CARDIAC TROPONINS IN CRITICAL ILLNESS

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ABSTRACT

Troponin elevations are frequent during critical illness and associated with higher short-term mortality. Whether troponin elevations in that population independently confer a worse prognosis remains a matter of debate and how to manage patients with troponin elevations in the intensive care unit is unknown. Myocardial injury after noncardiac surgery is a well-defined entity, but can the same criteria be applied in patients who transition in the intensive care unit? Most patients present a troponin elevation early after coronary artery bypass surgery. How should a myocardial infarction be defined in these patients? This thesis comprises 7 chapters that inform these knowledge gaps.

Chapter 1 is an introduction providing the rationale for conducting each of the included studies.

Chapter 2 reports on the PROTROPIC pilot study evaluating the feasibility of a larger study to assess whether troponin elevations in critical illness independently predict mortality.

Chapter 3 presents the use of secondary cardiovascular prevention medications and cardiac risk stratification in the PROTROPIC pilot study participants.

Chapter 4 is a systematic review and meta-analysis of randomized controlled trials evaluating the efficacy and safety of statins in critically ill patients.

Chapter 5 describes patients admitted to the intensive care unit after noncardiac surgery in the VISION cohort. This substudy also evaluates whether admission to the intensive care unit modifies the prognosis associated with myocardial injury after noncardiac surgery.

Chapter 6 evaluates the prevalence and prognosis associated with different definitions of myocardial infarction after coronary artery bypass grafting using data from the CORONARY trial.

Finally, Chapter 7 discusses the conclusion, limitation, and implications of the research presented in this PhD thesis.

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CONTRIBUTIONS BY OTHERS

At the end of each chapter is a full account of authors' contributions.

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LIST OF ABBREVIATIONS

ACEI	Angiotensin-converting enzyme inhibitor
Afib	Atrial fibrillation
aHR	Adjusted hazard ratio
ALI	Acute lung injury
ALT	Alanine aminotransferase
aOR	Adjusted odds ratio
APACHE II	Acute Physiology and Chronic Health Evaluation-II
ARB	Angiotensin II receptor blocker
ARDS	Acute respiratory distress syndrome
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
BMI	Body mass index
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCB	Calcium channel blocker
CI	Confidence interval
CK	Creatine kinase
CK-MB	Creatine kinase-MB isoezyme
CORONARY trial	CABG Off or On Pump Revascularization
COPD	Chronic obstructive pulmonary disease
cTn	Cardiac troponin
df	Degree of freedom
ECG	Electrocardiogram

EuroSCORE	European System for Cardiac Risk Operative Risk Evaluation
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard ratio
HMG-CoA	Hydroxyl-methyl-glutaryl-CoA
hs-cTn	High-sensitivity cardiac troponin
hs-cTnI	High-sensitivity cardiac troponin I
ICU	Intensive care unit
IQR	Interquartile range
IV	Intravenous
LBBB	Left bundle branch block
LMWH	Low molecular weight heparin
LV	Left ventricular
MANAGE trial	Management of Myocardial Injury after Noncardiac Surgery
MD	Mean difference
MI	Myocardial infarction
MICS	Myocardial injury after cardiac surgery
MINS	Myocardial injury after noncardiac surgery
MINS*ICU	Interaction term for MINS and ICU
N	Number
N/A	Not available, could not be completed
NR	Not reported
OR	Odd ratio
OVATION65 study	Optimal Vasopressor TItratiON
PAD	Peripheral arterial disease

Pre-op	Preoperative
PROTROPIC study	Prognostic value of elevated troponins in critical illness
RCT	Randomized controlled trial
RR	Relative risk/ Risk ratio
SAH	Subarachnoid hemorrhage
SD	Standard deviation
SE	Standard error
SIRS	Systemic inflammatory response syndrome
SIRS trial	Steroids In cardiac Surgery
ULN	Upper limit of normal
VIF	Variance inflation factor
VISION study	Vascular events In Surgery patIents cOhort evaluation
yr	year

CHAPTER 1: Introduction

1.1 Background

Patients in the intensive care unit (ICU) are the sickest patients in the hospital. Despite improvements in mechanical ventilation,[1] new technologies for hemodynamic support[2] and implementation of interventions proven to decrease ICU-related complications,[3] about 15% of patients die during their ICU stay.[4] More than a fifth of patients admitted to the ICU die during their hospital stay. Risk prediction models for ICU mortality have been validated but their discrimination is not perfect.[5,6] Having a better understanding of the relationship between widely available biomarkers and mortality in the ICU may better identify patients at risk of poor outcomes and aid in the evaluation of therapies that may be beneficial, thereby decreasing the risk of death.

In clinical practice, troponins are used in the diagnosis of myocardial infarction.[7] However, troponins can be elevated in other conditions such as heart failure, acute kidney injury, and pulmonary embolism. These causes of non-primary coronary elevation of troponins are common in the ICU. Critical illness is also an inflammatory and pro-coagulant condition;[8] this may lead to coronary thrombosis. Further, critically ill patients are under extremely high levels of physiologic stress, potentially leading to imbalances in myocardial oxygen supply and demand. The combination of these factors, and other factors not yet identified, could contribute to troponin elevations.

1.2 Troponin elevations in general medical-surgical ICU patients

After pooling 20 studies (3278 patients), a 2006 systematic review on this topic reported troponin elevations in a median of 43% (interquartile range 29 to 51%) of critically ill patients.[9] A 2-month, single center screening study reported that 50.5% of 103 consecutive ICU patients had elevated troponin measurements at some point in their ICU stay.[10] More than a half of these medical-surgical critically ill patients with elevated troponins met the criteria for myocardial infarction (one or more elevated troponin measurement **and** ischemic ECG [electrocardiogram] changes).[11] In another single center screening study (144 patients), 84% of patients presented at least one troponin value above the upper limit of normal and 41% had a possible or definite myocardial infarction.[12]

Distinguishing patients with elevated troponins (myocardial injury) from those with myocardial infarction (primary coronary-related) in the critically ill population is difficult. The Third and Fourth Universal definitions of myocardial infarction require elevated troponins with a rise and/or fall pattern in combination with either ischemic symptoms, ischemic ECG changes, new Q waves, new loss of viable myocardium, new regional wall motion abnormalities or evidence of intracoronary thrombus.[7,13] In many critically ill patients, symptoms cannot be elicited because of sedation or other distracting factors such as post-operative analgesic medications and delirium.

Troponin elevations in critical illness seem to be associated with increased mortality. Troponin screening is not currently recommended or part of usual clinical practice.

However, a meta-analysis of 6 prospective and retrospective cohort studies, including a total of 1706 patients, reports a pooled adjusted odds ratio (OR) for mortality in critically ill patients of 2.5 (95% CI 1.9 to 3.4; P<0.001).[9] The factors adjusted for were different across studies; however, the meta-analysis results demonstrate no heterogeneity ($I^2 = 0\%$; P=0.58). Many of these studies did not undertake screening of all patients for troponin elevations which may have biased their estimate of the mortality risk associated with troponin elevations. Studies in critically ill patients published since that systematic review support the association between elevated troponins and mortality.[11,14,15] In their systematic review in sepsis, Bessière et al reported a pooled adjusted OR for mortality associated with elevated troponin of 1.92 (95% CI 1.63-2.24).[16] The 4 studies included in this pooled estimate adjusted for validated prognostic scores, but statistical heterogeneity was observed ($I^2 = 52\%$; P=0.1). A few recent sepsis studies cast doubt on the prognostic value of elevated troponins by showing no independent association with mortality after adjustment for critical care risk prediction scores.[17-19] Two of these studies measured high sensitivity troponin T.[18,19] The third study combined the results of troponin I, troponin T and high sensitivity troponin T assays.[17] These studies raise the question of whether all troponin assays provide the same prognostic information.

Chapter 2 presents the feasibility and optimal design of a large prospective cohort study evaluating the epidemiology and prognostic significance of troponin elevations in critically ill patients, assessed in a 1-month pilot cohort study of systematic troponin and

ECG screening in patients admitted to 4 medical-surgical ICUs of 3 adult hospitals in Hamilton, Ontario.

1.3 Current treatment and risk stratification of critically ill patients with clinically recognized troponin elevations

The optimal work-up and treatment of patients with elevated troponins during a critical illness is unclear. Critical care physicians and cardiologists are frequently faced with seemingly asymptomatic elevated troponin levels and have little evidence whether this confers a risk of a poor outcome, whether further testing is warranted to prognosticate, and whether additional treatment is needed. The optimal treatment of patients with myocardial infarction due to atherosclerotic plaque rupture, however, has been extensively studied,[20,21] but no studies inform on the optimal management of myocardial infarction due to oxygen supply and demand imbalances or isolated troponin elevations during critical illness.[22,23,13] It is unknown whether treating these patients as if they had an acute coronary syndrome may favorably modulate their prognosis.

To our knowledge, the proportion of patients with elevated troponins during a critical illness who undergo risk stratification using myocardial perfusion scan or cardiac catheterization has not been reported. From our clinical experience and discussions with colleagues across the country, we believe that these risk-stratifying exams are obtained in a low proportion of medical-surgical ICU patients with elevated troponins.

In the third chapter, using the PROTROPIC Feasibility Study cohort, we describe the use of secondary cardiovascular prevention medications and cardiac investigations in critically ill patients with clinically recognized troponin elevations.

1.4 Statins in critically ill patients

Statins are known to be effective in the primary and secondary prevention of cardiovascular events.[24] Their lipid lowering effects occur through the inhibition of HMG-CoA reductase, reducing cholesterol production in the liver.[25] However, statins also modulate immunity and inflammation.[26] Observational data suggest statins may be of benefit in critically ill patients.[27] A few randomized controlled trials have been published evaluating statin treatment in specific critical diseases.[28-30] Whether statins are of benefit in critical illness in general remains uncertain.

Although systematic reviews on statins in sepsis have been published,[27,31,32] we were interested in a broader critically ill population. In chapter 4, we present a systematic review and meta-analysis of randomized controlled trials evaluating statins versus control or placebo in critically ill patients. The main objective of this study was to summarize information on both the safety and potential efficacy of these drugs in the critical care setting.

1.5 Troponin elevations after noncardiac surgery in patients admitted to the ICU

The Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study, a large prospective cohort, has established that troponin elevations, even in the absence of ischemic signs or symptoms - myocardial injury after noncardiac surgery (MINS) - were independently associated with a threefold increase in the risk of mortality at 30 days.[33,34] Patients may require admission to the ICU after noncardiac surgery for high level monitoring or after they have experienced a complication. The association of MINS with short-term mortality in patients admitted to the ICU after noncardiac surgery is unknown. In the fifth chapter of this thesis, using the VISION cohort, we described patients who were admitted to the ICU after noncardiac surgery and evaluated whether, in these patients, MINS was associated with the same mortality risk as in the overall cohort

1.6 Myocardial injury after cardiac surgery

Creatine kinase and troponin elevations are ubiquitous when patients are in the ICU after coronary artery bypass (CABG) surgery. This makes the diagnosis of myocardial infarction in this population challenging. The Third and Fourth Universal definitions for myocardial infarction after CABG surgery are based on a cardiac biomarker elevation greater than 10 times the 99th percentile concentration (designated as the upper limit of normal; ULN) from a healthy population.[13,35] These diagnostic criteria for myocardial infarction after CABG, even though widely accepted, are based on an arbitrary biomarker elevation threshold in association with signs of cardiac necrosis either on ECG or imaging or with angiographic evidence of new graft or native coronary artery occlusion.[35] Definitions for myocardial infarction after CABG have been proposed and updated.

Chapter 6 presents an evaluation of the incidence of myocardial injury and the prognostic implication of post-CABG myocardial injury as determined using different diagnostic criteria utilized by clinicians and in clinical studies of cardiac surgery using data from the CABG Off or On Pump Revascularization Study (CORONARY).[36]

1.7 Conclusion and future directions

Chapter 7 presents conclusions based on this thesis work, describes its limitations, and summarizes future research planned based on this thesis work.

References

1. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. The New England journal of medicine 2000;342:1301-8.

2. Sayer GT, Baker JN, Parks KA. Heart rescue: the role of mechanical circulatory support in the management of severe refractory cardiogenic shock. Current opinion in critical care 2012;18:409-16.

3. Muscedere J, Dodek P, Keenan S, et al. Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: prevention. Journal of critical care 2008;23:126-37.

4. Group PIftCCCT, the A, New Zealand Intensive Care Society Clinical Trials G, et al. Dalteparin versus unfractionated heparin in critically ill patients. The New England journal of medicine 2011;364:1305-14.

5. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Critical care medicine 1985;13:818-29.

6. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA : the journal of the American Medical Association 2001;286:1754-8.

7. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Journal of the American College of Cardiology 2012;60:1581-98.

8. Esmon CT. The normal role of Activated Protein C in maintaining homeostasis and its relevance to critical illness. Critical care 2001;5:S7-12.

9. Lim W, Qushmaq I, Devereaux PJ, et al. Elevated cardiac troponin measurements in critically ill patients. Archives of internal medicine 2006;166:2446-54.

10. Lim W, Whitlock R, Khera V, et al. Etiology of troponin elevation in critically ill patients. J Crit Care 2010;25:322-8.

11. Lim W, Holinski P, Devereaux PJ, et al. Detecting myocardial infarction in critical illness using screening troponin measurements and ECG recordings. Critical care 2008;12:R36.

12. Ostermann M, Lo J, Toolan M, et al. A prospective study of the impact of serial troponin measurements on the diagnosis of myocardial infarction and hospital and six-

month mortality in patients admitted to ICU with non-cardiac diagnoses. Critical care 2014;18:R62.

13. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). European heart journal 2018.

14. Reynolds T, Cecconi M, Collinson P, Rhodes A, Grounds RM, Hamilton MA. Raised serum cardiac troponin I concentrations predict hospital mortality in intensive care unit patients. British journal of anaesthesia 2012;109:219-24.

15. Babuin L, Vasile VC, Rio Perez JA, et al. Elevated cardiac troponin is an independent risk factor for short- and long-term mortality in medical intensive care unit patients. Critical care medicine 2008;36:759-65.

16. Bessiere F, Khenifer S, Dubourg J, Durieu I, Lega JC. Prognostic value of troponins in sepsis: a meta-analysis. Intensive care medicine 2013;39:1181-9.

17. Mehta S, Granton J, Gordon AC, et al. Cardiac ischemia in patients with septic shock randomized to vasopressin or norepinephrine. Critical care 2013;17:R117.

18. Landesberg G, Jaffe AS, Gilon D, et al. Troponin Elevation in Severe Sepsis and Septic Shock: The Role of Left Ventricular Diastolic Dysfunction and Right Ventricular Dilatation. Critical care medicine 2013.

19. Rosjo H, Varpula M, Hagve TA, et al. Circulating high sensitivity troponin T in severe sepsis and septic shock: distribution, associated factors, and relation to outcome. Intensive care medicine 2011;37:77-85.

20. Anderson JL, Adams CD, Antman EM, et al. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with

unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology 2013;61:e179-347.

21. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the American College of Emergency Physicians and Society for Cardiovascular Angiography and Interventions. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 2013;82:E1-27.

22. Lim W. JOE DOUPE LECTURE: Cardiac troponin in the intensive care unit. Clinical and investigative medicine Medecine clinique et experimentale 2009;32:E405-10.

23. Alpert JS, Thygesen KA, White HD, Jaffe AS. Diagnostic and therapeutic implications of type 2 myocardial infarction: review and commentary. The American journal of medicine 2014;127:105-8.

24. Wilt TJ, Bloomfield HE, MacDonald R, et al. Effectiveness of statin therapy in adults with coronary heart disease. Arch Intern Med 2004;164:1427-36.

25. Slater EE, MacDonald JS. Mechanism of action and biological profile of HMG CoA reductase inhibitors. A new therapeutic alternative. Drugs 1988;36 Suppl 3:72-82.

26. Liao JK, Laufs U. Pleiotropic effects of statins. Annu Rev Pharmacol Toxicol 2005;45:89-118.

27. Janda S, Young A, Fitzgerald JM, Etminan M, Swiston J. The effect of statins on mortality from severe infections and sepsis: a systematic review and meta-analysis. J Crit Care 2010;25:656 e7-22.

28. National Heart L, Blood Institute ACTN, Truwit JD, et al. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. The New England journal of medicine 2014;370:2191-200.

29. Page VJ, Casarin A, Ely EW, et al. Evaluation of early administration of simvastatin in the prevention and treatment of delirium in critically ill patients undergoing mechanical ventilation (MoDUS): a randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2017;5:727-37.

30. McAuley DF, Laffey JG, O'Kane CM, et al. Simvastatin in the acute respiratory distress syndrome. The New England journal of medicine 2014;371:1695-703.

31. Gross AK, Dunn SP, Feola DJ, et al. Clopidogrel treatment and the incidence and severity of community acquired pneumonia in a cohort study and meta-analysis of antiplatelet therapy in pneumonia and critical illness. Journal of thrombosis and thrombolysis 2013;35:147-54.

32. Wan YD, Sun TW, Kan QC, Guan FX, Zhang SG. Effect of statin therapy on mortality from infection and sepsis: a meta-analysis of randomized and observational studies. Critical care 2014;18:R71.

33. Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Study I, Devereaux PJ, Chan MT, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA 2012;307:2295-304.

34. Writing Committee for the VSI, Devereaux PJ, Biccard BM, 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.

35. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. European heart journal 2012;33:2551-67.

36. Lamy A, Devereaux PJ, Prabhakaran D, et al. Off-pump or on-pump coronary-artery bypass grafting at 30 days. The New England journal of medicine 2012;366:1489-97.

CHAPTER 2

The PROTROPIC Feasibility Study: Prognostic value of elevated troponins in critical illness (Accepted Canadian Journal of Anesthesia)

The PROTROPIC Feasibility Study:
Prognostic value of elevated troponins in critical illness

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Abstract

Background

Elevated cardiac troponin concentrations in critical illness are associated with an increased risk of death. We aimed to assess the feasibility of a larger study to ascertain the utility of cardiac troponin as a prognostic tool for mortality in critically ill patients.

Methods

Patients admitted to participating intensive care units (ICUs) during the 1-month enrolment period were eligible. We excluded cardiac surgical patients and patients who were admitted and either died or were discharged within 12 hours. In enrolled patients, we measured high-sensitivity cardiac troponin I (hs-cTnI), obtained ECGs and ascertained the incidence of myocardial infarction (MI), and isolated troponin elevation. Our feasibility objectives were to measure recruitment rate, the proportion of patients who consented under a deferred consent model and time required for data collection and study procedures.

Results

Over a 4-week enrollment period, 280 patients were enrolled using a deferred consent model. We obtained subsequent consent from 81% of patients. Study procedures and data collection required 1.7 hours per participant. Overall, 86 (38%) suffered a myocardial infarction (MI), 23 (10%) had an isolated hs-cTnI elevation, and 117 (52%) had no hs-cTnI elevation. Crude hospital mortality rate was 10% without an hs-cTnI elevation, 29% with an isolated hs-cTnl elevation (relative risk [RR] 2.2, 95% confidence interval [CI] 1.0, 6.0), and 29% with an MI (RR 2.6, 95%CI 1.4, 5.1).

Conclusion

Myocardial injury with elevated hs-cTnI concentrations and MIs occur frequently during critical illness. This pilot study has established the feasibility of conducting a large-scale investigation addressing this issue.

Introduction

Critically ill patients frequently have elevated cardiac troponin concentrations. Previous systematic screening studies suggest incidences of troponin elevations as high as 84% in this population.[1,2] Critically ill patients often receive life-support interventions such as mechanical ventilation, renal replacement therapy, vasopressors and/or inotropes, which in combination with the underlying illness, result in extremely high levels of physiologic stress. Excess sympathetic activity with an imbalance of myocardial oxygen supply and demand is hypothesized to be the cause of troponin elevations in a variety of critical illnesses such as sepsis, intracranial catastrophes, and severe burns.[3-5] Troponins can be elevated in conditions associated with increased cardiac preload or afterload such as pulmonary embolism, pulmonary hypertension and heart failure.[6-8] However, critical illness is an inflammatory and pro-coagulant condition, thereby theoretically increasing the risk for coronary thrombotic events.[9]

Whether fulfilling criteria for myocardial infarction (MI) or not, observational evidence suggests that elevated cardiac troponin concentrations in critical illness are associated with an increased risk of death even when adjusted for confounding factors.[10] We conducted a pilot study to assess the feasibility of a large cohort study to evaluate whether troponin elevations have independent prognostic value for mortality in critically ill patients.

Methods

Study Design

The PROTROPIC Feasibility Study (Prognostic value of elevated troponins in critical illness, NCT02285686) was a multicentre prospective cohort of consecutive critically ill patients conducted in 4 medical-surgical ICUs at 3 university-affiliated hospitals in Hamilton, Ontario (St. Joseph's Healthcare Hamilton, Hamilton General Hospital and Juravinski Hospital).

Study objectives

The pre-defined pilot study objectives were to assess the feasibility of recruiting patients efficiently in 4 ICUs, to evaluate the time required for data collection and study procedures, and to assess the deferred consent success rate. Pre-specified feasibility criteria were: 1) average recruitment rate (defined as the number of patients enrolled in the study per week) of 50 patients/week or more, 2) if the deferred consent rate (defined as the number of patients or substitute decision makers who provided consent divided by the total number of approached patients) was $\geq$80%, and 3) average time for completion of data collection of 6 hours or less. *A posteriori*, we measured compliance with study procedures (ability to assess serum high-sensitivity cardiac troponin I [hs-cTnI] levels and ECG screening at the protocolized time points) as an additional feasibility objective (calculated as the number of tests obtained as a proportion of the number that should have been obtained based on the study protocol).

The secondary objectives of the PROTROPICS Pilot were the primary objectives of a larger future study – to describe the incidence of hs-cTnI elevations and their impact on crude in-hospital mortality, to evaluate the proportion of critically ill patients with elevated hs-cTnI who met the Third Universal Definition for Myocardial Infarction,[11] and to assess the association of hs-cTnI elevations with in-hospital mortality (meeting MI criteria or not) upon adjusting for confounders known to influence mortality.

Eligibility Criteria

All adult patients admitted to participating ICUs during the study enrollment period were eligible. We excluded cardiac surgical patients, patients who were not expected to be alive or in ICU >12 hours and patients re-admitted to the ICU during the study period. The Hamilton Integrated Research Ethics Board approved the study and allowed either *a priori* or deferred informed consent.

Patient Recruitment

During the 1-month study enrolment period, the research team in the participating ICUs screened all new admissions, including on the weekends. We enrolled eligible patients using deferred consent, and obtained explicit consent from the patients or their substitute decision makers at the earliest possible time following enrolment. We recorded the occasions when study participation was declined, and the reasons why patients or substitute decision makers were not approached.

Procedures

Study data points were entered into a REDCap database.[12] Upon enrolment into the study, we collected demographic and baseline clinical data (diagnosis for admission, Acute Physiology and Chronic Health Evaluation-II [APACHE II] score[13], comorbidities, cardiovascular risk factors and home medications). During the ICU stay, we collected data on life support (mechanical ventilation, vasopressors and/or inotropes and dialysis), treatments (medications, blood product transfusions), laboratory tests (creatinine, hemoglobin) and cardiovascular events (MI, stroke, arrhythmia, major bleeding, pulmonary edema and non-fatal cardiac arrest). For the duration of hospital stay or up to 3 months after study enrolment, we collected data on vital status, ICU discharge, and risk stratification strategies (echocardiograms, stress tests, myocardial perfusion scans and cardiac catheterization). The time required for data collection was measured every day upon completion of study procedures by all data collectors during the fourth week of recruitment. Collecting these data in the fourth week allowed research staff sufficient time to familiarize themselves with study procedures.

Upon admission to and while participants were in the ICU, we obtained hs-cTnI measurements and ECGs daily for 1 week, every other day for 3 weeks and then weekly for 2 months. The hs-cTnI assay (a chemiluminescent microparticle assay from Abbott Diagnostics) was measured in fresh EDTA plasma on the ARCHITECT i2000SR analyzers at all three centres with laboratory performance in agreement with the latest recommendations.[14] We collected data on all cardiac troponin measurements and ECGs

ordered based on clinical care and data on whether patients had associated cardiac symptoms. We followed patients until hospital discharge, death or for a maximum of 3 months. Patients transferred to other hospitals were censored at the time of transfer.

The clinical team had access to all hs-cTnI results and ECGs that they ordered for clinical purposes, but were blinded to the non-clinical hs-cTnI and ECGs taken per the study protocol. If a non-clinical research ECG demonstrated significant new ST depressions or ST elevations, a copy of the ECG was provided to the clinical team immediately.

Adjudication

An hs-cTnI result >30 ng/L was considered elevated, which corresponds to the 99th percentile upper limit of normal based on healthy populations.[15,16] Physicians who were blinded to the hs-cTnI results adjudicated all ECGs independently and in duplicate. They evaluated ECGs chronologically for ischemic changes meeting the Third Universal Myocardial Infarction Definition criteria.[11] A cardiologist, also blinded to hs-cTnI results, resolved any disagreements. Patients were considered to have had an MI if they had elevated hs-cTnI with a rise and/or fall pattern in combination with either ischemic symptoms, ischemic ECG changes, new Q waves, new loss of viable myocardium, new regional wall motion abnormalities or evidence of intracoronary thrombus.[11] We divided the patients into three groups: MI, isolated hs-cTnI elevation and no hs-cTnI elevation.

Statistical Analyses

We included a convenience sample to inform our feasibility objectives. We used descriptive statistics to report the feasibility outcomes and baseline characteristics of participants: mean and standard deviation (SD), median and interquartile range (IQR) and counts with associated proportions. For crude comparisons, we compared proportions using Pearson's Chi-square or Fisher's exact test and continuous variables using 2-sample t-test or Wilcoxon rank-sum test as appropriate for the data distribution. We built a logistic regression model to assess the relationship between isolated hs-cTnI elevations, MI and mortality with adjustment for known prognostic factors. We chose the adjustment variables based on previous literature[17,18] and limited them to ensure a ratio of 10 events per variable; we forced them in the model. APACHE II was an obvious choice as it allowed the adjustment for multiple factors at once. We added troponin elevation and MI as they were the focus of the study. For the final variable, we chose to include vasopressor at baseline as opposed to another variable because it is not captured in the APACHE II score and may cause myocardial injury. A p value <0.05 was considered statistically significant. We report crude associations using relative risk (RR) and adjusted associations using adjusted odds ratio (OR) with the associated 95% confidence interval (CI).

Results

Recruitment and Feasibility Objectives

Over four consecutive weeks in the four ICUs, we screened 304 admissions; 282 patients were eligible but 2 were missed. Full consent was provided by 80.5% (214/266) of

patients/substitute decision makers. One patient initially consented, but later withdrew consent. Of approached patients, 13.9% (37/266) consented to the use of data that had already been collected but declined further study participation. No consent was sought for 14 patients: 13 due to perceived substitute decision maker burden and imminent death (these patients are included in the cohort) and 1 patient had no identified substitute decision maker. Details on the consent model and rate are published separately.[19] The patient flow chart is reported in **Figure 1**.

During the 4-week recruitment, we enrolled 266 patients, corresponding to 66.5 patients/week. Data collection took an average of 1 hour on a patient's first study day and 20 minutes on subsequent study days, for a median data collection time per patient of 1.7 hours throughout the entire study. One thousand and seventy-six hs-cTnI measurements occurred, which represents 74.6% of the troponin measurements that were supposed to occur based on the protocol. One thousand, two hundred and thirty-two ECGs were measured, which represents 85.4% of the ECG measurements that were supposed to occur based on the protocol.

Baseline Characteristics

Of the 226 participants with complete follow-up, mean age was 61.5 years (SD 17.3) and 133 (58.8%) were men. The mean APACHE II score was 14.9 (SD 7.6). Most patients were admitted with medical diagnoses (54.4%), while 38.1% were within 72 hours of a surgery and 7.5% had suffered a trauma. Of the participants, 54.9% had hypertension,

27.4% had diabetes, 33.6% had hypercholesterolemia, and 16.4% had a history of coronary artery disease. On the first ICU day, 43.4% of participants received invasive mechanical ventilation and 19.0% vasopressors; 1.8% received intermittent hemodialysis or continuous renal replacement therapy (Table 1). A table comparing the characteristics of patients with full consent and those who declined follow-up is presented in Appendix 1.

Clinical Outcomes

The median length of ICU stay was 3 days (IQR 2-7). Of the participants with complete follow-up, 97.8% (221/226) had at least one research hs-cTnI result with the median number of research hs-cTnI results being 5 (IQR 2 – 8). All participants with complete follow-up had at least one clinical or research hs-cTnI result. Of the patients with any data (those with complete follow-up and those who allowed us to use the data we had already collected, but declined further participation), 99.6% (262/263) had at least one hs-cTnI result, with the median number of research hs-cTnI results being 4 (IQR 2 to 7.75). Of 226 participants with complete follow-up, 109 patients (48.0%) had at least one hs-cTnI concentration exceeding the upper limit of normal cutoff (30 ng/L) during their ICU stay. Eighty-six patients (38.1%) met MI criteria and 23 (10.2%) had an isolated hs-cTnI elevation; 117 patients (51.7%) had no hs-cTnI elevation. The characteristics of the patients based on whether they suffered a MI, had an isolated hs-cTnI elevation or neither are presented in **Table 1**. APACHE II, vasopressors requirement on day 1, invasive and non-invasive ventilation differed significantly when the 3 groups were compared.

The crude hospital mortality rate was 9.5% in those without a hs-cTnI elevation, 28.6% for those with an isolated hs-cTnI elevation (RR, 2.2; 95% CI, 0.98-6.0) and 29.1% with an MI (RR, 2.6; 95% CI, 1.4-5.1) (**Table 2**). Neither isolated hs-cTnI elevation (aOR, 0.5; 95% CI, 0.21-1.22; p=0.13) nor MI (aOR, 1.38; 95% CI, 0.44-4.35; p=0.58) were found to be independent predictors of hospital mortality after adjusting for confounders (**Table 3**).

Discussion

The PROTROPICS pilot study has three key findings. First, cardiac troponin elevations are common in the ICU, occurring in 48% of patients enrolled. Second, such elevations may be associated with a three-fold increase in mortality. Finally, this pilot demonstrates the feasibility of a large-scale cohort aiming to determine the threshold at which cardiac troponin elevation is an independent prognostic factor for mortality in critically ill patients.

Despite improvements in mechanical ventilation[20], new technologies for hemodynamic support[21] and implementation of interventions that have been proven to decrease complications of critical illness,[22] about 15% of patients die during their ICU stay.[23] More than a fifth of patients admitted to the ICU die during their hospital stay. Risk prediction models for mortality have been validated but their discrimination is imperfect.[13,24] Having a better understanding of the relationship between widely available laboratory tests and mortality in the ICU may lead to identification of patients at risk of poor outcomes, and

evaluation of therapies in these patients at risk of poor outcomes, potentially decreasing the risk of death.

Studying cardiac troponin elevations during critical illness should be a priority. Clinicians need to understand a phenomenon that, based on our pilot study results, affects nearly half of all critically ill patients and is associated with an almost threefold increase in hospital mortality. The estimates seen in our pilot are consistent with previous reports on prospective systematic screening studies,[1,2,25] systematic reviews[4,10,26,27] and more recent non-systematic/retrospective cohorts.[28-31]

Currently, whether troponin elevations in the ICU hold an etiologic prognostic value of their own, or whether they are a marker of higher illness severity in general remains unclear. In many critically ill patients, cardiac symptoms cannot be elicited because of sedation or other distracting factors such as post-operative analgesic medications and delirium, making the distinction between isolated troponin elevations and MI in this population problematic and potentially spurious. If cardiac troponin elevation and MI identified in critically ill patients share the pathophysiology of type 1 (spontaneous, due to ruptured atherosclerosis plaque) or type 2 (secondary, caused by an imbalance of myocardial oxygen supply and demand) myocardial infarction,[11] - and they likely do - then these two conditions underscore the need for evaluation of treatments to improve the short and long-term outcomes of patients in the ICU. Cardiac troponin elevation as a potentially modifiable mediator of death is the focus of the OVATION65 trial

(NCT03431181) evaluating whether permissive hypotension in vasodilatory shock, by sparing catecholaminergic agents, decreases myocardial injury and, consequently, improves survival. As a parallel, cardiac troponin elevations after non-cardiac surgery are independently associated with mortality at 30 days as demonstrated in a large cohort study.[32] In a subsequent randomized controlled trial,[33] dabigatran was shown to lower the risk of major vascular complications when administered to patients with cardiac troponin elevations after non-cardiac surgery. Meanwhile, in the absence of ICU specific trials, applying data from the acute coronary syndrome literature in the ICU population could be considered given the strength of the body of evidence supporting the treatment of patients with MI whether perceived to be primary or secondary.[34]

A large, multicenter prospective cohort study with built-in ancillary mechanistic studies will improve our understanding of cardiac troponin elevations in critical illness. Such a cohort study with systematic laboratory testing and ECG screening will confirm if elevated cardiac troponins in critically illness, whether meeting other criteria for MI or not, are independently associated with a worse prognosis. Given the multiplicity of confounding factors, a large cohort is required to adjust for these confounders. The current literature consists of relatively small single center observational studies spread over almost 20 years using different types of cardiac troponin assays that have either been taken off the market or are bound to disappear in the future, with the majority of the major diagnostic companies producing hs-cTn assays.[35] A contemporary evaluation of the prevalence, incidence and risk factors for elevated cardiac troponin concentrations, how

patients with elevated concentrations are treated as a baseline, and the incidence of MI in critically ill patients are needed. Knowing the prognosis of these conditions and understanding current management will guide researchers and clinicians in evaluating potential risk-modifying therapies.

Our results demonstrate that conducting such a large cohort study with systematic cardiac troponin and ECG screening is feasible. The high consent rate is reassuring for the main cohort's external validity. The rapid accrual of participants confirms that a large cohort can be recruited efficiently. With data collection requiring on average less than 2 hours per participant, the study procedures are pragmatic. While compliance with screening cardiac troponin and ECG was suboptimal, we have identified it as a key study procedures to monitor in the main cohort.

Strengths and Limitations

Strengths of this study include demonstrating feasibility of a study to ascertain the utility of cardiac troponin as a prognostic tool for mortality in critically ill patients, using a larger sample size than previous studies using a similar design.[1,2] The study also provided estimates of the incidence of cardiac troponin elevation and MI that will inform a rigorous future evaluation. Using a deferred consent model, we avoided selection bias enrolling consecutive patients fulfilling eligibility criteria in 4 ICUs. Blinded adjudicators assessed serial ECGs for ischemia. The study also has several limitations. We evaluated feasibility in teaching centres; different practical issues may occur in community hospitals. In

addition, this pilot study was not powered to evaluate clinical outcomes and thus should generate further hypotheses rather than change practice.

Conclusions

Myocardial injury and MI are frequent during critical illness and these patients have an unadjusted higher risk of mortality compared to patients who do not have a cardiac troponin elevation. Whether the association of cardiac troponin elevation with death in the ICU is independent of other prognostic factors remains uncertain. This pilot study has established the feasibility of conducting a large-scale investigation addressing this issue.

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Figures

Figure 1 – Patient Flow Chart

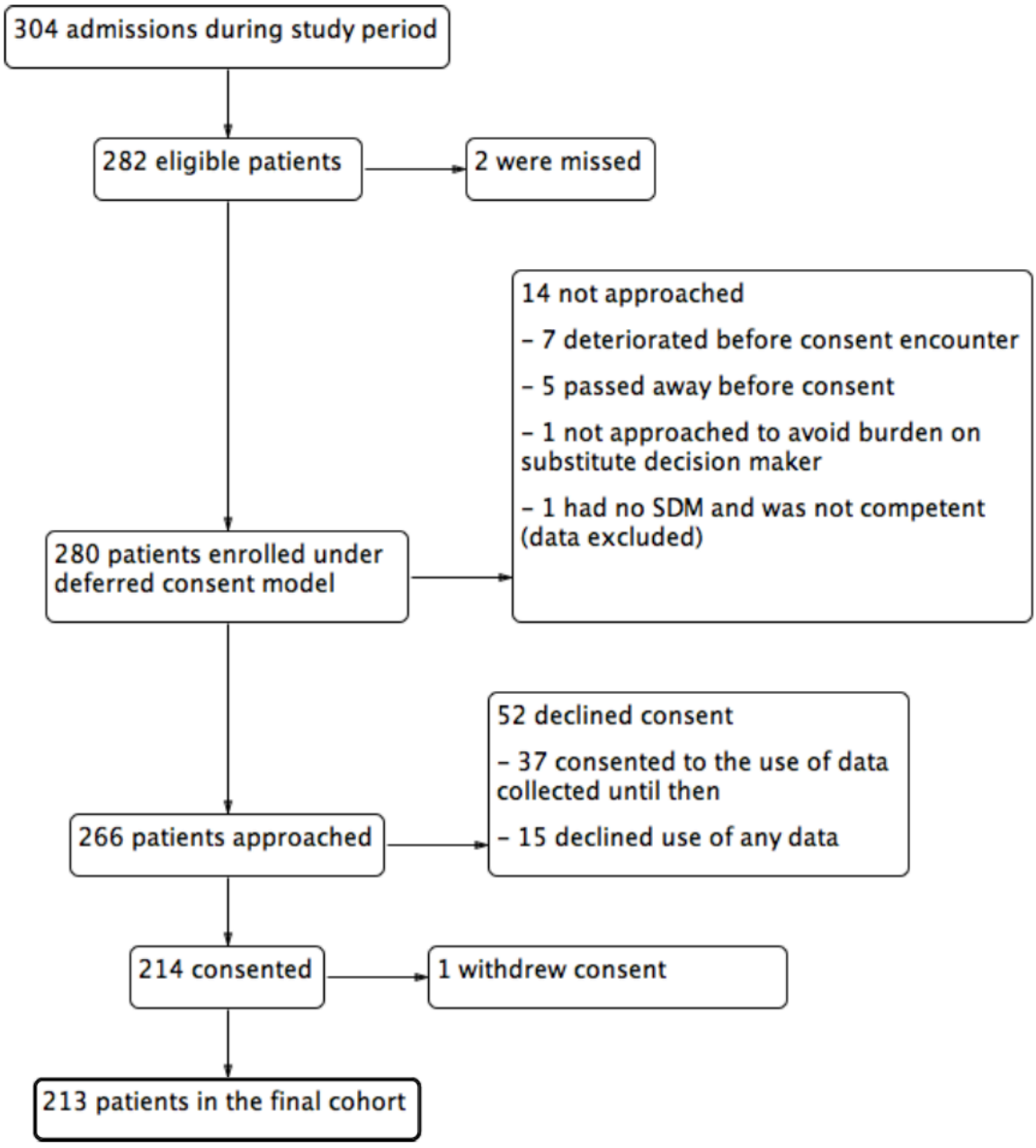

Table 1 – Baseline Characteristics of Participants with Complete Follow-up

	Total	Myocardial infarction	Isolated troponin elevation	No troponin elevation	P value for 3-group comparison
N (%)	226	86 (38.0)	23 (10.2)	117 (51.8)	
Age, years (SD)	61.5 (17.3)	63.4 (17.3)	65.5 (17.8)	59.4 (16.2)	0.12
Male sex, N (%)	133 (58.8)	48 (55.8)	13 (56.5)	72 (61.5)	0.66
BMI, kg/m^2 (SD)	30.2 (8.4)	28.4 (5.3)	26.8 (4.0)	31.7 (10.0)	0.21
APACHE II (SD)	14.9 (7.6)	18.2 (7.5)	19.2 (8.0)	11.5 (5.9)	<0.001
Patient type, N (%)					
Medical	123 (54.4)	59 (68.6)	16 (69.6)	48 (41.0)	0.002*
Surgical	86 (38.1)	22 (25.6)	6 (26.1)	58 (49.6)	
Trauma	17 (7.5)	5 (5.8)	1 (4.3)	11 (9.4)	
Diagnosis category on admission, N (%)					
Cardiovascular	34 (15.0)	18 (20.9)	4 (17.4)	12 (10.2)	**
Respiratory	67 (29.6)	21 (24.4)	7 (30.4)	39 (33.3)	
Gastrointestinal	33 (14.6)	13 (15.1)	1 (4.3)	19 (16.2)	
Neurologic	45 (19.9)	17 (18.9)	3 (13.0)	25 (21.4)	
Sepsis	19 (8.4)	11 (12.8)	3 (13.0)	5 (4.3)	
Metabolic	11 (4.8)	4 (4.7)	2 (8.7)	5 (4.3)	
Other	17 (7.5)	2 (2.3)	3 (13.0)	12 (10.2)	
Past medical history, N (%)					
Smoker	34 (15.0)	15 (17.4)	1 (4.3)	18 (15.3)	0.35*
Hypertension	124 (54.9)	50 (58.1)	15 (65.2)	59 (50.4)	0.29
Diabetes	62 (27.4)	29 (33.7)	8 (34.8)	25 (21.3)	0.10
Atrial fibrillation	28 (12.4)	17 (19.8)	2 (8.7)	9 (7.7)	0.03*
Hypercholesterolemia	76 (33.6)	31 (36.0)	11 (47.8)	34 (29.1)	0.17
Coronary artery disease	37 (16.4)	17 (19.8)	3 (13.0)	17 (14.5)	0.54*
Venous thromboembolism	10 (4.4)	3 (3.5)	0 (0)	7 (6.0)	0.57*
Congestive heart failure	26 (11.5)	14 (16.3)	3 (13.0)	9 (7.7)	0.14*
Moderate or severe valvular heart disease	5 (2.2)	3 (3.5)	0 (0)	2 (1.7)	0.80*
Peripheral vascular disease	14 (6.2)	5 (5.8)	1 (4.3)	8 (6.8)	1.00*
Stroke/Transient ischemic attack	34 (15.0)	22 (25.6)	4 (17.4)	8 (6.8)	0.001*
Chronic obstructive pulmonary disease/Asthma	51 (22.6)	18 (20.9)	7 (30.4)	26 (22.2)	0.62
Baseline life support, N (%)					
Inotropes	1 (0.4)	1 (1.2)	0 (0)	0 (0)	0.48*
Vasopressors	43 (19.0)	28 (32.6)	3 (12.0)	12 (10.2)	<0.001*
Non-invasive ventilation	29 (12.8)	17 (19.8)	0 (0)	12 (10.2)	0.02*
Invasive mechanical ventilation	98 (43.4)	45 (52.3)	15 (65.2)	38 (32.5)	0.001
Intermittent dialysis	2 (0.9)	2 (2.3)	0 (0)	0 (0)	0.34*
Continuous renal replacement therapy	2 (0.9)	2 (2.3)	0 (0)	0 (0)	0.34*

*at least 1 cell count with an expected count less than 5, Fisher's exact test used
** not calculated
SD: standard deviation, BMI: body mass index

Table 2 – Clinical Outcomes with Complete Follow-up

	Total	Myocardial infarction	Isolated troponin elevation	No troponin elevation	P value for 3-group comparison
Hospital mortality, N (%)	42 (18.8)	25 (29.1)	6 (28.6)	11 (9.5)	0.001*
Intensive care unit length of stay, days (IQR)	3 (2 – 7)	6 (2 – 12)	4 (2 – 5.25)	2 (1 – 5)	0.02
Hospital length of stay, days (IQR)	11 (5 – 22)	16 (8 – 34.75)	12 (3.75 – 18.25)	9 (4 – 14)	0.28

*at least 1 cell count with an expected count less than 5, Fisher's exact test used
IQR: interquartile range

Table 3 – Logistic Regression Model for In-Hospital Mortality

	B	S.E.	Wald	df	p	Odds ratio	95% CI lower	95%CI upper
Isolated troponins elevation	-0.69	0.46	2.30	1	0.13	0.50	0.21	1.22
Myocardial infarction	0.32	0.59	0.30	1	0.58	1.38	0.44	4.35
APACHE II	0.05	0.03	3.88	1	0.049	1.05	1.0	1.11
Vasopressor use on day 1	1.44	0.42	11.99	1	0.001	4.21	1.87	9.50
Constant	-2.45	0.59	17.13	1	0.000	0.09		

S.E.: Standard error
df: degree of freedom
CI: confidence interval

References

1. Ostermann M, Lo J, Toolan M, et al. A prospective study of the impact of serial troponin measurements on the diagnosis of myocardial infarction and hospital and six-month mortality in patients admitted to ICU with non-cardiac diagnoses. Critical care 2014;18:R62.

2. Lim W, Qushmaq I, Cook DJ, et al. Elevated troponin and myocardial infarction in the intensive care unit: a prospective study. Critical care 2005;9:R636-44.

3. Chen YN, Luo ZR, Zeng LJ, Wu MY, Wu YZ, Lin ZY. Cardiac troponin I: a marker for post-burn cardiac injury. Annals of clinical biochemistry 2000;37 (Pt 4):447-51.

4. Bessiere F, Khenifer S, Dubourg J, Durieu I, Lega JC. Prognostic value of troponins in sepsis: a meta-analysis. Intensive care medicine 2013;39:1181-9.

5. Wybraniec MT, Mizia-Stec K, Krzych LJ. Neurocardiogenic injury in subarachnoid hemorrhage: a wide spectrum of catecholamine-mediated brain-heart interactions. Cardiology journal 2014.

6. Muller-Bardorff M, Weidtmann B, Giannitsis E, Kurowski V, Katus HA. Release kinetics of cardiac troponin T in survivors of confirmed severe pulmonary embolism. Clinical chemistry 2002;48:673-5.

7. Horwich TB, Patel J, MacLellan WR, Fonarow GC. Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates in advanced heart failure. Circulation 2003;108:833-8.

8. Torbicki A, Kurzyna M, Kuca P, et al. Detectable serum cardiac troponin T as a marker of poor prognosis among patients with chronic precapillary pulmonary hypertension. Circulation 2003;108:844-8.

9. Esmon CT. The normal role of Activated Protein C in maintaining homeostasis and its relevance to critical illness. Critical care 2001;5:S7-12.

10. Lim W, Qushmaq I, Devereaux PJ, et al. Elevated cardiac troponin measurements in critically ill patients. Archives of internal medicine 2006;166:2446-54.

11. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Journal of the American College of Cardiology 2012;60:1581-98.

12. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377-81.

13. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Critical care medicine 1985;13:818-29.

14. Wu AHB, Christenson RH, Greene DN, et al. Clinical Laboratory Practice Recommendations for the Use of Cardiac Troponin in Acute Coronary Syndrome: Expert Opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine. Clinical chemistry 2018;64:645-55.

15. Keller T, Zeller T, Ojeda F, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. JAMA : the journal of the American Medical Association 2011;306:2684-93.

16. Kavsak PA, Worster A, Ma J, et al. High-Sensitivity Cardiac Troponin Risk Cutoffs for Acute Cardiac Outcomes at Emergency Department Presentation. Can J Cardiol 2017;33:898-903.

17. Capuzzo M, Valpondi V, Sgarbi A, et al. Validation of severity scoring systems SAPS II and APACHE II in a single-center population. Intensive care medicine 2000;26:1779-85.

18. Li G, Thabane L, Cook DJ, et al. Risk factors for and prediction of mortality in critically ill medical-surgical patients receiving heparin thromboprophylaxis. Ann Intensive Care 2016;6:18.

19. Honarmand K, Belley-Cote, E. P., Ulic D., Khalifa A., Gibson A., McClure G. R., Savija N., Alshamsi F., D'Aragon F., Rochwerg B., Duan E. H., Karachi T., Lamontagne F., Devereaux PJ, Whitlock R. P., Cook, D. J. The Deferred Consent Model in a Prospective Observational Study Evaluating Myocardial Injusry in the Intensive Care Unit. Journal of Intensive Care Medicine 2018;33:475-80.

20. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. The New England journal of medicine 2000;342:1301-8.

21. Sayer GT, Baker JN, Parks KA. Heart rescue: the role of mechanical circulatory support in the management of severe refractory cardiogenic shock. Current opinion in critical care 2012;18:409-16.

22. Muscedere J, Dodek P, Keenan S, et al. Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: prevention. Journal of critical care 2008;23:126-37.

23. The PROTECT investigators, the Canadian Critical Care Trials Group, New Zealand Intensive Care Society Clinical Trials G, et al. Dalteparin versus unfractionated heparin in critically ill patients. The New England journal of medicine 2011;364:1305-14.

24. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA : the journal of the American Medical Association 2001;286:1754-8.

25. Docherty AB, Sim M, Oliveira J, et al. Early troponin I in critical illness and its association with hospital mortality: a cohort study. Critical care 2017;21:216.

26. Zochios V, Valchanov K. Raised cardiac troponin in intensive care patients with sepsis, in the absence of angiographically documented coronary artery disease: A systematic review. J Intensive Care Soc 2015;16:52-7.

27. Sheyin O, Davies O, Duan W, Perez X. The prognostic significance of troponin elevation in patients with sepsis: a meta-analysis. Heart Lung 2015;44:75-81.

28. Vallabhajosyula S, Sakhuja A, Geske JB, et al. Role of Admission Troponin-T and Serial Troponin-T Testing in Predicting Outcomes in Severe Sepsis and Septic Shock. J Am Heart Assoc 2017;6.

29. Iqbal U, Siddique O, Jameel A, Anwar H, Chaudhary A. Prognostic Significance of Elevated Cardiac Troponin in Acute Gastrointestinal Bleeding. Gastroenterology Res 2017;10:238-43.

30. Masson S, Caironi P, Fanizza C, et al. Sequential N-Terminal Pro-B-Type Natriuretic Peptide and High-Sensitivity Cardiac Troponin Measurements During Albumin Replacement in Patients With Severe Sepsis or Septic Shock. Critical care medicine 2016;44:707-16.

31. Frencken JF, Donker DW, Spitoni C, et al. Myocardial Injury in Patients With Sepsis and Its Association With Long-Term Outcome. Circ Cardiovasc Qual Outcomes 2018;11:e004040.

32. 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.

33. 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 2018;391:2325-34.

34. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;130:2354-94.

35. Andruchow JE, Kavsak PA, McRae AD. Contemporary Emergency Department Management of Patients with Chest Pain: A Concise Review and Guide for the High-Sensitivity Troponin Era. Can J Cardiol 2018;34:98-108.

Contributorship Statement

Emilie Belley-Côté contributed significantly to the study's concept and design, data collection and analysis, and interpretation of the results. She wrote the first draft of the manuscript, provided critical revisions, and gave final approval of the submitted manuscript.

Richard Whitlock contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Diana Ulic contributed to the data collection and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Kimia Honarmand contributed to the data collection and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Abubaker Khalifa contributed to the data collection and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Graham McClure contributed to the data collection and analysis, and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Andrew Gibson contributed to the data collection and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Fayez Alshamsi contributed to the data collection and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Frédérick D'Aragon contributed to the data collection and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Bram Rochwerg contributed to the data collection and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Erick Duan contributed to the data collection and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Nevena Savija contributed to the data collection and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Tim Karachi contributed to the data collection and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

François Lamontagne contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Pete Kavsak contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Deborah Cook contributed to the study's concept and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Appendix 1 – Comparison of patients will complete follow-up and patients with partial consent

	Total	Complete follow-up	Partial consent with data	P value
N (%)	261	226	35	
Age, years (SD)	61.4 (17.8)	61.5 (17.3)	60.2 (23.1)	0.69
Male sex, N (%)	145 (55.6)	133 (58.8)	12 (34.3)	0.006
BMI, kg/m^2 (SD)	29.7 (8.1)	30.2 (8.4)	26.2 (4.4)	0.17
APACHE II (SD)	15.1 (7.7)	14.9 (7.6)	16.7 (8.6)	0.19
Patient type, N (%)				
Medical	142 (54.2)	123 (54.4)	18 (51.4)	0.39*
Surgical	98 (37.4)	86 (38.1)	12 (34.3)	
Trauma	22 (8.4)	17 (7.5)	5 (14.3)	
Diagnosis category on admission, N (%)				
Cardiovascular	38 (14.5)	34 (15.0)	4 (11.4)	0.95*
Respiratory	77 (29.4)	67 (29.5)	10 (28.6)	
Gastrointestinal	37 (14.1)	33 (14.6)	4 (11.4)	
Neurologic	53 (20.2)	45 (19.9)	8 (22.9)	
Sepsis	23 (8.8)	19 (8.4)	4 (11.4)	
Metabolic	12 (4.6)	11 (4.8)	1 (2.9)	
Other	22 (8.4)	17 (7.5)	4 (11.4)	
Past medical history, N (%)				
Smoker	38 (14.5)	34 (15.0)	4 (11.4)	0.80*
Hypertension	141 (53.8)	124 (54.9)	17 (48.6)	0.50
Diabetes	71 (27.1)	62 (27.4)	9 (25.7)	0.84
Atrial fibrillation	31 (11.8)	28 (12.4)	3 (8.6)	0.78*
Hypercholesterolemia	89 (34.0)	76 (33.6)	13 (37.1)	0.67
Coronary artery disease	40 (15.3)	37 (16.4)	3 (8.6)	0.24
Venous thromboembolism	11 (4.2)	10 (4.4)	1 (2.9)	1.00*
Congestive heart failure	30 (11.5)	26 (11.5)	4 (11.4)	1.00*
Moderate or severe valvular heart disease	5 (1.9)	5 (2.2)	0 (0)	0.75
Peripheral vascular disease	17 (6.5)	14 (6.2)	3 (8.6)	0.59*
Stroke/Transient ischemic attack	38 (14.5)	34 (15.0)	4 (11.4)	0.58*
Chronic obstructive pulmonary disease/Asthma	60 (22.9)	51 (22.6)	9 (25.7)	0.67*
Baseline life support, N (%)				
Inotropes	2 (0.8)	1 (0.4)	1 (2.9)	0.25*
Vasopressors	58 (22.1)	43 (19.0)	15 (42.9)	0.002
Non-invasive ventilation	32 (12.2)	29 (12.8)	3 (8.6)	0.48*
Invasive mechanical ventilation	120 (45.8)	98 (43.4)	22 (62.9)	0.03
Intermittent dialysis	3 (1.1)	2 (0.9)	1 (2.9)	0.35*
Continuous renal replacement therapy	2 (0.8)	2 (0.9)	0 (0)	0.75*
Outcomes				
Isolated troponin elevation	31	23 (10.1)	8 (22.9)	0.045*
Myocardial infarction	99	86 (37.9)	13 (37.1)	0.93

*at least 1 cell count with an expected count less than 5 – Fisher's exact test used

CHAPTER 3

Use of Secondary Cardiovascular Prevention Medications and Cardiac Risk Stratification in a Cohort of Critically Ill Patients with Cardiac Troponin Elevations

Use of Secondary Cardiovascular Prevention Medications and Cardiac Risk Stratification in a Cohort of Critically Ill Patients with Cardiac Troponin Elevations

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Under review

Abstract

Background

Optimal treatment and risk stratification for critically ill patients with troponin elevations are unknown. We aimed to describe the treatment, risk stratification, and factors associated with cardiac-risk stratification during critical illness.

Methods

The PROTROPIC Feasibility Study (Prognostic value of elevated troponins in critical illness) prospectively enrolled consecutive critically ill adults at four medical-surgical intensive care units (ICUs) in Canada. The study team gathered data on administered medications, laboratory tests, cardiac investigations, and vital status during the hospital stay or for up to 3 months after enrolment.

Results

Of the 226 participants with complete follow-up, 83 had a cardiac troponin elevation. Patients who experienced cardiac troponin elevation had higher mean APACHE II scores (19 vs. 13, $p<0.001$) and were more likely to have invasive mechanical ventilation (53% vs. 38%, $p=0.03$) and vasopressors (29% vs. 13%, $p=0.005$). At the time of ICU discharge, 37% of patients with a troponin elevation were receiving an antiplatelet agent, 32% a beta-blocker, 32% a statin, and 19% an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker. Patients with a troponin elevation were more likely to have an echocardiogram 65% vs 27%, $p<0.001$ and coronary angiogram (10% vs 0%,

$p<0.001$) compared to other patients. These cardiac investigations were more common among patients with troponin elevations and a history of congestive heart failure.

Conclusion

The use of secondary prevention medications is low in patients who experience troponin elevation during critical illness. Echocardiograms are frequently performed in this population, but few patients undergo coronary angiography.

Introduction

Preliminary evidence suggests that elevated troponin measurements in patients with critical illness portend a poor prognosis.[1,2] In clinical practice, it is our impression that among some patients, these troponin elevations are ignored, while other patients receive one or more treatments of proven benefit in acute coronary syndrome. Patient characteristics, clinician preferences, and local norms likely influence clinicians' decision making. Uncertainty exists regarding the optimal therapeutic and risk stratification approaches for critically ill patients who have a troponin measurement increase. Interpreting the available evidence regarding myocardial injury and type 2 myocardial infarction management in light of critical illness is challenging, and thus, the balance of risks and benefits when ordering cardiac medications or investigations in this population is unclear. In perioperative medicine, however, the Management of Myocardial Injury after Noncardiac Surgery (MANAGE) trial demonstrated that treatment with dabigatran can modify the risk of major vascular complications after myocardial injury after noncardiac surgery (MINS).[3] This raises the question of whether outcomes can be improved with cardiac medications in patients experiencing a troponin elevation during a critical illness. Before addressing this question, we must first understand current practice patterns in the intensive care unit (ICU). However, there is a lack of contemporary data regarding how physicians manage and risk stratify these patients. Using data from a multicentre cohort, we aimed to describe the treatment and risk stratification of patients with troponin elevations during a critical illness as well as factors associated with cardiac risk stratification.

Methods

Study Design

The PROTROPIC Feasibility Study (Prognostic value of elevated troponins in critical illness, NCT02285686) was a prospective cohort study that enrolled consecutive critically ill adult patients from four medical-surgical ICUs at three university-affiliated hospitals in Ontario, Canada (St. Joseph's Healthcare Hamilton, Hamilton General Hospital and Juravinski Hospital). The primary objective of the PROTROPIC Feasibility Study was to assess the feasibility of a large cohort study evaluating whether troponin elevations have independent prognostic value for mortality in critically ill patients; we have previously reported the procedures and results from the full feasibility study.[4]

Study Objectives

In this substudy, we aimed to describe the medical treatment and cardiac-risk stratification of patients with clinically identified troponin elevations during a critical illness. We also aimed to identify independent predictors of cardiac-risk stratification (echocardiograms, stress tests, myocardial perfusion scans and cardiac catheterization) in this population.

Screening and Eligibility Criteria

All patients newly admitted to participating ICUs were screened during the 1-month study enrolment period. Adult patients admitted to participating ICUs during the recruitment period were eligible. Cardiac surgical patients, patients who were not expected to be alive

or in ICU >12 hours, and patients re-admitted to the ICU during the study period were excluded. Patients or substitute decision makers provided either *a priori* or deferred informed consent at the earliest possible time following enrolment[5] as approved by the Hamilton Integrated Research Ethics Board. Patients who were enrolled based on the deferred consent process who died before they could provide consent and without a substitute decision maker were included in the study. In this substudy, we only included patients with complete follow-up.

Procedures

After enrolment, the study team collected demographic and baseline clinical data (diagnosis for admission, Acute Physiology and Chronic Health Evaluation-II [APACHE II] score,[6] comorbidities, cardiovascular risk factors and home medications). During participants' ICU stay, study personnel collected information on life support (mechanical ventilation, vasopressors and/or inotropes and dialysis), treatments (medications, blood product transfusions), laboratory tests (creatinine, hemoglobin) and cardiovascular events (myocardial infarction, arrhythmia, non-fatal cardiac arrest, pulmonary edema, stroke, and major bleeding). During the hospital stay or for up to 3 months after enrolment (whichever was shorter), study team documented vital status, ICU discharge, and cardiac investigations (echocardiograms, stress tests, myocardial perfusion scans and cardiac catheterization). If patients were transferred to another hospital, data collection was censored at the time of transfer from the index hospital. Data were entered into a REDCap database.[7]

The study team collected data on all cardiac troponin measurements and ECGs ordered by the clinical ICU team, and data on whether patients had associated cardiac symptoms. As part of the study protocol, cardiac troponin levels were also measured for research purposes. However, clinicians were blind to these measurement results and this substudy focuses on cardiac troponin measurement ordered by the clinical team.

Adjudication

Patients were considered to have a cardiac troponin elevation (i.e., myocardial injury) if they had a high sensitivity cardiac troponin I result >30 ng/L, which corresponds to the 99th percentile upper limit of normal based on healthy populations.[8,9] All ECGs were adjudicated independently and in duplicate by physicians who were blind to the cardiac troponin results. ECGs were evaluated chronologically for ischemic changes meeting the Third Universal Myocardial Infarction Definition criteria.[10] A cardiologist, also blinded to cardiac troponin results, resolved disagreements.

Statistical Analyses

This feasibility study used a convenience sample size.

The primary analysis focused on patients with a cardiac troponin elevation greater than the upper limit of normal. In secondary analyses, we considered patients to have an

elevated troponin measurement only if they had a cardiac troponin measurement >10 times the upper limit of normal.

Baseline characteristics of the patients, medications, and cardiac investigations are reported using descriptive statistics: mean and standard deviation (SD), median and interquartile range (IQR) and counts with associated proportions. We compared proportions with Pearson's Chi-square or Fisher's exact test and continuous variables with 2-sample t-test or Wilcoxon rank-sum test as appropriate for the data distribution. To compare the medications at three time points (before ICU admission, on the day of the troponin elevation, on ICU discharge), we used the Cochran-Q test. To evaluate predictors of cardiac investigations (echocardiogram, coronary angiogram, myocardial perfusion scans, or exercise stress test), we built a logistic regression model including troponin elevation (yes/no), ischemia on ECG (yes/no), ischemic symptoms (yes/no), age, APACHE II (Acute Physiology And Chronic Health Evaluation) score, sex (male/female), medical patient (versus trauma and surgical), and history of coronary artery disease (yes/no) or history of congestive heart failure or left ventricular dysfunction (yes/no). We chose these variables *a priori* based on clinical experience, limited them to ensure a ratio of 10 events per variable, and forced them into the model. We evaluated these variables for collinearity using the variance inflation factor (VIF) and tolerance. A p value <0.05 was considered statistically significant. We report adjusted odds ratio (OR) with the associated 95% confidence interval (CI). Analyses were performed using SPSS version 25.0 (IBM Corp) and the RVAideMemoire (v0.9-55) package in RStudio.

Results

Of the 261 patients who consented to provide data for the PROTROPIC Feasibility Study, 226 had complete follow-up and were included in this substudy. These participants all had at least one clinical cardiac troponin measurement.

Baseline characteristics

The baseline characteristics of patients with and without clinically recognized cardiac troponin elevations are compared in **Table 1**. Eighty-three patients (37%) had a clinically recognized cardiac troponin elevation. Patients who experienced a clinically recognized cardiac troponin elevation were more acutely ill, with significantly higher mean APACHE II scores, and a higher use of invasive mechanical ventilation and vasopressors ($p<0.05$ for all). They were more likely to have a medical diagnosis on admission, a history of atrial fibrillation, congestive heart failure, and stroke or transient ischemic attack. Baseline characteristics of patients with cardiac troponin elevation >10 times the upper limit of normal (n=30) compared to all other patients are presented in **Appendix 1**.

Cardiac medications use

Prior to ICU admission, a significantly higher proportion of patients who experienced a clinically recognized troponin elevation were taking an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker compared to patients without a troponin elevation. There was no significant difference in the use of other cardiac medications at baseline between patients with and without cardiac troponin elevations (**Table 2**). A

similar table focused on patients with a troponin elevation >10 times the upper limit of normal is presented in **Appendix 2**.

The use of cardiac medications before ICU admission, on the day of the troponin elevation, and on the last day in the ICU for patients with clinically recognized cardiac troponin elevations is presented in **Table 3**. Use of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker and oral anticoagulants was significantly lower during the ICU stay. Meanwhile, low-molecular weight heparin, unfractionated heparin and fondaparinux use significantly increased after ICU admission. Although the proportions of patients receiving beta-blockers and statins initially decreased, on the last day in ICU, these proportions increased to levels similar to pre-ICU admission. Of patients who experienced a clinically recognized cardiac troponin elevation, 36.7% were on an antiplatelet agent on the last day of ICU, 31.6% on a beta-blocker, 19.0% an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, and 31.6% on a statin. We present the use of cardiac medications at the same time-points in patients who had clinically recognized cardiac troponin elevations >10 times the upper limit of normal in **Appendix 3**.

Cardiac investigations

Overall, 93 patients (41.2%) underwent an echocardiogram and 8 patients (3.5%) underwent a coronary angiogram while no patients had exercise stress tests or nuclear perfusion scans done during their index hospital admission. Of patients with clinically

detected cardiac troponin elevations, 65.1% had an echocardiogram and 9.6% had a coronary angiogram, significantly more than patients without clinically detected troponin elevations (**Table 4**). Of patients with clinically detected troponin elevations >10 times the upper limit of normal, 66.7% had an echocardiogram and 16.7% had a coronary angiogram (**Appendix 4**).

Of the 8 patients who had a coronary angiogram, one patient (12.5%) was found to have a significant stenosis of the left main artery and 4 patients (50%) had significant stenosis of other vessels. Two patients (25.0%) underwent percutaneous coronary intervention and 2 patients (25.0%) required coronary artery bypass surgery. One patient with single-vessel disease was managed medically. The three other patients had no coronary stenosis > 30%.

Predictors of cardiac investigations

We present the regression model evaluating predictors of cardiac investigations in critically ill patients in **Table 5**. Independent predictors of cardiac risk stratification were cardiac troponin elevation and history of congestive heart failure. In a sensitivity analysis limited to patients with cardiac troponin elevations, the only significant predictor of cardiac investigation was APACHE II score (**Appendix 5**). We found no multicollinearity for the variables forced in the model (**Appendix 6**).

In-hospital outcomes

Of the 83 patients with clinically recognized troponin elevations, 29 (34.9%) died during the index hospital stay as compared to 13 (9.1%) patients without a clinically recognized troponin elevation. Eighteen of the 30 patients (60.0%) with troponin elevations >10 times the upper limit of normal died during the index hospital stay, as compared with 24 patients (12.2%) without a troponin elevation >10 times the upper limit.

Discussion

Key findings

Approximately one third of patients admitted to the ICU had a clinically recognized troponin elevation. Patients who experienced a clinically recognized cardiac troponin elevation, compared to those who did not, were more acutely ill, with significantly higher mean APACHE II scores, and a higher use of invasive mechanical ventilation and vasopressors. On discharge from ICU, medications of proven benefit in secondary prevention (antiplatelet agents, angiotensin II receptor blockers and angiotensin-conversion-enzyme inhibitor, beta-blockers, and statins) were infrequently prescribed in these patients. Of these patients, 10% had a coronary angiogram to stratify cardiac risk, significantly more than patients without clinically detected cardiac troponin elevations. In-hospital cardiac investigations were significantly more likely among patients with cardiac troponin elevations and a history of congestive heart failure. No patient underwent an exercise stress test or nuclear perfusion imaging.

Interpretation in the Context of Previous Literature

Other studies have suggested that cardiac troponin elevations during a critical illness are associated with an increased risk of in-hospital mortality.[1,2] However, a considerable knowledge gap persists regarding the long-term outcomes of these patients and whether these outcomes can be modified with medications that are effective in other types of myocardial injury. In a cohort of 1570 patients in France and Belgium, high-sensitivity cardiac troponin elevations on the day of discharge from medical-surgical ICU were associated with a two-fold increase in the risk of mortality at 1 year.[11]

This risk of death may be modifiable with targeted treatment[3] or with aggressive cardiovascular secondary prevention therapy as previously demonstrated for patients with myocardial injury after noncardiac surgery (MINS).[12] We found a low use of secondary cardiovascular prevention medication prescription on ICU discharge in this study; antiplatelet therapy was the most frequently prescribed at 36.7%. Moreover, there was negligible increase in the use of these secondary prevention cardiovascular medications between baseline and ICU discharge. Given the absence of evidence specific for myocardial injury during critical illness, extrapolation from studies in other populations with myocardial injury and from the acute coronary syndrome literature should be considered. Patients with type 2 myocardial infarction are commonly found to have coronary atherosclerosis on coronary angiogram.[13] Those patients who develop cardiac troponin elevation during critical illness likely warrant use of secondary prevention medications more consistently than observed in this cohort, but evidence informing such decisions is sparse.

Some medications used in the management of acute coronary syndromes and secondary cardiovascular prevention have been shown to be potentially beneficial in critically ill populations. In a systematic review and meta-analysis evaluating the effect of antiplatelet therapy in 10 cohort studies including 689,897 patients with sepsis, antiplatelet drugs were associated with reduced in-hospital mortality (OR 0.71, 95% confidence interval [CI] 0.59-0.84, $p<0.05$).[14] Another systematic review and meta-analysis of 25 randomized controlled trials evaluating statins in 2692 critically ill patients had similar findings; statins were associated with a significantly lower in-hospital mortality (risk ratio 0.77, 95% CI 0.68-0.87, $p<0.0001$) without an associated increase in adverse events such as myopathy, liver dysfunction, or delirium.[15] Short acting beta-blockers may also be of benefit to critically ill patients; two small randomized controlled trials investigated the effect of esmolol in patients in septic shock.[16,17] The larger trial (144 patients)[16] found lower 28-day mortality in the esmolol group, while the other trial (41 patients)[17] demonstrated significantly lower troponin levels with esmolol treatment. Critically ill patients are at higher risk of major bleeding than non-critically ill hospitalized patients; this should be taken into account when ordering therapeutic dose anticoagulation or dual antiplatelet therapy.[18,19] However, as thromboprophylaxis is standard of care in critical care, using low-dose fondaparinux could be considered and would be consistent with the dose demonstrated effective for acute coronary syndrome.[20] Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are usually not prescribed during a critical illness; however, their prescription on discharge has been independently

associated with lower mortality at 1 year in a cohort of 611 patients with acute kidney injury during a critical illness.[21] Although in broader populations, the balance of benefit and harm may be in their favor, when deciding whether to initiate these medications for critically ill patients, clinicians should weigh their risks and benefits in each individual.[22]

In this cohort, echocardiograms were more frequently obtained in patients with clinically recognized cardiac troponin elevations, but non-invasive testing for ischemia (e.g., exercise stress test and nuclear perfusion studies) was not obtained during the index hospital stay. This finding, combined with the absence of increased prescription of secondary prevention medications, may reflect clinicians' disbelief that cardiac troponin elevations in critical illness represent an ischemic phenomenon, which is concordant with a propensity to avoid further testing for underlying coronary artery disease in this setting.

Strengths and Limitations

This study has some strengths. We are reporting on consecutive patients in 4 ICUs in 3 centres. As the primary objective of the study was not to evaluate the treatment and cardiac investigations of patients with troponin elevations, our results are unlikely to be affected by the Hawthorne effect.[23] This study also has several limitations. The small sample size did not allow the exploration of possible associations between treatment and outcomes. In addition, the short follow-up prevented post-hospital assessment of cardiac risk stratification, medications, and outcomes. All participating centres were in the same city, and regional variations in practice likely exist.

Conclusions

The use of secondary prevention medications is low in patients who experience a cardiac troponin elevation during critical illness. Echocardiograms are frequently obtained and coronary angiograms infrequently obtained in this population, whereas non-invasive testing for ischemia is not undertaken during the index hospital stay.

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Disclosures

EPBC, DJC, AQ, DU, KH, AK, GRM, AG, FA, FDA, BR, ED, NS, TK, FL and RPW have no relevant conflicts of interest.

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PJD is a member of a research group with a policy of not accepting honorariums or other payments from industry for their own personal financial gain. They do accept honorariums/payments from industry to support research endeavours and costs to participate in meetings. Based on study questions he has originated and grants he has written, he has received grants from Abbott Diagnostics, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb, Coviden, Octapharma, Philips Healthcare, Roche

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References:

1. Lim W, Holinski P, Devereaux PJ, et al. Detecting myocardial infarction in critical illness using screening troponin measurements and ECG recordings. Critical care 2008;12:R36.

2. Ostermann M, Lo J, Toolan M, et al. A prospective study of the impact of serial troponin measurements on the diagnosis of myocardial infarction and hospital and six-month mortality in patients admitted to ICU with non-cardiac diagnoses. Critical care 2014;18:R62.

3. 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 2018;391:2325-34.

4. Belley-Cote EP, Whitlock RP, Ulic DV, et al. P2748 The PROTROPICS feasibility: prognostic value of elevated troponins in critical illness. European heart journal 2017;38:ehx502.P2748-ehx502.P.

5. Honarmand K, Belley-Cote, E. P., Ulic D., Khalifa A., Gibson A., McClure G. R., Savija N., Alshamsi F., D'Aragon F., Rochwerg B., Duan E. H., Karachi T., Lamontagne F., Devereaux PJ, Whitlock R. P., Cook, D. J. The Deferred Consent Model in a Prospective Observational Study Evaluating Myocardial Injusry in the Intensive Care Unit. Journal of Intensive Care Medicine 2018;33:475-80.

6. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Critical care medicine 1985;13:818-29.

7. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377-81.

8. Keller T, Zeller T, Ojeda F, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. JAMA : the journal of the American Medical Association 2011;306:2684-93.

9. Kavsak PA, Worster A, Ma J, et al. High-Sensitivity Cardiac Troponin Risk Cutoffs for Acute Cardiac Outcomes at Emergency Department Presentation. Can J Cardiol 2017;33:898-903.

10. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Journal of the American College of Cardiology 2012;60:1581-98.

11. Gayat E, Cariou A, Deye N, et al. Determinants of long-term outcome in ICU survivors: results from the FROG-ICU study. Critical care 2018;22:8.

12. 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.

13. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). Circulation 2018;138:e618-e51.

14. Ouyang Y, Wang Y, Liu B, Ma X, Ding R. Effects of antiplatelet therapy on the mortality rate of patients with sepsis: A meta-analysis. Journal of critical care 2018;50:162-8.

15. Belley-Cote EP, Cook DJ, Honarmand K, et al. Statins in Critically Ill Patients: A systematic review and meta-analysis. 2018.

16. Morelli A, Ertmer C, Westphal M, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. JAMA : the journal of the American Medical Association 2013;310:1683-91.

17. Yang S, Liu Z, Yang W, et al. [Effects of the beta-blockers on cardiac protection and hemodynamics in patients with septic shock: a prospective study]. Zhonghua wei zhong bing ji jiu yi xue 2014;26:714-7.

18. Lauzier F, Arnold DM, Rabbat C, et al. Risk factors and impact of major bleeding in critically ill patients receiving heparin thromboprophylaxis. Intensive care medicine 2013;39:2135-43.

19. Decousus H, Tapson VF, Bergmann JF, et al. Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. Chest 2011;139:69-79.

20. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive care medicine 2017;43:304-77.

21. Gayat E, Hollinger A, Cariou A, et al. Impact of angiotensin-converting enzyme inhibitors or receptor blockers on post-ICU discharge outcome in patients with acute kidney injury. Intensive care medicine 2018.

22. Chapman AR, Shah ASV, Lee KK, et al. Long-Term Outcomes in Patients With Type 2 Myocardial Infarction and Myocardial Injury. Circulation 2018;137:1236-45.

23. McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. J Clin Epidemiol 2014;67:267-77.

Table 1 – Baseline Characteristics of Participants

	Total	Clinically recognized cardiac troponin >ULN	No clinically recognized cardiac troponin elevation	P value
N (%)	226	83	143	
Age, years (SD)	61.5 (17.3)	64.9 (17.1)	59.6 (16.5)	0.02
Male sex, N (%)	134 (59.3)	45 (54.2)	88 (61.5)	0.33
APACHE II (SD)	14.9 (7.6)	18.9 (7.7)	12.5 (6.4)	<0.001
Patient type, N (%)				
Medical	123 (54.4)	56 (67.5)	67 (46.9)	0.01
Surgical	86 (38.1)	22 (26.5)	64 (44.8)	
Trauma	17 (7.5)	5 (6.0)	12 (8.4)	
Diagnosis category on admission, N (%)				
Cardiovascular	34 (15.0)	21(25.3)	13 (9.1)	<0.001*
Respiratory	67 (29.6)	19 (22.9)	48 (33.6)	
Gastrointestinal	33 (14.6)	7 (8.4)	26 (18.2)	
Neurologic	45 (19.9)	17 (20.5)	28 (19.6)	
Sepsis	19 (8.4)	11 (13.3)	8 (5.6)	
Metabolic	11 (4.8)	6 (7.2)	5 (3.5)	
Other	17 (7.5)	2 (2.4)	15 (10.5)	
Past medical history, N (%)				
Smoker	34 (15.0)	10 (12.0)	24 (16.8)	0.44
Hypertension	124 (54.9)	52 (62.7)	72 (50.3)	0.07
Diabetes	62 (27.4)	26 (31.3)	36 (25.2)	0.35
Atrial fibrillation	28 (12.4)	16 (19.3)	12 (8.4)	0.02
Hypercholesterolemia	76 (33.6)	33 (39.8)	43 (30.1)	0.15
Coronary artery disease	37 (16.4)	17 (20.5)	20 (14.0)	0.26
Venous thromboembolism	10 (4.4)	3 (3.6)	7 (4.9)	0.75*
Congestive heart failure	26 (11.5)	15 (18.1)	11 (7.7)	0.03
Moderate or severe valvular heart disease	5 (2.2)	2 (2.4)	3 (2.1)	1.00*
Peripheral vascular disease	14 (6.2)	5 (6.0)	9 (6.3)	1.00
Stroke/Transient ischemic attack	34 (15.0)	20 (24.1)	14 (9.8)	0.004

Chronic obstructive pulmonary disease/Asthma	51 (22.6)	18 (21.7)	33 (23.2)	0.87
Baseline life support, N (%)				
Inotropes	1 (0.4)	1 (1.2)	0 (0)	0.37*
Vasopressors	43 (19.0)	24 (28.9)	19 (13.3)	0.005
Non-invasive ventilation	29 (12.8)	14 (16.9)	15 (10.5)	0.22
Invasive mechanical ventilation	98 (43.4)	44 (53.0)	54 (37.8)	0.03
Intermittent dialysis	2 (0.9)	1 (1.2)	1 (3.8)	1.00*
Continuous renal replacement therapy	2 (0.9)	2 (2.4)	0 (0)	0.13*

* Fisher's exact test
APACHE: Acute Physiology And Chronic Health Evaluation
N: number
SD: standard deviation
ULN: upper limit of normal

Table 2 – Cardiac Medications Pre-Intensive Care Unit Admission

	Clinically recognized troponin elevation >ULN	**No clinically recognized troponin elevation**	**p-value**
Total N	83	143	
ASA, n (%)	27 (32.5)	40 (28.0)	0.47
P2Y12 inhibitor, n (%)	5 (6.0)	4 (2.8)	0.29*
Any antiplatelet agent, n (%)	28 (33.7)	42 (29.4)	0.49
Oral anticoagulant, n (%)	12 (14.5)	11 (7.7)	0.11
Diuretic, n (%)	26 (31.3)	36 (25.2)	0.32
Beta-blocker, n (%)	25 (30.1)	35 (24.5)	0.35
ACEI/ARB, n (%)	40 (48.2)	47 (32.9)	0.02
Non-dihydropyridine CCB, n (%)	7 (8.4)	5 (3.5)	0.13
Dihydropyridine CCB, n (%)	12 (14.5)	23 (16.1)	0.75
Amiodarone, n (%)	2 (2.4)	0 (0)	0.13
Digoxin, n (%)	7 (8.4)	4 (2.8)	0.10
Statin, n (%)	34 (41.0)	46 (32.2)	0.18
Nitrates, n (%)	2 (2.4)	1 (0.7)	0.56
IV heparin, n (%)	0 (0)	1 (0.7)	1.00*
Fondaparinux, n (%)	0 (0)	0 (0)	N/A
Therapeutic LMWH, n (%)	0 (0)	1 (0.7)	1.00*
IV heparin or fondaparinux or therapeutic LMWH, n (%)	0 (0)	2 (1.4)	0.53

**Fisher's exact test*
ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker
ASA: aspirin
CCB: calcium channel blocker
IV: intravenous
LMWH: low molecular weight heparin
N: number
N/A: not available, could not be computed
ULN: upper limit of normal

Table 3 – Cardiac Medications at Three Timepoints in Patients with Cardiac Troponin Elevations

	Before ICU admission	**On the day of troponin elevation**	**On the last ICU day**	p-value
ASA, n (%)	24 (30.4)	28 (35.4)	29 (36.7)	0.47
P2Y12 inhibitor, n (%)	4 (5.1)	7 (8.9)	8 (10.1)	0.11
Any antiplatelet agent, n (%)	25 (31.6)	28 (35.4)	29 (36.7)	0.64
Oral anticoagulant, n (%)	11 (13.9)	5 (6.3)	6 (7.6)	0.03
Beta-blocker, n (%)	24 (30.4)	13 (16.5)	25 (31.6)	0.01
ACEI/ARB, n (%)	37 (46.8)	12 (15.2)	15 (19.1)	<0.001
Non-dihydropyridine CCB, n (%)	7 (8.9)	1 (1.3)	4 (5.1)	0.02
Dihydropyridine CCB, n (%)	11 (13.9)	6 (7.6)	12 (15.2)	0.09
Amiodarone, n (%)	2 (2.5)	9 (11.4)	9 (11.4)	0.02
Diuretic, n (%)	24 (30.4)	18 (22.8)	20 (25.3)	0.41
Digoxin, n (%)	6 (7.6)	2 (2.5)	6 (7.6)	0.14
Statin, n (%)	31 (39.2)	20 (25.3)	25 (31.6)	0.01
Nitrates, n (%)	2 (2.5)	2 (2.5)	2 (2.5)	1.00
IV heparin, n (%)	0 (0)	5 (6.3)	4 (5.1)	0.03
Fondaparinux, n (%)	0 (0)	6 (7.6)	6 (7.6)	0.02
Therapeutic LMWH, n (%)	0 (0)	0 (0)	3 (3.8)	N/A
IV heparin or fondaparinux or therapeutic LMWH, n (%)	0 (0)	11 (13.9)	13 (16.5)	<0.001

ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin II receptor blocke
ASA: aspirin
CCB: calcium channel blocker
ICU: intensive care unit
IV: intravenous
LMWH: low molecular weight heparin
N: number
N/A: not available, could not be computed

Table 4 – Use of Cardiac Investigations

	Clinically recognized troponin elevation >ULN	**No clinically recognized troponin elevation**	**p-value**
N	**83**	**143**	
Exercise stress test, n (%)	0 (0)	0 (0)	N/A
Echocardiogram, n (%)	54 (65.1)	39 (27.3)	<0.001
Nuclear perfusion study, n (%)	0 (0)	0 (0)	N/A
Coronary angiogram, n (%)	8 (9.6)	0 (0)	<0.001*

**Fisher's exact test*
N: number
N/A: not applicable, could not be computed
ULN: upper limit of normal

Table 5 – Logistic Regression Model - Predictors of Cardiac Investigation

	B	S.E.	Wald	df	p	Odds ratio	95%CI lower	95%CI upper
ECG changes	0.164	0.313	0.274	1	0.601	1.178	0.638	2.175
Troponin elevation >ULN	1.358	0.341	15.856	1	<0.001	3.890	1.993	7.592
Ischemic symptoms	0.395	0.352	1.259	1	0.262	1.484	0.745	2.956
Age	0.005	0.009	0.232	1	0.630	1.005	0.986	1.023
History of coronary artery disease	0.189	0.441	0.185	1	0.668	1.208	0.509	2.867
History of congestive heart failure	1.168	0.515	5.155	1	0.023	3.216	1.173	8.817
APACHE II	0.047	0.024	3.814	1	0.051	1.048	1.000	1.098
Medical vs. trauma and surgical	0.30	0.334	0.008	1	0.928	1.031	0.535	1.985
Sex	0.143	0.319	0.202	1	0.653	1.154	0.618	2.156
Constant	-1.847	0.825	5.018	1	0.25	0.158		

APACHE II: Acute Physiology And Chronic Health Evaluation
CI: confidence interval
df: degree of freedom
ECG: electrocardiogram
ULN: upper limit of normal

Contributorship Statement

Emilie Belley-Côté contributed significantly to the study's concept and design, data collection and analysis, and interpretation of the results. She wrote the first draft of the manuscript, provided critical revisions, and gave final approval of the submitted manuscript.

Deborah Cook contributed to the study's concept and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

PJ Devereaux contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Anila Qasim contributed to the data analysis and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Diana Ulic contributed to the data collection and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Kimia Honarmand contributed to the data collection and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Abubaker Khalifa contributed to the data collection and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Graham McClure contributed to the data collection and analysis, and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Andrew Gibson contributed to the data collection and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Fayez Alshamsi contributed to the data collection and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Fayez D'Aragon contributed to the data collection and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Bram Rochwerg contributed to the data collection and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Erick Duan contributed to the data collection and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Nevena Savija contributed to the data collection and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Tim Karachi contributed to the data collection and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

François Lamontagne contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Pete Kavsak contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Richard Whitlock contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Appendix 1 - Baseline Characteristics of Participants, >10xULN

	Total	Clinically recognized cardiac troponin >10 ULN	No clinically recognized cardiac troponin elevation	P value
N (%)	226	30	196	
Age, years (SD)	61.5 (17.3)	63.5 (19.2)	61.2 (16.5)	0.49
Male sex, N (%)	134 ()	17 (56.7)	117 (59.7)	<0.01
APACHE II (SD)	14.9 (7.6)	20.2 (7.4)	14.0 (7.3)	
Patient type, N (%)				
Medical	123 (54.4)	21 (70.0)	102 (52.0)	0.17*
Surgical	86 (38.1)	7 (23.3)	79 (40.3)	
Trauma	17 (7.5)	2 (6.7)	15 (7.7)	
Diagnosis category on admission, N (%)				
Cardiovascular	34 (15.0)	10 (33.3)	24 (12.2)	0.004*
Respiratory	67 (29.6)	3 (10.0)	64 (32.7)	
Gastrointestinal	33 (14.6)	4 (13.3)	29 (14.8)	
Neurologic	45 (19.9)	7 (23.3)	38 (19.4)	
Sepsis	19 (8.4)	5 (16.7)	14 (7.1)	
Metabolic	11 (4.8)	1 (3.3)	10 (5.1)	
Other	17 (7.5)	0 (0)	17 (8.7)	
Past medical history, N (%)				
Smoker	34 (15.0)	3 (10.0)	31 (15.8)	0.59*
Hypertension	124 (54.9)	19 (63.3)	105 (53.6)	0.30
Diabetes	62 (27.4)	9 (30.0)	53 (27.0)	0.72
Atrial fibrillation	28 (12.4)	2 (6.6)	26 (13.3)	0.55*
Hypercholesterolemia	76 (33.6)	12 (40.0)	64 (32.7)	0.42
Coronary artery disease	37 (16.4)	8 (26.7)	29 (14.8)	0.11*
Venous thromboembolism	10 (4.4)	1 (3.3)	9 (4.6)	1.00*
Congestive heart failure	26 (11.5)	4 (13.3)	22 (11.2)	0.76*
Moderate or severe valvular heart disease	5 (2.2)	1 (3.3)	4 (2.0)	0.51*
Peripheral vascular disease	14 (6.2)	1 (3.3)	13 (6.6)	0.70*
Stroke/Transient ischemic attack	34 (15.0)	7 (23.3)	27 (13.8)	0.18*
Chronic obstructive pulmonary disease/Asthma	51 (22.6)	5 (16.7)	46 (23.5)	0.41
Baseline life support, N (%)				
Inotropes	1 (0.4)	1 (3.3)	0 (0)	0.13*
Vasopressors	43 (19.0)	16 (53.3)	27 (13.8)	<0.01

Non-invasive ventilation	29 (12.8)	6 (20.0)	23 (14.8)	0.24*
Invasive mechanical ventilation	98 (43.4)	19 (63.3)	79 (40.3)	0.02
Intermittent dialysis	2 (0.9)	1 (3.3)	1 (0.5)	0.25*
Continuous renal replacement therapy	2 (0.9)	1 (3.3)	1 (0.5)	0.25*

* Fisher's exact test
APACHE: Acute Physiology And Chronic Health Evaluation
N: number
SD: standard deviation
ULN: upper limit of normal

Appendix 2 – Medications Pre-Intensive Care Unit Admission Limited to Elevations >10xULN

	Clinically recognized troponin elevation >10xULN	**No clinically recognized troponin elevation >10xULN**	**p-value**
Total N	30	196	
ASA, n (%)	8 (27)	59 (30)	0.70
P2Y12 inhibitor, n (%)	3 (10)	6 (3)	0.10*
Any antiplatelet agent, n (%)	8 (27)	62 (32)	0.58
Oral anticoagulant, n (%)	2 (7)	21 (11)	0.75
Diuretic, n (%)	7 (23)	55 (28)	0.59
Beta-blocker, n (%)	10 (33)	50 (26)	0.37
ACEI/ARB, n (%)	13 (43)	74 (38)	0.56
Non-dihydropyridine CCB, n (%)	2 (7)	10 (5)	0.66*
Dihydropyridine CCB, n (%)	4 (13)	31 (16)	1.00*
Amiodarone, n (%)	0 (0)	2 (1)	1.00*
Digoxin, n (%)	1 (3)	10 (5)	1.00*
Statin, n (%)	12 (40)	68 (35)	0.57
Nitrates, n (%)	2 (7)	1 (0.5)	0.05*
IV heparin, n (%)	0 (0)	1 (0.5)	1.00*
Fondaparinux, n (%)	0 (0)	0 (0)	N/A
Therapeutic LMWH, n (%)	0 (0)	1 (0.5)	1.00*
IV heparin or fondaparinux or therapeutic LMWH, n (%)	0 (0)	2 (1)	1.00*

**Fisher's exact test*
ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker
ASA: aspirin
CCB: calcium channel blocker
IV: intravenous
LMWH: low molecular weight heparin
N: number
N/A: not available, could not be computed
ULN: upper limit of normal

Appendix 3 – Medications Pre-Intensive Care Unit Admission Limited to Elevations >10xULN

	Clinically recognized troponin elevation >10xULN	**No clinically recognized troponin elevation >10xULN**	**p-value**
Total N	30	196	
ASA, n (%)	8 (27)	59 (30)	0.70
P2Y12 inhibitor, n (%)	3 (10)	6 (3)	0.10*
Any antiplatelet agent, n (%)	8 (27)	62 (32)	0.58
Oral anticoagulant, n (%)	2 (7)	21 (11)	0.75
Diuretic, n (%)	7 (23)	55 (28)	0.59
Beta-blocker, n (%)	10 (33)	50 (26)	0.37
ACEI/ARB, n (%)	13 (43)	74 (38)	0.56
Non-dihydropyridine CCB, n (%)	2 (7)	10 (5)	0.66*
Dihydropyridine CCB, n (%)	4 (13)	31 (16)	1.00*
Amiodarone, n (%)	0 (0)	2 (1)	1.00*
Digoxin, n (%)	1 (3)	10 (5)	1.00*
Statin, n (%)	12 (40)	68 (35)	0.57
Nitrates, n (%)	2 (7)	1 (0.5)	0.05*
IV heparin, n (%)	0 (0)	1 (0.5)	1.00*
Fondaparinux, n (%)	0 (0)	0 (0)	N/A
Therapeutic LMWH, n (%)	0 (0)	1 (0.5)	1.00*
IV heparin or fondaparinux or therapeutic LMWH, n (%)	0 (0)	2 (1)	1.00*

**Fisher's exact test*
ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker
ASA: aspirin
CCB: calcium channel blocker
IV: intravenous
LMWH: low molecular weight heparin
N: number
N/A: not available, could not be computed
ULN: upper limit of normal

Appendix 4 – Use of cardiac risk stratification limited to patients with a troponin elevation >10xULN

N	Clinically recognized troponin elevation >10XULN 30	No clinically recognized troponin elevation >10XULN 196	p-value
Exercise stress test, n (%)	0	0	N/A
Echocardiogram, n (%)	20 (66.7)	73 (37.2)	0.003
Nuclear perfusion study, n (%)	0	0	N/A
Coronary angiogram, n (%)	5 (16.7)	3 (1.5)	0.001*

N: number
N/A: not applicable, could not be computed
ULN: upper limit of normal

Appendix 5 – Logistic Regression Model - Predictors of Cardiac Stratification in Patients with Troponin Elevations

	B	S.E.	Wald	df	p	Odds ratio	95%CI lower	95%CI upper
ECG changes	- 0.198	0.564	0.123	1	0.726	0.821	0.272	2.478
Ischemic symptoms	1.068	0.610	3.067	1	0.080	2.909	0.881	9.613
Age	0.016	0.016	0.969	1	0.325	1.016	0.984	1.050
History of coronary artery disease	0.194	0.730	0.070	1	0.791	1.214	0.290	5.076
History of congestive heart failure	-0.001	0.713	0.000	1	0.999	0.999	0.247	4.043
APACHE II	0.080	0.038	4.598	1	0.034	1.083	1.006	1.166
Medical vs. trauma and surgical	0.533	0.555	0.925	1	0.336	1.705	0.575	5.056
Sex	0.049	0.516	0.009	1	0.925	1.050	0.382	2.885
Constant	- 0.300	1.463	0.042	1	0.837	0.741		

APACHE II: Acute Physiology And Chronic Health Evaluation
CI: confidence interval
df: degree of freedom
ECG: electrocardiogram
ULN: upper limit of normal

Appendix 6 – Collinearity evaluation for the logistic regression model

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			Collinearity Statistics	
		B	Std. Error	Beta	t	Sig.	Tolerance	VIF
1	(Constant)	-.053	.163		-.326	.745		
	medical_vs_other	.122	.066	.122	1.835	.068	.786	1.273
	clin_trop_any	.386	.065	.377	5.900	.000	.859	1.164
	sympt_any	.041	.069	.038	.605	.546	.866	1.154
	ischemia_ECG_any	.049	.061	.050	.810	.419	.935	1.069
	age_years	.000	.002	.015	.234	.816	.890	1.124
	sex	.015	.061	.014	.240	.811	.962	1.040
	prior_location	.073	.017	.277	4.370	.000	.874	1.145
	htn___6	.234	.095	.152	2.452	.015	.912	1.097
	htn___7	.060	.084	.044	.709	.479	.895	1.117

a. Dependent Variable: stratification

CHAPTER 4

Association of Statins with Mortality in Critically Ill Patients: A systematic review and meta-analysis

Association of Statins with Mortality in Critically Ill Patients: A systematic review and meta-analysis
Short title: Statins in Critical Care

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The authors have not published, posted, or submitted any related papers from the same study.

All authors have no relevant conflict of interest.

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Under review

Abstract

Purpose

Conflicting evidence exists on the effect of statins within subtypes of critically ill patients. We performed a systematic review and meta-analysis of randomized controlled trials evaluating statins in critically ill patients.

Methods

We searched for randomized controlled trials evaluating the effect of statins versus placebo or control in critically ill patients. Outcomes of interest included mortality, stroke, myocardial infarction, liver dysfunction, myopathy, and delirium. In duplicate, reviewers screened titles and abstracts and then relevant full-texts. They then collected data and assessed risk of bias in duplicate. We pooled study results using a random effects model and evaluated the quality of evidence.

Results

We included 30 reports on 25 trials. Twenty trials (n=2692) reported on mortality at latest follow-up; the relative risk (RR) for mortality was 0.92 (95% CI [0.84,1.01], p=0.07, moderate quality evidence). In 15 trials (n=2403), the RR for in-hospital mortality was 0.77 (95%CI [0.68, 0.87], p<0.0001, high quality evidence). We found no significant difference in stroke (RR 0.74 [0.52, 1.05], p=0.09, moderate quality evidence), myocardial infarction (RR 0.81, 95% CI [0.45,1.47], p=0.49, moderate quality evidence), liver dysfunction (RR 1.25 [0.88, 1.77], p=0.22, low quality evidence), myopathy (RR

1.12 [0.66, 1.92], low quality evidence) and delirium (RR 0.99 [0.90, 1.07], p=0.73, high quality evidence).

Conclusion

Statins appear safe and decrease in-hospital mortality in critical illness. They may also confer a long-term mortality benefit. A large trial with follow-up and treatment beyond hospital discharge is required in order to properly evaluate the impact of statins in critical illness.

Keywords: statins, critical care, mortality, HMG-CoA reductase

Introduction

Statins are cholesterol-lowering agents that act by inhibiting hydroxyl-methyl-glutaryl-CoA (HMG-CoA) reductase, the enzyme that catalyzes cholesterol biosynthesis by the liver.[1] In addition to their established role in the prevention and treatment of cardiovascular disease, evidence suggests additional therapeutic effects that are independent of their cholesterol lowering effect.[2] These pleiotropic effects, which have been studied in both animal and human models, include improving or restoring vascular endothelial function, augmenting the stability of atherosclerotic plaques, lowering oxidative stress, attenuating vascular inflammation, and inhibiting platelet aggregation and the thrombogenic response.[3]

Despite heterogeneous pathologies characterizing critical illness, patients in the intensive care unit (ICU) have both a pro-inflammatory and procoagulant state. In the last decade, there has been increasing interest in the possible benefits of statin therapy among critically ill patients. In 2010, a meta-analysis of 20 cohort studies including 265,558 patients receiving statin therapy during sepsis suggested a protective effect for in-hospital mortality (odds ratio [OR] 0.38, 95% confidence interval [CI] [0.13, 0.64]) and 30-day mortality (OR 0.61, 95% CI [0.48, 0.73]).[4] Although promising, these effects have to be confirmed or refuted by data from randomized controlled trials (RCTs).

Evidence is conflicting across subtypes of critically ill patients. RCTs have shown that statins were associated with a significant reduction in mortality in those with ventilator

associated pneumonia[5] and that statins reduce non-pulmonary organ dysfunction in patients with acute lung injury.[6] Other RCTs have shown no benefit of statins in sepsis,[7] sepsis-associated acute respiratory distress syndrome (ARDS),[8] and ventilator-associated pneumonia.[8] One small RCT (80 patients) suggested that a statin in patients with subarachnoid hemorrhage reduced rescue therapy for vasospasm.[9] A larger RCT did not demonstrate a benefit of statin therapy on disability, and mortality.[10] In light of these inconsistent results, we performed a systematic review and meta-analysis of RCTs evaluating the impact of statins on mortality and cardiovascular morbidity and their safety in critically ill patients.

Methods

We preregistered our protocol with PROSPERO (CRD42015020847). Our detailed protocol with pre-specified selection criteria, outcomes, and analysis plan is available as supplementary material (**Appendix 1**).

Search strategy

With the assistance of a medical librarian, we developed a broad search strategy without language restriction, but including the pre-tested SIGN filter for RCTs (http://www.sign.ac.uk) (**Appendix 2**). Using electronic databases (MEDLINE, EMBASE, and CENTRAL) from inception to January 2018, we identified relevant references. We also searched clinical trial registries (Clinicaltrials.gov, ISRCTN Registry, WHO ICTRP), relevant conference proceedings for the last two years, and references of

the included trials and previous disease-specific systematic reviews for potentially eligible studies.

Study selection

In duplicate, two reviewers independently screened the identified references' title and abstract. Reviewers then assessed study eligibility of the full-text reports of all references deemed potentially relevant by either reviewer based on the screening process. To be included, trials had to randomize critically ill adults to either statin initiation or continuation (in those who were taking a statin prior to enrolment) versus standard care without a statin or placebo. We considered a study population to be critically ill if >50% of patients were being ventilated or required vasopressors or were admitted to an intensive care unit or neurological critical care unit at the time of randomization. In addition, trials had to report at least one of the following outcomes: mortality, myocardial infarction or injury, stroke, venous thromboembolism, delirium, liver dysfunction, myopathy, intensive care unit (ICU) and hospital length of stay.

Data extraction and risk of bias assessment

Independently and in duplicate, two reviewers extracted data using pre-designed abstraction forms. A third reviewer verified the data in case of discrepancy. When necessary, we contacted study authors to clarify methods or obtain additional data.

Two reviewers also evaluated the risk of bias for each trial using the Cochrane risk of bias evaluation tool.[11] They evaluated the following six criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other potential sources of bias (non intention-to-treat analysis, stopping early, etc.) They rated the risk of bias for each criterion as high, low or unclear. In the absence of individual RCT protocols for the included trials, reviewers judged a study at low risk of bias for selective reporting if it reported at least on mortality, liver dysfunction and myopathy. Disagreements were resolved by discussion.

Outcomes

Our *a priori* primary outcome was mortality at the longest follow-up period. Other efficacy outcomes of interest included in-hospital mortality, stroke, myocardial infarction, ICU and hospital length of stay. Adverse effects included myopathy, liver dysfunction and delirium. For all outcomes, we used the authors' definitions. When possible, we applied the intention-to-treat principle by re-introducing in our analyses patients who had been excluded because they had died during the study period.

Statistical analyses

With Review Manager (RevMan 5.3),[12] we meta-analyzed studies using a random effects model for each outcome when data were available from two or more studies. The results are presented in forest plots and as relative risks (RRs) and as mean differences (MDs) for

continuous outcomes with associated 95% CIs. We used a 5% significance level for all analyses.

We assessed for heterogeneity by inspecting the forest plots and using the Chi-squared test for homogeneity. We evaluated chance-independent heterogeneity with the I^2 statistic; we considered heterogeneity significant when I^2 was 50% or greater.
We conducted pre-specified subgroup analyses to explore potential sources of clinical and methodological heterogeneity. Risk of bias (high and unclear versus low), clinical condition (sepsis, subarachnoid hemorrhage, trauma), previous statin users versus statin-naïve patients, and patients with myocardial infarction or injury before randomization versus others were evaluated as interaction terms. *A posteriori*, we elected to add ARDS to the clinical conditions for the subgroup analyses.

To evaluate whether it was a moderator variable for mortality, we conducted a meta-regression according to the mean APACHE II score in each study using the metafor package[13] in RStudio (Version 1.0.136).

We screened for publication bias by visually evaluating funnel plots of effect size versus standard error for outcomes that were reported in 10 studies or more. When it was suspected, we used the arcsine test and Egger test to test for plot asymmetry for dichotomous and continuous variables, respectively.

Sensitivity analysis

We conducted a sensitivity analyses focusing on studies evaluating simvastatin. In vitro, simvastatin inhibits leukocyte adhesion[14] and it is hypothesized to have greater anti-inflammatory and antibacterial effects than some other statins.[15]

Quality of evidence

We evaluated the quality of the evidence for each outcome using the GRADE approach and rating system.[16] Our confidence in the estimates of effect could be impacted by risk of bias, imprecision, inconsistency, indirectness, and publication bias. We asked 10 intensivists to judge the patient-importance of each outcome; we report the mean importance based on physician responses.

Results

Literature search

Our search strategy identified 10,359 references in databases (**Figure 1**). After title and abstract and full-text review, 25 trials reported in 29 papers were included. We identified one ongoing trial and eight unpublished trials that had either never recruited patients (one trial), stopped early (four trials) or had an unknown status (three trials). Trial registry data allowed the inclusion of one trial stopped early. More detailed information on these trials is presented in **Appendix 3**.

Study characteristics and risk of bias

The 25 included trials (3319 patients) are described in **Table 1**. Follow-up ranged from 72 hours to 12 months. The disease states of interest for the trials were sepsis (10 trials), [7,17-25] ventilator acquired pneumonia (1 trial),[26], influenza (1 trial),[27] ARDS (3 trials), [6,8,28-32] patients undergoing mechanical ventilation (2 trials),[5,33] subarachnoid hemorrhage (6 trials),[34-39] traumatic brain injury (1 trial),[40] and intracerebral hemorrhage (1 trial).[41] The duration of statin treatment was 15 days or less in 8 trials,[6,7,18,20,23,25,28-30,38] and over 21 days in 11 trials.[5,8,19,26,27,31-35,37,39,41] The maximal duration of statin treatment was 42 days.[41] Five trial authors did not report the duration of statin therapy.[17,21,22,36,40] Thirteen RCTs studied the effects of simvastatin,[6,19,21,22,26,28-30,33-35,38-41], while 6,[7,17,20,23,25,37] 3,[8,18,27,31,32] and 2[5,36] studied atorvastatin, rosuvastatin, and pravastatin, respectively.

We describe the risk of bias for each domain in the included trials in **Table 2**. Nine trials were at low risk of bias[6-8,18,26,28-35], 15 were at high risk of bias[5,17,19-21,23-25,27,36-41] and one was at unclear risk of bias.[22] In five trials, blinding was inadequate.[5,17,24,37,39] Selective outcome reporting was likely present in 11 trials that did not report on myopathy, liver dysfunction and mortality.[19-21,24,25,27,36-38,40,41] Seven trials were judged at risk for attrition bias because of loss to follow-up or post-randomization exclusions.[17,20,23-25,39,41]

Mortality

Twenty studies[5-8,17-20,22,23,25,26,28,30-37,39,41] (2692 patients) reported on mortality at the longest follow-up period with a total of 1015 deaths. The RR for mortality at the longest follow-up period was 0.92 (95% CI [0.84,1.01], p=0.07, **Figure 2**). Heterogeneity was

low as evaluated by a X^2=20.36 (p=0.37) and I^2 of 7%. When limiting the analysis to trials at low risk of bias,[6-8,18,26,28-35] RR was 0.99 (95% CI[0.85,1.16], p=0.94, **Table 3A**). The quality of evidence is moderate, downgraded for risk of bias. Subgroup effects for clinical condition and previous statin use were not significant (p for interaction 0.62 and 0.52, respectively). In a meta-regression, APACHE II score was not a significant moderator variable for mortality (p=0.44, **Appendix 4**). The pooled estimate of effect was similar when only including trials evaluating simvastatin [6,19,22,26,28-30,33-35,39,41](RR 0.89, 95% CI[0.75, 1.05], p=0.16).

In-hospital mortality was reported in 15 trials (2403 patients, 698 events)[5-8,17-20,25,26,28,34-36,39] and it was significantly lower with statin therapy (RR 0.77, 95% CI[0.69, 0.87], p<0.0001, I^2=0%, high quality evidence). Sensitivity analysis of trials at low risk of bias[6-8,18,26,28,34,35] yielded a similar effect estimate (RR 0.79, 95% CI[0.68, 0.92], p=0.003, I^2=0%). The p for interaction evaluating the subgroups by clinical condition was not significant (p=0.99).

Stroke

Five trials[8,23,31,32,34,36,37] (1025 patients) reported on stroke with 36 events in the statin group and 57 in the control group. There was no significant difference in the risk of stroke RR 0.74 (95% CI [0.52,1.05], p=0.09, heterogeneity X^2=2.18 [p=0.54] and I^2=0%). This result was robust when the analysis was limited to the trials at low risk of bias [8,31,32,34](RR 0.81, 95% CI 0.39, 1.67], p=0.57). We found no significant subgroup effect

by clinical condition or previous statin use. Limiting the analysis to the trial assessing simvastatin[34] did not change the significance of the pooled estimate (RR 0.42, 95% CI[0.09, 1.92], p=0.26). After downgrading for imprecision, we have low confidence in the estimate of effect.

Myocardial infarction and injury

Three trials (846 patients)[8,23,31,32,34] evaluated myocardial infarction and injury with 19 events in the statin arm and 23 in the control arm. When pooled, there was no difference between groups: RR 0.81 (95% CI [0.45,1.47], p=0.49), heterogeneity X^2=0.04 (p=0.85) and I^2=0%. There was no significant subgroup effect for this outcome, but analyses were limited by the number of studies reporting this outcome. Only one 39-patient trial[34] evaluating simvastatin reported on myocardial infarction and injury (RR 1.05, 95%CI[0.07, 15.66], p=0.97). The quality of evidence for this outcome is moderate due to imprecision.

Venous thromboembolism

Only one trial reported on this outcome and found no significant difference in incidence with 6.9% in the placebo group versus 6.3% in the statin group (p=0.72).[8] These results yield moderate quality evidence due to imprecision.

Length of stay

We found no significant difference in ICU length of stay as reported in 12 trials[5-8,18,20,23,26,29-34,40] (2067 patients) with a MD -0.48 days (95% CI [-1.55, 0.58], p=0.37). Heterogeneity was substantial for this outcome (X^2=26.88 [p=0.005] and I^2=59%). This heterogeneity resolved when the trials were divided by clinical condition, in all subgroups except the 'other' category (I^2=58%). Subgroup analyses demonstrated that clinical condition and previous statin use were not effect modifiers (p for interaction 0.11 and 0.99 respectively). The only clinical condition in which statins were associated with a significantly reduced ICU length of stay was sepsis (MD -1.44 days, 95%CI [-2.63, -0.25]). Our confidence in the estimate of effect for ICU length of stay is moderate after taking inconsistency into account.

We found no significant difference in hospital length of stay as reported in 8 trials (1752 patients)[6-8,18,23,26,28-34] with a MD -1.10 days (95% CI [-2.95, 0.74], p=0.24, heterogeneity X^2=7.39 [p=0.39] and I^2=5%, high quality evidence). For this outcome, we found no significant interaction between hospital length of stay and clinical condition or previous statin use (p for interaction 0.08 and 0.58 respectively.) Sepsis was the only condition in which hospital length of stay was significantly shorter with statin treatment (MD -4.14 days, 95%CI [-7.04, -1.25]).

Adverse Events

We summarized the meta-analysis results for adverse events in **Table 3B**.

Delirium

Only two trials (222 patients) reported on the incidence of delirium and found no difference between groups (RR 0.99, 95%CI [0.90, 1.07], high quality evidence).[23,26] A single trial at low risk of bias contributed all events for this outcome.[33] In another trial, the proportion of ICU days with delirium was 34% in the statin group and 31% in the placebo arm (Hazard Ratio [HR] 1.14, 95%CI [0.92, 1.41], p=0.22).[32]

Liver dysfunction

All trials assessed for liver dysfunction by measuring transaminase levels, but the degree of elevation considered to represent dysfunction varied across studies. The definitions used for liver dysfunction in each trial are detailed in **Appendix 5**. When pooling thirteen trials (2164 patients),[6,8,18,21-23,26,27,29-35,38] liver dysfunction occurred in 66 patients in the statins group and 55 patients in the control group for a RR 1.25 (95% CI [0.88, 1.77], p=0.22, heterogeneity X^2=6.06 [p=0.22] and I^2=0%). Analysis limited to low risk of bias trials[6,8,18,26,28-35] and to trials evaluating simvastatin[6,21,22,26,28-30,33-35,38] also found no significant difference in liver dysfunction with statins (RR 1.23, 95% CI [0.86, 1.75], p=0.25 and RR 1.32, 95%CI [0.86, 2.03], p=0.21 respectively). In a subgroup analysis, clinical condition was not a significant effect modifier (p=0.59). Because of imprecision and indirectness, we have low confidence in the estimate of effect for this outcome.

Myopathy

Thirteen trials[6-8,18,21-23,26,29-35,38,39] reported on myopathy. All trials assessed for myopathy by measuring creatine kinase (CK) levels. The definitions used for myopathy in each trial

varied; they are detailed in **Appendix 5**. When pooled, 60 events occurred in the statin arm and 57 in the control arm for a RR 1.12 (95% CI [0.66, 1.92], p=0.67, heterogeneity X^2=12.45 [p=0.19] and I^2=28%). These results were robust in sensitivity analyses limited to trials at low risk of bias and those evaluating simvastatin. We found no significant subgroup difference based on the clinical condition studied. The evidence for this outcome is of low quality after accounting for imprecision and indirectness.

We did not conduct the pre-specified subgroup analysis for patients with myocardial infarction or injury because no trial reported on that specific patient population.

Quality of evidence

We summarize our judgements for each domain of the GRADE framework and the overall quality of evidence in **Appendix 6**.

Discussion

Key findings

Based on this systematic review and meta-analysis of randomized controlled trials, the use of statins in critically ill patients may reduce in-hospital mortality. A mortality benefit beyond hospital discharge was not demonstrated, but cannot be excluded, with a RR of 0.92 (95% CI [0.84,1.01], p=0.07, moderate quality evidence). Although we found no significant differences in myocardial infarction and injury, stroke and deep venous thrombosis/pulmonary embolism, these outcomes were assessed and reported in few

included studies and there were a limited number of events. The study results are reassuring regarding the safety of statins in the ICU setting in the absence of significant increases in liver dysfunction, myopathy and delirium in patients randomized to statin therapy.

The number of included trials and the diversity of health conditions in which statins have been evaluated underscore interest in the pleiotropic effects of statins during inflammatory and prothrombotic states associated with critical illnesses. Several observational studies describing improved mortality in statin-treated patients drove early hypotheses that statins may be beneficial in conditions that are not primarily cardiovascular.[42-44] These observational data may, however, be confounded by selection bias, and the healthy user effect.[45] Subsequent randomized trials showing no benefit of statins in ARDS, sepsis and subarachnoid hemorrhage have tempered clinicians' enthusiasm for prescribing statins for diverse conditions associated with critical illness. Individually, however, these trials were relatively small.

Statins are well established in the secondary prevention of cardiovascular events, where they lead to a 16% relative risk reduction in mortality over long-term follow-up, translating to a 1.8% absolute risk reduction.[46] The critical care population may be perceived as a "high risk/high response" population where, for varying risks of death, this relative risk reduction will be preserved. However, while death due to critical illness is common, the mechanisms leading to death often involve several concomitant acute and

chronic disease processes.[47] As a result, only a set fraction of risk of death in this population will be statin-modifiable. Although, in general, it may be conservative to power a study to detect a 20% relative risk reduction in the primary outcome, it is not the case for mortality in critical illness. Because this statin-modifiable fraction of the risk of death cannot be measured independently, for a significant effect to become apparent, the signal of benefit would have to overcome the noise of the non-modifiable risk of death, and power calculations would ideally reflect this.

For critically ill patients, the body of trial evidence to date suggests a survival benefit for statins regarding in-hospital mortality, and a longer-term mortality benefit cannot be excluded. Why would statins impact mortality in critical illness? Pleiotropic effects have been the popular hypothesis so far. We wonder, however, given the frequent troponin elevations and cited myocardial infarction rates in critically ill patients up to 50%,[48-50] whether the subgroup of patients[48,51] with myocardial injury may derive the most benefit. Through either anti-inflammatory effects or lipid-lowering properties, statins may derive their effect. Since no trials in the ICU setting have reported separately on the subgroup of patients with myocardial injury or infarction, this warrants further evaluation.

Statins may decrease short-term in-hospital mortality without impacting on mortality beyond this point because the maximal duration of statin therapy in the included trials was 30 days, and outcomes of patients who receive statins after a critical illness beyond hospital discharge are limited. While decreasing mortality in the immediate horizon is

worthwhile, death after discharge from the ICU remains substantial, reported to be 21% at 1 year,[52] 44% at 5 years.[53] In a 1500-patient cohort of patients discharged from ICU after a critical illness, cardiac biomarkers (high-sensitivity cardiac troponin and NT-proBNP) on ICU discharge were independent predictors of mortality during follow-up.[52] These findings may direct investigators to explore potentially modifiable mechanisms of death in this population.

Strengths and limitations

To our knowledge, this is the first systematic review of RCTs assessing statin use in a diverse population of critically ill patients; this leads to increased generalizability of the safety findings and increased power to evaluate the impact of statins on patient-important outcomes. Previous systematic reviews of statin therapy in critically ill patients focused on disease-specific subsets of patients.[54-56] Although this approach decreased the heterogeneity of the included studies and answered a more focused question, it limited the clinicians' perspective on the efficacy and safety of statin therapy in critically ill patients. We used a rigorous pre-specified protocol and conducted a broad search including the grey literature. Aiming to provide guidance for clinicians, we evaluated the quality of evidence for each outcome using the GRADE framework.[16]

This study does have several limitations. Despite contacting study authors, our results are limited by the limited number of trials reporting on outcomes such as myocardial infarction, stroke, delirium and deep venous thrombosis. In addition, the relatively short-

term follow-up and brief treatment duration precludes conclusions on the long-term effect of statin therapy in ICU survivors.

Conclusion

Statins appear safe and may decrease in-hospital mortality in critical illness. A large trial evaluating statin therapy given to critically ill patients for a long duration of time with long-term follow-up is needed.

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References

1. Slater EE, MacDonald JS. Mechanism of action and biological profile of HMG CoA reductase inhibitors. A new therapeutic alternative. Drugs 1988;36 Suppl 3:72-82.

2. Davies JT, Delfino SF, Feinberg CE, et al. Current and Emerging Uses of Statins in Clinical Therapeutics: A Review. Lipid Insights 2016;9:13-29.

3. Liao JK, Laufs U. Pleiotropic effects of statins. Annu Rev Pharmacol Toxicol 2005;45:89-118.

4. Janda S, Young A, Fitzgerald JM, Etminan M, Swiston J. The effect of statins on mortality from severe infections and sepsis: a systematic review and meta-analysis. J Crit Care 2010;25:656 e7-22.

5. Makris D, Manoulakas E, Komnos A, et al. Effect of pravastatin on the frequency of ventilator-associated pneumonia and on intensive care unit mortality: open-label, randomized study. Critical care medicine 2011;39:2440-6.

6. Craig TR, Duffy MJ, Shyamsundar M, et al. A randomized clinical trial of hydroxymethylglutaryl- coenzyme a reductase inhibition for acute lung injury (The HARP Study). American journal of respiratory and critical care medicine 2011;183:620-6.

7. Kruger P, Bailey M, Bellomo R, et al. A multicenter randomized trial of atorvastatin therapy in intensive care patients with severe sepsis. American journal of respiratory and critical care medicine 2013;187:743-50.

8. National Heart L, Blood Institute ACTN, Truwit JD, et al. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. The New England journal of medicine 2014;370:2191-200.

9. Tseng MY, Hutchinson PJ, Czosnyka M, Richards H, Pickard JD, Kirkpatrick PJ. Effects of acute pravastatin treatment on intensity of rescue therapy, length of inpatient stay, and 6-month outcome in patients after aneurysmal subarachnoid hemorrhage. Stroke 2007;38:1545-50.

10. Kirkpatrick PJ, Turner CL, Smith C, Hutchinson PJ, Murray GD, Collaborators S. Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): a multicentre randomised phase 3 trial. Lancet Neurol 2014;13:666-75.

11. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

12. Collaboration TC. Review Manager (RevMan). 5.3 ed. Copenhagen: The Nordic Cochrane Centre2014.

13. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. 2010 2010;36:48.

14. Sparrow CP, Burton CA, Hernandez M, et al. Simvastatin has anti-inflammatory and antiatherosclerotic activities independent of plasma cholesterol lowering. Arterioscler Thromb Vasc Biol 2001;21:115-21.

15. Masadeh M, Mhaidat N, Alzoubi K, Al-Azzam S, Alnasser Z. Antibacterial activity of statins: a comparative study of atorvastatin, simvastatin, and rosuvastatin. Ann Clin Microbiol Antimicrob 2012;11:13.

16. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401-6.

17. Choi HS, Park MJ, Kang HM, et al. Statin use in sepsis due to pneumonia. 2008.

18. El Gendy HA, Elsharnouby NM. Safety and vasopressor effect of rosuvastatin in septic patients. Egyptian Journal of Anaesthesia 2014;30:311-7.

19. Mirjalili MR, Shiranian F, Rahimian M, Borjani L, Dehghani A. The effect of simvastatin on the outcome of patients with sepsis: A clinical trial study. Acta Medica Mediterranea 2016;32:1203-6.

20. Prado K, Ribeiro C, Furian T, et al. A clinical randomized trial on the use of atorvastatin in patients with sepsis or septic shock: effects on endothelial function. Critical care 2013;17:P61.

21. Shao H, Wang C, Zhu W, et al. [Influence of simvastatin treatment on Toll-like receptor 4 in monocytes of peripheral blood in patients with sepsis and severe sepsis]. Zhonghua wei zhong bing ji jiu yi xue 2016;28:159-63.

22. Donnino M, Cocchi M, Salciccioli J, Akuthota P, Chase M, Cutlip D. Prospective, Double-blind Randomized Pilot Study of Statin Therapy in Septic Shock. Academic Emergency Medicine 2011;18:S4-S249.

23. Singh RK, Agarwal V, Baronia AK, Kumar S, Poddar B, Azim A. The Effects of Atorvastatin on Inflammatory Responses and Mortality in Septic Shock: A Single-center, Randomized Controlled Trial. Indian J Crit Care Med 2017;21:646-54.

24. Eladawy S, El-Hamamsy M, Bazan N, Elgendy M. The clinical outcome of simvastatin plus standard therapy versus

standard therapy alone in critically ill septic patients: randomized controlled clinical trial. Intensive Care Medicine Experimental 2016;4:A:895.

25. Heydari B, Khalili H, Beigmohammadi MT, Abdollahi A, Karimzadeh I. Effects of atorvastatin on biomarkers of acute kidney injury in amikacin recipients: A pilot, randomized, placebo-controlled, clinical trial. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences 2017;22:39.

26. Papazian L, Roch A, Charles PE, et al. Effect of statin therapy on mortality in patients with ventilator-associated pneumonia: a randomized clinical trial. JAMA : the journal of the American Medical Association 2013;310:1692-700.

27. Bernard GR. Randomized, Placebo Controlled Trial of the Effectiveness of Statins for Preventing Mortality Following ICU Admission for Influenza Complications. 2013;

.

28. McAuley DF, O'Kane CM, Craig TR, Shyamsundar M, Herwald H, Dib K. Simvastatin decreases the level of heparin-binding protein in patients with acute lung injury. BMC pulmonary medicine 2013;13:47.

29. Agus A, Hulme C, Verghis RM, et al. Simvastatin for patients with acute respiratory distress syndrome: long-term outcomes and cost-effectiveness from a randomised controlled trial. Critical care 2017;21:108.

30. McAuley DF, Laffey JG, O'Kane CM, et al. Simvastatin in the Acute Respiratory Distress Syndrome. New England Journal of Medicine 2014;371:1695-703.

31. Dinglas VD, Hopkins RO, Wozniak AW, et al. One-year outcomes of rosuvastatin versus placebo in sepsis-associated acute respiratory distress syndrome: prospective follow-up of SAILS randomised trial. Thorax 2016;71:401-10.

32. Needham DM, Colantuoni E, Dinglas VD, et al. Rosuvastatin versus placebo for delirium in intensive care and subsequent cognitive impairment in patients with sepsis-associated acute respiratory distress syndrome: an ancillary study to a randomised controlled trial. The Lancet Respiratory medicine 2016;4:203-12.

33. Page VJ, Casarin A, Ely EW, et al. Evaluation of early administration of simvastatin in the prevention and treatment of delirium in critically ill patients undergoing mechanical ventilation (MoDUS): a randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2017;5:727-37.

34. Chou SH, Smith EE, Badjatia N, et al. A randomized, double-blind, placebo-controlled pilot study of simvastatin in aneurysmal subarachnoid hemorrhage. Stroke 2008;39:2891-3.

35. Diringer MN, Dhar R, Scalfani M, et al. Effect of High-Dose Simvastatin on Cerebral Blood Flow and Static Autoregulation in Subarachnoid Hemorrhage. Neurocritical care 2016;25:56-63.

36. Jaschinski U, Scherer K, Lichtwarck M, Forst H. Impact of treatment with pravastatin on delayed ischemic disease and mortality after aneurysmal subarachnoid hemorrhage. Critical care 2008;12:P112.

37. Luo R, Fan J, Duan J, Feng L, Yin X. Combination Treatment of Atorvastatin and Fasudil Ameliorate Cerebral Vasospasm

after Subarachnoid Hemorrhage. Journal of Neurological Sciences [Turkish] 2015;32:40-8.

38. Lynch JR, Wang H, McGirt MJ, et al. Simvastatin reduces vasospasm after aneurysmal subarachnoid hemorrhage: results of a pilot randomized clinical trial. Stroke 2005;36:2024-6.

39. Macedo S, Bello Y, Silva A, Siqueira C, Siqueira S, Brito L. Effects of simvastatin in prevention of vasospasm in nontraumatic subarachnoid hemorrhage: preliminary data. Critical care 2009;13:P103.

40. Naghibi T, Madani S, Mazloomzadeh S, Dobakhti F. Simvastatin's effects on survival and outcome in traumatic braininjury patients: a comparative study. Turkish journal of medical sciences 2016;46:1-5.

41. Zhou X, Chen J, Wang C, Wu L. Anti-inflammatory effects of Simvastatin in patients with acute intracerebral hemorrhage in an intensive care unit. Experimental and therapeutic medicine 2017;14:6193-200.

42. Christensen S, Thomsen RW, Johansen MB, et al. Preadmission statin use and one-year mortality among patients in intensive care - a cohort study. Critical care 2010;14:R29.

43. Dobesh PP, Klepser DG, McGuire TR, Morgan CW, Olsen KM. Reduction in mortality associated with statin therapy in patients with severe sepsis. Pharmacotherapy 2009;29:621-30.

44. Bajwa EK, Malhotra CK, Thompson BT, Christiani DC, Gong MN. Statin therapy as prevention against development of acute respiratory distress syndrome: an observational study. Critical care medicine 2012;40:1470-7.

45. Miano TA, Lam S. The Healthy User Effect in Studies of Statins in the Critically Ill. Crit Care Med 2018;46:e95.

46. Wilt TJ, Bloomfield HE, MacDonald R, et al. Effectiveness of statin therapy in adults with coronary heart disease. Arch Intern Med 2004;164:1427-36.

47. Shankar-Hari M, Harrison DA, Rowan KM, Rubenfeld GD. Estimating attributable fraction of mortality from sepsis to inform clinical trials. Journal of critical care 2018;45:33-9.

48. Ostermann M, Lo J, Toolan M, et al. A prospective study of the impact of serial troponin measurements on the diagnosis of myocardial infarction and hospital and six-month mortality in patients admitted to ICU with non-cardiac diagnoses. Critical care 2014;18:R62.

49. Lim W, Holinski P, Devereaux PJ, et al. Detecting myocardial infarction in critical illness using screening troponin measurements and ECG recordings. Critical care 2008;12:R36.

50. Belley-Cote EP, Whitlock RP, Ulic DV, et al. P2748 The PROTROPICS feasibility: prognostic value of elevated troponins in critical illness. European heart journal 2017;38:ehx502.P2748-ehx502.P.

51. Bessiere F, Khenifer S, Dubourg J, Durieu I, Lega JC. Prognostic value of troponins in sepsis: a meta-analysis. Intensive care medicine 2013;39:1181-9.

52. Gayat E, Cariou A, Deye N, et al. Determinants of long-term outcome in ICU survivors: results from the FROG-ICU study. Critical care 2018;22:8.

53. Haines KJ, Berney S, Warrillow S, Denehy L. Long-term recovery following critical illness in an Australian cohort. J Intensive Care 2018;6:8.

54. Pasin L, Landoni G, Castro ML, et al. The effect of statins on mortality in septic patients: a meta-analysis of randomized controlled trials. PloS one 2013;8:e82775.

55. Jansen JO, Inaba K, Resnick S, et al. Selective non-operative management of abdominal gunshot wounds: survey of practise. Injury 2013;44:639-44.

56. Liu Z, Liu L, Zhang Z, Chen Z, Zhao B. Cholesterol-reducing agents for aneurysmal subarachnoid haemorrhage. The Cochrane database of systematic reviews 2013;4:CD008184.

Figure 1 - Flow of Study Selection for Trials Comparing Statins with Placebo or Control in Critically Ill Patients

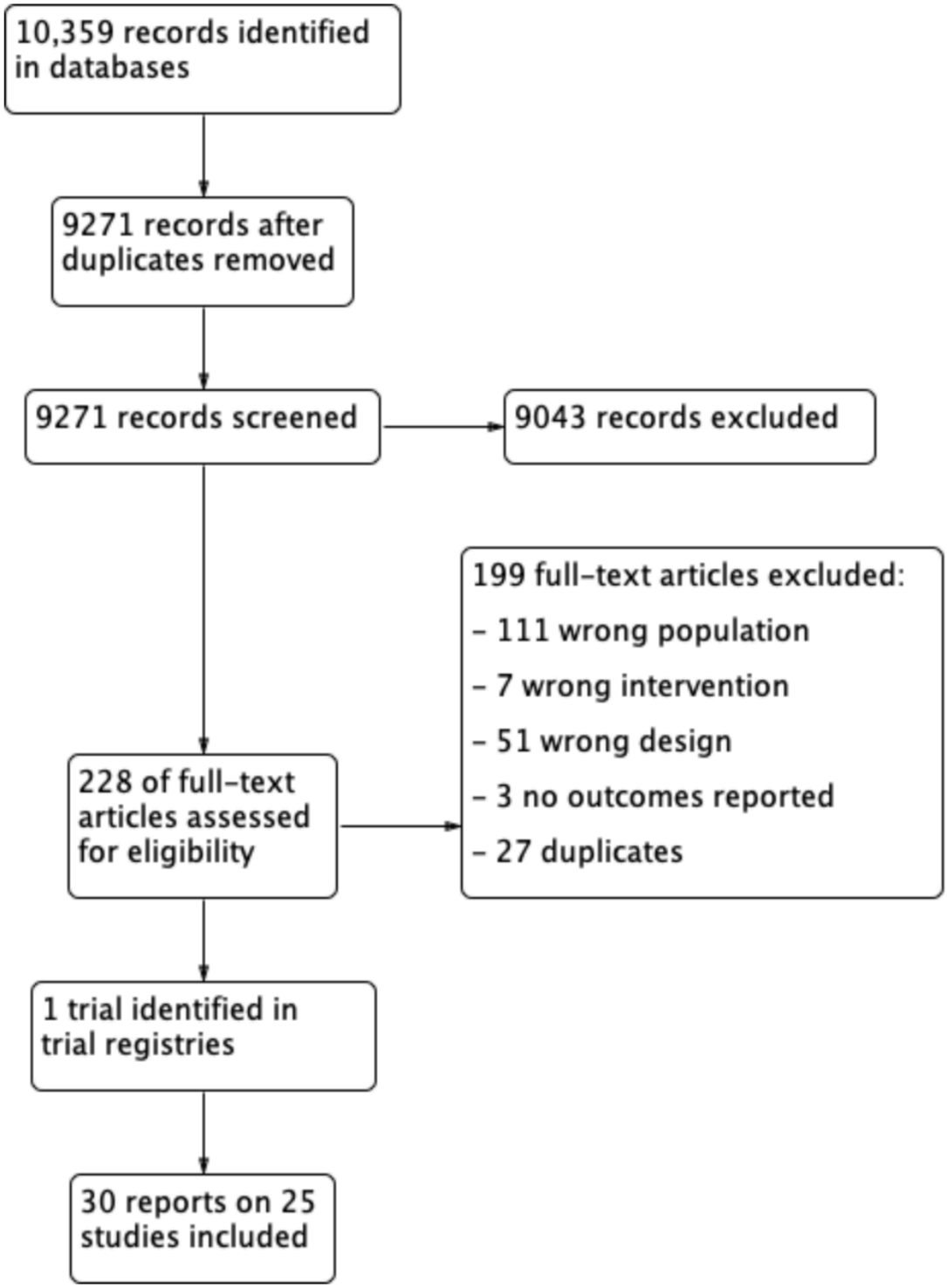

Figure 2 - Relative Risks for Mortality at Latest Follow-up of All Trials Comparing Statins with Placebo or Control in Critically Ill Patients

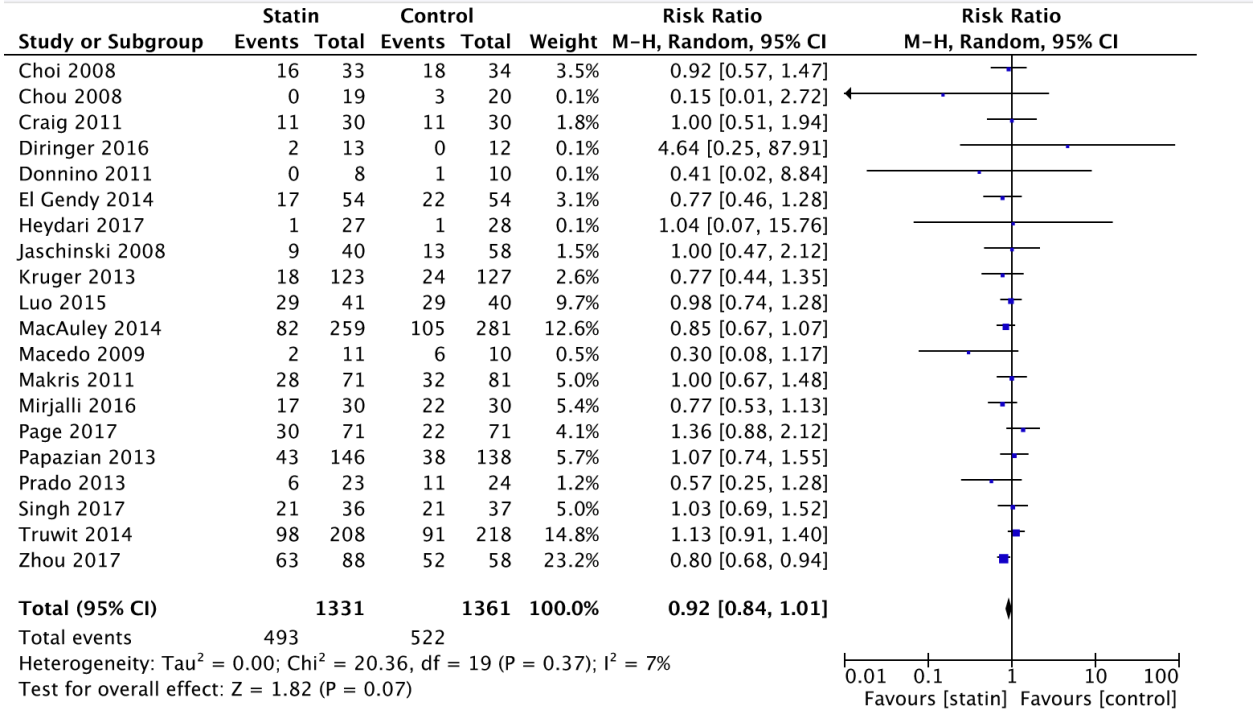

Table 1- Characteristics of Included Studies

Study	N	Primary critical illness	Statin	Primary Outcome	Follow-up	APACHE II
Bernard 2011 Unpublished	7	Influenza	Rosuvastatin 20 mg 28 days	Hospital mortality to day 28 or time to achieve resolution of respiratory failure	28 days	Statin – NR Placebo – NR
Choi 2008	67	Sepsis due to pneumonia	Atorvastatin 10 mg	NR	NR	Statin – NR Placebo – NR
Chou 2008	39	SAH	Simvastatin 80 mg 21 days	Death and drug morbidity (CK/AST/ALT elevation)	NR	Statin – NR Placebo – NR
Craig 2011 & McAuley 2013	60	ALI or ARDS	Simvastatin 80 mg 14 days	Reduction in extravascular lung water indexed to actual body weight	NR	Statin – 25.1 (6.5) Placebo – 23.3 (6.8)
Diringer 2016	25	Aneurysmal SAH	Simvastatin 80 mg 21 days	NR	21 days	Statin – NR Placebo – NR
Donnino 2011	18	Septic shock	Simvastatin 40 mg	Time to shock reversal	72 hours	Statin – 21 (6) Placebo – 20 (5)
El Gendy 2014	108	Sepsis	Rosuvastatin 20 mg 14 days	Number of acceptable blood pressure and systemic perfusion days	14 days	Statin – 25 (59)* Placebo – 24 (50)* *median (mean rank)
Eladawi 2016	100	Sepsis/severe sepsis	Simvastatin 40 mg	Mortality and total ICU length of stay	28 days	Statin – NR Standard treatment – NR
Heydari 2017	55	Documented gram negative infection sensitive to amikacin	Atorvastatin 40 mg 7 days	Urine neutrophil gelatinase-associated lipocalin	28 days	Statin – 20.3 (5.3) Placebo – 19.7 (4.4)
Jaschinski 2008	98	Aneurysmal SAH	Pravastatin 40 mg	Incidence of delayed ischemic disease and	NR	Statin – NR Placebo – NR

				extent of disability measured by the Glasgow Outcome Scale		
Kruger 2013	250	Severe sepsis	Atorvastatin 20 mg 14 days	Interleukin-6 concentrations	90 days	Statin – 22.1 (7.7) Placebo – 23.5 (7.8)
Luo 2015	120	Aneurysmal SAH	Atorvastatin 20 mg 21 days	Cerebral infarction or symptomatic vasospasm	6 months	Statin – NR Control – NR Combination therapy – NR
Lynch 2005	39	Aneurysmal SAH	Simvastatin 80 mg 14 days	Cerebral vasospasm	NR	Statin – NR Placebo – NR
McAuley 2014 & Agus 2017	540	ARDS	Simvastatin 80 mg 14 days	Ventilator-free days to day 28	28 days	
Macedo 2009	21	Nontraumatic SAH	Simvastatin 80 mg 21 days	Cerebral vasospasm	21 days	Statin - 14.3 Placebo -10.7
Makris 2011	152	Mechanical ventilation	Pravastatin 40 mg 30 days	Frequency of ventilator-associated pneumonia	6 months	Statin – 14.7 (0.5) Placebo – 14.8 (0.7)
Mirjalili 2016	60	Sepsis	Simvastatin NR 30 days	Mortality	30 days	Statin - 15.4 (4.76) Placebo – 15.33 (7.15)
Naghibi 2016	43	Traumatic brain injury	Simvastatin 80 mg on day 1, then 40 mg	ICU mortality	NR	Statin - 14.2 (6.6) Placebo - 14.8 (6.8)
Page 2017	142	Invasive mechanical ventilation	Simvastatin 80 mg 28 days	Number of days alive (i.e., number of delirium-free and coma-free days)	28 days	Statin - 17.2 (5.3) Placebo - 16.7 (6.4)
Papazian 2013	251	Suspected ventilator acquired pneumonia	Simvastatin 60 mg	Day-28 mortality	90 days	Statin – 7.2 (3.6)† Placebo – 6.7 (2.9)†

			28 days			
Prado 2013	47	Severe sepsis or septic shock	Atorvastatin 80 mg	Endothelial dysfunction	NR	Statin – 23 (6.9) Placebo – 23.5 (7.3)
Shao 2016	106	Sepsis and severe sepsis	Simvastatin 40 mg 15 days	NR	NR	Statin – 12.2 (4.1) Placebo – 11.4 (4.8)
Singh 2017	80	Septic shock	Atorvastatin 40 mg 7 days	28-day mortality	28 days	Statin – 16 (13-21)* Placebo – 15 (12-21)*
Truwit 2014, Dinglas 2016 & Needham 2016	745	ARDS	Rosuvastatin loading 40 mg, then 20 mg 28 days	Mortality before hospital discharge or until study day 60	12 months	Statin – 92.1 (28.4) Placebo – 94.8 (27.9)
Zhou 2017	146	Intracerebral hemorrhage	Simvastatin 0.08, 0.16, 0.24, 0.30 and 0.36 mg/kg 42 days	NR	NR	Stain – NR Placebo – NR

†SOFA score. APACHE score NR
*median (interquartile range) reported
ALI: acute lung injury
ALT: alanine aminotransferase
ARDS: acute respiratory distress syndrome
AST: aspartate aminotransferase
CK: creatine kinase
ICU: intensive care unit
NR: not reported
SAH: subarachnoid hemorrhage
SIRS: systemic inflammatory response syndrome

Table 2 – Risk of Bias of Included Studies

Study	Randomization sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Selective reporting
Bernard unpublished	unclear	unclear	low	low	unclear	high
Choi 2008	unclear	unclear	low	high	high	low
Chou 2008	low	low	low	low	low	low
Craig 2011 & McAuley 2013	low	low	low	low	low	low
Diringer 2016	low	low	low	low	low	low
Donnino 2011	unclear	unclear	low	low	low	low
Eladawy 2016	unclear	unclear	high	high	high	high
El Gendy 2014	low	low	low	low	low	low
Heydari 2017	low	unclear	low	low	high	high
Jaschinski 2008	unclear	unclear	unclear	unclear	unclear	high
Kruger 2013	low	low	low	low	low	low
Luo 2013	unclear	unclear	high	high	low	high
Lynch 2005	unclear	unclear	low	low	low	high
McAuley 2014 & Agus 2017	low	low	low	low	low	low
Macedo 2009	unclear	unclear	high	high	high	low
Makris 2011	low	unclear	high	high	low	low
Mirjalili 2016	low	unclear	low	low	low	high
Naghibi 2016	low	low	low	low	low	high
Page 2017	low	low	low	low	low	low
Papazian 2013	low	low	low	low	low	low
Prado 2013	unclear	unclear	low	low	high	high
Shao 2015	unclear	unclear	unclear	unclear	unclear	high
Singh 2017	low	low	low	low	high	low
Truwit 2014/ Dinglas 2016/ Needham 2016/ Hough 2015	low	low	low	low	low	low


Zhou 2017
unclear
unclear
low
low
high
high

Table 3 A – Summary of Meta-analysis for Efficacy Outcomes

Outcome	Number of studies	Number of participants	Effect estimate [95% CI]	p-value	I^2	p-value subgroup differences
MORTALITY AT LONGEST FOLLOW-UP						
All included studies	20	2692	0.92 [0.84, 1.01]	0.07	7%	
Risk of bias						0.12
Low risk of bias	9	1874	0.99 [0.85, 1.16]	0.94	18%	
High & unclear risk of bias	11	818	0.85 [0.76, 0.95]	0.005	0%	
Clinical conditions						0.62
ARDS	3	1026	0.99 [0.80, 1.22]	0.90	37%	
Sepsis	7	623	0.84 [0.69, 1.01]	0.07	0%	
SAH	5	264	0.85 [0.51, 1.41]	0.53	30%	
Trauma	0	0	Not estimable			
Other	5	779	0.99 [0.76, 1.30]	0.97	56%	
Simvastatin	10	1335	0.89 [0.75, 1.05]	0.16	29%	
Statin use						0.52
No previous statin use	13	2223	0.96 [0.86, 1.08]	0.48	0%	
Previous statin use	3	212	0.82 [0.32, 2.13]	0.68	61%	
IN-HOSPITAL MORTALITY						
All included studies	15	2403	0.77 [0.69, 0.87]	<0.0001	0%	
Risk of bias						0.62
Low risk of bias	8	1903	0.79 [0.68, 0.92]	0.003	7%	
High & unclear risk of bias	7	500	0.74 [0.58, 0.94]	0.01	0%	
Clinical conditions						0.99
ARDS	3	1197	0.75 [0.63, 0.88]	0.0005	0%	
Sepsis	5	532	0.78 [0.62, 0.97]	0.03	0%	
SAH	4	183	0.67 [0.24, 1.87]	0.44	40%	

Trauma	0	0	Not estimable			
Other	3	491	0.77 [0.40, 1.50]	0.45	55%	
Simvastatin			0.85 [0.69, 1.06]	0.15	14%	
Statin use						Not applicable
No previous statin use	10	2115	0.77 [0.67, 0.89]	0.0003	6%	
Previous statin use	0	0	Not estimable			
STROKE						
All included studies	5	1025	0.74 [0.52, 1.05]	0.09	0%	
Risk of bias						0.82
Low risk of bias	2	766	0.81 [0.39, 1.67]	0.57	0%	
High & unclear risk of bias	3	259	0.73 [0.46, 1.17]	0.19	13%	
Clinical conditions						0.09
ARDS	1	727	0.98 [0.43, 2.23]	0.96	Not applicable	
Sepsis	1	80	Not estimable		Not applicable	
SAH	3	218	0.69 [0.46, 1.02]	0.06	0%	
Trauma	0	0	Not estimable			
Other	0	0	Not estimable			
Simvastatin	1	39	0.42 [0.09, 1.92]	0.26	Not applicable	
Statin use						0.79
No previous stain use	3	200	0.83 [0.35, 2.00]	0.68	14%	
Previous statin use	1	727	0.98 [0.43, 2.23]	0.96	Not applicable	
MYOCARDIAL INFARCTION						
All included studies	3	846	0.81 [0.45, 1.47]	0.49	0%	
Risk of bias						Not estimable
Low risk of bias	2	766	0.81 [0.45, 1.47]	0.49	0%	
High & unclear risk of bias	1	80	Not estimable			

Clinical conditions						0.85
ARDS	1	727	0.80 [0.44, 1.47]	0.48	Not estimable	
Sepsis	1	80	Not estimable		Not estimable	
SAH	1	39	1.05 [0.07, 15.66]	0.97	Not estimable	
Trauma	0	0	Not estimable			
Other	0	0	Not estimable			
Simvastatin	1	39	1.05 [0.07, 15.66]	0.97	Not estimable	
Statin use						0.85
No previous stain use	2	119	1.05 [0.07, 15.66]	0.97	Not applicable	
Previous statin use	1	727	0.80 [0.44, 1.47]	0.48	Not estimable	
INTENSIVE CARE UNIT LENGTH OF STAY						
All included studies	12	2067	-0.48 [-1.55, 0.58]	0.37	59%	
Risk of bias						0.38
Low risk of bias	8	1752	-0.21 [-1.23, 0.80]	0.68	23%	
High & unclear risk of bias	4	315	-1.17 [-3.05, 0.71]	0.22	55%	
Clinical conditions						0.11
ARDS	3	929	0.39 [-1.03, 1.82]	0.59	0%	
Sepsis	3	431	-1.44 [-2.63, -0.25]	0.02	0%	
SAH	1	39	2.00 [-0.85, 4.85]	0.17	Not estimable	
Trauma	1	43	0.30 [-1.91, 2.51]	0.79	Not estimable	
Other	3	578	-0.95 [-3.44, 1.54]	0.45	58%	
Simvastatin	6	1108	0.45 [-0.79, 1.69]	0.48	0%	
Statin use						0.99

No previous stain use	8	1265	-1.01 [-2.13, 0.11]	0.08	55%	
Previous statin use	1	250	-1.00 [-2.58, 0.58]	0.22	Not applicable	
HOSPITAL LENGTH OF STAY						
All included studies	8	1752	-1.10 [-2.95, 0.74]	0.24	5%	
Risk of bias						Not estimable
Low risk of bias	8	1752	-1.10 [-2.95, 0.74]	0.24	5%	
High & unclear risk of bias	0	0	Not applicable			
Clinical conditions					56.4%	0.08
ARDS	3	929	0.27 [-2.37, 2.92]	0.84	0%	
Sepsis	2	358	-4.14 [-7.04, -1.25]	0.005	0%	
SAH	1	39	2.00 [-4.68, 8.68]	0.56	Not estimable	
Trauma	0	0	Not estimable			
Other	2	426	1.07 [-3.74, 5.88]	0.66	0%	
Simvastatin	5	1065	1.60 [-1.90, 5.10]	0.37	0%	
Statin use						0.58
No previous stain use	5	920	-2.27 [-5.34, 0.80]	0.15	14%	
Previous statin use	1	77	0.20 [-8.04, 8.44]	0.96	Not applicable	

ARDS: acute respiratory distress syndrome
CI: confidence interval
SAH: subarachnoid hemorrhage

Table 3B – Summary of Meta-Analysis for Safety Outcomes

Outcome	N studies	N participants	Effect estimate RR [95% CI]	p-value	p-value subgroup differences	I%
LIVER DYSFUNCTION						
All included studies	13	2164	1.25 [0.88, 1.77]	0.22		0%
Risk of bias					0.92	
Low risk of bias	8	1925	1.23 [0.86, 1.75]	0.25		0%
High & unclear risk of bias	5	239	1.13 [0.18, 6.91]	0.90		0%
Clinical conditions					0.59	
ARDS	3	1327	1.03 [0.48, 2.21]	0.95		54%
Sepsis	4	305	1.57 [0.66, 3.75]	0.31		Not applicable
SAH	3	103	2.52 [0.51, 12.46]	0.26		0%
Trauma	0	0	Not estimable			
Other	3	429	0.91 [0.44, 1.88]	0.80		0%
Simvastatin	9	1253	1.32 [0.86, 2.03]	0.21		0%
Statin use					Not applicable	
No previous statin use	7	863	1.53 [0.97, 2.43]	0.07		0%
Previous statin use	0	0	Not estimable			
MYOPATHY						
All included studies	13	2411	1.12 [0.66, 1.92]	0.67		28%
Risk of bias					0.51	
Low risk of bias	9	2175	1.09 [0.62, 1.91]	0.77		33%
High & unclear risk of bias	4	236	3.15 [0.14, 72.88]	0.47		Not applicable
Clinical conditions					0.99	
ARDS	3	1327	1.05 [0.41, 2.69]	0.92		67%
Sepsis	5	555	0.91 [0.14, 6.00]	0.92		36%
SAH	3	63	1.46 [0.24, 8.90]	0.68		0%

Trauma	0	0	Not estimable			Not applicable
Other	2	426	1.07 [0.16, 7.25]	0.94		71%
Simvastatin	10	1253	1.39 [0.67, 2.89]	0.38		21%
Statin use					Not applicable	
No previous statin use	7	863	1.70 [0.89, 3.23]	0.11		0%
Previous statin use	0	0	Not estimable			
DELIRIUM						
All included studies	2	222	0.99 [0.90, 1.07]	0.73		Not applicable
Risk of bias					Not applicable	
Low risk of bias	1	142	0.99 [0.90, 1.07]	0.73		Not applicable
High & unclear risk of bias	1	80	Not estimable			Not estimable
Clinical conditions					Not applicable	
ARDS	0	0	Not estimable			
Sepsis	1	80	Not estimable			
SAH	0	0	Not estimable			
Trauma	0	0	Not estimable			
Other	1	142	0.99 [0.90, 1.07]	0.73		Not applicable
Simvastatin	1	142	0.99 [0.90, 1.07]	0.73		Not applicable
Statin use					Not applicable	
No previous statin use	1	80	Not estimable			
Previous statin use	0	0	Not estimable			

ARDS: acute respiratory distress syndrome
CI: confidence interval
N: number
SAH: subarachnoid hemorrhage

Contributorship Statement

Emilie Belley-Côté contributed significantly to the study's concept and design, data collection and analysis, and interpretation of the results. She wrote the first draft of the manuscript, provided critical revisions, and gave final approval of the submitted manuscript.

Deborah Cook contributed to the study's concept and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

PJ Devereaux contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Kimia Honarmand contributed to the study's concept, data collection and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Diana Ulic contributed to the data collection and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Graham McClure contributed to the data collection and analysis, and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Kevin An contributed to the data collection and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Frédérick D'Aragon contributed to the interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Anila Qasim contributed to the data analysis and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Shreyash Dalmia contributed to the data collection and analysis, and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Arnav Agarwal contributed to the data collection and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

François Lamontagne contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Richard Whitlock contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Association of Statins with Mortality in Critically Ill Patients: A systematic review and meta-analysis

SUPPLEMENTARY MATERIALS

APPENDIX 1: Statins in Critically Ill Patients: A Systematic Review and Meta-Analysis Protocol

Background

Statins are known to be effective in the primary and secondary prevention of cardiovascular events.[1-3] Their lipid lowering effects occur through the inhibition of HMG-CoA reductase, reducing cholesterol production in the liver. However, statins also modulate immunity and inflammation. The anti-inflammatory effects of statins have been studied in both animal and human models of sepsis.[4] Critically ill patients, although heterogeneous in their individual pathologies, share a pro-inflammatory and pro-coagulant state.[5]

Observational data suggest statins may be beneficial in some critical care populations. In 2010, a meta-analysis of 20 cohort studies including 265,558 patients on statin therapy during sepsis suggested a protective effect for in-hospital mortality (OR 0.38, 95% CI 0.13-0.64) and 30-day mortality (OR 0.61, 95% CI 0.48-0.73).[6] Another systematic review conducted in the trauma population included 4 cohort studies.[7] Two of those studies were conducted in traumatic brain injury and both suggested a

significantly lower in-hospital mortality with statin therapy.[8,9] A cohort of 233 patients with burns also suggested a decreased in-hospital mortality in patients exposed to statins.[10] In the fourth cohort of 295 blunt trauma patients, statins were not associated with improved mortality.[11] Although promising, any protective signals need to be confirmed in randomized controlled trials (RCTs).

In 2013, a meta-analysis of 5 RCTs (650 patients) failed to demonstrate a benefit of statins on mortality in septic patients (RR 0.9, 95% CI 0.65-1.26).[12] However, it was not powered to exclude a significant benefit, neither a significant harm from statin therapy. A small trial of simvastatin in patients with acute lung injury (60 patients) suggested improvements in non-pulmonary organ dysfunction.[13] Recently, a larger RCT (745 patients) of rosuvastatin in sepsis-associated acute respiratory distress syndrome (ARDS) was stopped early for futility.[14] One small RCT (80 patients) had suggested that statins could also be beneficial in patients with subarachnoid hemorrhage.[15] A larger study (803 patients) published in 2014 did not demonstrate a benefit of statin therapy.[16]

Previous systematic reviews of statin therapy in critically ill patients focused on disease-specific subsets of patients.[7,12,17] Although this approach decreases the heterogeneity of the included studies and answers a more focused question, it limits the perspective clinicians currently have on the efficacy and safety of statin therapy in critically ill patients in general, since this

population often carries several of the above pathologies. Given our interest in the treatment of heteroegeneous critically ill patients with elevated troponins, we aim to systematically review and meta-analyze RCTs evaluating the effect of statin therapy on mortality in critically ill patients.

Our objective is to identify and appraise all randomized controlled trials evaluating statins in critically ill patients with respect to mortality, myocardial infarction, venous thromboembolic events (deep venous thrombosis/pulmonary embolism), stroke, adverse events (e.g., myopathy, liver dysfunction, delirium) as well as ICU and hospital length of stay in critically ill patients.

Methods

Eligibility criteria:

We will include studies that meet all of the following criteria:

Population

Critically ill adults (≥18 years old), defined as a study population where >50% of patients are being ventilated or require vasopressor therapy or are admitted to an intensive care unit or neurologic critical care unit at the time of randomization. For studies focused on patients with subarachnoid hemorrhage, we will include studies if >50% of patients have significant impairment (Hunt and Hess grade >2).

We will exclude studies of patients who have undergone cardiac surgery because most of these patients have a short length of ICU stay and a known benefit from statin therapy on the long term.

Intervention

Statins: atorvastatin, rosuvastatin, fluvastatin, lovastatin, simvastatin, pravastatin, pitavastatin, lovastatin

Statins can either be newly started or continued if the patient was already treated with a statin.

Comparator

Placebo or control

Outcomes

Mortality at the longest available follow-up (primary)

In-hospital mortality

Myocardial infarction at the longest available follow-up (as defined in each study)

Stroke at the longest available follow-up (as defined in each study)

Hospital length of stay

ICU length of stay

Myopathy (as defined in each study)

Liver dysfunction (as defined in each study)

Delirium (as defined in each study)

Study design

Randomized controlled trial

Duplicate publications of the same patients will be included if they report some new data.

We will apply no language constraints.

Search strategy

Databases: CENTRAL, MEDLINE and EMBASE

See Appendix 2 for complete MEDLINE search strategies. We will use the pre-tested SIGN filters (http://www.sign.ac.uk) for randomized controlled trials for our MEDLINE and EMBASE searches.

Other sources (grey literature):

We will review clinical trial registries: Clinicaltrials.gov, ISRCTN Register, WHO ICTRP for relevant unpublished studies.

We will review the references of included trials for other potentially relevant research.

Selection Process

Duplicate screening of retrieved references' titles and abstracts by two independent reviewers. Full-text reports for all references deemed relevant by any reviewer will be retrieved.

Two reviewers will independently assess trial eligibility in duplicate after full-text article review using a pre-designed eligibility forms. Trials will be included if they fulfill all eligibility criteria. For excluded trials, the most important justification for exclusion will be documented. Conflicts will be resolved using discussion. If no consensus can be reached, a third party will be involved. In the event a publication does not provide appropriate information for one or more eligibility criteria, but meets all other criteria, further information will be sought from the authors. Pending that information, the trial will be classified as unclear eligibility.

Data Collection and Missing Data

Two reviewers will extract data independently using pre-designed data collection forms. We will collect data related to randomization methods, blinding of treatment and assessment, use of intention-to-treat analyses, treatment group characteristics focusing on factors associated with prognosis, the number of patients crossed over, or excluded from the final analyses, or lost to follow-up, the definition of outcomes, inclusion and exclusion criteria and the number of patients with the outcomes of interest. Consensus will be sought for discordant data. We will contact the corresponding authors if some data relevant to the systematic review are missing in the study report. If they fail to reply within two weeks of our first contact and after one reminder, we will acknowledge the missing data and proceed with the analyses.

Data Analyses and Assessment of Heterogeneity

A random effects model will be used to pool the relevant results. The pooled estimates will be presented as relative risk (RR) with 95% confidence intervals (CI) for dichotomous outcomes and as mean differences (MD) for continuous outcomes with 95% CI. We will use a 5% significance level for all analyses.

We will assess for heterogeneity using the Chi-squared test for homogeneity and the I^2 statistic. We will conduct subgroup analyses to assess clinical and methodological sources of heterogeneity in intervention effect.

To evaluate whether it is a moderator variable for the primary outcome, we will conduct a meta-regression according to the mean APACHE II score in each study.

We will evaluate for potential publication bias using visual inspection of funnel plots of effect size versus standard error for outcomes that are reported in 10 studies or more. If it is suspected, we will use the arcsine test and Egger test to test for plot asymmetry for dichotomous and continuous variables, respectively. Analyses will be conducted with Review Manager (RevMan 5.3) and in R.

Potential clinical sources of heterogeneity:

A Priori Hypotheses to Explain Heterogeneity:

Subgroup	Hypothesis
High and moderate risk of bias versus low risk of bias	Studies at high risk of bias will show a greater benefit of statins.
Sepsis versus other critical illnesses	Patients with sepsis will derive greater benefit of statin therapy.
Subarachnoid versus other critical illnesses	Patients with subarachnoid will derive less benefit of statin therapy.
Trauma patients versus other critical illnesses	Trauma patients will derive less benefit of statin therapy.
Prior statin users	Prior statin users will derive greater benefit of statin therapy.
Patients with elevated troponins prior to randomization	Patients with elevated troponins will derive greater benefit of statin therapy.

Assessment of Risk of Bias:

The risk of bias for each study will be evaluated independently by two reviewers using a modified Cochrane risk of bias evaluation tool. The following will be abstracted from trial reports: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other potential sources of bias (analyses violating the intention-to-treat principle, stopping early, etc.) Disagreements will be resolved by discussion.

Quality of evidence

At the end of the process, two reviewers will evaluate the risk of bias underlying the conclusion for each outcome using the GRADE approach.[18]

Sensitivity Analysis

A sensitivity analysis focusing on studies using simvastatin will be conducted. Simvastatin is hypothesized to have greater anti-inflammatory and antibacterial effects than other statins.[19]

Reporting

We plan to publish our systematic review as an abstract and as a full publication in a peer-reviewed journal. We will report the authors' potential conflicts of interest.

References

1. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. The New England journal of medicine 2008;359:2195-207.

2. Briel M, Schwartz GG, Thompson PL, et al. Effects of early treatment with statins on short-term clinical outcomes in acute coronary syndromes: a meta-analysis of randomized controlled trials. JAMA : the journal of the American Medical Association 2006;295:2046-56.

3. Amarenco P, Goldstein LB, Szarek M, et al. Effects of intense low-density lipoprotein cholesterol reduction in patients with stroke or transient ischemic attack: the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Stroke; a journal of cerebral circulation 2007;38:3198-204.

4. Terblanche M, Almog Y, Rosenson RS, Smith TS, Hackam DG. Statins and sepsis: multiple modifications at multiple levels. The Lancet Infectious Diseases 2007;7:358-68.

5. Esmon CT. The normal role of Activated Protein C in maintaining homeostasis and its relevance to critical illness. Critical care 2001;5:S7-12.

6. Janda S, Young A, Fitzgerald JM, Etminan M, Swiston J. The effect of statins on mortality from severe infections and sepsis: a systematic review and meta-analysis. J Crit Care 2010;25:656 e7-22.

7. Jansen JO, Inaba K, Resnick S, et al. Selective non-operative management of abdominal gunshot wounds: survey of practise. Injury 2013;44:639-44.

8. Efron DT, Sorock G, Haut ER, et al. Preinjury statin use is associated with improved in-hospital survival in elderly trauma patients. The Journal of trauma 2008;64:66-73; discussion -4.

9. Schneider EB, Efron DT, MacKenzie EJ, Rivara FP, Nathens AB, Jurkovich GJ. Premorbid statin use is associated with improved survival and functional outcomes in older head-injured individuals. The Journal of trauma 2011;71:815-9.

10. Fogerty MD, Efron D, Morandi A, Guy JS, Abumrad NN, Barbul A. Effect of preinjury statin use on mortality and septic shock in elderly burn patients. The Journal of trauma 2010;69:99-103.

11. Neal MD, Cushieri J, Rosengart MR, et al. Preinjury statin use is associated with a higher risk of multiple organ failure after injury: a propensity score adjusted analysis. The Journal of trauma 2009;67:476-82; discussion 82-4.

12. Pasin L, Landoni G, Castro ML, et al. The effect of statins on mortality in septic patients: a meta-analysis of randomized controlled trials. PloS one 2013;8:e82775.

13. Craig TR, Duffy MJ, Shyamsundar M, et al. A randomized clinical trial of hydroxymethylglutaryl- coenzyme a reductase inhibition for acute lung injury (The HARP Study). American journal of respiratory and critical care medicine 2011;183:620-6.

14. National Heart L, Blood Institute ACTN, Truwit JD, et al. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. The New England journal of medicine 2014;370:2191-200.

15. Tseng MY, Hutchinson PJ, Turner CL, et al. Biological effects of acute pravastatin treatment in patients after aneurysmal subarachnoid hemorrhage: a double-blind, placebo-controlled trial. Journal of neurosurgery 2007;107:1092-100.

16. Kirkpatrick PJ, Turner CL, Smith C, Hutchinson PJ, Murray GD. Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): a multicentre randomised phase 3 trial. The Lancet Neurology 2014;13:666-75.

17. Liu Z, Liu L, Zhang Z, Chen Z, Zhao B. Cholesterol-reducing agents for aneurysmal subarachnoid haemorrhage. The Cochrane database of systematic reviews 2013;4:CD008184.

18. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401-6.

19. Masadeh M, Mhaidat N, Alzoubi K, Al-Azzam S, Alnasser Z. Antibacterial activity of statins: a comparative study of atorvastatin, simvastatin, and rosuvastatin. Ann Clin Microbiol Antimicrob 2012;11:13.

APPENDIX 2: MEDLINE Search Strategy

1. exp Sepsis/
2. exp Shock, Septic/
3. exp Shock, Traumatic/ or exp Shock, Cardiogenic/ or exp Shock/ or exp Shock, Hemorrhagic/ or exp Shock, Surgical/
4. exp Critical Care/
5. exp Intensive Care/
6. exp Respiration, Artificial/
7. exp Brain Injuries/
8. exp Respiratory Distress Syndrome, Adult/
9. exp Burns/
10. exp Critical Illness/
11. exp Intensive Care Units/
12. Ventilators, Mechanical/
13. exp Trauma Centers/
14. Sepsis.mp.
15. septic shock.mp.
16. shock.mp.
17. septicemia.mp.
18. blood stream infection.mp.
19. toxic shock.mp.
20. severe sepsis.mp.
21. Critical Illness.mp.
22. Critical Care.mp.
23. Intensive Care Units.mp.
24. Intensiv*.mp.
25. critical.mp.
26. burn unit*.mp.
27. burn patient.mp.
28. critically ill.mp.

29. ventilator*.mp.
30. artificial ventilation.mp.
31. respirator.mp.
32. ICU.mp.
33. Trauma Centers.mp.
34. Injury.mp.
35. shot*.mp.
36. shoot*.mp.
37. stab*.mp.
38. trauma*.mp.
39. accident*.mp.
40. Burn*.mp.
41. Respiratory Distress Syndrome, Adult.mp.
42. Subarachnoid Hemorr*.mp.
43. Brain injury.mp.
44. or/1-43
45. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
46. exp Anticholesteremic Agents/
47. exp Simvastatin/
48. exp Pravastatin/
49. exp Lovastatin/
50. Hydroxymethylglutaryl-CoA Reductase Inhibitors.mp.
51. statin*.mp.
52. rosuvastatin.mp.
53. crestor.mp.
54. atorvastatin.mp.
55. lipitor.mp.
56. cerivastatin.mp.
57. baycol.mp.
58. zenas.mp.
59. dalvastatin.mp.

60. RG 12561.mp.
61. fluvastatin.mp.
62. lescol.mp.
63. fluindostatin.mp.
64. pitavastatin.mp.
65. livalo.mp.
66. pitava.mp.
67. lovastatin.mp.
68. mevinacor.mp.
69. mevacor.mp.
70. mevinolin.mp.
71. monacolin.mp.
72. pravastatin.mp.
73. mevalotin.mp.
74. pravachol.mp.
75. simvastatin.mp.
76. zocor.mp.
77. lipex.mp.
78. Anticholesteremic Agents.mp.
79. or/45-78
80. 44 and 79
81. Randomized Controlled Trials as Topic/
82. randomized controlled trial/
83. Random Allocation/
84. Double Blind Method/
85. Single Blind Method/
86. clinical trial/
87. clinical trial, phase i.pt.
88. clinical trial, phase ii.pt.
89. clinical trial, phase iii.pt.
90. clinical trial, phase iv.pt.

91. controlled clinical trial.pt.
92. randomized controlled trial.pt.
93. multicenter study.pt.
94. clinical trial.pt.
95. exp Clinical Trials as topic/
96. 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95
97. (clinical adj trial$).tw.
98. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
99. PLACEBOS/
100. placebo$.tw.
101. randomly allocated.tw.
102. (allocated adj2 random$).tw.
103. 97 or 98 or 99 or 100 or 101 or 102
104. 96 or 103
105. case report.tw.
106. letter/
107. historical article/
108. 105 or 106 or 107
109. 104 not 108
110. 80 and 109
111. animals/
112. humans/
113. 111 not (111 and 112)
114. 110 not 113

APPENDIX 3: *Table 1.* Ongoing and Unpublished Potentially Eligible Trials

Trial identifier	Population	Intervention	Status	Comments
VASTVALUS NCT 01073800	Critically ill patients	Atorvastatin 80 mg	Unpublished	Stopped after recruiting 4 patients *confirmed with authors
CHAT pilot NCT 01033955	Critically ill patients with suspected, probable or confirmed H1N1 influenza	Rosuvastatin 40 mg on the first day then 20 mg	Unpublished	Stopped after recruiting 8 patients *confirmed with authors
SETS trial NCT00528580	Patients with sepsis	Simvastatin 80 mg	Unpublished	Stopped after recruiting 68 patients *no results to pool on clinicaltrials.gov
NCT01550419	Patients with ischemic stroke	Atorvastatin 40 mg	Unpublished	Unknown

	admitted to the ICU			
NCT00450840	Patients with septic shock	Simvastatin	Unpublished	Unknown
NCT00357123	Patients with abdominal sepsis	Rosuvastatin 20 mg	Unpublished	Unknown
NCT00487461	Patients with subarachnoid hemorrhage	Simvastatin 80 mg or 40 mg	Unpublished	Stopped after recruiting 25 patients
BURNSTAT NCT00978419	Patients with thermal burn	Rosuvastatin 40 mg then 20 mg	Unpublished	Likely never recruited
STAT trial NCT02901067	Patients with trauma	Rosuvastatin 20 mg	Ongoing	Factorial with ASA 325 mg Target sample 440 participants

APPENDIX 4: Meta-analysis results

Table 2. Summary of Meta-analysis for Efficacy Outcomes

Outcome	N studies	N participants	Effect estimate [95% CI]	p-value	I^2	p-value subgroup differences
STROKE						
Clinical conditions						0.09
ARDS	1	727	0.98 [0.43, 2.23]	0.96	Not applicable	
Sepsis	1	80	Not estimable		Not applicable	
SAH	3	218	0.69 [0.46, 1.02]	0.06	0%	
Trauma	0	0	Not estimable			
Other	0	0	Not estimable			
Simvastatin	1	39	0.42 [0.09, 1.92]	0.26	Not applicable	
Statin use						0.79
No previous stain use	3	200	0.83 [0.35, 2.00]	0.68	14%	
Previous statin use	1	727	0.98 [0.43, 2.23]	0.96	Not applicable	
MYOCARDIAL INFARCTION						
Clinical conditions						0.85
ARDS	1	727	0.80 [0.44, 1.47]	0.48	Not estimable	
Sepsis	1	80	Not estimable		Not estimable	
SAH	1	39	1.05 [0.07, 15.66]	0.97	Not estimable	
Trauma	0	0	Not estimable			
Other	0	0	Not estimable			
Simvastatin	1	39	1.05 [0.07, 15.66]	0.97	Not estimable	
Statin use						0.85
No previous stain use	2	119	1.05 [0.07, 15.66]	0.97	Not applicable	
Previous statin use	1	727	0.80 [0.44, 1.47]	0.48	Not estimable	

INTENSIVE CARE UNIT LENGTH OF STAY						
Clinical conditions						0.11
ARDS	3	929	0.39 [-1.03, 1.82]	0.59	0%	
Sepsis	3	431	-1.44 [-2.63, -0.25]	0.02	0%	
SAH	1	39	2.00 [-0.85, 4.85]	0.17	Not estimable	
Trauma	1	43	0.30 [-1.91, 2.51]	0.79	Not estimable	
Other	3	578	-0.95 [-3.44, 1.54]	0.45	58%	
Simvastatin	6	1108	0.45 [-0.79, 1.69]	0.48	0%	
Statin use						0.99
No previous stain use	8	1265	-1.01 [-2.13, 0.11]	0.08	55%	
Previous statin use	1	250	-1.00 [-2.58, 0.58]	0.22	Not applicable	
HOSPITAL LENGTH OF STAY						
Clinical conditions					56.4%	0.08
ARDS	3	929	0.27 [-2.37, 2.92]	0.84	0%	
Sepsis	2	358	-4.14 [-7.04, -1.25]	0.005	0%	
SAH	1	39	2.00 [-4.68, 8.68]	0.56	Not estimable	
Trauma	0	0	Not estimable			
Other	2	426	1.07 [-3.74, 5.88]	0.66	0%	
Simvastatin	5	1065	1.60 [-1.90, 5.10]	0.37	0%	
Statin use						0.58
No previous stain use	5	920	-2.27 [-5.34, 0.80]	0.15	14%	
Previous statin use	1	77	0.20 [-8.04, 8.44]	0.96	Not applicable	

ARDS: acute respiratory distress syndrome
CI: confidence interval
SAH: subarachnoid hemorrhage

Table 3. Summary of Meta-Analysis for Adverse Events

Outcome	N studies	N participants	Effect estimate RR [95% CI]	p-value	p-value subgroup differences	I%
LIVER DYSFUNCTION						
Clinical conditions					0.59	
ARDS	3	1327	1.03 [0.48, 2.21]	0.95		54%
Sepsis	4	305	1.57 [0.66, 3.75]	0.31		Not applicable
SAH	3	103	2.52 [0.51, 12.46]	0.26		0%
Trauma	0	0	Not estimable			
Other	3	429	0.91 [0.44, 1.88]	0.80		0%
Simvastatin	9	1253	1.32 [0.86, 2.03]	0.21		0%
Statin use					Not applicable	
No previous statin use	7	863	1.53 [0.97, 2.43]	0.07		0%
Previous statin use	0	0	Not estimable			
MYOPATHY						
Clinical conditions					0.99	
ARDS	3	1327	1.05 [0.41, 2.69]	0.92		67%
Sepsis	5	555	0.91 [0.14, 6.00]	0.92		36%
SAH	3	63	1.46 [0.24, 8.90]	0.68		0%
Trauma	0	0	Not estimable			Not applicable
Other	2	426	1.07 [0.16, 7.25]	0.94		71%
Simvastatin	10	1253	1.39 [0.67, 2.89]	0.38		21%
Statin use					Not applicable	
No previous statin use	7	863	1.70 [0.89, 3.23]	0.11		0%
Previous statin use	0	0	Not estimable			

DELIRIUM						
Clinical conditions					Not applicable	
ARDS	0	0	Not estimable			
Sepsis	1	80	Not estimable			
SAH	0	0	Not estimable			
Trauma	0	0	Not estimable			
Other	1	142	0.99 [0.90, 1.07]	0.73		Not applicable
Simvastatin	1	142	0.99 [0.90, 1.07]	0.73		Not applicable
Statin use					Not applicable	
No previous statin use	1	80	Not estimable			
Previous statin use	0	0	Not estimable			

ARDS: acute respiratory distress syndrome
CI: confidence interval
N: number
SAH: subarachnoid hemorrhage

Table 4. Meta-regression results

Mixed-Effects Model (k = 12; tau^2 estimator: DL)

tau^2 (estimated amount of residual heterogeneity): 0 (SE = 0.0277)
tau (square root of estimated tau^2 value): 0
I^2 (residual heterogeneity / unaccounted variability): 0.00%
H^2 (unaccounted variability / sampling variability): 1.00
R^2 (amount of heterogeneity accounted for): NA%

Test for Residual Heterogeneity:
QE(df = 10) = 8.7135, p-val = 0.5595

Test of Moderators (coefficient(s) 2):
QM(df = 1) = 0.5931, p-val = 0.4412

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	0.1844	0.3962	0.4654	0.6417	-0.5921	0.9609
apache	-0.0164	0.0213	-0.7701	0.4412	-0.0583	0.0254

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

APPENDIX 5: *Table 5.* Definitions Used for Adverse Events

Study	Myopathy	Liver dysfunction
Bernard unpublished	Likely not measured	Increased AST/ALT
Choi 2008	Not measured	Not measured
Chou 2008	Unexplained 3-fold elevation of CK on 2 consecutive measurements 24 hours apart	Unexplained 3-fold elevation of ALT/ AST on 2 consecutive measurements 24 hours apart
Craig 2011 & McAuley 2013	Reported CK >x10 ULN	ALT and AST >3x ULN
Diringer 2016	CK >2 standard deviations above ULN	Liver function>2 standard deviations above ULN
Donnino 2011	Above normal range	Above normal range
Eladawy 2016	Not measured	Not reported
El Gendy 2014	CPK >5 XULN	ALT and AST >3X ULN
Heydari 2017	Not measured	Not measured
Jaschinski 2008	Not measured	Not measured
Kruger 2013	CK ≥10,000	ALT >110 IU/L on admission: ALT >2x initial value ALT ≤110 IU/L on admission: ALT >5x ULN
Luo 2013	Not measured	Not measured
Lynch 2005	CK >1000 U/L	AST or ALT >3XULN (>180 U/L)
McAuley 2014 & Agus 2017	Elevated CK considered by the investigator to have a possible, probable or definite relationship to the study drug or CK >10X ULN	Elevated transaminases considered by the site PI to have a possible, probable or definite relationship to the study drug or AST/ALT >8X ULN
Macedo 2009	Not reported	Transaminase > 3XULN
Makris 2011	Not reported	Data not available
Mirjalili 2016	Not measured	Not measured
Naghibi 2016	Not measured	Not measured
Page 2017	CK >10xULN	AST,ALT >8 XULN
Papazian 2013	CK levels > 5X ULN	AST, ALT > 5X ULN
Prado 2013	Not reported	Not reported
Shao 2015	Not reported	Not reported
Singh 2017	CK >10X ULN	ALT level to more than twice the initial value
Truwit 2014/ Dinglas 2016/ Needham 2016/ Hough 2015	CK > 10X ULN	ALT or AST > 8X ULN
Zhou 2017	Not measured	Not measured

ALT: alanine aminotransferase
AST: aspartate aminotransferase
CK: creatine kinase
ULN: upper limit of normal

APPENDIX 6: *Table 6.* GRADE Table

Question: Statins compared to placebo or no statin for critically ill patients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Statins**	**placebo or no statin**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
20	randomised trials	serious [a]	not serious	not serious	not serious	none	493/1331 (37.0%)	522/1361 (38.4%)	**RR 0.92** (0.84 to 1.01)	**31 fewer per 1,000** (from 4 more to 61 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
								25.0%		**20 fewer per 1,000** (from 3 more to 40 fewer)		

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Statins**	**placebo or no statin**	**Relative (95% CI)**	**Absolute (95% CI)**		
								50.0%		**40 fewer per 1,000** (from 5 more to 80 fewer)		
In-hospital mortality												
15	randomised trials	not serious	not serious	not serious	not serious	none	325/1258 (25.8%)	373/1145 (32.6%)	**RR 0.77** (0.69 to 0.87)	**75 fewer per 1,000** (from 42 fewer to 101 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Stroke												
5	randomised trials	not serious	not serious	not serious	very serious [b]	none	36/507 (7.1%)	57/518 (11.0%)	**RR 0.74** (0.52 to 1.05)	**29 fewer per 1,000** (from 6 more to 53 fewer)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Statins**	**placebo or no statin**	**Relative (95% CI)**	**Absolute (95% CI)**		
Myocardial infarction												
3	randomised trials	not serious	not serious	not serious	serious [c]	none	19/426 (4.5%)	23/420 (5.5%)	**RR 0.81** (0.45 to 1.47)	**10 fewer per 1,000** (from 26 more to 30 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Venous thromboembolism												
1	randomised trials	not serious	not serious	not serious	serious [c]	none	25/367 (6.8%)	23/360 (6.4%)	**RR 1.07** (0.62 to 1.84)	**4 more per 1,000** (from 24 fewer to 54 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Liver dysfunction												
13	randomised trials	not serious	not serious	serious [d]	serious [e]	none	66/1084 (6.1%)	55/1080 (5.1%)	**RR 1.25** (0.88 to 1.77)	**13 more per 1,000** (from 6 fewer to 39 more)	⨁⨁◯◯ LOW	IMPORTANT
Myopathy												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Statins**	**placebo or no statin**	**Relative (95% CI)**	**Absolute (95% CI)**		
13	randomised trials	not serious	not serious	serious [f]	serious [c]	none	60/1204 (5.0%)	57/1207 (4.7%)	**RR 1.12** (0.66 to 1.92)	**6 more per 1,000** (from 16 fewer to 43 more)	⨁◯◯ LOW	IMPORTANT
Delirium												
2	randomised trials	not serious	not serious	not serious	not serious	none	66/111 (59.5%)	67/111 (60.4%)	**RR 0.99** (0.90 to 1.07)	**6 fewer per 1,000** (from 42 more to 60 fewer)	⨁⨁⨁⨁ HIGH	IMPORTANT
Intensive care unit length of stay												
12	randomised trials	not serious	serious [g]	not serious	not serious	none	1018	1049	-	MD **0.48 lower** (1.55 lower to 0.58 higher)	⨁⨁⨁◯ MODERATE	NOT IMPORTANT
Hospital length of stay												
8	randomised trials	not serious	not serious	not serious	not serious	none	866	886	-	MD **1.1 lower** (2.95 lower to 0.74 higher)	⨁⨁⨁⨁ HIGH	NOT IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. The point estimate is different in the sensitivity analysis including only trials at low risk of bias.
b. Wide confidence interval that includes significant benefit and no effect.
c. Wide confidence interval that includes significant harm and significant benefit.
d. All studies defined liver dysfunction as an increase in transaminases.
e. Wide confidence interval that includes significant harm and no effect.
f. All studies defined myopathy as an increase in CK.
g. I^2=59%, consistent with substantial heterogeneity.

CHAPTER 5

Association Between Postoperative Troponin Levels and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery Admitted to the Intensive Care Unit

Association Between Postoperative Troponin Levels and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery Admitted to the Intensive Care Unit

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Abstract

Background: Myocardial injury after noncardiac surgery (MINS) is associated with 30-day mortality; however, it is unknown whether intensive care unit (ICU) admission after noncardiac surgery modifies the short-term increase in mortality risk associated with MINS.

Methods: We aimed to describe the characteristics and outcomes of patients enrolled in the VISION study who were admitted to the ICU for at least one night. Finally, we evaluated whether 30-day mortality associated with MINS differed for patients admitted to the ICU for at least one night versus patients not admitted to the ICU.

Results: Of 40,004 participants, 4488 (11%) spent at least one night in the ICU after surgery. Death occurred in 336 of patients who were admitted to the ICU (7%) and 379 of patients who were not (1%). Of the patients admitted to the ICU, 1220 (27%) had MINS, while 3971 patients (11%) who were not admitted to the ICU had MINS. In the ICU, 91% of MINS were asymptomatic. MINS was associated with an increased risk of 30-day mortality among patients admitted to the ICU (adjusted hazard ratio (HR), 2.22; 95% CI, 1.78-2.78) and patients not admitted to the ICU (adjusted HR, 3.88; 95% CI, 3.13-4.81) (p for interaction <0.001).

Conclusion: Among patients admitted to the ICU after noncardiac surgery, MINS was independently associated with a 2-fold increase in 30-day mortality. This risk was significantly lower than for patients who were not admitted to the ICU.

Introduction

Troponin elevations are frequent in patients admitted to the intensive care unit (ICU) with reported incidences greater than 50%.[1-3] It is hypothesized that extreme sympathetic activity with an imbalance of myocardial oxygen supply with demand causes troponin elevations in a variety of critical illnesses. Whether these troponin elevations in the ICU are independently associated with mortality or only characterize a more severe primary disease process remains a matter of debate.[4-6]

In patients who have undergone noncardiac surgery, large prospective cohorts undergoing systematic screening have established that troponin elevations judged to be due to an ischemic etiology, even in the absence of ischemic signs or symptoms - myocardial injury after noncardiac surgery (MINS) - are independently associated with a threefold increase in the risk of mortality at 30 days.[7,8] Further, we now know that this risk is modifiable. In the Management of myocardial injury After NoncArdiac surGEry (MANAGE) trial, dabigatran lowered the risk of major vascular complications in patients who had MINS.[9]

After noncardiac surgery, patients may require admission to the ICU, either for high-level monitoring or after they have experienced a complication. Whether requiring ICU admission after surgery modifies the short-term increase in mortality risk associated with MINS is unknown. Using the Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study, we aimed to describe patients who transit through the ICU

after surgery and to evaluate whether MINS in patients admitted to the ICU is associated with the same increase in mortality risk compared to patients not admitted to the ICU.

Methods

Study Design

The VISION study was a prospective cohort that recruited 40,004 patients undergoing noncardiac surgery in North and South America, Africa, Asia, Australia, and Europe. VISION was designed to recruit a representative sample of patients undergoing noncardiac surgery to evaluate major postoperative complications. The first 15,000 patients had fourth-generation troponin T measured after noncardiac surgery.[7] For the subsequent patients, fifth-generation high-sensitivity troponin T measurements were obtained.[8]

Study Objectives

In this secondary analysis, our objective was to describe the baseline characteristics and outcomes of the VISION participants who spent at least one night in the ICU and to compare them with those who did not. In addition, we compared the characteristics of patients meeting MINS criteria in the 2 groups. Finally, we evaluated whether the increase in risk of mortality at 30 days associated with MINS differed for patients who were admitted to the ICU for at least one day compared to those who were not.

Eligibility Criteria

In this study, we evaluated both patients in the fourth and fifth-generation troponin VISION cohorts. VISION recruited patients ≥45 years of age who underwent noncardiac surgery and received a general or regional anesthetic. Patients who underwent elective, urgent or emergent surgery during the day or at night on a weekday or weekend were included. Patients who did not require an overnight stay in hospital after surgery or who were previously enrolled in VISION were excluded. Research ethics boards in all participating centers approved the protocol before patient recruitment.

Patient Recruitment and Procedures

Details of the recruitment strategies and study procedures have previously been reported.[7,8] Briefly, patients were recruited using a mixed consent model (*a priori* or deferred) either consecutively or using a recruitment schedule including random non-recruiting weeks or randomly selected surgical services when the surgical volume exceeded the study team capacity.

Research personnel obtained data on baseline variables, type of surgery, and type of anesthesia from patient interviews and charts. Troponin levels were measured 6 to 12 hours post-operatively and on the first, second, and third day after surgery. Research personnel followed patients during their hospital stay and reviewed charts for study outcomes. Research staff telephoned patients at 30 days after surgery and obtained source documentation if they had experienced an outcome since hospital discharge. Our outcomes of interest for this study were: death, MINS, myocardial infarction (with and

without symptoms), non-fatal cardiac arrest, congestive heart failure, stroke, pneumonia, and acute kidney injury requiring dialysis.

For the analyses pertaining to MINS, we excluded patients who had no troponin measurement after noncardiac surgery. Patients were considered to have MINS if they had at least one troponin measurement that exceeded the thresholds derived from the definition of MINS for each assay and was adjudicated to have been due to an ischemic etiology.[7,8] For the fourth generation, this threshold is greater or equal to 0.03 ng/mL.[7] For the fifth generation, this threshold is greater or equal to 20 ng/L with an absolute change of 5 ng/L or more or a troponin measurement ≥65 ng/L.[8]

Adjudication

Non-blinded expert adjudicators assessed the clinical notes and laboratory data of all patients with an elevated troponin level to determine whether the troponin elevation was due to a non-ischemic cause (eg, sepsis, pulmonary embolus, atrial fibrillation, cardioversion, chronic elevation). If not then it was assumed ischemic, fulfilling the definition of MINS, and further determination was made as to whether the patient also met the Third Universal definition of myocardial infarction[10] (based on the presence of symptoms, ECG changes, or imaging evidence). Their adjudicators' decisions were used in the statistical analyses.

Statistical Analyses

To describe and compare patient groups, we used descriptive statistics reporting means and standard deviations, medians and interquartile ranges, and proportions as appropriate. For crude comparisons, we compared proportions using Pearson's Chi-square test or Fisher's exact test and continuous variables using 2-sample t-test or Wilcoxon rank-sum test as appropriate for the data distribution.

To evaluate the risk of mortality at 30 days associated with MINS for patients who were admitted to the ICU compared to those who were not, we excluded patients who were adjudicated as having a non-ischemic etiology for a troponin elevation. For patients with more than one episode of MINS, we only considered the first episode. For patients who had their first troponin elevation before surgery, that episode of elevation was excluded. We built a Cox proportional hazards model in which the dependent variable was mortality at 30 days. We included as independent variables, the significant predictors of 30-day mortality previously demonstrated in VISION analyses (i.e., age, recent high risk coronary artery disease, history of stroke, peripheral vascular disease, chronic obstructive pulmonary disease [COPD], urgent or emergent surgery, active cancer, general surgery vs other surgery, neurosurgery vs other surgery) and MINS based on the 4th and separately the 5th generation troponin measurement with an interaction term for admission to the ICU.[7,8] A priori, we had decided to build separate Cox proportional hazards models, using the same variables, for patients who were admitted to the ICU and those who were not if the interaction was significant. We report adjusted hazard ratios (aHR) with 95% confidence intervals (CI) for all independent predictors of 30-day mortality.

Results

From August 2007 to November 2013, patients were recruited at 28 centers in 14 countries in Europe, Asia, Africa, Australia, North and South America. Of the 40,037 VISION participants, 40,004 were included in this study. We were unable to determine mortality at hospital discharge or 30 days for 31 patients and 2 patients were missing predictors used in the model. Follow-up was complete for 39,651 patients (99%).

Baseline Characteristics

Of the 40,004 participants, 4488 (11%) spent at least one night in the ICU after surgery. The median ICU length of stay was 2 nights (interquartile range 1, 4). The patients' preoperative characteristics, types of surgery and anesthesia are presented in **Table 1**. Patients 45-64 years old represented 45% of the patients admitted to the ICU after surgery. In this age group, 9% of patients were admitted to the ICU. Patients 65-74 years old represented 30% of patients admitted to the ICU; in this age group, 13% of patients were admitted to the ICU. Patients 75 years and older represented 25% of patients admitted to the ICU; 15% of patients in this age group were admitted to the ICU.

As shown in **Table 1**, a significantly higher proportion of patients admitted to the ICU had a history of diabetes, hypertension, congestive heart failure, coronary artery disease, peripheral vascular disease, and stroke compared to those admitted post-operatively to surgical ward. Patients admitted to the ICU were also more likely to be in atrial fibrillation just before surgery. Other comorbidities such as active cancer, renal failure,

and chronic obstructive pulmonary disease were also significantly more frequent in patients admitted to the ICU compared to those cared for on a ward.

A significantly higher proportion of patients undergoing major vascular, major general, major thoracic, and major neurosurgery were admitted to the ICU than a surgical ward or step-down unit. Overall, 32% (842/2666) of patients undergoing major vascular, 18% (1485/8222) of those undergoing major general surgery, 19% (229/1193) of those undergoing major thoracic surgery and 24% (562/2341) of those undergoing major neurosurgery were admitted to the ICU. In contrast, 4% (639/15,308) of patients were admitted to the ICU after low-risk surgeries. Patients undergoing urgent or emergent surgery often spent at least one night in the ICU postoperatively – 14% (599/4189).

Outcomes

All complications were significantly more frequent in patients admitted to the ICU than the ward (**Table 2**). Specifically, death occurred in 336 of patients who were admitted to the ICU (7%) and 379 of patients who were not (1%). Of the patients admitted to the ICU, 1220 had MINS (27%) while 3956 patients who were not admitted to the ICU had MINS (11%). Myocardial infarction occurred in 489 patients admitted to the ICU (11%) and 889 patients who were not (3%). Most myocardial infarctions and MINS in patients with an ICU stay were asymptomatic (respectively, 76% [371/489] and 91% [1111/1220]). Among other complications, the most common in patients admitted to the

ICU were pneumonia (324 patients [7%]), and congestive heart failure (179 patients [4%]).

Among patients with MINS, all complications were significantly more frequent in patients admitted to the ICU than the ward (**Table 3**).

MINS

Among patients admitted to the ICU, 1393 (31%) had a troponin elevation. Of these, 1246 (89%) were adjudicated to be of ischemic etiology. The characteristics of patients admitted to the ICU with MINS, with a non-ischemic troponin elevation, and with neither are presented in **Appendix 1**. The 30-day mortality rate was 12.8% (156 deaths; 95%CI, 11.0-14.6) in patients with MINS admitted to the ICU and 4.0% (158 deaths; 95%CI, 3.8-4.2) in patients with MINS who were not admitted to the ICU.

In a Cox proportional hazard model where the dependent variable was mortality at 30 days and the independent predictors identified in previous VISION analyses, the interaction term for MINS and ICU admission was statistically significant (p for interaction <0.001, **Appendix 2**). **Table 4** reports the Cox proportional hazard ratio models including the same variables for patients who were admitted to the ICU and separately for those who were not. Urgent and emergent surgery, active cancer, and major general surgery were independently associated with 30-day mortality in patients admitted to the ICU. In that population, MINS was associated with an adjusted HR of 2.22 (95%

CI, 1.78-2.78) for 30-day mortality. In patients who were not admitted to the ICU, all independent predictors of 30-day mortality identified in previous VISION analyses were again significantly associated with death at 30 days. In that population, MINS was associated with an adjusted HR for 30-day mortality of 3.88 (95% CI 3.13-4.81). **Figure 1** presents Kaplan-Meier estimates for survival in patients with MINS admitted to the ICU and not admitted to the ICU.

Discussion

Key Findings

In this international cohort of patients who underwent noncardiac surgery, 11% of patients were admitted to the ICU post-operatively, and 31% of these had a troponin elevation, 89% of whom were adjudicated as having an ischemic etiology. Complications were more frequent among patients admitted to the ICU with 27% experiencing MINS (versus 11% in the non-ICU group) and 7% dying within 30 days (versus 1% in the non-ICU group). Admission to the ICU appears to modify the relationship between MINS and death; MINS was associated with an adjusted HR for 30-day mortality of 2.22 (95%CI 1.78-2.78) in patients who transitioned through the ICU and HR 3.88 (95%CI 3.13-4.81) in patients who were not admitted to the ICU. Ninety-one percent of MINS in ICU patients were asymptomatic.

There are differences in threshold for admission to the ICU following noncardiac surgery. In some centers, patients are routinely admitted to the ICU after high risk surgeries for

advanced monitoring and rapid response in the event of a complication, especially if they have comorbidities.[11] However, where critical care resources are limited, admission to the ICU is restricted to patients with serious complications requiring closer monitoring or life-support.[12] These differences in practice and potential differences in case-mix or local practices likely account for variability in the proportion of patients admitted to the ICU after noncardiac surgery. For example, in a multicenter prospective 7-day observational study of 11,422 patients undergoing surgery in Africa, 5% were admitted to the ICU[13] whereas in a single center cohort of 2018 patients undergoing 2546 surgeries in Switzerland, patients were admitted to the ICU after 18% of surgeries.[14] In VISION, 11% of patients transitioned through the ICU. As demonstrated on our study, patients treated in the ICU after surgery have a higher risk of short-term mortality and complications.

Prospective cohort studies with systematic screening indicate that troponin elevations are frequent in critically ill patients, with reported incidences ranging from 48 to 84%.[1-3] To our knowledge, this is the first study with systematic troponin screening focusing on myocardial injury after noncardiac surgery in an ICU population. In this group, myocardial injury was less frequent than in mixed medical-surgical critically ill populations, occurring in 31% of patients. With 89% of these events adjudicated as being of ischemic etiology, such that 27% of patients met criteria for MINS.

We validated the MINS definition in the ICU population. Our results confirm the prognostic importance of MINS in post-operative patients admitted to the ICU, but also

demonstrate that ICU admission is an effect modifier. MINS is associated with an adjusted HR of 2.2 for mortality at 30 days and an absolute risk of death of 12.8% in patients admitted to the ICU. The lower adjusted HR for mortality at 30 days observed in the group of patients admitted to the ICU may reflect advanced medical treatment in the ICU.[15] Our finding that other complications which increased the risk of death were more frequent in this population supports this hypothesis. Another plausible hypothesis is that these patients have a higher risk of death at baseline and multisystem problems that reduce the risk of death associated with MINS.

Our results indicate that troponin elevations in critically ill post-operative patients significantly impact short-term prognosis. Beyond detecting a subset of patients at higher risk for 30-day mortality, previous work in this area demonstrated that MINS identifies a group of patients who may benefit from intensive risk factor reduction as well as targeted therapy such as dabigatran as shown in the MANAGE trial.[9,16,17] The adoption of effective practices is lagging in ICU patients. Despite their relative safety and potential benefit,[18] antiplatelet agents and statins remain infrequently used in critically ill patients with myocardial injury. In a single-center cohort of 102 critically ill patients, 47% of those with elevated troponins and 70% of those with myocardial infarction received an antiplatelet agent.[1] The prescription of statins was 47% for patients with elevated troponins and 51% for those with MI. The generation of population-specific evidence about risk-modifying treatments in this context is also needed. Meanwhile, given the potential to modify this risk, routine monitoring for troponin levels in surgical patients

admitted to the ICU would help to detect this prognostically important postoperative complication, since MINS is asymptomatic in the majority of patients.

Strengths and Limitations

This study has several strengths. With over 40,000 patients and a representative sample of patients undergoing noncardiac surgery around the world, the VISION cohort has excellent external validity. The 4488 patients admitted to the ICU represent one of the largest cohorts of critically ill patients with systematic troponin screening and the only one focused on patients after noncardiac surgery. Physicians reviewed the clinical notes and ECGs of all patients with troponin elevations to adjudicate them as from an ischemic or non-ischemic etiology. This study also has limitations. First, because it is a secondary analysis of a prospective cohort, some data points of interest such as an illness severity score and reason for ICU admission (prophylactic high level monitoring vs. unrelated critical illness) were unavailable. Second, these data may not apply to medical ICU patients. Third, adjudicators may have missed non-ischemic etiologies for troponin elevations, leading to an overestimation of the incidence of MINS.

Conclusion

After noncardiac surgery, 11% of patients transition through the ICU with 27% suffering MINS. In this population, MINS is independently associated with a 2-fold increase in 30-day mortality. Because 91% of ICU patients with MINS present without ischemic symptoms, routine monitoring for troponin levels in patients admitted to the ICU after

noncardiac surgery would help to detect this prognostically important postoperative complication.

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Conflicts of interest

Dr. Devereaux is a member of a research group with a policy of not accepting honorariums or other payments from industry for their own personal financial gain. They do accept honorariums/payments from industry to support research endeavours and costs to participate in meetings. Based on study questions he has originated and grants I have written, I have received grants from Abbott Diagnostics, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb, Coviden, Octapharma, Philips Healthcare, Roche Diagnostics and Stryker. He has also participated in an advisory board meeting for GlaxoSmithKline and an expert panel meeting with AstraZeneca and Boehringer Ingelheim.

Table 1 - Patient Preoperative Characteristics, Types of Surgery and Anesthesia

	Patients with ICU Stay - n (%)	Patients without ICU Stay - n (%)	p-value
Age Group			
45-64	2014 (44.88)	20051 (56.46)	<0.0001
65-74	1324 (29.5)	8882 (25.01)	<0.0001
>=75	1150 (25.62)	6583 (18.54)	<0.0001
Gender			
Female	2638 (58.78)	17489 (49.24)	<0.0001
Pre-Op Afib			
In atrial fibrillation just before surgery	245 (5.46)	878 (2.47)	<0.0001
History of:			
Diabetes	1088 (24.24)	7244 (20.4)	<0.0001
Hypertension	2780 (61.94)	17372 (48.91)	<0.0001
Congestive Heart Failure	338 (7.53)	1086 (3.06)	<0.0001
Coronary Artery Disease	1100 (24.51)	4059 (11.43)	<0.0001
High-risk Coronary Artery Disease	125 (2.79)	259 (0.73)	<0.0001
Coronary Revascularization	188 (4.19)	675 (1.9)	<0.0001
Coronary Revascularization (within 6 months)	86 (1.92)	363 (1.02)	<0.0001
Cardiac Arrest	52 (1.16)	183 (0.52)	<0.0001
Peripheral Vascular Disease	744 (16.58)	2459 (6.92)	<0.0001
Stroke	370 (8.24)	1312 (3.69)	<0.0001
Chronic Obstructive Pulmonary Disease	697 (15.53)	2468 (6.95)	<0.0001
Cancer			
Active Cancer, n (%)	1054 (23.48)	5114 (14.4)	<0.0001
MDRD EGFR			
<30 ml/minute/1.73m^2 or on dialysis	276 (6.15)	1074 (3.02)	<0.0001
30-44 ml/minute/1.73m^2	358 (7.98)	1837 (5.17)	<0.0001
45-59 ml/minute/1.73m^2	668 (14.88)	4307 (12.13)	<0.0001
>=60 ml/minute/1.73m^2	1912 (42.6)	16395 (46.16)	<0.0001
Type of Surgery			
Major Vascular	842 (18.76)	1825 (5.14)	<0.0001
Major General	1485 (33.09)	6737 (18.97)	<0.0001
Major Thoracic	229 (5.1)	964 (2.71)	<0.0001
Major Urology or Gynecology	398 (8.87)	4593 (12.93)	<0.0001
Major Orthopedic	692 (15.42)	6305 (17.75)	0.0001
Major Neurosurgery	562 (12.52)	1779 (5.01)	<0.0001
Low Risk Surgery	639 (14.24)	14669 (41.3)	<0.0001
Urgency of Procedure			
Urgent or Emergent Surgery	599 (13.35)	3590 (10.11)	<0.0001
Type of Anesthesia			
General Only	2480 (55.26)	18263 (51.42)	<0.0001
Neuro-Axial (Spinal or Epidural) Only	589 (13.12)	8965 (25.24)	<0.0001
General and Nitrous Oxide Only	290 (6.46)	3515 (9.9)	<0.0001
General and Nerve Block Only	118 (2.63)	1139 (3.21)	0.0408

Afib: atrial fibrillation
ICU: intensive care unit
Pre-op: preoperative

Table 2 – 30-Day Perioperative Complications by Intensive Care Unit Admission

	Patients with ICU Stay - n (%)	Patients without ICU Stay - n (%)	p-value
Mortality, n (%)	336 (7.49)	379 (1.07)	<0.0001
Myocardial injury after non cardiac surgery (MINS), n(%)	1220 (27.18)	3956 (11.14)	<0.0001
MINS with symptoms	109 (2.43)	144 (0.41)	<0.0001
MINS without symptoms	1111 (24.75)	3812 (10.73)	<0.0001
Myocardial Infarction (MI), n(%)	489 (10.9)	889 (2.5)	<0.0001
MI with symptoms	118 (2.63)	184 (0.52)	<0.0001
MI without symptoms	371 (8.27)	705 (1.99)	<0.0001
Non-fatal Cardiac Arrest, n (%)	73 (1.63)	66 (0.19)	<0.0001
Congestive Heart Failure, n (%)	178 (3.97)	193 (0.54)	<0.0001
Stroke, n (%)	71 (1.58)	61 (0.17)	<0.0001
Pneumonia, n (%)	323 (7.2)	214 (0.6)	<0.0001
Acute Kidney Injury with Dialysis, n (%)	101 (2.25)	16 (0.05)	<0.0001

MI: myocardial infarction

MINS: myocardial injury after noncardiac surgery

Table 3 – 30-Day Perioperative Complications in Patients with Myocardial Injury after Noncardiac Surgery by Intensive Care Unit Admission

	Patients with ICU Stay - n (%)	Patients without ICU Stay - n (%)	p-value
Mortality, n (%)	156 (12.79)	158 (3.98)	<0.0001
Myocardial injury after non cardiac surgery (MINS), n(%)	1220 (100)	3971 (100)	NA
MINS with symptoms	109 (8.93)	144 (3.63)	<0.0001
MINS without symptoms	1111 (91.07)	3827 (96.37)	<0.0001
Myocardial Infarction (MI), n(%)	447 (36.64)	722 (18.18)	<0.0001
MI with symptoms	109 (8.93)	144 (3.63)	<0.0001
MI without symptoms	338 (27.7)	578 (14.56)	<0.0001
Non-fatal Cardiac Arrest, n (%)	64 (5.25)	51 (1.28)	<0.0001
Congestive Heart Failure, n (%)	98 (8.03)	91 (2.29)	<0.0001
Stroke, n (%)	26 (2.13)	12 (0.3)	<0.0001
Pneumonia, n (%)	130 (10.66)	58 (1.46)	<0.0001
Acute Kidney Injury with Dialysis, n (%)	54 (4.43)	8 (0.2)	<0.0001

MI: myocardial infarction

MINS: myocardial injury after noncardiac surgery

Table 4 – Perioperative Predictors of 30-Day Mortality

A. Patients who were admitted to the intensive care unit

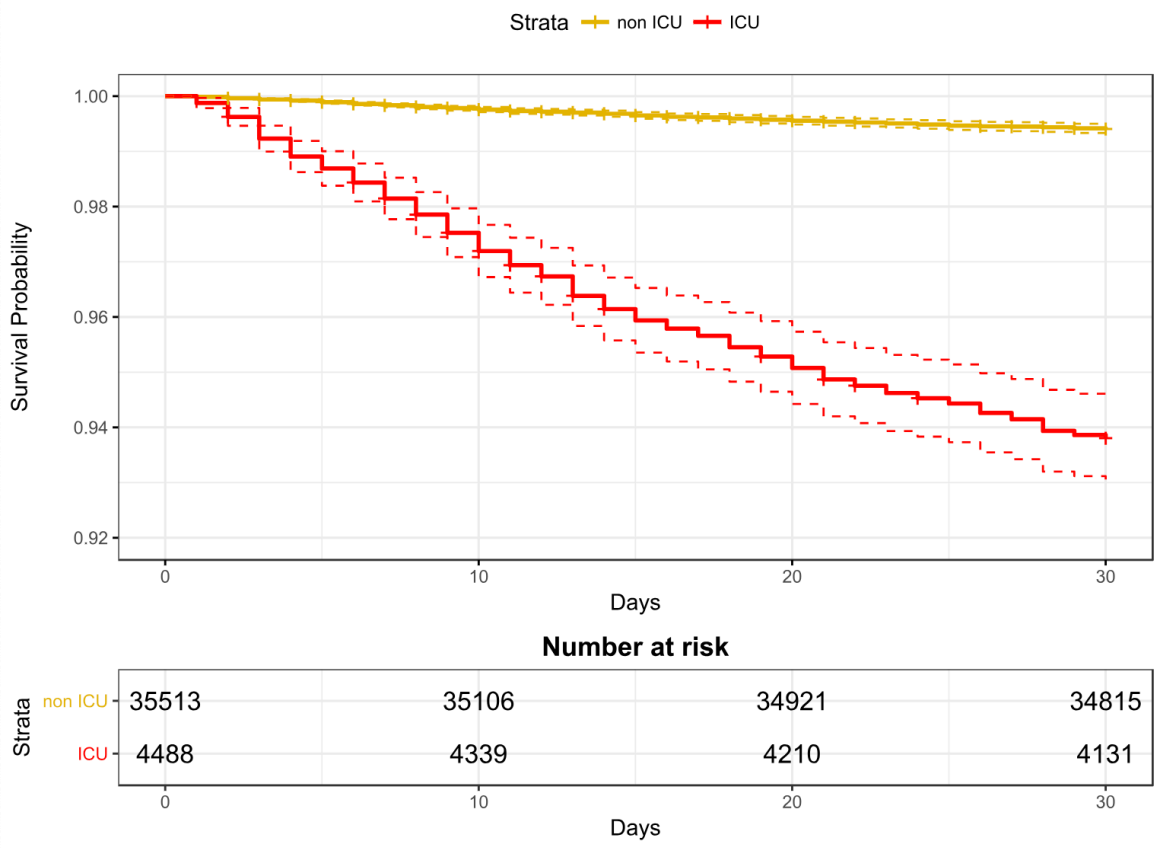
Preoperative characteristics and surgical categories	No. died/ total No.	% (95% CI)	Adjusted HR (95% CI)	p value
Age in years				
45-64	136/2014	6.75 (6.24-7.26)	Reference	
65-74	88/1324	6.65 (6.16-7.14)	0.91 (0.69-1.20)	0.50
≥75	112/1150	9.74 (8.70-10.78)	1.13 (0.86-1.47)	0.38
Recent high risk CAD	16/125	12.80 (11.02-14.58)	1.61 (0.97-2.68)	0.07
No recent high risk CAD	320/4363	7.33 (6.73-7.93)	Reference	
History of stroke	47/553	8.50 (7.70-9.30)	1.0 (0.73-1.38)	0.98
No history of stroke	289/3935	7.34 (6.74-7.94)	Reference	
History of PAD	58/744	7.80 (7.13-8.47)	1.10 (0.81-1.50)	0.53
No history of PAD	278/3744	7.43 (6.82-8.04)	Reference	
History of COPD	65/697	9.33 (8.37-10.29)	1.24 (0.94-1.65)	0.13
No history of COPD	271/3791	7.15 (6.58-7.72)	Reference	
Urgent/Emergent surgery	102/599	17.03 (13.92-20.14)	3.03 (2.38-3.85)	<0.001
Elective surgery	234/3889	6.02 (5.61-6.43)	Reference	
Active cancer	103/1054	9.77 (8.72-10.82)	1.62 (1.26-2.09)	<0.001
No active cancer	233/3434	6.79 (6.28-7.30)	Reference	
Major general surgery	136/1372	9.91 (8.83-10.99)	1.53 (1.20-1.96)	<0.001
Other surgeries	200/3116	6.42 (5.96-6.88)	Reference	
Major neurosurgery	36/562	6.41 (5.95-6.87)	1.08 (0.74-1.58)	0.69
Other surgeries	300/3926	7.64 (6.99-8.29)	Reference	
MINS	156/1220	12.79 (11.01-14.57)	2.22 (1.78-2.78)	<0.001
No MINS	180/3268	5.51 (5.17-5.85)	Reference	

B. Patients who were <u>not</u> admitted to the intensive care unit

Preoperative characteristics and surgical categories	No. died/ total No.	% (95% CI)	Adjusted HR (95% CI)	p value
Age in years				
45-64	128/20050	0.64 (0.63-0.65)	Reference	
65-74	92/8882	1.04 (1.03-1.05)	1.31 (1.00-1.72)	0.1
≥75	159/6583	2.42 (2.35-2.49)	2.21 (1.72-2.83)	<0.001
Recent high risk CAD	15/259	5.79 (5.41-6.17)	2.91 (1.72-4.90)	<0.001
No recent high risk CAD	364/35257	1.03 (1.02-1.04)	Reference	
History of stroke	51/2029	2.51 (2.44-2.58)	1.54 (1.14-2.09)	0.01
No history of stroke	328/33487	0.98 (0.97-0.99)	Reference	
History of PAD	68/2459	2.77 (2.68-2.86)	2.30 (1.74-3.05)	<0.001
No history of PAD	314/33048	0.94 (0.93-0.95)	Reference	
History of COPD	65/2468	2.63 (2.55-2.71)	1.78 (1.35-2.35)	<0.001
No history of COPD	314/33048	0.95 (0.94-0.96)	Reference	
Urgent/Emergent surgery	128/3590	3.57 (3.42-3.72)	4.56 (3.66-5.69)	<0.001
Elective surgery	251/31926	0.79 (0.78-0.80)	Reference	
Active cancer	104/5114	2.03 (1.98-2.08)	2.69 (2.12-3.42)	<0.001
No active cancer	275/30400	0.90 (0.89-0.91)	Reference	
Major general surgery	104/6578	1.58 (1.55-1.61)	1.65 (1.30-2.10)	<0.001
Other surgeries	275/28938	0.95 (0.94-0.96)	Reference	
Major neurosurgery	26/1779	1.46 (1.43-1.49)	2.31 (1.53-3.48)	<0.001
Other surgeries	353/33737	1.05 (1.04-1.06)	Reference	
MINS	158/3971	3.98 (3.80-4.16)	3.88 (3.13-4.81)	<0.001
No MINS	221/31545	0.70 (0.69-0.71)	Reference	

CAD: coronary artery disease
CI: confidence interval
COPD: chronic obstructive pulmonary disease
HR: hazard ratio
MINS: myocardial injury after noncardiac surgery
PAD: peripheral arterial disease

Figure 1 – Kaplan-Meier Estimates of 30-Day Mortality for Patients with Myocardial Injury after Noncardiac Surgery Based on Intensive Care Unit Admission



References

1. Lim W, Holinski P, Devereaux PJ, et al. Detecting myocardial infarction in critical illness using screening troponin measurements and ECG recordings. Critical care 2008;12:R36.

2. Lim W, Qushmaq I, Cook DJ, et al. Elevated troponin and myocardial infarction in the intensive care unit: a prospective study. Critical care 2005;9:R636-44.

3. Ostermann M, Lo J, Toolan M, et al. A prospective study of the impact of serial troponin measurements on the diagnosis of myocardial infarction and hospital and six-month mortality in patients admitted to ICU with non-cardiac diagnoses. Critical care 2014;18:R62.

4. Velasquez A, Ghassemi M, Szolovits P, et al. Long-term outcomes of minor troponin elevations in the intensive care unit. Anaesth Intensive Care 2014;42:356-64.

5. Markou N, Gregorakos L, Myrianthefs P. Increased blood troponin levels in ICU patients. Current opinion in critical care 2011;17:454-63.

6. Caujolle M, Allyn J, Brulliard C, et al. Determinants and prognosis of high-sensitivity cardiac troponin T peak plasma concentration in patients hospitalized for non-cardiogenic shock. SAGE Open Med 2018;8:2050312118771718.

7. Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Study I, Devereaux PJ, Chan MT, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA : the journal of the American Medical Association 2012;307:2295-304.

8. Writing Committee for the VSI, Devereaux PJ, Biccard BM, et al. Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. JAMA : the journal of the American Medical Association 2017;317:1642-51.

9. 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 2018;391:2325-34.

10. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Journal of the American College of Cardiology 2012;60:1581-98.

11. Ghaffar S, Pearse RM, Gillies MA. ICU admission after surgery: who benefits? Current opinion in critical care 2017;23:424-9.

12. Nates JL, Nunnally M, Kleinpell R, et al. ICU Admission, Discharge, and Triage Guidelines: A Framework to Enhance Clinical Operations, Development of Institutional Policies, and Further Research. Critical care medicine 2016;44:1553-602.

13. Biccard BM, Madiba TE, Kluyts HL, et al. Perioperative patient outcomes in the African Surgical Outcomes Study: a 7-day prospective observational cohort study. Lancet 2018;391:1589-98.

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

15. Shankar-Hari M, Harrison DA, Rowan KM, Rubenfeld GD. Estimating attributable fraction of mortality from sepsis to inform clinical trials. Journal of critical care 2018;45:33-9.

16. 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.

17. Relos RP, Hasinoff IK, Beilman GJ. Moderately elevated serum troponin concentrations are associated with increased morbidity and mortality rates in surgical intensive care unit patients. Critical care medicine 2003;31:2598-603.

18. Gross AK, Dunn SP, Feola DJ, et al. Clopidogrel treatment and the incidence and severity of community acquired pneumonia in a cohort study and meta-analysis of antiplatelet therapy in pneumonia and critical illness. Journal of thrombosis and thrombolysis 2013;35:147-54.

Contributorship Statement

Emilie P Belley-Côté contributed significantly to the study's concept and design, data collection and analysis, and interpretation of the results. She wrote the first draft of the manuscript, provided critical revisions, and gave final approval of the submitted manuscript.

Richard P Whitlock contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Daniel I Sessler contributed to the data collection and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Wojciech Szczeklik contributed to the data collection and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

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Appendix 1
Characteristics of patients admitted to the ICU with MINS, with a non-ischemic troponin elevation, and with neither

Age Group				
45-64	389 (31.89)	50 (33.33)	1375 (46.93)	0.7903
65-74	352 (28.85)	43 (28.67)	769 (26.25)	1.0000
>=75	505 (41.39)	54 (36)	697 (23.79)	0.2379
Gender				
Female gender	759 (62.21)	103 (68.67)	1684 (57.47)	0.1458
Pre-Op Afib				
In atrial fibrillation just before surgery	90 (7.38)	19 (12.67)	123 (4.2)	0.0358
History of:				
Diabetes	372 (30.49)	33 (22)	635 (21.67)	0.0398
Hypertension	873 (71.56)	104 (69.33)	1707 (58.26)	0.6365
Congestive Heart Failure	147 (12.05)	24 (16)	155 (5.29)	0.2111
Coronary Artery Disease	431 (35.33)	45 (30)	587 (20.03)	0.2292
High-risk Coronary Artery Disease	53 (4.34)	5 (3.33)	63 (2.15)	0.7148
Coronary Revascularization	71 (5.82)	4 (2.67)	110 (3.75)	0.1580
Coronary revascularization (within 6 months)	32 (2.62)	4 (2.67)	46 (1.57)	1.0000
Cardiac Arrest	18 (1.48)	2 (1.33)	28 (0.96)	1.0000
Peripheral Vascular Disease	299 (24.51)	43 (28.67)	392 (13.38)	0.3122
Stroke	131 (10.74)	9 (6)	208 (7.1)	0.0959
Chronic Obstructive Pulmonary Disease	249 (20.41)	26 (17.33)	411 (14.03)	0.4356
Cancer				
Active Cancer, n (%)	261 (21.39)	27 (18)	722 (24.64)	0.3918
MDRD EGFR				
<30 ml/minute/1.73m^2 or on dialysis	154 (12.62)	29 (19.33)	86 (2.94)	0.0314
30-44 ml/minute/1.73m^2	134 (10.98)	29 (19.33)	178 (6.08)	0.0044
45-59 ml/minute/1.73m^2	207 (16.97)	22 (14.67)	364 (12.42)	0.5507
>=60 ml/minute/1.73m^2	428 (35.08)	49 (32.67)	1337 (45.63)	0.6205
Type of Surgery				
Major Vascular	312 (25.57)	35 (23.33)	489 (16.69)	0.6199
Major General	335 (27.46)	65 (43.33)	1017 (34.71)	0.0001
Major Thoracic	72 (5.9)	6 (4)	148 (5.05)	0.4462
Major Urology or Gynecology	102 (8.36)	8 (5.33)	265 (9.04)	0.2592
Major Orthopedic	238 (19.51)	18 (12)	410 (13.99)	0.0344
Major Neurosurgery	94 (7.7)	5 (3.33)	436 (14.88)	0.0744
Low risk surgery	151 (12.38)	19 (12.67)	408 (13.92)	1.0000
Urgency of Procedure				
Urgent or emergent surgery	203 (16.64)	42 (28)	317 (10.82)	0.0009
Type of Anesthesia				
General only	658 (53.93)	93 (62)	1627 (55.53)	0.0741
Neuro-axial (spinal or epidural) only	447 (36.64)	48 (32)	1010 (34.47)	0.3048
General and Nitrous Oxide Only	88 (7.21)	8 (5.33)	262 (8.94)	0.4955
General and Nerve Block Only	39 (3.2)	4 (2.67)	80 (2.73)	0.9178

Afib: atrial fibrillation
ICU: intensive care unit
Pre-op: preoperative

Appendix 2: Cox Proportional Hazard Model for Mortality at 30 Days

Predictor	Adjusted HR (95% CI)	P value
Age 45-64 years	reference	
Age 65-74 years	1.12 (0.92-1.36)	1
Age ≥ 75 years	1.65 (1.38-1.98)	<0.001
Recent high risk CAD	2.04 (1.42-2.94)	<0.001
History of stroke	1.22 (0.97-1.52)	0.1
History of PAD	1.59 (1.29-1.96)	<0.001
History of COPD	1.49 (1.22-1.82)	<0.001
Urgent/Emergent surgery	3.73 (3.17-4.38)	<0.001
Active cancer	2.17 (1.82-2.58)	<0.001
Major general surgery	1.61 (1.35-1.91)	<0.001
Major neurosurgery	1.54 (1.17-2.04)	0.001
MINS	4.53 (3.67-5.58)	<0.001
ICU admission	5.68 (4.63-6.97)	<0.001
MINS*ICU admission	0.43 (0.32-0.58)	<0.001

CAD: coronary artery disease
COPD: chronic obstructive pulmonary disease
HR: hazard ratio
ICU: intensive care unit
MINS: myocardial injury after noncardiac surgery
MINS*ICU: interaction term for MINS and ICU
PAD: peripheral arterial disease

CHAPTER 6

Definitions of Post Coronary Artery Bypass Grafting Myocardial Infarction: Variations in Incidence and Prognostic Significance

Definitions of Post Coronary Artery Bypass Grafting Myocardial Infarction: Variations in Incidence and Prognostic Significance

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Abstract

Aim: Using data from the CORONARY trial (n=4752), we evaluated the incidence and prognostic significance of MI applying different definitions based on peak post-operative creatine kinase-MB isoezyme (CK-MB) and cardiac troponin levels. We then aimed to identify the peak cardiac troponin during the first 3 postoperative days that was independently associated with a 2-fold increase in 30-day mortality.

Methods: To combine different assays, we analysed cardiac troponins in multiples of their respective upper limit of normal (ULN). We identified the lowest threshold with a hazard ratio (HR) >2 for 30-day mortality independent of EuroSCORE and on- versus off-pump surgery.

Results: Depending on the definition used based on CK-MB, the incidence of MI after CABG ranged from 0.6 to 19 % and the associated HRs for 30-day mortality ranged from 2.7 to 6.9. Using cardiac troponin (1528 patients), the incidence of MI ranged from 1.7 to 13% depending on the definition used with HRs for 30-day mortality ranging from 5.1 to 7.2. The first cardiac troponin threshold we evaluated, 180xULN, was associated with an adjusted HR for 30-day mortality of 7.6 (95% CI 3.4-17.1) when compared to <130xULN. The next independent threshold was 130xULN with an adjusted HR for 30-day mortality of 7.8 (95% CI 2.3-26.1). The next cardiac troponin tested threshold (70xULN) did not meet criteria for significance.

Conclusion: Our results illustrate that the incidence and prognosis of a post-CABG MI varies based on the definition used. Validated post-CABG MI diagnostic criteria

formulated from their independent association with important clinical outcomes are needed.

Keywords: Cardiac Surgery, CK-MB, Myocardial Infarction, Troponin

The Universal definitions for myocardial infarction (MI) after coronary artery bypass (CABG) surgery are based on a cardiac biomarker elevation greater than 10 times the 99th percentile concentration (designated as the upper limit of normal; ULN) from a healthy population.[1,2] These post-CABG MI diagnostic criteria are based on an arbitrary biomarker elevation threshold in association with signs of cardiac necrosis.[1] In 2012, the Task Force elected to increase the biomarker elevation threshold for the Third Universal definition because the initial greater than 5xULN threshold was considered too sensitive.[1,3] In 2013, the Society for Cardiovascular Angiography and Interventions suggested another definition using different biomarker elevation thresholds depending on whether new pathologic Q waves or left bundle branch block (LBBB) were present.[4] These different MI definitions have never undergone rigorous validation in the context of CABG to assess their association with clinically important events.[1,2,4] They were also established when CK-MB was the biomarker of choice to diagnose post-CABG MI. In many centres, cardiac troponins have replaced CK-MB.[5] Given the ubiquitous release of cardiac troponin during CABG surgery, the prognostic value of using a 10-fold ULN threshold has been questioned by clinicians when diagnosing post-CABG MI.[6] Therefore, we aimed to identify a prognostically relevant cardiac troponin threshold post-CABG MI.

The CABG Off or On Pump Revascularization Study (CORONARY) was a large (n=4752) randomized controlled trial that compared CABG with and without cardiopulmonary bypass.[7-9] Using data from that trial, we aimed to evaluate the incidence

of MI and the prognostic implication of post-CABG MI as determined using different diagnostic criteria utilized by clinicians and in clinical studies of cardiac surgery.

Methods

Details of the CORONARY Trial (NCT 00463294) methods have been published previously and are briefly described below.[8]

Patients

Patients were recruited between 2006 and 2011 from 79 centers in 19 countries. Patients were eligible if they were scheduled to undergo CABG and had at least one of the following risk factors: age ≥70 years, peripheral artery disease, cerebrovascular disease, carotid stenosis ≥70%, or renal insufficiency. Patients 60 to 69 years of age were enrolled if they had diabetes, required urgent revascularization, had a left ventricular ejection fraction ≤ 35%, or a recent history of smoking. After the recruitment of 1700 patients, a protocol amendment allowed patients 55 to 59 years to be enrolled if they had one of the risk factors listed for patients aged 60 to 69 years. Patients were excluded if they required valve surgery, were not suitable for one of the two CABG techniques, had a life expectancy <2 years, required emergent revascularization or repeat CABG surgery, or were previously enrolled in CORONARY. Written informed consent was obtained for each participant. Research ethics board approval was obtained at each participating center.

Follow-up

In all patients, CK-MB measurements and ECG readings were mandated at 24 and 48 hours after surgery. Centres could report post-operative cardiac troponins at 24 and 48 hours on the standardized case report forms, but troponin measurement was not mandated. When reporting biomarker values, centres also provided the 99th percentile of the ULN for the assay used.

Patients were seen in clinic or at the hospital 30 days after their surgery. At one year, patients were assessed for death, nonfatal stroke, nonfatal myocardial infarction, or nonfatal renal failure requiring dialysis at 30 days after surgery. All deaths within 30 days of surgery were considered cardiovascular. Follow-up was complete for 4752 patients (100%) at 30 days and for 4690 patients (98.7%) at 1 year.[7]

Statistical Analyses

CK-MB

Using data from participants in the CORONARY Trial as a cohort, we evaluated the incidence of post-CABG MI according to five different definitions: the Second Universal MI definition,[3] the Third Universal MI definition,[1] the definition proposed by Moussa *et al.*,[4] the definition used in the CORONARY Trial,[8] and the definition used in the Steroids In cardiac Surgery (SIRS) Trial.[10] The detailed definitions are presented in **Table 1**. To evaluate the clinical relevance of the definitions, we calculated the adjusted hazard ratio

(aHR) for 30-day mortality adjusted for EuroSCORE associated with each of them. To determine if there was a significant interaction (i.e., $P<0.05$) between on-pump surgery and off-pump surgery with the MI definitions, we added an interaction term.

In the SIRS trial, a 7507-patient trial evaluating prophylactic steroid versus placebo in on-pump cardiac surgery, we observed that CK-MB mass and activity assays performed differently based on thresholds set by their ULN.[10] For this reason, a separate threshold for each assay type was established. We aimed to confirm this finding using CORONARY data by evaluating the incidence and aHR for 30-day mortality associated with MI as defined in CORONARY separately for patients in whom CK-MB mass and CK-MB activity were measured. Further, we determined the aHRs for 30-day mortality using the SIRS definitions for CK-MB mass and CK-MB activity using the CORONARY trial data.

Cardiac Troponin

In patients for whom cardiac troponin levels were available, we evaluated the incidence of post-CABG MI according to three different definitions: the Third[1] and Fourth[2] Universal MI definitions, and the definition proposed by Moussa *et al*[4] (**Table 1**). In order to combine different cardiac troponin assays, we analysed cardiac troponin in multiples of their respective ULN, as there is no standardization across assays.[11] For CORONARY trial participants with at least one cardiac troponin measurement in the first 48 hours after surgery, we calculated the proportion that had a peak cardiac troponin concentration >10

x ULN (the currently suggested threshold), the associated aHR for 30-day and 1-year mortality adjusting for EuroSCORE.

To identify a prognostically relevant cardiac troponin concentration threshold after CABG surgery, we used a proportional hazards Cox models with 30-day mortality as the dependent variable. We identified the lowest cardiac troponin threshold that had a statistically significant independent aHR greater than 2 by exploring peak cardiac troponin levels in multiples of the ULN, while adjusting for EuroSCORE and on-pump versus off-pump surgery. *A priori*, we specified that the first threshold we would test would be the peak postoperative troponin threshold close to the 95th percentile of the overall cohort. Additional cutoffs were chosen *a posteriori* based on the distribution of data. We conducted sensitivity analyses that repeated these thresholds identifying analyses but used 1-year mortality as the dependent variable,

Results

In CORONARY, 119 (2.5%) patients died during the first 30 days and 241 (5%) patients died within one year. The baseline characteristics of the CORONARY participants have been previously reported and are summarized **Table 2**.[9]

Three patients (0.06%) developed a new left bundle branch block and 55 developed new Q waves (1.16%) after surgery.

CK-MB

For each of the five definitions of interest for CK-MB, the incidence of MI and aHRs for 30-day and 1-year mortality are presented in **Table 3**. Depending on the diagnostic criteria used, the incidence of MI after CABG surgery ranged from 0.6 to 19% and the aHRs for 30-day mortality ranged from 2.7 to 6.9. The Third Universal definition was associated with the lowest post-CABG MI incidence and the SIRS trial definition with the highest. The SIRS trial definition resulted in the lowest aHR (2.7; 95% CI 1.9-4.0) for 30-day mortality and the Moussa definition had the highest aHR (6.9; 95% CI 4.2-11.5). There was no significant interaction between on-pump surgery and off-pump surgery with the MI definitions (i.e., all interaction p values were ≥0.2).

The aHRs for the CK-MB mass and activity assays using the assay-specific SIRS definitions and the CORONARY definition are presented in **Table 4**. Using the CORONARY definition, the incidence of MI in patients for whom CK-MB mass were reported was 4% while it was 14% when CK-MB activity were reported. The aHRs for 30-day mortality were 2.5 (95% CI 1.3-4.6) and 2.6 (95% CI 0.9-7.5), respectively.

Cardiac Troponin

Peak cardiac troponin results were available for 1528 patients who underwent on-pump (n=760) or off-pump CABG (n=768) in the CORONARY trial. For 1085 of these patients (71%), cardiac troponin I was reported; for the other patients, cardiac troponin T was reported. The characteristics of patients with and without cardiac troponins reported are

compared in **Supplemental material 1**. Patients who had cardiac troponin reported were systematically different from those who did not. Patients who had a troponin measurement were significantly older and more likely to have a history of hypertension, diabetes, percutaneous coronary intervention, renal failure requiring dialysis, peripheral and cerebrovascular disease. Patients for whom cardiac troponin was reported had a significantly higher body mass index and were significantly less likely to have had urgent surgery.

Peak cardiac troponins were greater than 10xULN in 46% (705/1538) of patients. The positively skewed distribution of peak post-operative cardiac troponin concentrations is shown in **Figure 1**. The mean for the peak cardiac troponin results was 53.0xULN (standard deviation 328.8). The median for peak cardiac troponin results was 8.7xULN (interquartile range 2.3- 30.1). After adjustment for EuroSCORE and on and off-pump surgery, the aHR for mortality associated with a peak cardiac troponin >10xULN was 4.0 (95% CI 0.8-19.3) at 30 days. There was no significant interaction between on-pump surgery and off-pump surgery with the MI definitions (i.e., the interaction p value was 1).

For each of the three definitions of interest for cardiac troponins, the incidence of MI and aHR for 30-day and 1-year mortality are presented in **Table 3**. Depending on the diagnostic criteria used, the incidence of MI ranged from 1.7% to 13% and the aHRs for 30-day mortality ranged from 5.1 to 7.2. The Fourth Universal definition was associated with the lowest post CABG MI incidence while the Moussa definition resulted in the

highest incidence. The Fourth Universal definition resulted in the lowest aHR for 30-day mortality 5.1 (95% CI 1.5-17.6), while the Third Universal definition resulted in the highest aHR, 7.2 (95% CI 2.4-21.3).

To identify a prognostically relevant threshold, the first threshold we evaluated was 180xULN because 177xULN corresponded to the 95th percentile. This threshold was associated with an aHR for 30-day mortality of 7.6 (95% CI 3.4-17.1) when compared to <130xULN. The next independent threshold that we evaluated was 130xULN to 180xULN with an adjusted HR for 30-day mortality of 7.8 (95% CI 2.3-26.1) when compared to <130xULN. The next threshold (>70xULN) did not meet criteria for significance with an adjusted HR of 2.5 (95% CI 0.7-8.5). The HRs for 1-year mortality are presented in **Table 5**.

Discussion

Key Results

We examined the incidence and associated mortality of different post-CABG MI definitions within the CORONARY trial dataset. The incidence and associated mortality varied substantially based on which definition of MI after CABG surgery was applied. Based on the CORONARY trial dataset, definitions based on CK-MB measures were associated with a 2.7 to 6.9-fold increase in 30-day mortality. However, some definitions were found to result in a high incidence of MI (SIRS definition, incidence of 19% which included CK-MB levels determined by enzyme activity and mass), while others much less

so (Third Universal Definition, incidence of 0.6% which does not endorse CK-MB activity assays).

Cardiac troponin elevations >10xULN after CABG surgery occurred in 46% patients in the CORONARY trial and were not significantly associated with 30-day mortality when adjusting for EuroSCORE and on- versus off-pump CABG. When adding new Q waves or new left bundle branch block, as per the Third and Fourth Universal definitions, the incidence of MI decreased to less than 2% and the HR for 30-day mortality was more than 5. These results suggest that a clinically relevant cardiac troponin threshold for post-CABG MI should be higher than >10xULN, the value advocated in the Universal Definition of MI. Including new Q waves or left bundle branch block to post CABG MI criteria leads to a higher HR for 30-day mortality; however, with a 5-fold increase in 30-day mortality, mandating these ECG changes in the criteria likely misses a stratum of the population who have suffered an MI and are at substantial risk for short-term death.

Existing Studies

An association between cardiac biomarker elevations and mortality after CABG was demonstrated in a systematic review of seven studies (18,908 patients) by Domanski *et al*.[12] Their adjusted and unadjusted pooled results suggested that post-operative CK-MB and cardiac troponin increases were associated with increased short and long-term mortality. With increasing biomarker elevations, mortality increased: for CK-MB, a doubling in risk occurred with CK-MB ≥5xULN while for cardiac troponin the risk

doubled with elevations 20 to 40 xULN.[12] Another systematic review of 23 studies (29,483 patients) by Petaja also demonstrated worse outcomes with post-operative biomarker elevations.[13]

Diagnosing an MI after a cardiac surgery is complicated for multiple reasons. MI after CABG surgery can be caused by early graft failure, distal embolization of plaque material and inadequate myocardial protection.[14] Based on different mechanisms, these events can have different clinical presentations. The surgical "trauma" to the myocardium in itself causes some biomarker release. Cardiac and pericardial manipulation can result in ECG changes. The assessment for typical symptoms is confounded by normal post-operative pain, delirium and analgesia. Accordingly, biomarker elevations are important as they can be the main reliable manifestation of significant myocardial injury. In the noncardiac perioperative setting, where assessment for symptoms is also unreliable, isolated cardiac biomarker elevations are associated with substantial mortality.[15]

The SIRS definition is the only prognostic-based definition, but also the only definition that relies solely on biomarkers.[10,16] The SIRS biomarker threshold was derived with the explicit goal of identifying patients at risk of a poor outcome. Using blinded data from the first 7000 participants, the SIRS investigators undertook a planned analysis used a modified Mazumdar approach to identify the lowest peak post-operative CK-MB threshold independently associated with a HR >2 for 30-day mortality when adjusting for EuroSCORE.[17] Separate analyses of CK-MBs measured with the mass and the activity

assays is another strength of the SIRS MI definition. Other MI definitions do not differentiate between these assays even though they produce significantly different results, and the CK-MB mass assay being recommended over activity.[10,18]

Our analysis using the CORONARY data validates the SIRS definition when using the CKMB mass assay by demonstrating that the thresholds identified in SIRS were also associated with a more than 2-fold increase in 30-day mortality in the CORONARY cohort. In the absence of ECG, imaging or angiographic criteria, it could be argued that the SIRS definition identifies patients with myocardial injury rather than myocardial infarction. However, any definition that requires new Q waves or a new left bundle branch block is likely to demonstrate an MI incidence of less than 2%, no matter what is the required increase in the biomarker, and these data suggest such a definition is going to miss prognostically important events. As for the imaging and angiographic criteria, they cannot be assessed routinely in all patients and are therefore likely under detect MI.

Myocardial injury after cardiac surgery (MICS) may actually be a better designation for the pathophysiologic mechanisms that lead to biomarker release after cardiac surgery. A minority of cardiac surgery patients have classic myocardial infarction with acute coronary or graft occlusion with resulting necrosis in a specific myocardial territory.[19,20] Most cardiac injury after cardiac surgery is related to the extent of the procedure as demonstrated with higher biomarkers after valvular surgery or combined surgery compared to isolated CABG.[21] The quality of myocardial protection may also play a role;

inadequate administration of cardioplegia may result in greater myocardial injury. Clinicians should recognize that troponin elevations above established thresholds after cardiac surgery provide important prognostic information. To what extent this risk is modifiable is still unknown and warrants further research. The ongoing VISION (Vascular events In Surgery patIents cOhort evaluatioN) Cardiac Surgery Study, a 15,000-patient cohort will allow derivation of a more precise estimate for the optimal event-driven MI definition after cardiac surgery using high sensitivity cardiac troponins.

Strengths and Limitations

Our work represents the first comparison of the incidence and prognostic value of different post-CABG MI definitions. Using patients from a large cardiac surgery randomized trial as a cohort provided us with a large sample size and high quality data. The excellent follow-up (100% at 30-days and 98.7% at 1-year), allowed evaluation of the association of the MI definitions with important clinical outcomes.

Important limitations of this study include the absence of information on cardiac surgery procedures other than CABG. The subgroup of patients with cardiac troponin measurements was smaller and the overall CORONARY cohort, and this sample size limited our ability to explore potential thresholds. In addition, the CORONARY trial was conducted before the widespread use of high-sensitivity cardiac troponins and we cannot comment on reported differences in ULN between men and women and those older than 70 years than younger when using high-sensitivity cardiac troponin assays.[22] While these

data of non-high-sensitivity cardiac troponins provide insights, further research is needed using high sensitivity cardiac troponins.

Conclusions

The various definitions for MI after CABG result in substantial variations in the incidence of MI and in the associated aHRs for mortality. These variations have important implications for clinical practice; depending on diagnostic criteria used, an absolute difference of 18% of patients will be labelled as having a perioperative MI. Our current study validates the prognostic impact of the SIRS diagnostic criteria, which are the only criteria established based on clinical data. Further work is needed to clarify the underlying pathophysiology of these events and help differentiate across the various pathophysiological mechanisms. Clinically relevant post-CABG MI diagnostic criteria should be independently associated with mortality. Our results illustrate the need for validated post-CABG MI diagnostic criteria formulated from their independent association with important clinical outcomes.

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Disclosures

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Dr. Devereaux is a member of a research group with a policy of not accepting honorariums or other payments from industry for their own personal financial gain. They do accept honorariums/payments from industry to support research endeavours and costs to participate in meetings. Based on study questions he has originated and grants I have written, I have received grants from Abbott Diagnostics, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb, Coviden, Octapharma, Philips Healthcare, Roche Diagnostics and Stryker. He has also participated in an advisory board meeting for GlaxoSmithKline and an expert panel meeting with AstraZeneca and Boehringer Ingelheim.

The other authors have no relevant conflict of interest to declare.

References

1. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. European heart journal 2012;33:2551-67.

2. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). European heart journal 2018.

3. Thygesen K, Alpert JS, White HD, Joint ESCAAHAWHFTFftRoMI. Universal definition of myocardial infarction. European heart journal 2007;28:2525-38.

4. Moussa ID, Klein LW, Shah B, et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). Journal of the American College of Cardiology 2013;62:1563-70.

5. Prochaska MT, Hohmann SF, Modes M, Arora VM. Trends in Troponin-Only Testing for AMI in Academic Teaching Hospitals and the Impact of Choosing Wisely(R). J Hosp Med 2017;12:957-62.

6. van Beek DE, van Zaane B, Buijsrogge MP, van Klei WA. Implementation of the third universal definition of myocardial infarction after coronary artery bypass grafting: a survey study in Western Europe. Journal of the American Heart Association 2015;4:e001401.

7. Lamy A, Devereaux PJ, Prabhakaran D, et al. Effects of off-pump and on-pump coronary-artery bypass grafting at 1 year. The New England journal of medicine 2013;368:1179-88.

8. Lamy A, Devereaux PJ, Prabhakaran D, et al. Rationale and design of the coronary artery bypass grafting surgery off or on pump revascularization study: a large international randomized trial in cardiac surgery. American heart journal 2012;163:1-6.

9. Lamy A, Devereaux PJ, Prabhakaran D, et al. Off-pump or on-pump coronary-artery bypass grafting at 30 days. The New England journal of medicine 2012;366:1489-97.

10. Whitlock RP, Devereaux PJ, Teoh KH, et al. Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial. Lancet 2015;386:1243-53.

11. Estis J, Wu AHB, Todd J, Bishop J, Sandlund J, Kavsak PA. Comprehensive Age and Sex 99th Percentiles for a High-Sensitivity Cardiac Troponin I Assay. Clin Chem 2018;64:398-9.

12. Domanski MJ, Mahaffey K, Hasselblad V, et al. Association of myocardial enzyme elevation and survival following coronary artery bypass graft surgery. Jama 2011;305:585-91.

13. Petaja L, Salmenpera M, Pulkki K, Pettila V. Biochemical injury markers and mortality after coronary artery bypass grafting: a systematic review. The Annals of thoracic surgery 2009;87:1981-92.

14. Brener SJ, Lytle BW, Schneider JP, Ellis SG, Topol EJ. Association between CK-MB elevation after percutaneous or surgical revascularization and three-year mortality. Journal of the American College of Cardiology 2002;40:1961-7.

15. 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.

16. Writing Committee for the VSI, Devereaux PJ, Biccard BM, et al. Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. JAMA : the journal of the American Medical Association 2017;317:1642-51.

17. Whitlock R, Teoh K, Vincent J, et al. Rationale and design of the steroids in cardiac surgery trial. American heart journal 2014;167:660-5.

18. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. Journal of the American College of Cardiology 2000;36:959-69.

19. Rasmussen C, Thiis JJ, Clemmensen P, et al. Significance and management of early graft failure after coronary artery bypass grafting: feasibility and results of acute angiography and re-re-vascularization. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 1997;12:847-52.

20. Fabricius AM, Gerber W, Hanke M, Garbade J, Autschbach R, Mohr FW. Early angiographic control of perioperative ischemia after coronary artery bypass grafting. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2001;19:853-8.

21. Mastro F, Guida P, Scrascia G, et al. Cardiac troponin I and creatine kinase-MB release after different cardiac surgeries. Journal of cardiovascular medicine 2015;16:456-64.

22. Welsh P, Preiss D, Shah ASV, et al. Comparison Between High-Sensitivity Cardiac Troponin T and Cardiac Troponin I in a Large General Population Cohort. Clin Chem 2018.

Table 1: Criteria used in each definition of post-CABG MI

Definition	**Rationale for biomarker threshold**	**Biomarker and ECG Crite**
CK-MB		
Universal Definition 2007	Arbitrary	CK-MB >5xULN **with** ECG abnormalities **or** angiographic evidence of new graft or native coronary artery occlusion **or** imaging evidence of new loss of viable myocardium
Universal Definition 2012	Arbitrary	CK-MB >10xULN **with** ECG abnormalities **or** angiographic evidence of new graft or native coronary artery occlusion **or** imaging evidence of new loss of viable myocardium
Moussa Definition 2013	Arbitrary	CK-MB ≥10xULN **or** ≥5xULN with ECG abnormalities
CORONARY Definition 2012	Arbitrary	CK-MB ≥5xULN **or** angiographic evidence of new graft or native coronary artery occlusion **or** imaging evidence of new loss of viable myocardium
SIRS Study Definition 2015	Event-driven	CK-MB mass ≥ 6xULN **or** CK-MB activity ≥40
Cardiac troponin		

Definition	**Rationale for biomarker threshold**	**Biomarker and ECG Crite**
CK-MB		
Universal Definition 2012	Arbitrary	Cardiac troponin >10xULN **with** ECG abnormalities **or** angiographic evidence of new graft or native coronary artery occlusion **or** imaging evidence of new loss of viable myocardium
Universal Definition 2018	Arbitrary	Cardiac troponin values >10xULN **with** pathological Q waves **or** angiographic evidence of new graft or native coronary artery occlusion **or** imaging evidence of new loss of viable myocardium
Moussa 2013	Arbitrary	Cardiac troponin values ≥70xULN **or** ≥35XULN **with** ECG abnormalities

ULN: 99th percentile upper limit of normal
ECG abnormalities: new pathologic Q waves or new left bundle branch block

Table 2: Baseline Characteristics for all participants in CORONARY

Total N	4752
Age – yr – mean (SD)	68 (7)
Male sex – no. (%)	3843 (80.9)
Body Mass Index kg/m2 - mean (SD)	26.7 (4.4)
Clinical history – no. %	
Prior myocardial infarction	1641 (34.5)
Prior percutaneous coronary intervention (PCI)	463 (9.7)
Cerebrovascular disease	456 (9.8)
Peripheral arterial disease	385 (8.1)
Smoking (never)	2187 (46.0)
Diabetes	2228 (46.9)
Renal failure (dialysis)	66 (1.4)
Congestive heart failure	296 (6.2)
Hypertension	3604 (75.8)
Chronic atrial fibrillation	128 (2.7)
LV Function (EF%)	
Grade 1 (≥ 50%)	3294 (70.7)
Grade 2 (35-49%)	1103 (23.7)
Grade 3 (20-34%)	244 (5.2)

Grade 4 (<20%)	11 (0.2)
EuroSCORE grade – no.	
0 to 2	1339 (28.2)
3 to 5	1932 (40.7)
> 5	1412 (29.7)
Urgent surgery	1842 (38.8)
Any antiplatelet agent (pre-op)	3620 (76.2)
Numbers of vessels diseased	
Left main	1001 (21.5)
Triple vessel disease	2711 (58.2)
Double vessel disease	817 (17.5)
Single vessel disease	119 (2.6)

Table 3: MI Incidence and Associated Mortality According to Diagnostic Criteria Used

Definition		Incidence N (%)	Unadjusted Mortality 1y N (%)	30-day aHR for mortality (95%CI)*	1-year aHR for mortality (95%CI)*
CK-MB					
Universal Definition 2007	MI	50 (1.1)	8 (16.0)	5.1 (2.2-11.4)	2.8 (1.4-6.0)
	No MI	4702 (98.9)	233 (5.0)		
Universal Definition 2012	MI	29 (0.6)	5 (17.2)	5.3 (2.0-14.2)	2.5 (1.0-6.5)
	No MI	4723 (99.4)	236 (5.0)		
Moussa Definition 2013	MI	127 (2.7)	22 (17.3)	6.9 (4.2-11.5)	3.9 (2.5-6.0)
	No MI	4625 (97.3)	219 (4.7)		
CORONARY Definition 2012	MI	328 (6.9)	41 (12.5)	4.0 (2.6-6.2)	2.9 (2.1-4.1)
	No MI	4424 (93.1)	200 (4.5)		
SIRS Study Definition 2015	MI	902 (19.0)	73 (8.1)	2.7 (1.9-4.0)	1.9 (1.4-2.5)
	No MI	3850 (81.0)	168 (4.4)		
Cardiac troponin					
Universal Definition 2012	MI	27 (1.8)	5 (18.5)	7.2 (2.4-21.3)	3.7 (1.5-9.3)
	No MI	1473 (98.2)	79 (4.4)		
Universal Definition 2018	MI	26 (1.7)	4 (15.4)	5.1 (1.5-17.6)	2.9 (1.1-8.1)
	No MI	1474 (98.3)	80 (5.4)		
Moussa 2013	MI	196 (13.1)	23 (11.7)	5.6 (2.8-11.0)	3.0 (1.8-4.8)
	No MI	1304 (86.9)	61 (4.7)		

CI: confidence interval
HR: hazard ratio
*adjusted for EuroSCORE

Table 4: MI Associated Mortality According to the SIRS and CORONARY Definition for CK-MB Mass and Activity Assays

CK-MB Assay	Incidence N (%)	HR for 30-day mortality (95%CI)*	HR for 1-year mortality (95%CI)*
CORONARY definition			
Mass	103 (3.5)	2.5 (1.3-4.6)	2.4 (1.5-3.9)
Activity	215 (14.2)	2.6 (0.9-7.5)	1.2 (0.6-2.4)
SIRS definition			
Mass	713 (24.5)	3.8 (1.6-8.9)	2.2 (1.1-4.2)
Activity	175 (11.6)	3.3 (2.1-5.2)	2.0 (1.5-2.8)

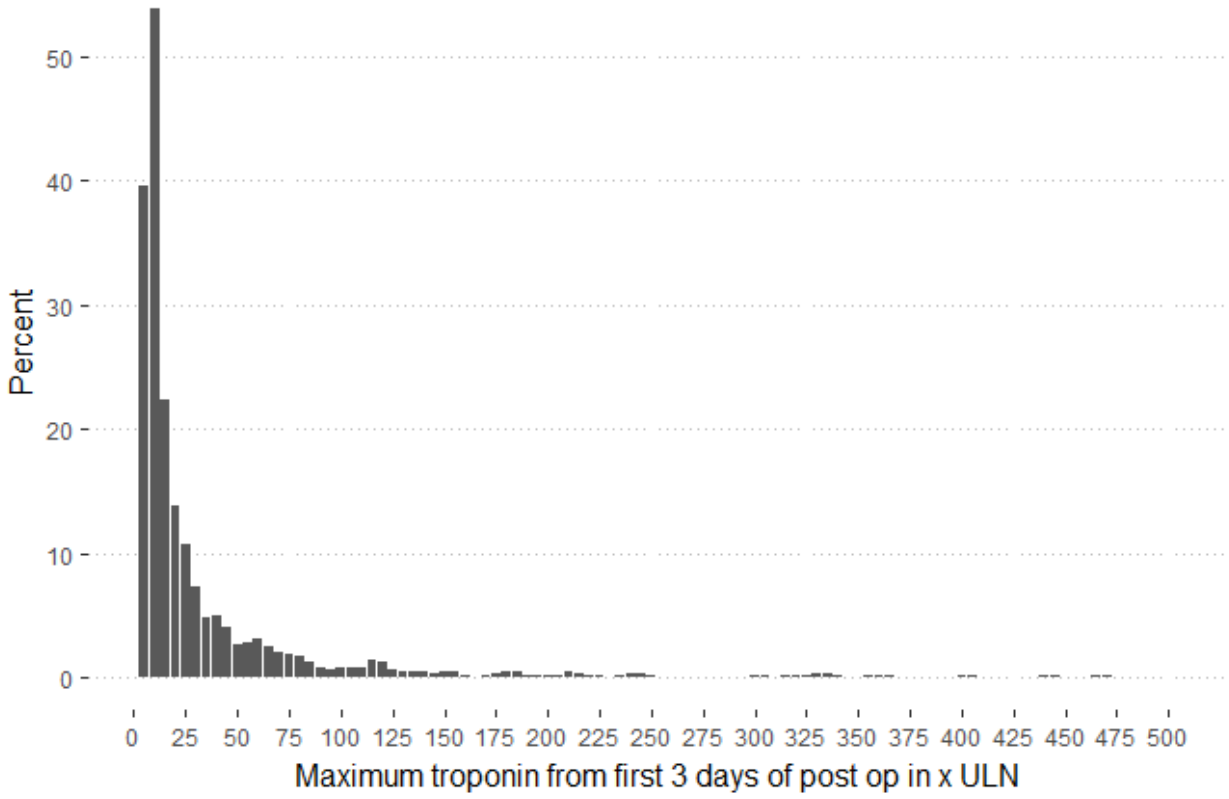
CI: confidence interval
HR: hazard ratio
*adjusted for EuroSCORE

Table 5: Association of Cardiac Troponins with Mortality

	Covariate	HR (95% CI)*	P-value
30-day Mortality	130≤ cTn <180xULN	7.8 (2.3-26.1)	0.0009
	cTn ≥ 180xULN	7.6 (3.4-17.1)	<0.0001
	Off-Pump	1.3 (0.7-2.5)	0.5
	EuroSCORE	1.1(1.0-1.2)	0.0002
1-year Mortality	130≤ cTn <180xULN	3.7 (1.4-10.3)	0.01
	cTn ≥180 xULN	4.2 (2.3-7.8)	<0.0001
	Off-Pump	1.0 (0.7-1.6)	1.0
	EuroSCORE	1.1 (1.1-1.1)	<0.0001

*reference is cardiac troponin <130XULN
CI: confidence interval
cTn: troponin
HR: hazard ratio
ULN: 99th percentile upper limit of normal

Figure 1



This table shows the distribution of cardiac troponins in multiples of the 99th percentile of the upper limit of normal.

Contributorship Statement

Emilie Belley-Côté contributed significantly to the study's concept and design, data collection and analysis, and interpretation of the results. She wrote the first draft of the manuscript, provided critical revisions, and gave final approval of the submitted manuscript.

André Lamy contributed to the study's concept, data collection and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

PJ Devereaux contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Pete Kavsak contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

François Lamontagne contributed to the interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Deborah Cook contributed to the interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Kevin Kennedy contributed to the data analysis, and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.
Jessica Vincent contributed to data collection and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

Yongning Ou contributed to data collection and interpretation of the results. She provided critical revisions and gave final approval of the submitted manuscript.

George Tagarakis contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Richard Whitlock contributed to the study's concept and interpretation of the results. He provided critical revisions and gave final approval of the submitted manuscript.

Appendix 1 - **Baseline Characteristics for Patients who had a Cardiac Troponin Reported in CORONARY**

	With troponin reported (n=1528)	Without troponin reported (n=3224)	P-value
Age – years (SD)	68.1 (7.3)	67.3 (6.5)	<0.001
Male sex – no. (%)	1217 (79.6)	2626 (81.5)	0.14
Body Mass Index – kg/m^2 (SD)	27.4 (4.5)	26.4 (4.3)	<0.001
Clinical history – no. %			
Prior myocardial infarction	546 (35.7)	1095 (34.0)	0.23
Prior percutaneous coronary intervention	194 (12.7)	269 (8.3)	<0.001
Cerebrovascular disease	198 (13.0)	258 (8.2)	<0.001
Peripheral arterial disease	178 (11.6)	207 (6.4)	<0.001
Smoking (never)	555 (36.3)	1632 (50.6)	<0.001
Diabetes	676 (44.2)	1552 (48.1)	0.01
Renal failure (dialysis)	33 (2.2)	33 (1.0)	0.002
Congestive heart failure	105 (6.9)	191 (5.9)	0.21
Hypertension	1238 (81.0)	2366 (73.4)	<0.001
Chronic atrial fibrillation	51 (3.3)	77 (2.5)	0.09
Left ventricular function			0.06
Grade 1 (≥ 50%)	1046 (68.5)	2248 (71.8)	
Grade 2 (35-49%)	384 (25.1)	719 (23.0)	
Grade 3 (20-34%)	94 (6.2)	150 (4.8)	
Grade 4 (<20%)	3 (0.2)	8 (0.3)	
EuroSCORE grade – no. (%)			<0.001
0 to 2	334 (21.9)	1005 (31.2)	
3 to 5	605 (39.6)	1327 (41.2)	
> 5	560 (36.6)	852 (26.4)	
Urgent surgery	486 (31.8)	1356 (42.1)	<0.001
Any antiplatelet agent (pre-op)	1312 (85.9)	2308 (71.6)	<0.001
Numbers of vessels diseased			<0.001
Left main	402 (26.3)	599 (19.1)	
Triple vessel disease	829 (54.3)	1882 (60.1)	
Double vessel disease	272 (17.8)	545 (17.4)	
Single vessel disease	24 (1.6)	95 (3.0)	
Trial allocation			
On-pump	760 (49.7)	1617 (50.2)	
Off-pump	768 (50.3)	1607 (49.8)	
Troponin I	1085 (71.0)		
Troponin T	443 (29.0)		

No : number; SD : standard deviation

CHAPTER 7
Conclusions and Future Directions

7.1 Background

This doctoral thesis explored problems related to troponin elevations in critically ill patients. The presented studies describe the prevalence of troponin elevations in medical-surgical critically ill patients and their association with in-hospital mortality, provide insight into the current management of patients with clinically recognized troponin elevations in the intensive care unit (ICU), evaluate the safety of statins in the ICU setting, and explore definitions for significant myocardial injury in ICU patients who have recently undergone noncardiac or cardiac surgery.

7.2 The Need and Feasibility of a Large Cohort Evaluating the Incidence of Troponin Elevations in Critical Illness

In Chapter 2, a pilot study was presented demonstrating the feasibility of a large cohort study with systematic troponin and electrocardiogram (ECG) screening to evaluate whether troponin elevations were independently associated with a worse prognosis in critically ill patients. Myocardial injury and myocardial infarction were frequent during critical illness and these patients had an unadjusted higher risk of mortality compared to patients who did not have a cardiac troponin elevation. Whether the association of cardiac troponin elevation with death in the ICU was independent of other prognostic factors remained uncertain. This pilot study has established the feasibility of conducting a large-scale investigation addressing this issue.

The high consent rate was reassuring for the main cohort's external validity. The rapid accrual of participants confirmed that a large cohort can be recruited efficiently. With data collection requiring on average less than 2 hours per participant, the study procedures were pragmatic. While compliance with screening cardiac troponin and ECG was suboptimal, we have identified it as a key study procedures to monitor in the main cohort.

The results of this pilot will inform the design of a large prospective cohort with built-in ancillary mechanistic studies aiming to improve our understanding of cardiac troponin elevations in critical illness. Such a cohort study with systematic laboratory testing and ECG screening will confirm whether elevated cardiac troponins in critically illness, whether meeting other criteria for myocardial infarction or not, are independently associated with a worse prognosis.

The sample size for the large study will depend on the number of variables we will aim to adjust for and the funding we will be able to secure. Given the multiplicity of factors that impact mortality during critical illness and their interplay, we expect to recruit more than 6000 patients in the main cohort. This sample size, with an expected 1000 events, should allow us to adjust for baseline characteristics, in-ICU events as time-dependent variables and interactions between variables.

7.3 Secondary Cardiovascular Prevention and Risk Stratification in Critically Ill Patients with Troponin Elevations

In Chapter 3, we describe the use of secondary cardiovascular prevention medications and cardiac investigations during the index hospital stay in a cohort of patients with clinically identified troponin elevations during a critical illness from the pilot study presented in Chapter 2.

About one third of patients admitted to the ICU had a clinically recognized troponin elevation. These patients were more acutely ill, with significantly higher mean APACHE II scores, and a higher use of invasive mechanical ventilation and vasopressors than patients without clinically recognized troponin elevations. On discharge from ICU, medications of proven benefit in secondary cardiovascular prevention (antiplatelet agents, angiotensin II receptor blockers and angiotensin-conversion-enzyme inhibitor, beta-blockers, and statins) were infrequently prescribed in patients with a troponin elevation. Of these patients, 10% had a coronary angiogram to stratify cardiac risk, significantly more than patients without clinically detected cardiac troponin elevations. No patient underwent an exercise stress test or nuclear perfusion imaging. In-hospital cardiac investigations were significantly more likely among patients with troponin elevations and a history of congestive heart failure.

These results demonstrated that the use of secondary cardiovascular prevention medications was low in patients who experience a troponin elevation during critical illness. Echocardiograms were frequently performed and coronary angiograms

infrequently obtained in this population, whereas non-invasive testing for ischemia was not undertaken during the index hospital stay.

7.4 Safety and Efficacy of Statins in Critically Ill Patients

In Chapter 4, a systematic review and meta-analysis of randomized controlled trials evaluated the safety and efficacy of statins in critically ill patients.

Based on the pooled estimates of risk, the use of statins in critically ill patients may reduce in-hospital mortality. A mortality benefit beyond hospital discharge was not demonstrated, but could not be excluded. We found no significant differences in myocardial infarction and injury, stroke and deep venous thrombosis/pulmonary embolism, but these outcomes were assessed and reported in few included studies and there were a limited number of events. The pooled results were reassuring regarding the safety of statins in the ICU setting in the absence of significant increases in liver dysfunction, myopathy and delirium in patients randomized to statin therapy.
These data suggest statin therapy in critically ill patients is safe and beneficial.

These results support the need for a large high-quality trial to definitively establish the effects of a statin in critically ill patients. In this trial, we will evaluate whether the subgroup of patients with myocardial injury derives the most benefit. Given the high mortality during and early after a critical illness, studying interventions that may improve these patients' outcomes should be a priority. Meanwhile, the results of this systematic

review and meta-analysis may reassure clinicians regarding the safety of statins in the ICU.

7.5 Myocardial Injury after Noncardiac Surgery in Patients Admitted to the Intensive Care Unit

In Chapter 5, we described patients who transit through the ICU after noncardiac surgery and evaluated whether, in the subset of patients admitted to the ICU, troponin elevations were associated with the same mortality risk as in the overall cohort.

In this international cohort of 40,004 patients who underwent noncardiac surgery, 11% of patients were admitted to the ICU post-operatively, and 31% of these had a troponin elevation, 89% of whom were adjudicated as having an ischemic etiology. Complications were more frequent among patients admitted to the ICU with 27% experiencing myocardial injury after noncardiac surgery (MINS) (versus 11% in the non-ICU group) and 7% dying within 30 days (versus 1% in the non-ICU group). Admission to the ICU modified the relationship between MINS and death; MINS was associated with an adjusted hazard ratio (HR) for 30-day mortality of 2.22 (95%CI 1.78-2.78) in patients who transitioned through the ICU and HR 3.88 (95%CI 3.13-4.81) in patients who were not admitted to the ICU. Ninety-one percent of MINS in ICU patients were asymptomatic.

The lower adjusted HR for mortality at 30 days observed in the group of patients admitted to the ICU may reflect advanced medical treatment in the ICU. Our finding that other complications which increased the risk of death were more frequent in this population supports this hypothesis. Another plausible hypothesis is that these patients had a higher risk of death at baseline and multisystem problems that reduced the risk of death associated with MINS. Given the potential to modify this risk, routine monitoring for troponin levels in surgical patients admitted to the ICU would help to detect this prognostically important postoperative complication, since MINS is asymptomatic in the majority of patients.

7.6 Defining Myocardial Infarction after Coronary Artery Bypass Surgery

In Chapter 6, the incidence and prognostic significance of myocardial infarction after coronary artery bypass surgery (CABG) are reported applying different definitions based on peak post-operative creatine kinase-MB isoezyme (CK-MB) and cardiac troponin levels. In addition, a peak cardiac troponin during the first 3 postoperative days that was independently associated with a 2-fold increase in 30-day mortality was identified.

The incidence and prognosis of a post-CABG myocardial infarction varied based on the definition used within the CORONARY trial dataset. Cardiac troponin elevations meeting the threshold criterion were frequent after CABG and were not significantly associated with short-term outcomes. These results re-inforce that validated post-CABG myocardial

infarction diagnostic criteria formulated from their independent association with important clinical outcomes are needed.

The ongoing VISION (Vascular events In Surgery patIents cOhort evaluatioN) Cardiac Surgery Study, a 15,000-patient cohort will allow derivation of a more precise estimate for the optimal event-driven myocardial infarction definition after cardiac surgery using high sensitivity cardiac troponins. The definitions derived from the VISION Cardiac Surgery Study will have broader generalizability due to the inclusion of non-CABG patients.

7.7 Future directions

By conducting the studies included in this thesis, I have acquired the methodological knowledge and experience required to answer important research questions using a multi-design programmatic approach. I will apply this knowledge throughout my career to inform questions from different angles.

In addition, in the process of answering the research questions in this thesis, I have discovered other unanswered key clinical questions requiring further investigations. For example, after seeing the low uptake of secondary cardiovascular prevention medications in the cohort of patients with clinically identified troponin elevation during critical illness, I decided to evaluate how clinicians manage these patients when the elevation occurs after noncardiac surgery. I will explore this question in the VISION cohort, leading to

greater generalizability of the results than from the smaller and single country PROTROPIC pilot study cohort. Another example, is that after noticing that the incidence of new Q waves after cardiac surgery was very low, I started wondering what was the prognostic relevance of ischemic ECG changes after cardiac surgery. Developing validated separate definitions for myocardial infarction after CABG and other cardiac surgical procedures should be a priority. These definitions have to identify patients with a worse post-operative prognosis. Identifying patients at higher risk of short-term mortality will allow clinicians to intensify monitoring for signs of early complications. It will also allow researchers to explore strategies and therapies to modify these risks. I will explore whether ischemic ECG changes provide prognostic information in addition to troponin release in the VISION Cardiac Surgery cohort.

Other important research areas stemming from this thesis that warrant addressing include: 1) assessing the prognostic importance of troponin elevations during critical illness in a cohort large enough to adjust for the multiple confounders in this heterogeneous and complex population, 2) definitively evaluating whether statins improve outcomes when administered during a critical illness. These objectives could even be achieved concomitantly by a pragmatic randomized controlled trial of statin therapy nested in a very large cohort of critically ill patients with systematic troponin monitoring.