movements per day.
Community-Acquired Pneumonia	The diagnosis of community acquired pneumonia requires that the pneumonia was obtained in the community and not in a nursing home or hospital and any one of the following: 1. Rales or dullness to percussion on physical examinations of chest AND any of the following: A. New onset of purulent sputum or change in character of sputum B. Isolation of organism from blood culture C. Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy 2. Chest radiography showing new or progressive infiltrate, consolidation, cavitation, or pleural effusion AND any of the following:

	A. New onset of purulent sputum or change in character of sputum B. Isolation of organism from blood culture C. Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy D. Isolation of virus or detection of viral antigen in respiratory secretions E. Diagnostic single antibody titer (IgM) or fourfold increase in paired serum samples (IgG) for pathogen F. Histopathologic evidence of pneumonia
Fracture	The diagnosis of a fracture requires a physician diagnosis of a bone fracture.

CABG = coronary artery bypass graft ; CT = computed tomography; DVT = deep vein thrombosis; ECG = electrocardiogram; Hb = hemoglobin; LBBB = left bundle branch block; MI = myocardial infarction; MINS = myocardial injury after noncardiac surgery; MRI = magnetic resonance imaging; NIHSS = National Institutes of Health Stroke Scale; PCI = percutaneous coronary intervention; PE = pulmonary embolism; URL = upper reference limit; VTE = venous thromboembolism.

APPENDIX 5: Trial Groups

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Data Monitoring Committee (DMC): G. Wyse (Chairperson), D. Cheng, D. Johnstone, G. Wells.

APPENDIX 6. Countries and participating centres (recruitment in brackets)
CANADA (745) – *Juravinski Hospital and Cancer Centre (255):* V. Tandon, P. Joseph, A. Patel, D. Leong, K. Gregus, K. Lawrence, L. Doharris; *St. Joseph's Healthcare Hamilton (174):* J.D. Neary, D. Conen, J. Cheung, J. Douketis, D. Wright, S. Wikkerink, W. Dechert; *Hamilton General Hospital (168):* P. Magloire, M. Panju, K. Azzam, T. Rapanos, T. Van Helder, A. Shroff, J. Hare; *Health Sciences Centre (53):* S. Srinathan; *Kingston General Hospital (50):* J. Erb; *CHUM (19):* E. Duceppe; *London Health Sciences (15):* M. Mrkobrada; *University of Alberta Hospital (6):* M. Jacka; *Victoria Hospital (2):* A. Garg; *Montreal General Hospital (2):* D. Hornstein; *Grey Nuns Community Hospital (1):* G.B. Winkelaar; **INDIA (259)** – *Rahate Surgical Hospital (86):* R.P. Vithalrao; *Christian Medical College, Ludhiana (78):* N.K. Chowdary; *Surat Institute of Digestive Sciences (50):* K. Bhatt; *Amrita Institute of Medical Sciences and Research Institute (15):* A.B. Pillai; *M. S. Ramaiah Medical College & Hospitals (9):* S.C. Desai; *Sidhu Hospital (8):* R. Sidhu; *MV Hospital (7):* S. Mohan; *NH Hospital (5):* R. George; *Ramana Maharishi Rangammal Hospital (1): T.R.* Gurunath; **SOUTH AFRICA (185)** – *Inkosi Albert Luthuli Central Hospital, University of KwaZulu-Natal (83):* L.W. Drummond, B.S. Kusel, D.P. Naidoo, P. Naidoo, A.M. Torborg; *Grey's Hospital (University of KwaZulu-Natal) (51):* C. Rajah, Z. Farina, R.P. von Rahden, S. Gumede; *University of Cape Town (50):* B. Mayosi, C. Chishala, E. Coetzee, R.A. Dyer; *University of Free State (1)*: J. Diedericks; **POLAND (131)** – *Szpital Zakonu Bonifratrów św. Jana Grandego w Krakowie (47):* W. Szczeklik; *Samodzielny Publiczny Zakład Opieki Zdrowotnej Ministerstwa Spraw Wewnętrznych w Krakowie (32):* M. Libura; *Spzoz w Myslenicach (12):* J. Salwa; *Zakład Opieki Zdrowotnej im. Jana Pawła II (9):* J. Górka; *Szpital św. Anny w Miechowie (6):* J. Władarczyk; *Szpital im Rydygiera (6):* W. Mudyna; *Specjalistyczny Szpital im. E. Szczeklika (6):* P. Grudzien; *SPZOZ "Szpital Powiatowy" im Marty Wieckiej (5):* J. Gucwa; *OrtoMed sp. Z.o.o. (4):* M. Slowiaczek; *Spzoz w Brzesku (4):* P. Dobosz; **DENMARK (120)** – *Køge-Roskilde Hospital (31):* I. Gogenur; *Rigshospitalet (27):* D. Isbye; *Bispejberg and Frederiksberg Hospital (24):* C. Meyhoff; *Herlev Hospital (23):* C. Meyhoff; *Vejle Hospital (11):* K. Martinsen; *Nordsjællands Hospital Hillerød (4)*: M. Bestle; **SPAIN (90)** – *Hospital Universatario Valle Hebron (45):* M. de Nadal; *Hospital de la Santa Creu I Sant Pau (26):* P. Paniagua-Iglesias; *Bellvitge University Hospital (11):* M. Vives; *Hospital Ramón y Cajal (8):* A. Serrano; **ITALY (73)** – *IRCCS Istituto Ortopedico Galeazzi (34):* M. Turiel; *U.O.C. di Cardiologia - Ospedale Sant'Antonio (19):* L. Mos; *IRCCS San Raffaele Scientific Institute (15):* G. Landoni; *A.O. Niguarda Ca'Granda (3):* S. Passarani; *Ospedale San Gerardo (2):* Z. Mokini; **BRAZIL (37)** – *Lifecenter Hospital (13):* E.L. Figueiredo; *Hospital Barra D'Or (8):* J.L.F. Petriz; *Hospital de Base (6):* L.N. Maia; *Hospital Santa Lúcia (4):* R.R. Bergo; *Sociendade Hospitalar Angelina Caron (3):* D.B. Précoma; *Hospital e Maternidade Celso Pierro - PUCCAMP (3):* J.F.K. Saraiva; **ARGENTINA (28)** – *Sanatorio San Martín (15):* O.G. Vilamajó; *Fundacion Cardiovascular de Buenos Aires (6):* M. Benzadón; *San Roque Hospital (5):* M. Parody; *Fundacion Favaloro (1)*: E. Duronto; *Clinica Parra (1)*: Adrian Ingaramo; **COLOMBIA (26)** – *Fundación oftalmologica de Santander Clinica Carlos Ardila Luile (FOSCAL) (20)*: G. A. Parra; *Fundación Cardioinfantil - Instituto de Cardiología (6):* D.

Novoa; **UNITED STATES (20)** – *Wake Forest University School of Medicine (6):* S. Miller; *University of Rochester Medical Center (6):* S. Thomas; *Oregon Health (3):* A. O'Glasser; *Western New York Healthcare System (VA) (2):* M. Bourji; *VA North Texas (1)*: S. Banerjee; *Drexel University College of Medicine (1)*: A. Gupta*; Kansas University Medical Center (1)*: I. Opole; **CZECH REPUBLIC (11)** – *Regional Hospital Liberec (6):* M. Fischer; *University Hospital Motol (5):* P. Jansky; **PHILIPPINES (9)** – *De La Salle University Medical Center (6):* V. Mendoza; *Philippine General Hospital E Reyes (3)*: E. Reyes; **UNITED KINGDOM (7)** – *Russell Halls Hospital Dudley Group NHS Foundation Trust (5):* R.J. Pierson; *Royal Victoria Hospital (2):* M. Shields; **AUSTRALIA (4)** – *Westmead Hospital (4):* C. Chow; **FRANCE (4) -** *Groupe Hospitalier Pitié Salpétrière (3)*: P. Coriat; *Centre Hospitalier Lyon (1)*: V. Piriou; **GERMANY (2) -** *Universitätsklinikum Bon*n (1): A. Hoeft; *Klinikum der J. W. Goethe-Universität Frankfurt (1)*: K. Zacharowski; **KENYA (2) -** *Aga Khan University Hospital Nairobi (2)*: G. Yonga; **PERU (1)** – *Hospital Nacional Cayetano Heredia (1):* A. Rotta.

SUPPLEMENTAL REFERENCES

1. Devereaux PJ, Biccard BM, Sigamani A, et al. Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. Jama. 2017;317:1642-51.
2. Puelacher C, Lurati Buse G, Seeberger D, et al. Perioperative Myocardial Injury After Noncardiac Surgery: Incidence, Mortality, and Characterization. Circulation. 2017.
3. Reed GW, Horr S, Young L, et al. Associations Between Cardiac Troponin, Mechanism of Myocardial Injury, and Long-Term Mortality After Noncardiac Vascular Surgery. J Am Heart Assoc. 2017;6.
4. Botto F, Alonso-Coello P, Chan MT, et al. 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.
5. van Waes JA, Nathoe HM, de Graaff JC, et al. Myocardial injury after noncardiac surgery and its association with short-term mortality. Circulation. 2013;127:2264-71.
6. Redfern G, Rodseth RN, Biccard BM. Outcomes in vascular surgical patients with isolated postoperative troponin leak: a meta-analysis. Anaesthesia. 2011;66:604-10.
7. Levy M, Heels-Ansdell D, Hiralal R, et al. 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.

CO-AUTHORS' CONTRIBUTORSHIP – CHAPTER 4

Emmanuelle Duceppe's contribution is detailed in the Declaration of Academic Achievement.

The contributorship of other authors is detailed in the table below.

Authors' contributorship						
	Conception and Design	Data Acquisition (for the main trial)	Analysis and Interpretation of Data	Drafting Manuscript	Critical Manuscript Revision	Approval of Final Manuscript
SY	X		X		X	X
VT		X			X	X
RR	X	X	X		X	X
BB	X	X	X		X	X
DX	X	X	X		X	X
WS	X	X	X		X	X
CSM	X	X	X		X	X
MGF		X			X	X
JV	X	X	X		X	X
SS		X			X	X
JP		X			X	X
PM		X			X	X
JN		X			X	X
MR		X			X	X
NKC		X			X	X
BM		X			X	X
MN		X			X	X
EP		X			X	X
JCV	X	X	X		X	X
FB		X			X	X
OB	X	X	X		X	X
GG	X		X		X	X
JWE	X		X		X	X
DIS	X	X	X		X	X
CK	X		X		X	X
SP	X	X	X		X	X
SJC	X		X		X	X
MS		X			X	X
SIB			X		X	X
PJD	X	X	X		X	X

CHAPTER 5

A RANDOMIZED PLACEBO-CONTROLLED TRIAL OF OMEPRAZOLE IN PATIENTS WITH MYOCARDIAL INJURY AFTER NONCARDIAC SURGERY

CHAPTER 5 - A randomized placebo-controlled trial of omeprazole in patients with myocardial injury after noncardiac surgery

Manuscript unpublished

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ABSTRACT

Importance: Myocardial injury after noncardiac surgery (MINS) is common and associated with a poor prognosis. In the MANAGE Trial, we previously reported that dabigatran 110 mg twice daily reduces the risk of major vascular complications in patients with MINS.

Objective: To determine the impact of omeprazole 20 mg daily compared to placebo in patients with MINS on the occurrence of major upper gastrointestinal events.

Design: MANAGE was an international, randomized, placebo-controlled trial of dabigatran versus placebo and, using a partial factorial, omeprazole versus placebo. Patients were followed for a mean of 17 months. Patients, investigators, healthcare providers and outcome assessors were blinded to treatment allocation.

Setting: Multicentre, international trial in 84 centres in 19 countries

Participants: Eligible patients were 45 years or older and were enrolled within 35 days of having a MINS. Patients with a hemorrhagic disorder, bleeding diathesis, or who were taking a proton pump were excluded.

Interventions: Omeprazole 20 mg orally once daily versus placebo.

Main outcomes and measures: Primary outcome of major upper gastrointestinal complication (i.e., composite of overt gastroduodenal bleeding, overt upper gastrointestinal bleeding of unknown origin, or upper gastrointestinal perforation).

Results: From the 1754 patients enrolled in the MANAGE trial, we randomized 556 patients to omeprazole (n=286) versus placebo (n=270.) Mean patient's age was 69.2 years and 73.5% took an antiplatelet agent during follow-up. The primary outcome occurred in 1 (0.3%) patient in the omeprazole group and 0 patient in the placebo group. There was no difference between groups

for the occurrence of dyspepsia (38 patients [13.3%] in the omeprazole group and 42 patients [15.6%] in the placebo group; hazard ratio 0.84; 95% confidence interval, 0.54-1.31).

Conclusion and Relevance: Omeprazole did not demonstrate an effect on major upper gastrointestinal events. Although the trial was underpowered to rule out an effect of omeprazole, major upper gastrointestinal events were so rare in patients who had MINS that it is unlikely similar patients would benefit from omeprazole.

Trial Registration: NCT01661101

INTRODUCTION

Myocardial injury after noncardiac surgery (MINS) is common and associated with a poor prognosis.[1,2] Of the >200 million adults worldwide who are undergoing major surgery annually, approximatively 15% will suffer MINS.[3,4] Studies have demonstrated that MINS is independently associated with an increased risk of 30-day and 1-year mortality and major cardiovascular complications.[4,5] We have previously reported the dabigatran results of the MANAGE Trial, which randomized 1754 patients with MINS to dabigatran 110 mg twice daily or placebo. The primary efficacy outcome (i.e., a composite of vascular mortality and nonfatal myocardial infarction, non-hemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic venous thromboembolism) occurred in significantly fewer patients randomized to dabigatran than placebo (97 of 877 patients [11%] versus 133 of 877 patients [15%]; hazard ratio [HR], 0.72; 95% confidence interval [CI], 0.55-0.93; p=0.01).

The major limitation of anticoagulation therapy is the risk of bleeding, and a significant proportion of bleeding events are gastrointestinal in origin.[6-9] Perioperative major bleeding is associated with 30-day mortality and myocardial injury and infarction.[9,10] Dyspepsia is also a common consequence of antithrombotic therapy, which can impact medication compliance.[11] In patient taking acetylsalicylic acid (ASA), proton pump inhibitors have been shown to significantly reduce the risk of dyspepsia and peptic ulcer disease.[12,13] Omeprazole – a proton pump inhibitor– has been shown in patients with coronary artery disease taking dual antiplatelet therapy to reduce the risk of gastrointestinal events and overt gastrointestinal bleeding at 6 months.[8]

Considering the potential benefit of proton pump inhibitors to reduce perioperative gastrointestinal complications and bleeding, we hypothesized that omeprazole would reduce the

risk of major upper gastrointestinal complications (i.e., a composite of overt gastrointestinal bleeding, overt upper gastrointestinal bleeding of unknown origin, or upper gastrointestinal perforation) in patients who have MINS. Therefore, we undertook a partial factorial in the MANAGE Trial and randomized patients who were not on a gastroprotective drug to omeprazole or placebo. We report the results of the omeprazole factorial in this publication.

METHODS

The MANAGE Trial was an international, randomized, placebo-controlled trial to determine the impact of dabigatran on the risk of major vascular complications and, using a partial factorial, omeprazole on the risk of major upper gastrointestinal complications. The rationale and design and the MANAGE trial and the results of the dabigatran trial have been reported elsewhere.[14,15]

Patients

Eligible patients were 45 years or older, underwent noncardiac surgery with overnight hospital stay, and had MINS within the preceding 35 days. MINS was defined either by meeting the Third Universal Definition of Myocardial Infarction[16] or as an elevated troponin measurement after surgery believed to be due to ischemia (i.e., no evidence of a non-ischemic etiology like sepsis, pulmonary embolism). Patients were excluded from the main trial if they required a therapeutic dose anticoagulant, had a history of bleeding diathesis or intracranial, intraocular or spinal bleeding, or had an estimated glomerular filtration rate <35 mL/min. Patients were also excluded from the omeprazole partial factorial if they were taking or required a proton pump inhibitor or another gastroprotective drug. The full inclusion and exclusion criteria for both components of the trial are presented in Supplemental Appendix I.

Patient enrollment and follow-up

Eligible patients who provided written informed consent were randomized using a 24-hour centralized randomization system that used blocked randomization, stratified by centres. All patients were allocated to either dabigatran 110 mg orally twice daily or corresponding placebo, and patients who participated in the partial factorial were allocated to omeprazole 20 mg orally once daily or corresponding placebo. Patients, investigators, health care providers, data collectors, and adjudicators were blind to treatment allocation. Medication was provided to patients by the research team at baseline and resupplied every 6 months until completion of the trial. Patients were followed in person at 1, 6, 12, 18, and 24 months and by phone every 3 months between office visits. Patients continued their study drug and follow-up until 24 months, or until trial termination on November 30, 2017.

Outcomes

The primary outcome was the occurrence of major upper gastrointestinal complications (i.e., a composite of overt gastroduodenal bleeding, overt upper gastrointestinal bleeding of unknown origin, or upper gastrointestinal perforation). Secondary outcomes are reported in Supplemental Appendix II. The safety outcomes were Clostridium difficile-associated diarrhea, diarrhea, community-acquired pneumonia, and fracture. Supplemental Appendix III reports the outcomes definitions.

Adjudicators evaluated the outcomes reported in Supplemental Appendix IV. We used the decisions of the outcome adjudicators for all statistical analyses.

Sample size

The main trial had planned initially to recruit 3200 patients followed for an average of 1 year. Due to slowness in recruitment, the funding for the trial was curtailed and the main dabigatran trial's sample size was reduced to 1750 patients; this occurred without knowledge of the trial results. A third of the patients were expected to be enrolled in the omeprazole partial factorial component of the trial. We thus anticipated to enroll approximatively 600 patients in the omeprazole trial based on the revised sample size. We assumed a HR of 0.30 with omeprazole for the reduction of major gastrointestinal complications based on the COGENT Trial[8], a primary outcome incidence of 10% at 1 year, a 15% discontinuation rate in the omeprazole group and 15% proton pump inhibitor starting rate in the placebo group, which would provide 81% power to detect a difference with a two-sided alpha = 0.05.

Statistical analysis

We present the primary outcome as the time-to-the first occurrence of any one of the components of the composite primary outcome using the Kaplan-Meier estimator. We used the log-rank test to compare the rate of occurrence of the primary outcome between the omeprazole versus placebo groups. We also undertook a Cox proportional hazard model to estimate the effect of omeprazole on the hazard of the primary outcome with stratification according to whether patients were also treated with dabigatran. The secondary and safety outcomes were analyzed using a similar approach to the primary outcome. For all Cox proportional hazards models, we calculated the HRs, corresponding 95% confidence intervals (CI), and associated p-values. Patients were analyzed according to the group they were randomized to, following the intention-to-treat principle. Patient lost to follow-up were censored on the last day their status was known. Our threshold for inferring statistical significance in all analyses was if the computed nominal 2-sided p-value was less than alpha 0.05. All analyses were performed as

detailed in a pre-defined statistical analysis plan. Analyses were undertaken using SAS (version 9.4).

Three interim analyses were performed when 25%, 50%, and 75% of the 1-year follow-up data were available for the main trial and reviewed by an independent Data Monitoring Committee (DMC). The modified Haybittle-Peto rule of four standard deviations (SDs) for the first and second interim analyses ($\alpha = 0.0001$) and three SDs for the third interim analysis ($\alpha = 0.00047$) was used.

Trial organization and funding

The MANAGE Trial was an investigator-initiated, multicentre, international trial. All centres obtained National Regulatory Authorities and ethics approval before initiating recruitment. The sponsor was the Population Health Research Institute (PHRI) in Hamilton, Ontario, Canada. The PHRI obtained a grant from Boehringer Ingelheim to fund the trial. A Canadian Institutes of Health Research Foundation Grant also supported the trial. The sponsor purchased the omeprazole and placebo study drug from Liconsa, Guadalajara, Spain. The PHRI was responsible for the trial coordination, conduct, data collection, and analyses. The sponsor originated the research idea and drafted the protocol and Boeringher Ingelheim provided feedback on the protocol. No funding source had a role in data collection, analyses, manuscript drafting, or decision for publication. Supplemental Materials lists the trial committees, participating centres, and investigators.

RESULTS

Figure 1 shows the patient flow diagram. We enrolled 556 patients in the omeprazole factorial trial; 286 patients were randomized to omeprazole and 270 patients to placebo. The mean duration of follow-up was 17 months and 2% (11 patients) were lost to follow-up.

Table 1 reports participants' baseline characteristics and concomitant medication at the time of enrollment, by treatment group. Among participants, 77.9% met the MINS criteria through an isolated ischemic troponin elevation that did not fulfill the Third Universal Definition of Myocardial Infarction[16] and 8.5% experienced an ischemic signs or symptoms with their MINS event. Patient's mean age was 69.2 years (standard deviation 10.7), 55.6% were male, 11.0% had a prior history of myocardial infarction, 15.6% had a current or prior history of peripheral vascular disease, 27.2% had diabetes, and 5.2% had a prior history of cerebrovascular disease. Among participants, 6.1% had a history of dyspepsia within the last 6 months and 1.1% had a prior documented gastrointestinal bleed. Most participants (78.8%) underwent elective surgery and the common types of surgery were orthopedic (40.3%), general (23.0%), and vascular surgery (17.1%). At randomization, 57.7% of patients were taking aspirin, which subsequently increased to 72.5% during follow-up. During a follow-up visit, 5.5% of patients were taking a Cox-2 inhibitor and 17.8% were taking a non-steroidal anti-inflammatory drug (NSAID).

In patients randomized to the omeprazole group, 1 patient (0.3%) suffered the primary outcome of major upper gastrointestinal complication compared to no patient (0.0%) in the placebo group. The individual event from the primary composite outcome was an overt gastroduodenal bleed. The secondary outcome of upper gastrointestinal complication occurred in 0.7% (2/286) patients in the omeprazole group versus 0.4% (1/270) patients in the placebo group (HR 1.92; 95% CI 0.17-21.1; p=0.60). There was no difference between groups for the occurrence of individual components of the secondary outcome (Table 2). In patients allocated to omeprazole, 13.3% (38/286) had dyspepsia, compared to 15.6% (42/270) allocated to placebo (HR 0.84; 95% CI 0.54-1.31; p=0.44).

Thirty-six (12.6%) patients in the omeprazole group and 41 patients (15.2%) in the placebo group experienced a major vascular complication (HR 0.83; 95% CI 0.53-1.31; p=0.43). There was no difference in the incidence of the individual components of this composite outcome or mortality between the two treatment groups (Table 2). There was no significant difference between groups on the any of the safety outcomes (Table 3). Only 2 (0.7%) patients in the omeprazole group had Clostridium Difficile-associated diarrhea compared to no (0.0%) patient in the placebo group. There was no difference in diarrhea (7.7% versus 6.7%; HR 1.18, 95% CI 0.63-2.20), community-acquired pneumonia (3.8% versus 2.6%; HR 1.53, 95% CI 0.59-3.94), and fracture (3.8% versus 2.6%; HR 1.50, 95% CI 0.58-3.87) between omeprazole and placebo group.

During the trial, 126 (44.1%) patients in the omeprazole group and 124 (45.9%) patients in the placebo group permanently discontinued study drug at some point during the trial and did not resume. The main reason for discontinuation was patient request (49.1% and 52.7% for omeprazole and placebo, respectively). Patient requiring an open label proton pump inhibitor explained the permanent discontinuation in 7 (6.1%) patients in the omeprazole group and 8 (7.1%) patients in the placebo group.

Post hoc exploratory analyses

To determine the impact of permanent drug discontinuation on patient outcomes, we performed a post-hoc, per-protocol analysis, which censored patients 7 days after permanent drug discontinuation. We undertook a per-protocol analysis for upper gastrointestinal complications and dyspepsia. We did not perform a per-protocol analysis on the primary outcome due to low event rate (only one event). The per-protocol analyses did not demonstrate a statistically significant difference between treatment groups (Table 4).

We also explored in a post-hoc analysis if omeprazole had an impact on severe dyspepsia compared to placebo. We defined severe dyspepsia as dyspepsia occurring more than once a week. We did not find a difference between treatment groups on risk of severe dyspepsia (HR 0.95; 95% CI, 0.55-1.61).

DISCUSSION

Statement of Principal Findings

Among patients who had MINS and were followed for a mean of 17 months, major upper gastrointestinal complications were very uncommon, with only 1 (0.3%) event occurring in the omeprazole group, and no event in the placebo group. Dyspepsia occurred more frequently than major upper gastrointestinal complications, but we did not find a difference between patients randomized to omeprazole (13.3%) compared to placebo (15.6%). Major vascular complications were frequent in both groups, but omeprazole did not significantly change the risk of a major vascular event.

Our Trial in Relation to Other Studies

In our patient sample, 72.5% of patients were on aspirin during follow-up. In the PEP trial, 13,356 patients undergoing surgery for a hip fracture or elective arthroplasty were randomized to aspirin or placebo for 35 days after surgery for the prevention of venous thromboembolism.[17] In patients allocated to aspirin, the incidence of hematemesis or melena requiring a transfusion was 0.2% (29 events); in the hip fracture subgroup, the incidence of hematemesis or melena not requiring a transfusion was 2.7% (182/6679). Our definition of major upper gastrointestinal bleeding did not require a transfusion but rather imaging

confirmation of bleeding or drop in ≥3.0 g/dL in hemoglobin. Although definitions differ, the incidence of major upper gastrointestinal bleeding was significantly lower in our trial than seen in the PEP Trial. In the RE-LY trial, 6015 patients with atrial fibrillation were randomized to dabigatran 110 mg orally twice daily for the prevention of ischemic stroke and 40.0% were taking ASA concomitantly. At 30 months follow-up, 133 (2.2%) suffered a major gastrointestinal bleeding and 707 (11.8%) dyspepsia.[6] We observed a similar rate of dyspepsia in our population but did not demonstrate a reduction in dyspepsia with omeprazole. Previous trials in patients taking aspirin have shown that esomeprazole (a proton pump inhibitor) reduces the risk of peptic ulcer disease and dyspepsia (HR 0.14; 95% CI 0.07-0.30).[12,13] In the COGENT trial, 3873 patients with coronary artery disease receiving dual antiplatelet therapy were randomized to omeprazole 20 mg orally daily or placebo.[8] Omeprazole was associated with a reduction in the composite of overt or occult bleeding, symptomatic gastroduodenal ulcers or erosions, obstruction, or perforation (HR 0.34; 95% CI 0.03-0.56) at 6 months.

Strengths and Limitations

The incidence of upper gastrointestinal bleeding was lower than expected in our trial that included a population of postoperative patients who had MINS and in which most patients received an antiplatelet. One of the potential explanations for our low event rate could be a selection bias in including patients at lower risk of gastrointestinal events in the partial omeprazole factorial of the trial. In the main dabigatran trial, 44.9% (788/1754) of patients were on a gastroprotective drug (i.e., non-study proton-pump inhibitor, H2-receptor antagonist, or antacid) at randomization and were excluded from the omeprazole trial. It is possible that these patients were believed to be at higher risk of upper gastrointestinal complications and prescribed a gastroprotective drug by their treating physician. In this subset of 788 patients who were

excluded from the omeprazole trial, the incidence of significant lower gastrointestinal bleeding was 1.9% (15/788), and non-significant lower gastrointestinal bleeding 3.0% (24/788). These was no significant difference in the occurrence of dyspepsia between this subset of patients (12.6%; 99/788) and patients randomized in the omeprazole component of this trial (13.3%; 38/286) (p=0.75). Therefore, even in patients that were believed to be at higher risk and treated with a gastroprotective drug and not enrolled in the omeprazole trial, the event rate remained very low.

The lack of impact of omeprazole on dyspepsia could also be explained by the high rate of non-compliance observed, where 44.1% in the omeprazole arm permanently discontinued study drug and did not resume during follow-up. We did not, however, demonstrate in per-protocol analysis a difference between groups in the occurrence of upper gastrointestinal events or dyspepsia.

CONCLUSION

The MANAGE Trial is the first randomized, placebo-controlled trial to study the impact of omeprazole in patients who had MINS. During 17 months of follow-up, we did not demonstrate an impact of omeprazole on major upper gastrointestinal bleeding, with the limitation of a very low event rate. We also did not find a significant difference in the occurrence of major vascular events and dyspepsia between omeprazole and placebo. Although the trial was underpowered to rule out an effect of omeprazole, major upper gastrointestinal events were so rare in patients who had a MINS that it is unlikely that patients would benefit from omeprazole.

REFERENCES – CHAPTER 5

1. Devereaux PJ, Szczeklik W. Myocardial injury after non-cardiac surgery: diagnosis and management. European heart journal 2019.

2. Devereaux PJ, Sessler DI. Cardiac Complications in Patients Undergoing Major Noncardiac Surgery. The New England journal of medicine 2015;373:2258-69.

3. Devereaux PJ, Biccard BM, Sigamani A, et al. Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. Jama 2017;317:1642-51.

4. Puelacher C, Lurati Buse G, Seeberger D, et al. Perioperative Myocardial Injury After Noncardiac Surgery: Incidence, Mortality, and Characterization. Circulation 2018;137:1221-32.

5. Levy M, Heels-Ansdell D, Hiralal R, et al. 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.

6. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. The New England journal of medicine 2009;361:1139-51.

7. Connolly SJ, Eikelboom JW, Bosch J, et al. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet (London, England) 2017.

8. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. The New England journal of medicine 2010;363:1909-17.

9. Devereaux PJ, Mrkobrada M, Sessler DI, et al. Aspirin in patients undergoing noncardiac surgery. The New England journal of medicine 2014;370:1494-503.

10. Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet (London, England) 2008;371:1839-47.

11. Yeomans ND, Lanas AI, Talley NJ, et al. Prevalence and incidence of gastroduodenal ulcers during treatment with vascular protective doses of aspirin. Aliment Pharmacol Ther 2005;22:795-801.

12. Yeomans N, Lanas A, Labenz J, et al. Efficacy of esomeprazole (20 mg once daily) for reducing the risk of gastroduodenal ulcers associated with continuous use of low-dose aspirin. Am J Gastroenterol 2008;103:2465-73.

13. Scheiman JM, Devereaux PJ, Herlitz J, et al. Prevention of peptic ulcers with esomeprazole in patients at risk of ulcer development treated with low-dose acetylsalicylic acid: a randomised, controlled trial (OBERON). Heart 2011;97:797-802.

14. Duceppe E, Yusuf S, Tandon V, et al. Design of a Randomized Placebo-Controlled Trial to Assess Dabigatran and Omeprazole in Patients with Myocardial Injury after Noncardiac Surgery (MANAGE). The Canadian journal of cardiology 2018;34:295-302.

15. Devereaux PJ, Duceppe E, Guyatt G, et al. Dabigatran in patients with myocardial injury after non-cardiac surgery (MANAGE): an international, randomised, placebo-controlled trial. Lancet (London, England) 2018;391:2325-34.

16. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation 2012;126:2020-35.

17. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. Lancet (London, England) 2000;355:1295-302.

Figure 1. Patient flow diagram

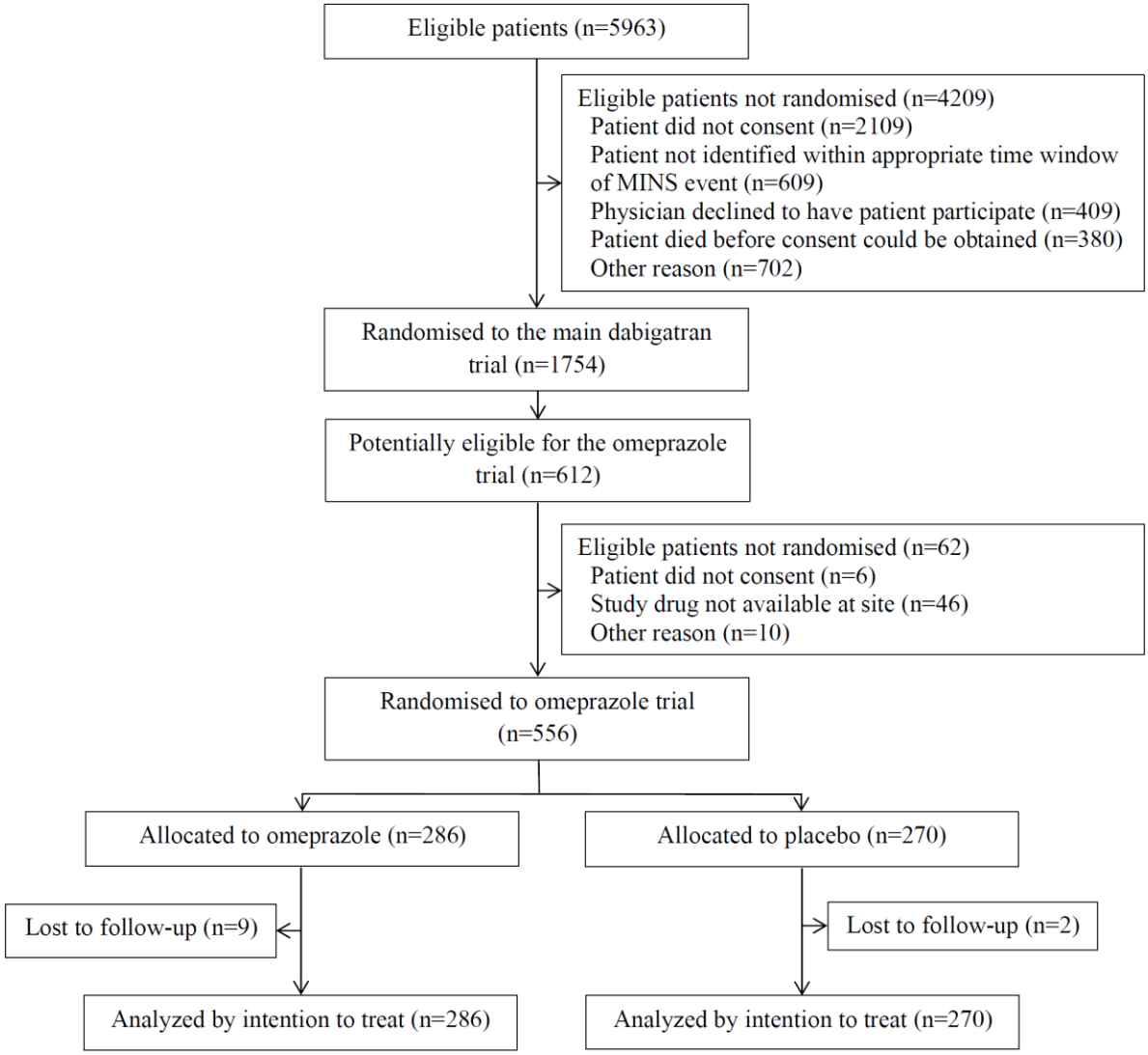

Table 1. Baseline Characteristics

Characteristics	Omeprazole N=286	Placebo N=270
Age (years, mean [± SD])	68.5 (10.5)	69.9 (10.8)
Gender (male) – no. (%)	149 (52.1)	160 (59.3)
MINS diagnostic criteria – no. (%)		
myocardial infarction	65 (22.7)	58 (21.5)
isolated ischemic troponin elevation	221 (77.3)	212 (78.5)
Time from surgery to MINS diagnosis (days, median [IQR])	1.0 (1.0-2.0)	1.0 (1.0-2.0)
Time from MINS diagnosis to randomization (days, median [IQR])	4.0 (2.0-11.0)	4.0 (2.0-13.0)
History – no. (%)		
prior myocardial infarction	31 (10.8)	30 (11.1)
recent high-risk coronary artery disease*	7 (2.4)	5 (1.9)
prior stroke	10 (3.5)	8 (3.0)
prior peripheral arterial disease	41 (14.3)	46 (17.0)
prior pulmonary embolism	2 (0.7)	3 (1.1)
prior deep venous thrombosis	5 (1.7)	5 (1.9)
diabetes	76 (26.6)	75 (27.8)
hypertension	181 (63.3)	170 (63.0)
dyspepsia within the last 6 months	21 (7.3)	13 (4.8)
peptic ulcer disease within the last 6 months	1 (0.3)	0 (0.0)
prior gastrointestinal bleeding	9 (3.1)	4 (1.5)
recent/active cancer within the last 6 months	32 (11.2)	38 (14.1)
Laboratory measurements prior to randomization		
hemoglobin (g/L), median (IQR)	10.9 (9.7-12.2)	10.7 (9.3-12.1)
calculated creatinine clearance (mL/min), median (IQR)	78.7 (60.1-105.3)	77.3 (55.7-98.3)
Type of surgery preceding MINS – no. (%)		
orthopedic	119 (41.6)	105 (38.9)
general	62 (21.7)	66 (24.4)
vascular	47 (16.4)	48 (17.8)
urologic or gynecologic	35 (12.2)	32 (11.9)
thoracic	14 (4.9)	8 (3.0)
spinal	4 (1.4)	5 (1.9)
low risk surgery	15 (5.2)	15 (5.6)
Urgent/emergent surgery – n (%)	57 (19.9)	61 (22.6)
Medications at randomization – no. (%)		

aspirin	156 (54.5)	165 (61.1)
any antiplatelet agent	159 (55.6)	167 (61.9)
ACE inhibitor or ARB	120 (42.0)	110 (40.7)
beta-blocker	89 (31.1)	80 (29.6)
statin	147 (51.4)	147 (54.4)
cox-2 inhibitor	5 (1.7)	2 (0.7)
non-cox-2 inhibitor/NSAID	41 (14.3)	29 (10.7)
Regions – no. (%)		
North America	85 (29.7)	84 (31.1)
Europe, Australia	64 (22.4)	53 (19.6)
Asia	46 (16.1)	43 (15.9)
Africa	80 (28.0)	76 (28.1)
South America	11 (3.8)	14 (5.2)

ACE = angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; IQR = interquartile range; MINS = myocardial injury after noncardiac surgery; NSAID = nonsteroidal anti-inflammatory drug; SD = standard deviation.

***** A physician diagnosis ≤6 months before noncardiac surgery of: a myocardial infarction, acute coronary syndrome, Canadian Cardiovascular Society Class (CCSC) III angina, or CCSC IV angina: CCSC III angina - angina occurring with level walking of 1-2 blocks or climbing ≤1 flight of stairs at a normal pace; CCSC IV angina - inability to carry on any physical activity without the development of angina.

Table 2. Efficacy Outcomes

Outcome	Omeprazole (N=286)	Placebo (N=270)	Hazard Ratio (95% CI)	P Value
Primary efficacy outcome – no. (%)				
composite of overt gastroduodenal bleeding, overt upper gastrointestinal bleeding of unknown origin, or upper gastrointestinal perforation	1 (0.3)	0 (0.0)	-	-
Secondary efficacy outcomes – no. (%)				
upper gastrointestinal complication*	2 (0.7)	1 (0.4)	1.92 (0.17-21.1)	0.60
dyspepsia	38 (13.3)	42 (15.6)	0.84 (0.54-1.31)	0.44
overt gastroduodenal bleeding	1 (0.3)	0 (0.0)	-	-
overt upper gastrointestinal bleed of unknown origin	0 (0.0)	0 (0.0)	-	-
symptomatic gastroduodenal ulcer	1 (0.3)	1 (0.4)	0.97 (0.06-15.5)	0.98
gastrointestinal pain with underlying multiple gastroduodenal erosions	0 (0.0)	0 (0.0)	-	-
upper gastrointestinal perforation	0 (0.0)	0 (0.0)	-	-
overt esophageal bleeding	0 (0.0)	1 (0.4)	-	-
bleeding of assumed occult gastrointestinal origin with a drop in hemoglobin ≥3.0 g/dL	1 (0.3)	1 (0.4)	0.94 (0.06-15.1)	0.97
major vascular complication†	36 (12.6)	41 (15.2)	0.83 (0.53-1.31)	0.43
all-cause mortality	38 (13.3)	39 (14.4)	0.94 (0.60-1.47)	0.79
vascular mortality	25 (8.7)	28 (10.4)	0.86 (0.50-1.48)	0.59
non-fatal myocardial infarction	9 (3.1)	10 (3.7)	0.87 (0.35-2.13)	0.76
non-fatal non-hemorrhagic stroke	1 (0.3)	2 (0.7)	0.49 (0.04-5.47)	0.57
non-fatal peripheral arterial thrombosis	0 (0.0)	1 (0.4)	-	-
non-fatal symptomatic venous thromboembolism	3 (1.0)	4 (1.5)	0.71 (0.16-3.18)	0.66
non-fatal symptomatic pulmonary embolism	1 (0.3)	3 (1.1)	0.31 (0.03-3.02)	0.32
non-fatal symptomatic proximal deep vein thrombosis	2 (0.7)	1 (0.4)	1.94 (0.18-21.4)	0.59

CI, confidence interval
*Upper gastrointestinal complication is a composite of overt gastroduodenal bleeding, overt upper gastrointestinal bleeding of unknown origin, symptomatic gastroduodenal ulcer, gastrointestinal pain with underlying multiple gastroduodenal erosions or upper gastrointestinal perforation
†Major vascular complication is a composite of vascular mortality, non-fatal myocardial infarction, non-fatal non-hemorrhagic stroke, non-fatal peripheral arterial thrombosis or non-fatal symptomatic venous thromboembolism

Table 3. Safety Outcomes

Outcome	Omeprazole (N=286)	Placebo (N=270)	Hazard Ratio (95% CI)	P Value
Primary safety outcome – no. (%)				
Clostridium difficile-associated diarrhea	2 (0.7)	0 (0.0)	-	-
Diarrhea	22 (7.7)	18 (6.7)	1.18 (0.63-2.20)	0.60
Community-acquired pneumonia	11 (3.8)	7 (2.6)	1.53 (0.59-3.94)	0.38
Fracture	11 (3.8)	7 (2.6)	1.50 (0.58-3.87)	0.40

CI, confidence interval.

Table 4. Per-protocol analysis

Outcome	Omeprazole (N=286)	Placebo (N=270)	Hazard Ratio (95% CI)	P Value
Any gastrointestinal complication*	38 (13.3)	38 (14.1)	0.93 (0.60-1.47)	0.77
Dyspepsia	36 (12.6)	38 (14.1)	0.88 (0.56-1.40)	0.60

Patients were censored 7 days after permanent drug discontinuation in per-protocol analyses.
* Any gastrointestinal complication is a composite of overt gastroduodenal bleeding, overt upper gastrointestinal bleeding of unknown origin, symptomatic gastroduodenal ulcer, gastrointestinal pain with underlying multiple gastroduodenal erosions, upper gastrointestinal perforation, or dyspepsia

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SUPPLEMENTAL APPENDIX I – Eligibility criteria

Inclusion criteria – patients who had undergone noncardiac surgery were eligible if they fulfilled the following criteria

1. ≥45 years of age,
2. suffered MINS based upon fulfilling one of the following criteria
    A. elevated troponin or CK-MB measurement with one or more of the following defining features
        i. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema);
        ii. development of pathologic Q waves present in any two contiguous leads that are ≥30 milliseconds;
        iii. electrocardiogram (ECG) changes indicative of ischemia (i.e., ST segment elevation [≥2 mm in leads V_1, V_2, or V_3 OR ≥1 mm in the other leads], ST segment depression [≥1 mm], OR symmetric inversion of T waves ≥1 mm) in at least two contiguous leads;
        iv. new LBBB; or
        v. new or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging; OR
    B. elevated troponin measurement after surgery with no alternative non-ischemic explanation (e.g., pulmonary embolism, sepsis) to ischemic myocardial injury; AND
3. provided written informed consent to participate within 35 days of suffering their MINS.

Exclusion criteria – patients fulfilling any of the following criteria were excluded:

1. hypersensitivity or known allergy to dabigatran;
2. history of intracranial, intraocular, or spinal bleeding;
3. hemorrhagic disorder or bleeding diathesis;
4. known hepatic impairment or liver disease expected to have an impact on survival;
5. condition that required therapeutic dose anticoagulation (e.g., prosthetic heart valve, venous thromboembolism, atrial fibrillation);
6. using or plan to initiate rifampicin, cyclosporine, itraconazole, tacrolimus, ketoconazole, or dronedarone;
7. women who were pregnant, breastfeeding, or of childbearing potential who refused to use a medically acceptable form of contraception throughout the study;
8. investigator considered the patient unreliable regarding requirement for study follow-up or study drug compliance; OR
9. previously enrolled in the MANAGE Trial.

We also excluded patients in whom any of the following criteria persisted beyond 35 days of their suffering MINS:

1. the attending surgeon believed it was not safe to initiate therapeutic dose anticoagulation therapy;
2. the attending physician believed aspirin, intermittent pneumatic compression, or elastic stockings were not sufficient for venous thromboembolism prophylaxis and that the patient required a prophylactic-dose anticoagulant;
3. the patient had an indwelling epidural or spinal catheter that could not be removed, or the first dose of dabigatran would occur within 4 hours of epidural catheter removal;
4. estimated glomerular filtration rate was <35 ml/min, as estimated by calculated creatinine clearance; OR
5. the patient was awaiting cardiac catheterization beyond 35 days after their suffering MINS.

Exclusion Criteria Specific to Patients in the Omeprazole Factorial Component of the Trial

We excluded patients meeting any of the following criteria:

1. hypersensitivity or known allergy to omeprazole;
2. requirement for a proton pump inhibitor, an H2-receptor antagonist, sucralfate, atazanavir, clopidogrel, or misoprostol;
3. esophageal or gastric variceal disease; OR
4. patient declined participation in the omeprazole arm of MANAGE.

SUPPLEMENTAL APPENDIX II – Secondary outcomes

The secondary outcomes were upper gastrointestinal complication (i.e., composite of overt gastroduodenal bleeding, overt upper gastrointestinal bleeding of unknown origin, symptomatic gastroduodenal ulcer, gastrointestinal pain with underlying multiple gastroduodenal erosions, or upper gastrointestinal perforation), major vascular complication (i.e., a composite of vascular mortality, nonfatal myocardial infarction, nonfatal non-hemorrhagic stroke, nonfatal peripheral arterial thrombosis, nonfatal amputation, and nonfatal symptomatic venous thromboembolism [i.e., symptomatic pulmonary embolism and symptomatic proximal deep venous thrombosis]), overt gastroduodenal bleeding, overt esophageal bleeding, overt upper gastrointestinal bleeding of unknown origin, symptomatic gastroduodenal ulcer, gastrointestinal pain with underlying multiple gastroduodenal erosions, upper gastrointestinal perforation, bleeding of assumed occult gastrointestinal origin with a documented drop in hemoglobin of ≥3.0 g/dL, dyspepsia, and mortality.

SUPPLEMENTAL APPENDIX III - Outcomes definitions

Outcome	Definition
Subclassification of death	Vascular death was defined as any death with a vascular cause and included those deaths following a myocardial infarction, cardiac arrest, stroke, cardiac revascularisation procedure (i.e., PCI or CABG surgery), pulmonary embolus, hemorrhage, or deaths due to an unknown cause. Non-vascular death was defined as any death due to a clearly documented non-vascular cause (e.g. trauma, infection, malignancy).
Myocardial infarction	The diagnosis of myocardial infarction required any one of the following criterion: 1. Detection of a rise or fall of a cardiac biomarker (preferably troponin) with at least one value above the 99th percentile of the URL together with evidence of myocardial ischemia with at least one of the following: A. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath; or pulmonary edema); B. development of pathologic Q waves present in any two contiguous leads that were ≥30 milliseconds; C. new or presumed ECG changes indicative of ischemia (i.e., ST segment elevation [≥2 mm in leads V_1, V_2, or V_3 OR ≥1 mm in the other leads], ST segment depression [≥1 mm], or symmetric inversion of T waves ≥1 mm) in at least two contiguous leads; D. new LBBB; E. new cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging; or F. identification of intracoronary thrombus on angiography or autopsy. 2. Cardiac death, with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased. 3. PCI related myocardial infarction was defined by an elevation of a troponin value (>5 x 99th percentile URL) in patients with a normal baseline troponin value (≤99th percentile URL) or a rise of a troponin measurement >20% if the baseline values were elevated and were stable or falling. In addition, one of the following was required: (i) symptoms suggestive of myocardial ischemia, (ii) new ischemic ECG changes, (iii) angiographic findings consistent

	with a procedural complication, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion. 4. Stent thrombosis associated with myocardial infarction when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values, with at least one of value above the 99th percentile URL. 5. CABG surgery related myocardial infarction was defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with a normal baseline troponin value (≤99th percentile URL). In addition, one of the following was required: (i) new pathological Q waves or new LBBB, (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. 6. For patients who were believed to have suffered a myocardial infarction within 28 days of the index MINS event or within 28 days of a prior myocardial infarction, the following criterion for myocardial infarction was required: Detection of a rise or fall of a cardiac biomarker (preferably troponin) with at least one value above the 99th percentile of the URL and 20% higher than the last troponin measurement related to the preceding event together with evidence of myocardial ischemia with at least one of the following: A. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath; or pulmonary edema); B. development of pathologic Q waves present in any two contiguous leads that were ≥30 milliseconds; C. new or presumed new ECG changes indicative of ischemia (i.e., ST segment elevation [≥2 mm in leads V_1, V_2, or V_3 OR ≥1 mm in the other leads], ST segment depression [≥1 mm], or symmetric inversion of T waves ≥1 mm) in at least two contiguous leads; D. new LBBB; E. new cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging; or F. identification of intracoronary thrombus on angiography or autopsy.
Stroke	Stroke was defined as a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting more than 24 hours or leading to death. Stroke was sub-classified into non-hemorrhagic and hemorrhagic stroke.

Non-hemorrhagic stroke was sub-classified into ischemic, ischemic with secondary transformation, or stroke of uncertain classification.

Ischemic stroke was defined as a focal brain infarction caused by an arterial (or rarely venous) obstruction and documented by CT/MRI as normal or showing an infarct in the clinically expected area.

Ischemic stroke with secondary hemorrhagic transformation could have been symptomatic or asymptomatic.

C. Symptomatic transformation of ischemic stroke was defined as a hematoma occupying 30% or more of the infarcted tissue associated with a significant neurologic deterioration (consistent with a decrease of 4 points in the NIHSS) compared to immediately before the worsening and an absence of an alternative explanation for the deterioration.
D. Asymptomatic transformation of ischemic stroke was defined as a hemorrhagic transformation not meeting the criteria for symptomatic transformation.

Undetermined stroke was defined as a definite stroke that does not meet the criteria for ischemic or hemorrhagic stroke because CT scan or MRI are not done and there are no autopsy data. Rarely it cannot be determined with confidence whether the stroke was ischemic versus hemorrhagic, even after review of CT/MRI images (e.g., primary intracerebral hemorrhage versus severe hemorrhagic transformation); these stroke events were classified as undetermined.

The diagnosis of hemorrhagic stroke required neuroimaging or autopsy confirmation and includes two subcategories: primary intracerebral hemorrhage (i.e., intraparenchymal or intraventricular) and primary subarachnoid hemorrhage. Intracranial bleeding caused by head trauma, bleeding associated with tumors, hemorrhagic transformation of ischemic stroke, and subdural/epidural hematomas were not considered as hemorrhagic strokes but were considered critical organ bleeding. Micro-bleeds were not considered intracranial hemorrhage.

C. Primary intracerebral hemorrhage: These were symptomatic hemorrhagic strokes with CT/MRI or autopsy evidence of bleeding into the substance of the brain or ventricular spaces. Large or superficial intracerebral hemorrhages often are associated with minor amounts of subarachnoid hemorrhage, but these were classified as

	intracerebral hemorrhages. Primary intracerebral hemorrhage does not include secondary hemorrhage into cerebral infarct (i.e., hemorrhagic transformation, which was defined separately), intracerebral bleeding (i.e., contusions) due to trauma, or micro-bleeds detected by MRI. D. Primary subarachnoid hemorrhage: Typical clinical syndrome of sudden onset headache, with or without focal signs (subarachnoid hemorrhage may not have focal deficits), and CT or cerebrospinal fluid evidence of bleeding primarily into the subarachnoid space. Subarachnoid bleeding due to ruptured intracranial aneurysms and vascular malformation were counted as hemorrhagic strokes, but traumatic subarachnoid hemorrhage was not.
Peripheral arterial thrombosis	We considered a peripheral arterial thrombosis to have occurred when there was clear evidence of abrupt occlusion of a peripheral artery (i.e., not a stroke, myocardial infarction, or pulmonary embolism) consistent with either an acute local thrombotic event or a peripheral arterial embolism. To fulfill this definition we required at least one of the following objective findings of peripheral arterial thrombosis: 1. surgical report indicating evidence of arterial thrombosis/ peripheral arterial embolism, 2. pathological specimen demonstrating arterial thrombosis/ peripheral arterial embolism, 3. imaging evidence consistent with arterial thrombosis/ peripheral arterial embolism, or 4. autopsy reports documenting arterial thrombosis/ peripheral arterial embolism.
Amputation	Amputation was defined as an amputation procedure or auto amputation, subsequent to the initial surgery.
Symptomatic venous thromboembolism	Symptomatic venous thromboembolism was a composite of symptomatic pulmonary embolism or symptomatic proximal deep venous thrombosis. Symptomatic pulmonary embolism: The diagnosis of symptomatic pulmonary embolism required symptoms (e.g., dyspnea, pleuritic chest pain) and any one of the following: 1. a high probability ventilation/perfusion lung scan, 2. an intraluminal filling defect of segmental or larger artery on a helical CT scan, 3. an intraluminal filling defect on pulmonary angiography, or

	4. a positive diagnostic test for deep venous thrombosis (e.g., positive compression ultrasound) and one of the following: A. non-diagnostic (i.e., low or intermediate probability) ventilation/perfusion lung scan, or B. non-diagnostic (i.e., subsegmental defects or technically inadequate study) helical CT scan Symptomatic proximal deep venous thrombosis: The diagnosis of symptomatic proximal deep venous thrombosis required: 1. symptoms (e.g., leg pain), 2. thrombosis involving the popliteal vein or more proximal veins for leg deep venous thrombosis and axillary or more proximal veins for arm deep venous thrombosis, AND 3. evidence of vein thrombosis by any one of the following: D. a persistent intraluminal filling defect on contrast venography, E. noncompressibility of one or more venous segments on B mode compression ultrasonography, or F. A clearly defined intraluminal filling defect on contrast enhanced computed tomography.
Significant lower gastrointestinal bleeding	Significant lower gastrointestinal bleeding was defined as hematochezia or melena (if the latter was used no cause of bleeding was found on upper gastrointestinal endoscopy) with evidence of hemodynamic instability requiring fluid resuscitation or evidence of blood loss (>2.0 g/dL hemoglobin drop or a blood transfusion).
Non-significant lower gastrointestinal bleeding	Non-major lower gastrointestinal bleeding was defined as hematochezia or melena (if the latter was used no cause of bleeding was found on upper gastrointestinal endoscopy) without evidence of hemodynamic instability or evidence of blood loss (>2.0 g/dL hemoglobin drop or a blood transfusion).
Fracture	The diagnosis of a fracture required a physician diagnosis of a bone fracture.
Dyspepsia	Dyspepsia was a symptom reported by a patient in one or more of the following ways: 1. indigestion (a pain or discomfort in the upper abdomen), 2. heartburn (a burning feeling behind the breastbone), 3. regurgitation (an acid taste coming up into the mouth from the stomach), or 4. nausea (a feeling of sickness without being sick).

Overt gastroduodenal bleeding	The definition of overt gastroduodenal bleeding requires confirmation of bleeding, from a gastroduodenal lesion, by upper endoscopy or radiography.
Overt esophageal bleeding	The definition of overt esophageal bleeding requires confirmation of bleeding, from the esophagus, by upper endoscopy or radiography.
Overt upper gastrointestinal bleeding of unknown origin	The definition of overt upper gastrointestinal bleeding of unknown origin requires confirmed of the bleeding by upper endoscopy or radiography without localization of the culprit lesion and a drop in hemoglobin $\geq$3.0 g/dL.
Symptomatic gastroduodenal ulcer	The definition of symptomatic gastroduodenal ulcer requires confirmation of the ulcer on endoscopy or radiography and persistent pain of presumed gastrointestinal origin with a duration $\geq$3 days.
Gastrointestinal pain with underlying multiple gastroduodenal erosions	The definition of gastrointestinal pain with underlying multiple gastroduodenal erosions requires confirmation of $\geq$5 gastroduodenal erosions on endoscopy and persistent pain of presumed gastrointestinal origin with a duration $\geq$3 days.
Upper gastrointestinal perforation	To fulfill the definition of upper gastrointestinal perforation a patient requires radiographic or surgical evidence of upper gastrointestinal perforation.
Bleeding of assumed occult gastrointestinal origin with a documented drop in hemoglobin of $\geq$3.0 g/dL	This diagnosis requires a documented drop in hemoglobin of $\geq$3.0 g/dL and the investigator believes the bleed was due to an occult gastrointestinal source.
Clostridium Difficile associated diarrhea	This outcome requires laboratory documentation of Clostridium-difficile and diarrhea.
Diarrhea	This outcome is defined by new onset >3 loose bowel movements per day.
Community-acquired pneumonia	The diagnosis of community acquired pneumonia requires that the pneumonia was obtained in the community and not in a nursing home or hospital and any one of the following: 1. Rales or dullness to percussion on physical examinations of chest AND any of the following: A. New onset of purulent sputum or change in character of sputum B. Isolation of organism from blood culture C. Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy 2. Chest radiography showing new or progressive infiltrate, consolidation, cavitation, or pleural effusion AND any of the following: A. New onset of purulent sputum or change in character of sputum B. Isolation of organism from blood culture

	C. Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy D. Isolation of virus or detection of viral antigen in respiratory secretions E. Diagnostic single antibody titer (IgM) or fourfold increase in paired serum samples (IgG) for pathogen F. Histopathologic evidence of pneumonia

SUPPLEMENTAL APPENDIX IV – Adjudicated outcomes

The following outcomes were adjudicated by an independent adjudication event committee: significant lower gastrointestinal bleeding, overt gastroduodenal bleeding, overt upper gastrointestinal bleeding of unknown origin, symptomatic gastroduodenal ulcer, gastrointestinal pain with underlying multiple gastroduodenal erosions, upper gastrointestinal perforation, death (vascular versus non-vascular), myocardial infarction, non-hemorrhagic stroke, hemorrhagic stroke, peripheral arterial thrombosis, symptomatic pulmonary embolism, and symptomatic proximal deep vein thrombosis.

CO-AUTHOR'S CONTRIBUTORSHIP – CHAPTER 5

Emmanuelle Duceppe's contribution is detailed in the Declaration of Academic Achievement.

The contributorship of other authors is detailed in the table below.

Authors' contributorship						
	Conception and Design	Data Acquisition	Analysis and Interpretation of Data	Drafting Manuscript	Critical Manuscript Revision	Approval of Final Manuscript
GG	X		X		X	
VT		X			X	
RR	X	X	X		X	
BB	X	X	X		X	
WS	X	X	X		X	
CSM	X	X	X		X	
JV	X	X	X		X	
MGF	X	X	X		X	
SS		X			X	
JP		X			X	
AP		X			X	
MP		X			X	
EMC		X	X		X	
FKB		X	X		X	
PM		X	X		X	
VZ		X			X	
MR		X			X	
PVR		X			X	
NKC		X			X	
MN		X			X	
PPI		X			X	
OB	X	X	X		X	
JCV	X	X	X		X	
RD	X	X			X	
SP	X	X	X		X	
KB		X	X		X	
SY	X		X		X	
PJD	X	X	X		X	

CHAPTER 6

DISCUSSIONS AND FUTURE DIRECTIONS

CHAPTER 6 – Discussions and future directions

6.1 KEY FINDINGS OF THIS THESIS

Worldwide, an estimated >200 million surgeries are performed yearly, and of those undergoing inpatient noncardiac surgery, 1 in 17 patients will have a myocardial injury after noncardiac surgery (MINS).[1,2] MINS has been shown in previous studies to be mostly asymptomatic and associated with a significant increase in short- and long-term mortality.[2-4] In fact, MINS is one of the leading causes of 30-day mortality after inpatient surgery.[2] Despite the importance of the issue, MINS remains a relatively new clinical entity with several knowledge gaps. This thesis focuses on important aspects of the prediction, detection, and management of MINS.

Chapter 2 presents the results of a prospective cohort study that looked at the incremental value of using N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP) in addition to clinical evaluation for cardiac risk stratification of patients undergoing inpatient noncardiac surgery. Several small studies had established the association of NT-proBNP with major cardiovascular outcomes.[5-7] Our study (N=10,402) is by far the largest cohort to address this question, allowing for robust external validation in a representative sample of mixed noncardiac surgeries. We were able to perform risk-adjusted optimal cutpoint analyses[8] with a modification allowing for determination of more than one prognostically important threshold. We found that compared to NT-proBNP <100 ng/L (the reference group), values of ≥100 to <200 ng/L , ≥200 to <1500 ng/L, and ≥1500 ng/L were associated with adjusted hazard ratio of 2.27 (95% confidence interval [CI] 1.90-2.70), 3.63 (95% CI 3.13-4.21), and 5.82 (95% CI 4.81-7.05), and corresponding incidences of the primary outcome of MINS and vascular death in 12.3% (226/1843), 20.8% (542/2608), and 37.5% (223/595), respectively. We demonstrated that the

addition of NT-proBNP to a clinical risk score improved discrimination and preoperative cardiac risk stratification.

The 2017 Canadian Cardiovascular Society Perioperative Guidelines[9] recommend using a NT-proBNP threshold of 300 ng/L, based on a baseline risk of 5%, to define higher risk in patients who could benefit from closer postoperative monitoring, including systematic troponin measurement. We found that patients with preoperative NT-proBNP ≥200 ng/L had a perioperative risk of >5%. Based on these results, clinicians should consider using a NT-proBNP of 200 ng/L for preoperative cardiac risk stratification.

Chapter 3 details the findings from a multicentre, prospective, nested cohort and biobank study of 3953 patients who underwent noncardiac surgery with at least an overnight hospital stay after surgery and who had postoperative blood samples collected up to postoperative day 3 and tested for high-sensitivity troponin I (hsTnI) (Abbott Laboratories). We found that peak postoperative hsTnI measurements were associated with the occurrence of our primary outcome of major cardiac events and death at 30 days (i.e., composite of all-cause mortality, and non-fatal myocardial infarction after 3 days post-surgery, cardiac arrest, and congestive heart failure). Using a Cox proportional iterative process based on a modification of the optimal cutpoint Mazumdar approach, we found that peak hsTnI values of <60 ng/L, 60 ng/L to <700 ng/L, and ≥700 ng/L were associated with incidences of major cardiac events and death of 1.0% (95% CI, 0.7-1.3), 8.6% (95% CI 5.6-13.0) and 27.3% (95% CI 16.4-41.9), respectively. Compared to peak hsTnI <60 ng/L, hsTnI values 60 ng/L to <700 ng/L and ≥700 ng/L were associated with adjusted hazard ratios (aHR) of 7.54 (95% CI% 4.27-13.32) and 26.87 (95% CI 13.27-54.41). In patient who underwent in-hospital noncardiac surgery, a postoperative hsTnI ≥60 ng/L, with or without clinical signs or symptoms of myocardial ischemia, is associated with a 10% incidence

and 9-fold increased risk of subsequent major cardiac events and mortality at 30 days. This threshold could be used to define MINS when using Abbott hsTnI.

Chapter 4 presents the design and methods of the MANAGE trial, an international randomized controlled trial which enrolled 1754 patients who were randomized to dabigatran or matching placebo and, using a partial factorial design for eligible patients, to omeprazole or matching placebo, within 35 days of suffering MINS. Patients were followed for a maximum of 2 years for the occurrence of the primary composite outcome of major cardiovascular complications (dabigatran trial) and major upper gastrointestinal complications (omeprazole trial). We discussed sample size considerations secondary to slower than anticipated recruitment and trial budget constraints.

Chapter 5 discusses the results of the omeprazole factorial component of the MANAGE trial. The primary outcome occurred in 1 (0.3%) patient in the omeprazole group and 0 patient in the placebo group. There was no difference between groups for the occurrence of any of the secondary efficacy and safety outcomes, including dyspepsia (38 patients [13.3%] in the omeprazole group and 42 patients [15.6%] in the placebo group; hazard ratio 0.84; 95% CI, 0.54-1.31). We found that major upper gastrointestinal events were much rarer in patients who had MINS than anticipated.

6.2 LIMITATIONS OF THIS THESIS

Minimal p-value approach to identify "optimal" cutpoints for a continuous predictor variable

Both studies in Chapter 2 and 3 utilize a statistical method to identify optimal cutpoints for a continuous predictor (i.e., NT-proBNP and hsTnI) incorporated in a multivariable model. Categorization of a continuous variable in predictive models has been criticized by many from

statistical considerations.[10-12] Some of the issues raised regarding categorization of continuous variables and optimal cutpoints testing include loss of statistical power[13], inflation of type-1 error and false-positive results arising from multiple testing[11,14], unrealistic cutpoint model with individuals close to either sides of thresholds categorized as having very different risks[12], and residual confounding in multivariable models when including a dichotomized rather than continuous variable[12].

Nevertheless, categorization is often preferable for translation into clinical practice since it makes it easier for clinicians to use in clinical decision making.[15] The approach described by Mazumdar proposes several steps to mitigate several of these issues and also addresses other important considerations that we applied in our analyses: 1) visual inspection of exploratory scatter plot (i.e., proportion of binary outcome Y over intervals of prognostic variable X) to detect areas of obvious cutpoints; 2) p-value adjustment accounting for the inflation in type I error; 3) exclusion of extreme data values from the range of systematic search for thresholds; 4) cutpoint search using multivariable analysis, and 5) considering effect sizes and relative risk associated with potential cutpoints, in addition to p-values, to select candidate cutpoints.[8,15]

One limitation we had was that there is no available or validated formula for p-value adjustment to account for multiple testing with our modification of the Mazumdar minimal p-value approach. P-value correction formulas to adjust for multiple testing have been described, but apply when determining a single threshold from a maximum Chi-squared statistic.[15] Also, Bonferoni correction has been shown to be overly conservative with minimal P-value optimal cutpoint testing.[15] Thus, we used an empirical alpha=0.01. Additionally, instead of looking for significant thresholds at every unit of NT-proBNP or hsTnI, we used clinically meaningful increment that were at or above the assay's coefficient of variation. We also censored the

extremes (i.e., we did not search for thresholds above hsTnI above 1000 ng/L and NT-proBNP above 4000 ng/L). This significantly reduced the amount of testing; for example, instead of exploring every unit across the NT-proBNP detection range of 5 ng/L to 9000 ng/L, we only explored 38 thresholds, which somewhat mitigated the issue of multiple testing.

External validation of study findings

Chapter 2 and 3 identified new thresholds of NT-proBNP and hsTnI to predict 30-day MINS and vascular death, and major cardiac events and death, respectively. Although the association and prognostic importance of these two biomarkers in the perioperative setting have already been well-established as detailed above, these new thresholds would benefit from external validation in prospective cohorts, as recommended by the TRIPOD statement.[16] We were able to perform non-random split sample analysis in the NT-proBNP study, which may be considered an intermediary between internal and external validation[16], but the sample size was too limited in the hsTnI analysis to perform such analysis. Our limited statistical power for the hsTnI analysis likely also limited our ability to detect multiple significant hsTnI thresholds, particularly below our lower identified thresholds (i.e., 60 ng/L). External validation in a larger dataset with greater number of events would be beneficial.

Challenges in trial recruitment and sample requirement

It is not uncommon for trials to face challenges and delays in recruitment that can have major consequences.[17] Delays in trial enrollment can increase resource use and costs and result in an under powered trial.[17] The true intervention effect may be missed and falsely-negative trials can deprive patients of potential beneficial treatments. On the other hand, it can also limit the ability to detect a difference in less common adverse safety outcomes.

As discussed in Chapter 4 et 5, the MANAGE trial's recruitment was slower than anticipated. Reluctance on the part of some patients and clinicians to take dabigatran negatively impacted recruitment. Moreover, delays in regulatory approvals and some hospitals not being able to implement routine troponin measurement following noncardiac surgery impacted recruitment. Despite implementing various strategies that have been described to address issues hindering recruitment[17], the length of the trial was extended and funding for the trial was curtailed. This resulted in an approximative 50% reduction in planned sample size. Fortunately, the effect size was large enough for the main dabigatran trial to yield positive results for the primary efficacy outcome.[18] For the omeprazole partial factorial, the reduction in sample size, however, was much larger. The initial assumption was that 60% of patients enrolled in the dabigatran main trial would be eligible to the omeprazole trial. In fact, only 30% of patients in the main trial were enrolled in the partial factorial. With the reduction in sample size of the main trial, the omeprazole trial's sample size was further reduced and went from an anticipated 1920 to 600 enrolled patients.

Factorial and partial factorial trial designs have efficiency advantages by addressing multiple questions in the same study at reduced costs and resource use, and allow for the assessment of interactions between interventions.[19] Partial factorial trials allow for more flexible enrollment strategies and study two interventions that may differ in their eligibility criteria. However, the drawback is that recruitment in the partial factorial is dependent on successful enrolment the main intervention. In the MANAGE trial, the sample size reduction impacted both trials, but the loss of statistical power was greatest in the omeprazole component. Another caveat is the risk of selection bias in the factorial component when the second intervention is not mandatory (as in a full factorial). The MANAGE trial required patients to take dabigatran or

corresponding placebo orally twice daily for up to two years; some patients may have felt that taking a second pill for a long period was too much and refused participation in the factorial. These patients may differ in a non-random way from patients who agreed to enroll in both trials. The selection bias may also come from treating physicians who felt that higher risk patients should benefit from the intervention (a gastroprotective drug) rather than enrolling their patients in the trial. This may explain in part the very low primary outcome event rate observed in the omeprazole trial.

The sample size calculation was made with the assumption of a 10% incidence of upper gastrointestinal complications (in the first ~400 patients who suffered MINS in the VISION Study, 7.6% had a gastrointestinal bleed within 30 days, unpublished data). Such a drastic difference in outcome incidence in patients with MINS between the early VISION study (7.6%) and the omeprazole trial (0.2%; 1 event) is difficult to explain but likely multifactorial in nature. Given the limitations discussed above, we were not able to answer the question if omeprazole in patients who had a MINS could prevent upper gastrointestinal bleeding but given how rare these events were, it is unclear if there would be value in exploring this in a subsequent trial.

6.3 FUTURE DIRECTIONS

Many aspects of MINS prediction, detection, and management remains to be elucidated. We have validated the utility of NT-proBNP for preoperative cardiac risk stratification but other biomarkers may also have incremental value, such as preoperative hsTnT[20,21] and growth differentiation factor 15 (GDF-15)[22,23] who have showed promising results for perioperative cardiac risk stratification in the perioperative setting. Brain natriuretic peptide (BNP) is also used in many centres who commonly do not have access to NT-proBNP; most hospital

laboratories opt to have one or the other made available in the clinical setting, but rarely both assays. Although BNP and NT-BNP reflect the same cardiac hormonal activity, their reference range differs, and there is no conversion factor between assays.[24] BNP would warrant investigation in the perioperative setting to inform on the thresholds and allow centres who do not have access to NT-proBNP but rather BNP to use it for perioperative cardiac risk stratification. Given the short half-life of BNP (20 minutes)[25], investigation in a prospective cohort with testing in real-time would be needed to answer this question.

Biomarkers have been shown to help risk stratification but could also be used to identify patients at higher risk who could benefit from perioperative interventions aimed at preventing MINS. Another important question is if interventions aimed at reducing preoperative NT-proBNP could impact perioperative patient prognosis. Trials in patients with chronic heart failure have demonstrated a significant reduction in all-cause mortality associated with NT-proBNP-guided therapy.[26] Such therapies could be adapted and explored in randomized controlled trials in patients undergoing surgery to determine the impact on postoperative major cardiovascular outcomes. The value of cardiac imaging in patients with elevated preoperative NT-proBNP could also be of interest. In unselected patients, the additional value of non-invasive cardiac imaging in addition to clinical evaluation alone has not been demonstrated[9,27], but could be valuable in patients with incidental finding of elevated NT-proBNP.

As mentioned in Chapter 3, there are various hsTnI assays available that differ in immunoassay method. Our study used hsTnI assays by Abbott Laboratories but other TnI and hsTnI are available in different centres that would require investigation to determine their thresholds to diagnose MINS. Exploration in large biobank studies using representative

sampling of noncardiac surgeries to ensure sufficient statistical power to detect prognostically important thresholds, in particular when using high-sensitivity assays would be preferable.

Management of patients with MINS is also of paramount importance to reduce the mortality burden in this population. We discussed the design and methods of a randomized controlled trial using an anticoagulant and proton pump inhibitor in patients who suffered a MINS, as well as several challenges in recruitment during the study's conduct. Strategies to mitigate these challenges have to be tailored to the intervention. These could include performing a feasibility pilot trial, conduct the trial in centres with systematic troponin monitoring already in place, involve stakeholders in the early phase of the trial's design and during study activation to improve uptake of the trial, consider patient partnership in patient recruitment, performing acceptability surveys with stakeholders and knowledge users on the proposed interventions and identifying barriers to trial implementation, etc. Acknowledging that some challenges encountered during the MANAGE trial's conduct were specific to particularities of the trial and timing of its conduct, learning from this experience can only benefit future trials addressing MINS therapies. There are many possible strategies to reduce mortality in patients who suffered a MINS that could be explored, such as dual antiplatelet therapy, cardiac imaging, outpatient monitoring for early detection of complications, and outpatient intensive secondary prevention strategies.

So far, research on MINS have focused on events occurring while patients are in hospital and all the evidence and studies discussed in this thesis relate to patients who underwent noncardiac surgery with overnight hospital stay. There has, however, been a shift in the recent decades for an increasing number of surgeries to be performed as ambulatory (outpatient) surgery in Canada and worldwide. Advances in surgical and anesthesia techniques and

limitations of hospital beds have resulted in moving some interventions to be performed as outpatient surgery, rather than inpatient. The VISION study enrolled patients between 2007 and 2013 and a third of patients underwent what was considered to be "low-risk" surgery[28]; the incidence of MINS and death in low-risk surgery was 9.3% (95% CI 8.8-9.8) and 1.2% (95% CI 1.1-1.4), respectively.[2] Given the fact that in recent decades, there has been a transition in surgeries deemed at low risk to be performed as same-day cases, it is likely that a substantial proportion of the interventions that made patients eligible to be enrolled in VISION are now being performed as same-day with no overnight admission. This raises the following questions. Are some patients undergoing outpatient surgery for "low-risk" interventions suffering asymptomatic and undetected MINS that could impact their short- and long-term prognosis? Could biomarkers such as preoperative NT-proBNP be used to identify patients at higher risk of perioperative complications who are not good candidate for ambulatory surgery? Would postoperative outpatient troponin monitoring be feasible and allow for the detection of undiagnosed, prognostically important events? These are all questions that need answering and will be part of my research program moving forward. There is a glaring gap in knowledge and evidence on this topic and these are a crucial question that need to be elucidated in future research endeavors.

Author's contribution: Emmanuelle Duceppe is the sole author of this chapter; this chapter is not published.

REFERENCES – CHAPTER 6

1. Weiser TG, Haynes AB, Molina G, et al. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. Lancet (London, England) 2015;385 Suppl 2:S11.

2. Association between complications and death within 30 days after noncardiac surgery. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2019;191:E830-e7.

3. Puelacher C, Lurati Buse G, Seeberger D, et al. Perioperative Myocardial Injury After Noncardiac Surgery: Incidence, Mortality, and Characterization. Circulation 2018;137:1221-32.

4. Smilowitz NR, Redel-Traub G, Hausvater A, et al. Myocardial Injury After Noncardiac Surgery: A Systematic Review and Meta-Analysis. Cardiol Rev 2019;27:267-73.

5. Rodseth RN, Biccard BM, Le Manach Y, et al. The prognostic value of pre-operative and post-operative B-type natriuretic peptides in patients undergoing noncardiac surgery: B-type natriuretic peptide and N-terminal fragment of pro-B-type natriuretic peptide: a systematic review and individual patient data meta-analysis. Journal of the American College of Cardiology 2014;63:170-80.

6. Kopec M, Duma A, Helwani MA, et al. Improving Prediction of Postoperative Myocardial Infarction With High-Sensitivity Cardiac Troponin T and NT-proBNP. Anesthesia and analgesia 2017;124:398-405.

7. Wijeysundera DN, Pearse RM, Shulman MA, et al. Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study. Lancet (London, England) 2018;391:2631-40.

8. Mazumdar M, Smith A, Bacik J. Methods for categorizing a prognostic variable in a multivariable setting. Statistics in medicine 2003;22:559-71.

9. Duceppe E, Parlow J, MacDonald P, et al. Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery. The Canadian journal of cardiology 2017;33:17-32.

10. Austin PC, Brunner LJ. Inflation of the type I error rate when a continuous confounding variable is categorized in logistic regression analyses. Statistics in medicine 2004;23:1159-78.

11. Barnwell-Menard JL, Li Q, Cohen AA. Effects of categorization method, regression type, and variable distribution on the inflation of Type-I error rate when categorizing a confounding variable. Statistics in medicine 2015;34:936-49.

12. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. Statistics in medicine 2006;25:127-41.

13. Faraggi D, Simon R. A simulation study of cross-validation for selecting an optimal cutpoint in univariate survival analysis. Statistics in medicine 1996;15:2203-13.

14. Altman DG, Lausen B, Sauerbrei W, Schumacher M. Dangers of using "optimal" cutpoints in the evaluation of prognostic factors. Journal of the National Cancer Institute 1994;86:829-35.

15. Mazumdar M, Glassman JR. Categorizing a prognostic variable: review of methods, code for easy implementation and applications to decision-making about cancer treatments. Statistics in medicine 2000;19:113-32.

16. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. Annals of internal medicine 2015;162:55-63.

17. Thoma A, Farrokhyar F, McKnight L, Bhandari M. Practical tips for surgical research: how to optimize patient recruitment. Canadian journal of surgery Journal canadien de chirurgie 2010;53:205-10.

18. Devereaux PJ, Duceppe E, Guyatt G, et al. Dabigatran in patients with myocardial injury after non-cardiac surgery (MANAGE): an international, randomised, placebo-controlled trial. Lancet (London, England) 2018;391:2325-34.

19. Dakin HA, Gray AM, MacLennan GS, Morris RW, Murray DW. Partial factorial trials: comparing methods for statistical analysis and economic evaluation. Trials 2018;19:442-.

20. Gillmann HJ, Meinders A, Grohennig A, et al. Perioperative levels and changes of high-sensitivity troponin T are associated with cardiovascular events in vascular surgery patients. Critical care medicine 2014;42:1498-506.

21. Weber M, Luchner A, Seeberger M, et al. Incremental value of high-sensitive troponin T in addition to the revised cardiac index for peri-operative risk stratification in non-cardiac surgery. European heart journal 2013;34:853-62.

22. Guenancia C, Kahli A, Laurent G, et al. Pre-operative growth differentiation factor 15 as a novel biomarker of acute kidney injury after cardiac bypass surgery. International journal of cardiology 2015;197:66-71.

23. Yuan Z, Li H, Qi Q, et al. Plasma levels of growth differentiation factor-15 are associated with myocardial injury in patients undergoing off-pump coronary artery bypass grafting. Scientific reports 2016;6:28221.

24. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. Heart (British Cardiac Society) 2006;92:843-9.

25. Weber M, Mitrovic V, Hamm C. B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide - Diagnostic role in stable coronary artery disease. Exp Clin Cardiol 2006;11:99-101.

26. Bajaj NS, Patel N, Prabhu SD, Arora G, Wang TJ, Arora P. Effect of NT-proBNP–Guided Therapy on All-Cause Mortality in Chronic Heart Failure With Reduced Ejection Fraction. Journal of the American College of Cardiology 2018;71:951-2.

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

28. Devereaux PJ, Biccard BM, Sigamani A, et al. Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. Jama 2017;317:1642-51.