MYOCARDIAL INJURY AFTER NONCARDIAC SURGERY

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By

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ABSTRACT

Worldwide, more than 2 million patients die within 30 days after noncardiac surgery anually. Postoperative ischemic myocardial injury is frequent, however, no consensus exists about its definition.

Objective: to develop a term Myocardial Injury after Noncardiac Surgery (MINS) caused by myocardial ischemia, requiring at least, troponin T (TnT) elevation, and with prognostic relevance at 30 days after surgery.

Methods: we performed a prospective study including 15,167 patients ≥45 years-old undergoing noncardiac surgery, who had fourth-generation TnT measurements during the first 3 postoperative days. We undertook Cox regression analyses with 30-day mortality after surgery as the dependent variable, using different TnT thresholds, clinical features and several perioperative variables. Non-ischemic etiologies were excluded. Furthermore, we developed a scoring system to predict risk in MINS patients.

Results: MINS was defined as TnT ≥0.03 ng/mL with or without clinical features, and it was an independent predictor of 30-day mortality (adjusted HR 3.82, CI 95% 2.84-5.10). We determined that MINS incidence was 8%, its population attributable risk 33.7%, and 30-days mortality rate 9.6%. Patients did not experience ischemic symptoms in 84% of MINS cases. Additionally, we developed a scoring system in patients suffering MINS with 3 independent predictors of death (age ≥75 years, new ST elevation or left bundle branch block, and anterior location of ECG changes),

Conclusion: Among patients undergoing noncardiac surgery, we defined MINS based on a TnT threshold ≥0.03 ng/mL. Mostly, MINS patients were asymptomatic. Therefore, this strongly suggests the importance of a troponin monitoring during the first few days after surgery.

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LIST OF ABBREVIATIONS AND SYMBOLS

ECG: Electrocardiographic

MI: Myocardial Infarction

MINS: Myocardial Injury after Noncardiac Surgery

TnI: Troponin I

TnT: Troponin T

VISION: Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Study

DECLARATION OF ACADEMIC ACHIEVEMENT

Dr Fernando Botto participated in different activities of VISION Study as member of the Operations Committee, i.e., coordination of Latin America countries, independent outcomes adjudication, control of data quality and monitoring of regional centers. I designed, together with Dr PJ Devereaux, the statistical analysis plan to develop the proposed Myocardial Injury after Noncardiac Surgery (MINS) concept, and I have also conceived the idea of developing a scoring system to predict risk in MINS patients. Further, I participated in the interpretation of results with Dr Devereaux and the statistician, Diane Heels-Ansdell, from McMaster University. Finally, I performed all the bibliographic searches, drafted all the chapters and incorporated the suggestions of my thesis committee members.

Dr. PJ Devereaux is the Principal Investigator of VISION Study and contributed with the conception and design of the study, obtained funding to support it, conceived the idea of troponin monitoring during the perioperative period, coordinated the activities for development of MINS, and critically reviewed all chapters of the manuscript.

Dr Gordon Guyatt, Dr Lehana Thabane and Dr Daniel Sessler have also reviewed the manuscript and made substantial suggestions. Diane Heels-Ansdell performed the statistical analysis and Shirley Petit coordinated all VISION activities and data management.

Chapter 1

INTRODUCTION

Worldwide, more than 200 million adults undergo a major noncardiac surgery annually.[1,2] Based on contemporary data from the largest prospective cohort[3] and the largest randomized trial[4], we estimate that each year more than 2 million patients die within 30 days after noncardiac surgery, and that almost 1 out of 2 occur due to a cardiovascular reason. Additionally, 6 to 10 million patients suffer a myocardial infarction (MI) during the same period. Therefore, cardiovascular complications after noncardiac surgery represent a major public health challenge.

Coronary artery disease is the progressive thickening of the wall of coronary arteries resulting from a chronic inflammatory process characterized mainly by the accumulation of fatty materials (e.g., cholesterol). In situations when the arterial lumen is significantly reduced due to a chronic narrowing and a high myocardial oxygen demand occurs, or when the blood flow is suddenly reduced by a thrombus formation or a significant blood pressure decrease, the cardiac cells or myocytes do not receive an adequate amount of oxygen and nutrients and suffer a process called "myocardial ischemia". Clinically, the patient may experience chest pain or shortness of breath, electrocardiographic (ECG) abnormalities, and elevation of cardiac biomarkers (i.e., proteins like creatine-kinase MB and troponin), as a consequence of the myocardial damage.

During the perioperative period of noncardiac surgery, a patient with a chronic severe coronary obstruction may suffer myocardial ischemia triggered by an increased oxygen demand due to increase in heart rate and blood pressure as a consequence of surgical stress (i.e., surgical trauma, anesthesia/analgesia, pain, bleeding, anemia, hypothermia, fasting, intubation/extubation).[5] Furthermore, a sudden coronary blood flow reduction caused by local thrombus formation, coronary vasospasm or significant hypotension, represents a second mechanism that may precipitate ischemia. Reasons are attributed to endothelial damage produced by an increased shear stress in an enhanced inflammatory and hypercoagulable environment due to the neurohumoral changes mentioned above, [5] and bleeding as a consequence of surgery.

Whatever the responsible mechanism, myocardial ischemia may be clinically symptomatic or silent.[6] Furthermore, it may be self-limited or aborted by treatment. However, if the blood flow is not quickly restored (i.e., within 30 minutes), the myocytes deprived of oxygen begin suffering a process of cell death. This process that takes from a few minutes up to 2 to 4 hours to be completed is called "myocardial infarction" and presume "myocardial necrosis", which means irreversible death of myocardial cells.[7]

During or after a MI the patient may experience electric disturbances of the heart, i.e., arrhythmias, or an extensive damage of the cardiac muscle with the subsequent risk of cardiac failure. Both mechanisms may result in short or long-term mortality.

Since MI has not only clinical, but also social, psychological, and economic implications, an accurate diagnosis is crucial. Traditionally, it was based on a requirement of two of the following three elements: clinical symptoms (e.g., chest pain,

shortness of breath), ischemic ECG abnormalities, and elevation of myocardial enzymes or biomarkers.[8] Currently, the most sensitive and specific serum biomarkers are a family of regulatory proteins called troponins (i.e., subunits T and I), found in the skeletal and cardiac muscle, but not smooth muscle, that have an important role during the contraction process of the heart. They have demonstrated a great diagnostic performance for detecting myocardial damage[7], and nowadays, they are overwhelmingly used in hospitals to diagnose MI.

1.1 The problem

First in 2000, and later in 2007, a joint committee of the leading international scientific societies in cardiovascular disease updated the universal definition of MI.[7,9] They stated that the term MI reflects necrosis or cell death of cardiac myocytes caused by ischemia, which is the result of a coronary perfusion imbalance between supply and demand. The term MI does not include myocardial cell death associated with mechanical injury from coronary artery bypass grafting (CABG) (e.g., ventricular venting or manipulation of the heart) nor does it include myocardial necrosis due to miscellaneous causes (e.g. heart failure, cardioversion, electrophysiological ablation, renal failure, sepsis, myocarditis, cardiac toxins, or infiltrative diseases).[7]

This consensus group developed the diagnostic criteria for acute MI presented in the **Table 1**. These criteria offer a specific definition for MI after cardiac procedures like percutaneous coronary interventions (PCI)) and CABG; however, they did not provide a specific criterion for MI after noncardiac surgery.[7]

Therefore, there are two main arguments to propose a new term related to the ischemic complications after noncardiac surgery. First, the spectrum of myocardial injury includes from a few minutes of myocardial ischemia up to the established MI with irreversible necrosis. Perioperative MI is a well known independent predictor of adverse results;[10] however, there is evidence demonstrating that intermediate reversible ischemic episodes, such as prolonged ischemia (i.e., 30 minutes of ST segment depression) are also independent predictors of short and long-term mortality.[11] Moreover, it is probable that small peak troponin values, which have important short-term prognostic implications,[3] do not represent myocardial necrosis but rather myocardial injury due to prolonged ischemia.[11-13]

Second, perioperative MI after noncardiac surgery frequently goes undetected. The POISE Trial investigators demonstrated than 65% of perioperative MIs were asymptomatic.[10] This likely occurs because the vast majority of them take place within the first 48 hours after surgery when most patients are receiving high dose analgesic medication that may mask ischemic symptoms. As a result, ECG or troponin measurements are not timely performed, making ECG abnormalities frequently absent, even when troponin is elevated, usually 12-24 hours after the MI onset.

Consequently, it might be argued that prognostically relevant asymptomatic myocardial injury patterns that happen early after noncardiac surgery may not fulfill the criteria of the universal definition of MI (i.e., cell death of cardiac myocytes caused by ischemia), therefore, the application of this definition is not suitable for the perioperative period of noncardiac surgery.

1.2 Thesis proposal

We propose that for any diagnosis to have clinical relevance, its definition and diagnostic criteria must fulfill, at least, the following two criteria: 1) there must be a perceived shared pathophysiology; and 2) it must have prognostic relevance.

We propose the term "Myocardial Injury after Noncardiac Surgery" (MINS), that is defined as *"myocardial cell injury caused by ischemia, which is the result of a coronary perfusion imbalance between supply and demand, has prognostic relevance and occurs during or within 30 days after noncardiac surgery, and is characterized, at least, by troponin elevation".* MINS does not include perioperative myocardial injury that is due to pulmonary embolism, sepsis, cardioversion, chronic troponin elevation or another known nonischemic etiology.

Although there are potential arguments as to why the noncardiac surgery community should utilize the universal definition of MI in the noncardiac surgery setting (e.g., this definition is highly referenced and known), by introducing a new term we could frame the definition to ensure we capture those prognostically relevant perioperative myocardial injuries due to myocardial ischemia that at present, would not fulfill that universal definition of MI.

Introducing a new term would also: 1) allow us to minimize the risk that individuals will assume that what is known about non-operative MIs (e.g., pathophysiology, treatment) applies to these perioperative myocardial events; 2) allow us to avoid the labeling and implications of the term MI that is based upon non-operative MIs (e.g. insurance, employment); 3) facilitate establishing diagnostic criteria based upon

research demonstrating prognostic relevance; and 4) bring attention to a topic that is relevant, and focus the medical community on the perioperative setting.

To establish our proposed diagnostic criteria we will evaluate a large international prospective cohort of adult patients undergoing major noncardiac surgery, who have had the same postoperative biomarker measurement with troponin T (TnT), thus avoiding inconsistency in prognostic thresholds across various troponin asssays.

Regarding the evidence about this concept, small studies have suggested that post-operative troponin elevation is related to myocardial damage and represent a significant predictor for adverse cardiovascular outcomes.[14,15] However, no individual study has evaluated if further clincial criteria is required (e.g., ischemic symptoms, ECG changes) beyond the biomarker elevation to demostrate prognostic relevance. Additionally, no study has addressed the ischemic versus non-ischemic etiology linked to the biomarker elevation.

Currently, the most robust evidence arises from the recent first publication of the Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Study that included more than 15,000 patients and demonstrated that a peak of TnT $\geq$0.02 ng/mL within the first 72 hours after noncardiac surgery, occurring in 11.6% of patients, was an independent predictor of death at 30 days.[3] This report carries an important prognostic message indicating that postoperative monitoring of TnT can enhance risk stratification after noncardiac surgery. This paper did not, however, explore the diagnostic criteria and prognostic relevance of TnT elevation associated to a shared ischemic pathophysiology, which are the aims of the present thesis.

1.3 Thesis objectives

1.3.1 Primary objective

Among patients undergoing major noncardiac surgery, we will develop diagnostic criteria for Myocardial Injury after Non-cardiac Surgery (MINS) using the VISION Study database through exploration of various criteria based upon an assumption of shared underlying ischemic pathophysiology and demonstrated prognostic relevance (established through independent impact on 30-day mortality).

1.3.2 Secondary objectives

We will describe the characteristics of patients suffering MINS (i.e., age, gender, cardiovascular risk profile, ischemic symptoms, ECG abnormalities) and determine its preoperative independent predictors. Finally, we will develop a clinical score to predict mortality risk at 30 days after surgery among patients suffering MINS.

1.4 References

1. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet 2008;372(9633):139-44.

2. Devereaux PJ, Chan M, Eikelboom J. Major vascular complications in patients undergoing noncardiac surgery: The magnitude of the problem, risk prediction, surveillance, and prevention. In: Yusuf S, Cairns JA, Camm AJ, Fallen EL, Gersh BJ, editors. Evidence based Cardiology. 3rd ed. London, England: BMJ Books, 2009.

3. Devereaux PJ, Chan M, Alonso-Coello P, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. The Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Study Investigators. JAMA 2012;307(21):2295-2304.

4. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008;371(9627):1839-47.

5. Devereaux PJ, Goldman L, Cook D et al. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. CMAJ 2005; 173 (6):627-634

6. Devereaux PJ, Goldman L, Yusuf S et al. Surveillance and prevention of major perioperative ischemic cardiac events in patients undergoing noncardiac surgery: a review CMAJ 2005; 173 (7):779-88.

7. Thygesen K, Alpert J, White H, on behalf of the joint ESC/ACCF/AHA/WHF task force for the Redefinition of Myocardial Infarction. Universal Definition of Myocardial Infarction. JACC 2007, 50(22): 2173-95.

8. Report of the Joint International Society and Federation of Cardiology/World Health Organization task force on standardization of clinical nomenclature. Nomenclature and criteria for diagnosis of ischemic heart disease. Circulation 1979;59:607–9

9. The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined - a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. J Am Coll Cardiol 2000;36:959–69.

10. Devereaux PJ, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, et al. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. Ann Intern Med 2011;154(8):523-8.

11. Landesberg G, Luria M, Cotev S et al. Importance of long-duration postoperative ST-segment depresión in cardiac morbidity after vascular surgery. Lancet 1993; 341:715-19.

12. Landesberg G, Shatz V, Akopnik I et al. Association of Cardiac Troponin, CK-MB, and Postoperative Myocardial Ischemia With Long-Term Survival After Major Vascular Surgery. J Am Coll Cardiol 2003;42:1547–54

13. Bottiger B, Motsch J, Teschendorf P et al. Postoperative 12-lead ECG predicts peri-operative myocardial ischaemia associated with myocardial cell damage. Anaesthesia, 2004, 59:1083–1090.

14. Levy M, Heels-Ansdell D, Hiralal R et al. Prognostic value of troponin and creatine

kinase muscle and brain isoenzyme measurement after noncardiac surgery: a systematic review and meta-analysis. Anesthesiology 2011;114(4):796-806

15. Redfern G, Rodseth R and Biccard B. Outcomes in vascular surgical patients with isolated postoperative troponin leak: a meta-analysis. Anaesthesia, 2011, 66: 604–610.

Table 1. Universal definition of Myocardial Infarction [7]

Criteria for Acute Myocardial Infarction

The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

1- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:

- *Symptoms of ischaemia;*
- *ECG changes indicative of new ischaemia (new ST-T changes or new left bundle branch block [LBBB]);*
- *Development of pathological Q waves in the ECG;*
- *Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.*

2- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

3- For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 _ 99th percentile URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognized.

4- For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 _ 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction.

5- Pathological findings of an acute myocardial infarction.

Criteria for Prior Myocardial Infarction

Any one of the following criteria meets the diagnosis for prior myocardial infarction:

1- Development of new pathological Q waves with or without symptoms.

2- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.

3- Pathological findings of a healed or healing myocardial infarction.

Chapter 2

THEORETICAL FRAMEWORK

2.0 Global burden of noncardiac surgery and relevance of cardiovascular complications

Recent estimations of the global volume of surgery obtained from the World Health Organization and the United Nations Population Fund based on data from 56 countries accounts for 234.2 million (95% CI 187.2-281.2) surgeries per year, which translates in 1 operation every 25 persons per year. [1] If we consider that a small number are cardiac or pediatric procedures, we can calculate that noncardiac surgery represents over 200 million cases per year. [2]

During the last few decades, surgery has experienced an impressive growth, particularly due to development and worldwide dissemination of significant advances that improved life expectancy and quality of life. Therefore, the primary increment in surgical volume has occurred among the elderly, which represent the highest risk population for adverse outcomes. Consequently, cardiovascular complications after noncardiac surgery have increased and represent a major public health challenge with substantial economic implications.

A prospective and relatively unselected cohort study published in 1999, including 4,315 patients undergoing elective major noncardiac surgeries, showed that major cardiac complications (ventricular fibrillation/cardiac arrest, complete heart block, acute

myocardial infarction and pulmonary edema) during the admission were 2.1%, cardiac death 0.3% and total death 1%.[3] The incidence of perioperative MI was 1%. For a long time, these results were the best available evidence. Nearly one decade later, POISE Trial, the largest cardiovascular randomized controlled trial performed in perioperative medicine (8351 patients undergoing major noncardiac surgery recruited in 23 countries), showed a higher complications rate, i.e., cardiac death (1.6 %) and MI (5%).[4] Given the restrictive nature of randomized trials (i.e., high risk patients), these results are not representative of the real world, therefore, a prospective large international cohort of patients of 45 years old or more undergoing non-cardiac surgery was designed to generate valid data from a contemporary representative sample (VISION Study).

Currently, VISION has recruited more than 32,000 patients. Among the first 16,000 patients, the observed rate of death and perioperative MI or elevated troponin at 30 days were 2% and 6.8%, respectively. [5] Thus, taking into account that more than 100 million adults over 45 years old undergo noncardiac surgery, [2] we can estimate that each year 2 million die and 6.8 million suffer a perioperative MI or troponin elevation. Furthermore, we may argue that given the scarcity of available data from poor countries and its higher rate of death [1,5], the number of complications may increase even more, reinforcing the need of improving the quality of health care during the perioperative period of noncardiac surgery.

2.1 Physiopathology of perioperative myocardial ischemia and infarction

Pre-operative factors that may influence post-operative cardiovascular

complications have been exhaustively investigated either to predict risk or to understand their physiopathology. As a consequence, several predictive risk models were developed.[3, 7-9] Coronary artery disease has emerged as an independent predictor of perioperative complications suggesting that myocardial ischemia may represent an essential pathway leading to perioperative MI and cardiac death.

In general terms, myocardial ischemia is defined as an imbalance between myocardial oxygen supply and demand. There are two different mechanisms to consider:

a) high-demand ischemia, caused by an increase in myocardial oxygen demand determined by an elevated heart rate or systolic blood pressure (e.g., exercise, emotion) in individuals with a severe fixed coronary artery obstruction.

b) low-supply ischemia, caused by a reduction in the oxygen supply determined by intracoronary thrombosis or coronary vasospasm, that is usually the consequence of plaque dysruption, platelet activation, and endothelial dysfunction of coronary atherosclerotic plaques with different degree of stenoses. Significant hypotension may be also included within this group.

In the non-operative setting, a chronic stable coronary artery disease, and an acute coronary syndrome (i.e., unstable angina, myocardial infarction) represent the first and the second mechanism, respectively. Traditionally, perioperative myocardial ischemia was mainly attributed to the first mechanism, triggered by surgical stress. Thus, preoperative stress-testing to detect myocardial ischemia and subsequent coronary revascularization of severe coronary stenoses before noncardiac surgery were recommended for risk reduction . [10,11]

Currently, evidence supports the second mechanism for a large proportion of these events. Several surgical conditions (i.e., surgical trauma, anesthesia and analgesia, pain, bleeding, anemia, hypothermia, fasting, intubation/extubation) increase levels of cortisol and catecholamines, which increase heart rate and blood pressure. These factors promote a stressful physiological situation and increase coronary shear stress across coronary arteries. Further, an inflammatory, hypercoagulable and hypoxic enviroment is generated by neurohumoral changes.[12] As results, both ischemic mechanisms may occur, leading to myocardial ischemia and potentially to MI (**Figure 1**). Finally, the apparent benefit of pharmacological agents without anti-ischemic properties (i.e., statins) supports the low-supply mechanism through endothelial dysfunction and anti-inflammatory pathways that can cause coronary thrombosis.[13]

In summary, among patients undergoing noncardiac surgery the resulting enviroment resembles performing an extreme myocardial stress-test, that may result in coronary thrombosis, ischemia, and MI.

2.1.1. Histopathological evidence

Autopsy heart specimens suggested that severe multivessel coronary disease and left main disease are highly prevalent in patients who suffer a perioperative fatal MI. Significant triple-vessel disease was observed in 54% and 59% of cases, and left main in 19% and 23% in two series (**Table 1**).[14,15] These observations might be interpreted as a cause for myocardial ischemia, which may often lead to MI. Further, as the number of diseased vessels increase, the places that may serve for plaque rupture and thrombosis

also increase. Thus, since both mechanisms, i.e., increased demand ischemia due to severe fix obstructions and reduced supply ischemia due to thrombosis in non-significant obstructions, are not mutually exclusive, they may coexist in the same patient. These autopsy studies showed an incidence of plaque rupture between 46 and 55%, and intracoronary thrombosis between 28 and 35% in patients that suffered a fatal peri-operative MI (Table 1).[14,15] Similar findings were observed in patients with a fatal non-operative MI.[14]

A limitation of these studies relied on a selection bias toward a mechanism of demand ischemia in patients with severe coronary obstructions rather than coronary thrombosis, and toward the sicker group of patients.[14,15] Further, both series included a very small sample size (total of 68 autopsies). Therefore, some degree of caution in the interpretation is required.

Additional evidence supporting coronary plaque rupture and thrombosis as a dominant mechanism in perioperative MI emerged from 2 observational clinical studies. The first, was a small case-control study that included patients who suffered a peri-operative MI or died in-hospital after vascular surgery and had a previous coronary angiogram (average of 6 days before surgery).[16] Peri-operative MIs were significantly related to inadequately collateralized total oclussions and to non-obstructive coronary lesions. Interestingly, no culprit artery had a severe obstruction between 70 and 99%, and multivariable analysis determined that the number of lesions >30% had the strongest association with the outcomes.

The second study, was recently published and included 120 consecutive patients

who were evaluated with a coronary angiography after suffering an acute coronary syndrome, mostly acute MI, after noncardiac surgery. Results demostrated that 45% of patients had a type of lesions with characteristics strongly associated with plaque rupture and trombosis (i.e., Ambrose's type II). Similar findings were observed in a second group of 120 patients who underwent angiography due to a nonoperative acute coronary syndrome. Further, both groups showed a significantly higher incidente of thrombotic obstructions when compared with a third participating group of 240 patients with stable coronary artery disease.[17]

2.1.2. Clinical evidence

Interpretation of physiopathological data emerged from clinical studies may also help to understand the mechanisms of peri-operative myocardial ischemia and infarction.

The high-demand ischemia mechanism is supported by ECG analysis of peri-operative MI. Most of these events were preceeded by prolonged myocardial ischemia (i.e., more than 30 or 60 minutes) accompanied by ST segment depression rather than ST elevation[18-24] and they showed no Q wave development in most cases (i.e., 60 to 100% were adjudicated as non-Q-wave myocardial infarctions).[18,25,26] Furthermore, tachycardia was a common finding and was associated to ST segment depression.[18,27] Although an increased heart rate could have favored thrombosis due to an increased coronary shear stress and plaque disruption, it is also a well-known determinant of myocardial oxygen demand.

The high-demand theory may, however be debated based on indirect data arisen from POISE Trial.[4] Pre-operative administration of beta-blockers reduced the rate of perioperative MI. This evidence is inconsistent with the high-demand theory because beta-blockers produced significant hypotension and this phenomenon should have increased the rate of perioperative MI due to a blood-flow reduction across severe fix coronary obstructions. Therefore, to explain the reduction of MI, it might be argued that beta-blockers improved the hypercoagulable state triggered by surgery.[28-30]

More conflicting data against the high-demand mechanism was revealed from trials evaluating prophylactic coronary revascularization. Bypass surgery and coronary angioplasty were traditionally advocated before noncardiac surgery in patients with inducible myocardial ischemia caused by severe fixed coronary stenoses.[31,32] However, two meta-analyses showing no reduction in death and MI at 30 days after noncardiac surgery challenged this approach[33,34] We recently conducted a systematic review including newly available randomized trial evidence. Four trials were included, comprising a total of 1245 patients.[35-38] Results showed that systematic coronary revascularization did not reduce the composite of death and MI at 30 days after noncardiac surgery compared to a conservative approach. Eighty-one (12.9%) events occurred among the 628 patients randomized to systematic coronary revascularization, and 79 (12.8%) among the 617 patients treated with a conservative approach (RR 0.83, 95% CI 0.40-1.71) (**Figure 2**). Regarding peri-operative MI, there were 59 (9.4%) events in the first group and 63 (10.2%) in the second (RR 0.91, 95% CI 0.50-1.67) (**Figure 3**). Therefore, in spite of the inconclusive evidence (i.e., underpowered meta-analysis,

substantial heterogeneity) we may speculate that treating preoperative fixed severe coronary obstructions with revascularization does not alter the incidence of perioperative ischemic complications, thus challenging the high-demand theory.

Finally, data emerging from VISION Study with more than 15,000 patients[39] showed that "recent high-risk coronary artery disease" (i.e., unstable angina, MI or CCSC III or IV angina) during the last 6 months was an independent predictor of death at 30 days after noncardiac surgery. However, stable coronary artery disease beyond 6 months before surgery was not an independent predictor. This evidence further supports that the severity of coronary artery stenoses does not represent the main underlying mechanism for perioperative myocardial ischemia leading to death.

2.1.3. Summary of the evidence

Although the existing evidence about the physiopathology of perioperative myocardial ischemia and infarction has substantial limitations, it does provide insights. The burden of coronary artery disease is apparently the strongest predictor of risk rather than focal severe obstructions. Regarding the ischemic mechanism, the surgical enviroment (i.e., stress, inflammation, hypercoagulability, hypoxia) may either promote plaque rupture and subsequent trombosis and vasoespasm, mostly occuring in non-obstructive coronary plaques, as it happens in 86% of non-operative MIs[40], or trigger myocardial ischemia upon severe pre-existing fixed coronary obstructions, which may finally turn into a MI, particularly in the presence of tachycardia, hypertension or hypotension, anemia or hypoxemia.

2.2 Clinical presentation and prognosis of perioperative myocardial ischemia in noncardiac surgery. Basis for the thesis proposal

The ischemic cascade was described more than 20 years ago. [41] It begins with an imbalance between myocardial oxygen supply and demand that produces ventricular diastolic and systolic dysfunction; thereafter, ECG changes (i.e., ST segment shifts) may happen, and finally, symptoms may appear (e.g., chest pain, dyspnea). The full sequence may take less than 1 minute. Importantly, ECG and ischemic symptoms not always occur and further, they are not specific for myocardial ischemia. If the ischemic process is not quickly resolved (i.e., in less than 30 minutes), myocardial cells begin to die. This process represents a MI, and cell death is pathologically defined as necrosis. Necrosis needs 2 to 4 hours or more to be completed in the involved coronary territory, depending on several factors, such as collateral circulation, persistent or intermittent coronary occlusion, sensitivity of myocytes to ischemia, pre-conditioning and individual myocardial demand for oxygen. As a result, different proteins or biochemical markers are released into the circulation, i.e., troponin, creatine-kinase MB, myoglobin.

Therefore, perioperative myocardial ischemia in the clinical practice may be monitored through symptoms, ECG, and biochemical markers. However, clinical features may be frequently absent or unrecognized, as we will describe later. Furthermore, imaging techniques (i.e., echocardiogram, nuclear scintigraphy) may be helpful, but just to confirm or discard individual diagnoses instead of being applied to every patient during the early postoperative hours.

2.2.1 The universal definition of MI. Does it fail to capture perioperative MIs and relevant ischemia after noncardiac surgery?

Refinements in the development of cardiac biomarkers, particularly troponin assays, made them even more sensitive and specific, allowing even minimal microscopic areas of necrosis of less than one gram of tissue to be detected. In 1999, and later on in 2007, a joint ESC/ACCF/AHA/WHF consensus updated the definition of acute MI as *"a typical rise and fall of troponin (indicates myocardial necrosis) as the preferred biomarker, plus one or more ischemic features between symptoms, new ST-T changes, new left bundle branch block, new Q waves, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality (indicates clinical setting consistent with myocardial ischemia)".* [42]

Troponin elevation was defined as a value exceeding the 99th percentile of a normal reference population (or URL= upper reference limit), with a coefficient of variation ≤10% at that threshold to improve precision. The guidelines also stated that *"if troponin is elevated in the absense of ischemic features, an alternative explanation for myocardial necrosis other than ischemia should be explored because the elevation by itself does not indicate the mechanism".* Later on, we will comprehensively discuss this concept because it is critical for the thesis development.

Other reported etiologies of troponin elevation are pulmonary embolism, congestive heart failure, myocarditis, aortic dissection, tachyarrhythmias or bradyarrhythmias, cardioversion, electrophysiological ablation, infiltrative diseases, renal

failure, drug toxicity, toxins, respiratory failure, and sepsis.[43]

This consensus established also definitions for peri-procedural MI after CABG and PCI.[42] In both settings, ischemic symptoms were not required criteria. After PCI, the definition was based only on troponin elevation, such as more than three times the 99th percentile URL; and after CABG, was based on troponin elevation, such as more than five times the 99th percentile URL during the first 72 hours, associated to ECG (i.e., new Q waves or LBBB), angiographic (i.e., new graft or native artery occlusion) or imaging (i.e., new loss of viable myocardium) evidence of MI. These definitions provided the basis for monitoring of ECG and biomarkers during the early post-procedural hours, and help physicians to take diagnostic and therapeutic decisions intended to reduce morbidity and mortality.

No specific criteria were included for MI after noncardiac surgery despite the known high rate of unrecognized perioperative MI. Pooled evidence based on prospective cohort studies with a sample size of more than 300 patients undergoing noncardiac surgery who had at least one post-operative measurement of a cardiac biomarker (total of 1309 patients and 38 perioperative MIs), showed that only 14% of perioperative MIs experienced chest pain, and 53% experienced any potential ischemic symptom or sign (**Table 2**).[25, 27, 44, 45] According to a recent POISE subanalysis including 8351 patients and 415 (5%) perioperative MIs, 65% did not experience ischemic symptoms.[46] Several factors may explain this high rate of asymptomatic perioperative MI, such as the use of potent analgesics, communication difficulties of patients under mechanical ventilation or conscious impairment, and physician's misinterpretations due

to the occurrence of nonspecific signs (e.g., tachycardia, hypoxia, hypotension) or symptoms (e.g., dyspnea, nausea).

Consequently, ECG abnormalities and troponin elevation required to fulfil the universal definition of MI are potentially missed in the majority of patients without ischemic symptoms during the postoperative period.

Perioperative MI without ischemic symptoms is an independent predictor of death at 30 days (adjusted OR 4.00, CI 95% 2.65-6.06). [46] Therefore, we believe that there is a great opportunity to improve medical care by a timely detection of patients suffering high-risk myocardial ischemia.

2.2.2 ST segment depression may independently predict either perioperative MI and mortality, but with a suboptimal performance

As mentioned above, clinically relevant ischemic episodes of myocardial ischemia are underestimated. Myocardial infarction is a well-known independent predictor of short-term mortality within the spectrum of postoperative myocardial ischemia. Similarly, prolonged ischemic periods detected by ECG monitoring are also independent predictors of cardiac short and long-term mortality.[18, 20, 23, 47]

We searched for studies that included more that 300 patients who underwent noncardiac surgery and evaluated myocardial ischemia through ST segment analysis (i.e., standard ECG, Holter recordings or continuous 12-lead ECG monitoring) and MI ascertained through cardiac biomarker assessment during the early postoperative days. We found 4 original studies,[19, 27, 48, 49] and 2 complementary analyses using a different

methodology in the same cohorts of patients.[50, 51] Two studies that included patients who underwent different types of noncardiac surgery (n=474) [27] and vascular surgery (n=385) [48] and were monitored with Holter recordings, demonstrated that the incidence of pre-operative ST segment depression ≥1 mm was 20% and 33.5%, intra-operatively 25% and 36%, and post-operatively 41% and 46%, respectively. Differences may represent the higher prevalence of coronary artery disease in vascular surgery patients.

Multivariable analysis determined that postoperative silent ischemia was the only independent predictor of in-hospital ischemic events (i.e., cardiac death, nonfatal MI, and unstable angina), with an OR of 9.2; CI 95%, 2.0-42.0; p=0.004. [27] Likewise, the occurrence of perioperative ischemic time ≥1% of patients' total perioperative time (OR 3.67; p<0.001), and age (OR 1.08; p<0.04) were the only independent predictors of perioperative MI in the second study.[48] In both studies, ST segment depression was suboptimal to predict adverse events since sensitivity was 80% and 84%, specificity 66% and 71%, positive predictive value 7% and 13% and negative predictive value 99% and 99%, respectively. Positive likelihood ratios were between 2 and 3 and likelihood ratios of absence of ST segment depression were between 0.2 and 0.3. The clinical utility was mainly related to the negative predictive value when ST depression was absent during monitoring.

More contemporary results from 447 patients undergoing vascular surgery under continuous 12-lead ECG monitoring demonstrated that prolonged episodes of ischemia >15 minutes, >30 minutes and >60 minutes were significantly associated with different threshold criteria defining MI, from the lower (troponin I [TnI] >0.6 ng/mL or troponin T

[TnT] >0.03 ng/mL) to the higher (TnI >3.1 ng/mL or TnT >0.2 ng/mL) cut-off points. Multivariable analysis including pre and postoperative variables indicated than prolonged ischemia >30 and >60 minutes were associated with long-term mortality (OR 2.59 CI 95% 1.51-4.45 and OR 3.75 CI 95% 2.07-6.82, respectively) independent of biomarker elevation.[50]

Finally, a multivariable analysis of data from 3564 patients who had ECGs performed immediately after noncardiac surgery demostrated that ST depression or elevation ≥1 mm in ≥2 leads, or T wave inversion consistent with ischemia, were independent predictors of adverse cardiac events (i.e., MI, pulmonary edema, ventricular fibrillation or primary cardiac arrest, and complete heart block) after adjusting for the pre-operative Revised Cardiac Risk Index (RCRI) and intraoperative variables (OR 2.2, CI 95% 1.2-3.9, $p<0.01$).[49] The low number of events (n=18) in the subgroup with ischemia on the ECG reduces the reliability of these estimations. Interestingly, this work considers T wave inversion as part of the definition of myocardial ischemia, but unfortunately, a separate analysis from ST abnormalities was not reported, probably due to the low number of cases. Regarding the predictive performance of ECG changes, sensitivity was 23%, specificity 93%, positive predictive value 7% and negative predictive value 98%. Resulting positive and negative likelihood ratios were 3.28 and 0.82, respectively, reinforcing once again the suboptimal prediction capabilities for cardiovascular complications.

In summary, in spite of the underpowered nature of the available evidence, prolonged and silent myocardial ischemia defined by ST segment depression of more than

30 minutes might be considered a strong predictor of short and long-term cardiac events, even in patients not fulfilling the universal definition of MI.

Unfortunately, reliable ST segment monitoring through a continuous 12-lead ECG performed in every patient after every surgery is unrealistic and requires advanced and expensive technology. Moreover, it has to be considered a substantial patient discomfort due to the cables glued to the chest, even with a wireless system. Regarding the indication of standard ECG, the silent nature of myocardial ischemia in this context makes it difficult deciding the most appropriate time for this practice, in addition to the aforementioned moderate diagnostic yield.

2.2.3 Post-operative troponin elevation independently predicts death regardless the diagnosis of MI

Similar to the ECG and ST segment monitoring, cardiac biomarkers (i.e., troponins, CK MB) surveillance after noncardiac surgery is not routinely performed. Therefore, among patients whithout symptoms there are no clues to inform the physician that the patient is having a silent ischemic event. Thus, regarding the universal definition of MI, relevant subclinical episodes of myocardial ischemia followed by necrosis commonly go undetected because ST segment depression and troponin elevation are usually missed. Moreover, if detected, biomarker elevation is frequently trivialized, as suggested by the underuse of cardiovascular medication at hospital discharge among patients who suffered a perioperative MI.[46]

A systematic monitoring of troponin measurements during the first few days after surgery would prevent physicians missing ischemic episodes. Such a proposal does, however, require evidence supporting the clinically significant prognostic implications of such findings.

Small studies have suggested the utility of post-operative troponin elevation as a significant predictor for cardiovascular adverse events and its relationship with myocardial damage. A meta-analysis of 14 studies performed in the noncardiac surgery setting was recently published.[52] It included 3318 patients who underwent post-operative TnT and I surveillance, 459 deaths occurred in the 1-2 years following surgery. Pooled data showed that a troponin elevation predicted death at 1 year (OR 6.7, CI 95% 4.1-10.9), and beyond 1 year of follow-up (OR 1.8, CI 95% 1.4-2.3). A second meta-analysis including 8 studies restricted to vascular surgery (7 measured TnI and one measured TnT) evaluated 1873 patients and 63 deaths, and demonstrated that a troponin elevation predicted all-cause mortality at 30 days (OR 5.03, CI 95% 2.88-8.79).[53]

Despite this encouraging evidence, several limitations weaken the validity of both meta-analyses, particularly that the models in each study were at substantial risk of overfitting. Further, the variable utilization of either TnT or I assays, with various cut-off points and analytical methods prevents generalization to clinical practice. Finally, no individual study adjusted for the predictive value of ischemic clinical variables (i.e., chest pain, ECG abnormalities).

To improve the specificity of the evidence supporting the utility of low TnT thresholds during the early hours after noncardiac surgery, we searched and reviewed

studies including more than 300 patients with TnT assessment, but not TnI, during the first postoperative days, using low cut-off points (i.e., below 0.1 ng/mL), and reporting prognostic implications at 30 days after surgery.

We found only 3 studies fulfilling our criteria. The first two were exclusively focused on vascular surgery and were performed in a single hospital. Landesberg et al., included 447 patients who underwent post-operative monitoring with continuous ST segment technology and CK-MB, TnT and I. The main results were focused on long-term follow-up, and the association between TnT, clinical features of MI and mortality at 30-days were not reported.[19] The second study included 513 patients and was also focused on long-term outcomes. Results demonstrated that low TnT values were independently associated with all-cause mortality after adjusting for gender, cardiac risk factors, site and type of surgery, post-operative ECG changes and clinical symptoms.[54] The prognostic impact of low-level TnT ≥0.01 ng/mL was not reported, but we calculated an OR of 11.6 (CI 95% 4.4-30.1, $p<0.001$) for 30-day mortality. Limitations of this study were: 1) the small sample size with only 20 deaths at 30 days, making estimates imprecise; 2) the etiology of TnT elevation was not considered (e.g., ischemia, sepsis, pulmonary embolism); 3) the association between TnT and clinical features (i.e., chest pain, ECG changes) was not comprehensively analyzed at the short-term follow-up; and 4) the low generalizability of results since all patients underwent vascular surgery in only one hospital.

The third study was recently published; it represents the first analysis of the ongoing multicenter VISION Study that included 15,133 patients evaluating the

prognostic value of post-operative TnT after noncardiac surgery.[39] Multivariable analyses demonstrated that a peak of TnT ≥0.02 μg/L within the first 72 hours after noncardiac surgery, occurring in 11.6% of patients, independently predicted death at 30 days when compared with a reference value of TnT ≤0.01 μg/L: peak TnT=0.02 μg/L (adjusted hazard ratio [aHR], 2.41; 95% CI, 1.33-3.77); 0.03-0.29 μg/L (aHR, 5.00; 95% CI, 3.72-6.76); and ≥0.30 μg/L (aHR, 10.48; 95% CI, 6.25-16.62). The observed population attributable risk suggested that the biomarker elevation explained 41.8% of deaths.

This first VISION analysis carries an important prognostic message, which indicates that post-operative monitoring of TnT can enhance the risk stratification process after noncardiac surgery. However, it does not support any therapeutic message because neither the etiology of troponin elevation, nor the association with the clinical features required by the universal definition of MI were explored. Thus, focusing on myocardial ischemia as the responsible etiology and excluding from the analysis those patients with sepsis (i.e, myocardial toxicity), pulmonary embolism (i.e., acute right ventricular overload) and electric cardioversion, we will be able to develop the concept of Myocardial Injury after Noncardiac Surgery (MINS) with a relatively homogeneous population regarding the cause of TnT elevation.

In summary, no adequately powered study has still completely addressed the relationship between conventional or even minor troponin elevation, ischemic features (i.e., clinical signs and symptoms and ECG changes) and prognosis in the first 30 days after noncardiac surgery. Moreover, no trial has excluded troponin elevation due to a

suspected pulmonary embolism or sepsis, and it is recognized that both conditions have a different physiopathology, prognosis, and treatment compared with myocardial ischemia. We have the opportunity in the VISION Study to explore these ischemic troponin elevations through the analysis of clinical and biochemical data on more than 15,000 patients.

2.2.4 Ischemic troponin leak without myocardial necrosis

Initially, investigators believed that troponin release was related to myocardial damage, even when small elevations were identified, but it was not considered criteria for MI. Later on, troponin elevation was associated with myocardial necrosis and thus included as an essential part of the universal definition of MI.[42] In the perioperative setting of noncardiac surgery, it was proposed as a risk predictor for cardiovascular complications, and also, as a marker of myocardial ischemia and infarction.[55-58]

Evidence has demostrated that release of creatine-kinase, the traditional marker of myocardial necrosis, may occur after short periods of coronary occlusion without signs of necrosis, meaning transient reversible ischemia. The explanation resides in the leak of creatine-kinase located in the cytosolic compartment of cardiac myocites.[59] Approximately 5 to 8 % of TnT or I is unbound in the cytosol,[60, 61] and after a reversible damage to the myocyte membrane by any cause, a similar phenomenom may result in the release of troponin from the cytosol. Since the half-life of troponin is short (i.e., 2 hours) small peaks may be observed in the blood lasting for short periods (i.e., 24 hours) rather than prolonged periods of 5 to 10 days that have been observed after degradation and

continuous leak of structural troponin (i.e., troponin linked to the contractile system). [62]

In the absense of myocardial necrosis, the exact mechanisms of troponin leak without irreversible rupture of the sarcolemma have not been explained. Recently, Dr H. White in an editorial comment has described six potential pathobiological mechanisms to explain troponin elevation; five out of them are not linked to myocardial necrosis and three are potentially caused by ischemia.[63] These mechanisms are:

1- Myocyte necrosis, the most frequent, caused by ischemic, inflammatory, infiltrative, direct trauma, and toxic causes including sepsis.

2- Apoptosis or programmed cell death, when enzymes called caspases break structural proteins and may cause troponin leaks. This mechanism has been associated to progression of end-stage cardiomyopathies.[64]

3- A normal myocyte cell turnover or regeneration process is apparently related to aging. However, uncertainty exists whether this slow process may determine circulating levels of troponin.[65]

4- Cellular release of small fragments of troponin due to proteolytic degradation without cell death and cellular membrane disruption. It was demostrated that TnI is degraded in stunned myocardium by an intrecellular calpain protease after 20 minutes of global ischemia followed by 20 minutes of reperfusion.[66,67] Others, observed a similar TnI degradation pattern mediated by calpains, however the trigger was an increased preload (i.e., left ventricular end-diastolic pressure) independent of the presence of ischemia.[68]

5- Increased cellular wall permeability of cytosolic troponin without cell necrosis

triggered by reversible myocyte membrane injury (i.e., myocardial stretch or ischemia).[67, 69]. Experiments performed by Hessel M. and colleagues in viable cultures cardiomyocytes have demostrated intact TnI release in the absense of necrosis by stimulation of stretch-responsive integrins (i.e., a type of adhesion molecules), which differs from necrotic troponin release explained by extensive troponin degradation.[69] This finding simulates myocardial strain, like volumen or pressure overload that usually occurs in heart failure and pulmonary embolism.

6- Development and release of membranous blebs with cytoplasmic contents from cardiac myocytes during ischemia, without suffering necrosis,[70-72] also associated to integrins stimulation.[69, 73] Experiments in animals have demostrated that hepatocytes develop membrane blebs over 1 to 3 hours after anoxia, and on reoxygenation early stages are fully reversible. Blebs are reabsorbed or shed into the circulation releasing cytoplasmic contents, but plasma membranes remain intact and there is no loss of cell viability.[74-76] Clinically, a rapid rise and fall of hepatocyte intracellular enzymes occurs when cardiac output is restored in ischemic hepatitis, and no hepatic necrosis occurs. Otherwise, if perfusion is not quickly improved, the blebs grow and finally break, with the consequent break of plasma membranes, thus hepatocelular necrosis occurs with a prolonged enzyme elevation.[71, 77, 78]

Evidence supporting the same pathophysiological process of reversible troponin release exists in cultured cardiac myocytes, showing bleb development and release without suffering myocardial necrosis.[70-72, 78] These results are consistent with the short or prolonged periods of TnT release after ischemic induction of perfused rat hearts,

depending on the faster or the slower myocardial re-oxygenation.[79] Unlike the first case of rapid re-oxygenation and myocytes survival, if prolonged ischemia occurs they become necrotic.

Uncertainty exists regarding whether the process of cell separation in-vitro may damage the membranes and that blebs may occur as a onsequence of this technical issue. However, in actual hearts bleb formation has been documented.[80-82]

In the clinical practice, the dynamic process of troponin release shows a biphasic curve; first, a fast peak as a consequence of an early cytosolic pool release, and later, a slow and prolonged leak cause by the structural troponin linked to the contractile system.[83] We may speculate that during acute MI, while the coronary artery is occluded, downstream myocytes become hypoxic and the initial troponin peak results from an early bleb release, which turns rapidly normal if reperfusion is restored due to a short cytosolic troponin half-life. However, if myocardial reperfusion is delayed, myocytes membranes break due to blebs rupture and a persistent troponin elevation determined by the structural long half-life troponin leak may last for 7 to 11 days, suggesting the presence of myocardial necrosis.[78, 83] In patients with unstable angina, some authors have suggested that transient myocardial ischemia has occurred after detecting troponin elevation which becomes normal a few hours later, attributed to the release of short half-life troponin from cytosol.[84]

We believe that troponin release by both ischemic and necrotic mechanisms are usually overlapped. Therefore, patients suffering ST-elevation MIs are expected to show a predominant necrotic release of troponin, as opposed to those with non-ST elevation,

who show a predominant ischemic troponin leak, as proposed by others.[85]

Troponin release due to a suspected ischemic cause may be observed across a wide spectrum of other clinical conditions without clear evidence of myocardial necrosis, such as the following:

1- Patients with supraventricular tachyarrhytmias may show troponin elevation with or without apparent severe coronary artery disease, suggesting a mechanism of demand ischemia.[86] Moreover, Turer et al., detected TnT release under conventional cut-off point using a High Sensitive TnT assay in response to pacing-induced stress, even in cases without ischemia ascertained through the quantification of myocardial lactate.[87] These findings may be interpreted as the consequence of ischemia without development of myocardial necrosis. However, evidence is not solid enough because it emerges from small studies with potential type I or II errors, and furthermore, it is not still clearly defined whether tachyarrhytmias, in the absence of severe CAD, may trigger troponin release due to underlying structural heart disease, inflammatory states or due to an imbalance between oxygen demand/supply.

2- Results recently reported from 120 patients included in TIMI 35 Study demostrated a troponin increase in the setting of stress test-induced transient myocardial ischemia using a novel ultrasensitive TnI assay, but not with less accurate TnT and I commercial assays. [88] The observed magnitude was proportional to the degree of ischemia on perfusion scans, and the duration of ischemia was brief (i.e., 2 minutes on average), suggesting a small amount of cytosolic troponin release.

3- Troponin elevation has been documented associated to strenuous exercise in

apparently healthy individuals, as demostrated by a meta-analysis, [89] supporting again a short-half life troponin leak since blood samples demostrated becoming normal shortly after the exercise. Further, no evidence of irreversible myocardial damage was ascertained by means of imaging methods.[90-92]

4- A disorder referred to as stress cardiomyopathy, Takotsubo disease, or "broken-heart" syndrome is characterized by transient reversible left ventricular dysfunction and no severe obstructions in coronary arteries. Clinical presentation includes acute chest pain or dyspnea, ST-T changes on ECG and a moderate elevation of cardiac biomarkers such as troponin or CK-MB, mimicking an acute myocardial infarction.[93-96] Furthermore, wall‑motion abnormalities are found on the echocardiogram usually demonstrating apical ballooning. Complete myocardial function recovery is achieved within 1 to 6 weeks in nearly all cases. The etiology remains nuclear, however catecholamines seem to have a pivotal role, probably generating coronary artery vasospasm, microcirculation dysfunction or transient obstruction of the left ventricular outflow tract.[93-96] This acutely developed cardiomyopathy clearly demonstrates myocardial disfunction due to a highly probable ischemic cause, troponin elevation, and no residual myocardial necrosis.

2.3 Myocardial Injury after Non-cardiac surgery (MINS). Thesis proposal summary

My thesis proposal will consist in developing a new term entitled MINS (Myocardial Injury after Noncardiac Surgery) to capture those perioperative myocardial injuries that occurs as a result of myocardial ischemia, and impact independently on the 30-day mortality after noncardiac surgery. For this purpose, we will use the data obtained

from approximately 15,000 patients recruited in an international multicenter prospective cohort study (VISION Study).

Defining MINS will hopefully become a pivotal step for deciding on routine postoperative monitoring with biomarkers, for establishing timely and appropriated therapeutic indications, and finally, for designing research projects in the field of perioperative medicine.

2.4 References

1. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet 2008;372(9633):139-44.

2. Devereaux PJ, Chan M, Eikelboom J. Major vascular complications in patients undergoing noncardiac surgery: The magnitude of the problem, risk prediction, surveillance, and prevention. In: Yusuf S, Cairns JA, Camm AJ, Fallen EL, Gersh BJ, editors. Evidence based Cardiology. 3rd ed. London, England: BMJ Books, 2009.

3. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999;100 (10):1043-9.

4. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008;371(9627):1839-47.

5. Bickler S, Ozgediz D, Gosselin R et al. Key Concepts for Estimating the Burden of Surgical Conditions and the Unmet Need for Surgical Care. World J Surg (2010) 34:374 - 380.

6. VISION Study (Vascular events In noncardiac Surgery patIents cOhort evaluatioN study). Population Health Research Institute/McMaster University. CANNECTIN investigators meeting. Hamilton, Canada. June 9th, 2011.

7. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in non-cardiac surgical procedures. N Engl J Med 1977;297(16):845-50.

8. Detsky AS, Abrams HB, McLaughlin JR, et al. Predicting cardiac complications in patients undergoing non-cardiac surgery. J Gen Intern Med 1986;1(4):211-9.

9. Kumar R, McKinney WP, Raj G, et al. Adverse cardiac events after surgery: assessing risk in a veteran population. J Gen Intern Med 2001;16:507-18.

10. Eagle K, Brundage B, Chaitman B et al. Guidelines for perioperative cardiovascular evaluation for noncardiac surgery. Report of the American College of Cardiology / American Heart Association Task Force on Practice Guidelines (Committee on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). J Am Coll Cardiol 1996;15:27(4):910-48.

11. Fleisher L, Eagle K. Lowering cardiac risk in non-cardiac surgery. N Engl J Med 2001;345 (23):1677-82.

12. Devereaux PJ, Goldman L, Cook D et al. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. CMAJ 2005; 173 (6):627-634.

13. Kaski JC, Aldama G, Cosín-Sales J. Cardiac syndrome X. Diagnosis, pathogenesis and management. Am J Cardiovasc Drugs 2004;4:179-94.

14. Cohen M and Aretz T. Histological Analysis of Coronary Artery Lesions in Fatal Postoperative Myocardial Infarction. Cardiovasc Pathol 1999;8:133-139.

15. Dawood M, Gutpa D, Southern J et al. Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. Int J Cardiol 1996; 57:37-44.

16. Ellis S, Hertzer N, MD, Young J. Angiographic Correlates of Cardiac Death and Myocardial Infarction Complicating Major Nonthoracic Vascular Surgery. Am J Cardiol 1996;77:1126-1128.

17. Gualandro D, Campos C, Calderaro D et al. Coronary plaque rupture in patients with myocardial infarction after noncardiac surgery: Frequent and dangerous. Atherosclerosis (2012), doi:10.1016/j.atherosclerosis.2012.02.021.

18. Landesberg G, Mosseri M, Zahger D et al. Myocardial Infarction After Vascular Surgery: The Role of Prolonged, Stress-Induced, ST Depression-Type Ischemia. J Am Coll Cardiol 2001;37:1839–45).

19. Landesberg G, Shatz V, Akopnik I et al. Association of Cardiac Troponin, CK-MB, and Postoperative Myocardial Ischemia With Long-Term Survival After Major Vascular Surgery. J Am Coll Cardiol 2003;42:1547–54

20. Landesberg G. Monitoring for myocardial ischemia. Best Practice & Research Clinical Anaesthesiology 2005; 19(1):77–95.

21. Lopez Jimenez, Goldman L, Sacks D et al. Prognostic Value of Cardiac Troponin T After Noncardiac Surgery: 6-Month Follow-Up Data. J Am Coll Cardiol 1997;29:1241–5).

22. McCann R and Clements F. Silent myocardial ischemia in patients undergoing peripheral vascular surgery: incidence and association with perioperative cardiac morbidity and mortality. J Vasc Surg 1989;9:583-7.

23. Ouyang P, Gerstenblith G, Furman WR et al. Frequency and significance of early postoperative silent myocardial ischemia in patients having peripheral vascular

surgery. Am J Cardiol 1989; 64: 1113–6.

24. Pasternack PF, Grossi EA, Baumann FG, et al. Beta blockade to decrease silent myocardial ischemia during Peripherals vascular surgery. Am J Surg 1989; 158: 113–6.

25. Badner NH, Knill RL, Brown JE, Novick TV, Gelb AW. Myocardial infarction after noncardiac surgery. Anesthesiology 1998; 88: 572–8.

26. Fleisher LA, Nelson AH, Rosenbaum SH. Postoperative myocardial ischemia: etiology of cardiac morbidity or manifestation of underlying disease? Journal of Clinical Anesthesia 1995; **7**: 97–102.

27. Mangano DT, Browner WS, Hollenberg M et al. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. N Engl J Med 1990; 323: 1781–8.

28. Von Kanel R, Dimsdale J. Effect of sympathetic activation by adrenergic infusions on hemostasis in vivo. Eur J Haematol 2000;65(6):357-69.

29. Von Kanel R, Mills P, Ziegler M, Dimsdale J. Effect of beta-2 adrenegic receptor functioning and increased norepinephrine on the hypercoagulable state with mental stress. Am Heart J 2002;144(1):68-72.

30. Hjemdahl P, Larsson P, Wallen N. Effect of stress and beta-blockade on paltelet function. Circulation 1991;84(6 suppl):vi 44-61.

31. Eagle K, Brundage B, Chaitman B et al. Guidelines for perioperative cardiovascular evaluation for noncardiac surgery. Report of the American College of

Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). J Am Coll Cardiol 1996;15:27(4):910-48.

32. Fleisher L, Eagle K. Lowering cardiac risk in non-cardiac surgery. N Engl J Med 2001;345 (23):1677-82.

33. Wong E, Lawrence H, Wong D. The effects of prophylactic coronary revascularization or medical management on patients outcomes after noncardiac surgery - a meta-analysis. Can J Anesth 207;54 (9):705-717.

34. Biccard B, Rodseth R. A meta-analysis of the prospective randomized trials of coronary revascularization before noncardiac vascular surgery with attention to the type of coronary revascularisation performed. Anesthesia 2009;64:1105-1113.

35. McFalls E, Ward H, Moritz T et al. Coronary artery revascularization before elective major vascular surgery. N Engl J Med 2004;351:2795-804.

36. Don Poldermans, Schouten O, Vidakovic R et al, for the DECREASE Study Group. A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery. The DECREASE-V Pilot Study. J Am Coll Cardiol 2007;49:1763-9.

37. Monaco M, Stassano P, Di Tommaso L et al. Systematic strategy of prophylactic coronary angiography improves long-term outcome after major vascular surgery in medium to high-risk patients. J Am Coll Cardiol 2009;54:989-96.

38. Illuminati G, Ricco J, Greco C et al. Systematic preoperative coronary angiography and stenting improves postoperative results of carotid endarterectomy in patients with

asymptomatic coronary artery disease: a randomised controlled trial. Eur J Vasc Endovasc Surg 2010;39:139-145.

39. Devereaux PJ, Chan M, Alonso-Coello P, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. The Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Study Investigators. JAMA 2012;307(21):2295-2304.

40. Falk E, Sha PK, Fuster V. Coronary plaque disruption. Circulation 1995;92(3):657-71

41. Nesto R and Kowalchuk G. The Ischemic Cascade: Temporal Sequence of Hemodynamic, Electrocardiographic and Symptomatic Expressions of lschemia. Am J Cardiol 1987;57:23C-30C.

42. Thygesen K, Alpert J, White H, on behalf of the joint ESC/ACCF/AHA/WHF task force for the Redefinition of Myocardial Infarction. Universal Definition of Myocardial Infarction. JACC 2007, 50(22): 2173-95.

43. Ammann P, Pfisterer M, Fehr T, Rickli H. Raised cardiac troponins. Causes extend beyond acute coronary síndromes. BMJ 2004;328:1028–9

44. Devereaux PJ, Goldman L, Yusuf S et al. Surveillance and prevention of major perioperative ischemic cardiac events in patients undergoing noncardiac surgery: a review CMAJ 2005; 173 (7):779-88.

45. Ashton CM, Petersen NJ, Wray NP, Kiefe CI, Dunn JK, Wu L, et al. The incidence of perioperative myocardial infarction in men undergoing noncardiac surgery. Ann Intern Med 1993;118:504-10.

46. Devereaux PJ, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, et al.

Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. Ann Intern Med 2011;154(8):523-8.

47. Bottiger B, Motsch J, Teschendorf P et al. Postoperative 12-lead ECG predicts peri-operative myocardial ischaemia associated with myocardial cell damage. Anaesthesia, 2004, 59:1083–1090.

48. Pasternack P, Grossi E, Baumann G, et al. Silent myocardial ischemia monitoring predicts late as well as perioperative cardiac events in patients undergoing vascular surgery. J Vasc Surg 1992;16:171-80.

49. Rinfret S, Goldman L, Polanczyk C, et al. Value of Immediate Postoperative Electrocardiogram to Update Risk Stratification After Major Noncardiac Surgery. Am J Cardiol 2004;94:1017–1022.

50. Landesberg G, Mosseri M, Shatz V, et al. Cardiac Troponin After Major Vascular Surgery. The Role of Perioperative Ischemia, Preoperative Thallium Scanning, and Coronary Revascularization. J Am Coll Cardiol 2004;44:569 –75.

51. Eisenberg M, London M, Leung J, et al. Monitoring for Myocardial Ischemia During Noncardiac Surgery. A Technology Assessment of Transesophageal Echocardiography and 12-Lead Electrocardiography. JAMA1992;268:210-216.

52. Levy M, Heels-Ansdell D, Hiralal R et al. Prognostic value of troponin and creatine kinase muscle and brain isoenzyme measurement after noncardiac surgery: a systematic review and meta-analysis. Anesthesiology 2011;114(4):796-806.

53. Redfern G, Rodseth R and Biccard B. Outcomes in vascular surgical patients with isolated postoperative troponin leak: a meta-analysis. Anaesthesia, 2011, 66: 604–610.

54. Winkel T, Schouten O, Hoeks S, et al. Prognosis of Vascular Surgery Patients Using a Quantitative Assessment of Troponin T Release: Is the Crystal Ball still Clear?. Eur J Vasc Endovasc Surg (2010) 40, 739-746.

55. Katus HA, Schoeppenthau M, Tanzeem A. Non-invasive asssessment of peri-operative cell damage by circulating cardiac troponin T. Br Heart J 1991;65:259-264.

56. Adams JE, Sigard GA, Allen BT. Diagnostic of perioperative myocardial infarction with measurements of cadiac troponin I. N Engl J Med 1994;330:670-674.

57. Lee TH, Thomas EJ, Ludwig LE. Troponin T as a marker for ischemia in patients undergoing major non-cardiac surgery. Am J Cardiol 1996;77:1031-1036.

58. Metzler H, Gries M, Rehak P et al. Peri-operative myocardial cell injury: the rol of troponins. Br J Anaesthesia 1997;78:386-390.

59. Heyndrickx GR, Amano J, Kenna T, et al. Creatine-kinase release not associated with myocardial necrosis after short periods of coronary artery occlusion in conscious baboons. J Am Coll Cardiol 1985;6:1299**e**303.

60. Katus HA, Remppis A, Scheffold T, et al. Intracellular compartmentation of cardiac troponin T and its release kinetics in patients with reperfused and nonreperfused myocardial infarction. Am J Cardiol 1991;67:1360 –7.

61. Vasile VC, Jaffe A. The biological basis of troponin in heart disease: possible uses for troponin fragmentology. Heart Metab 2009;43:5-8.

62. Gerhardt W, Katus H, Ravkilde J, et al. S-troponin T in suspected ischemic myocardial injury compared with mass and catalytic concentrations of S-creatine kinase isoenzyme MB. Clin Chem 1991;37:1405–11.

63. White H. Pathobiology of Troponin Elevations. Do Elevations Occur With Myocardial Ischemia as Well as Necrosis?. JACC 2011, 57(24): 2406-8.

64. Narula J, Haider N, Virmani R, et al. Apoptosis in myocytes in end-stage heart failure. N Engl J Med 1996;335:1182–9.

65. Bergmann O, Bhardwaj RD, Bernard S, et al. Evidence for cardiomyocyte renewal in humans. Science 2009;324:98-102.

66. Gao WD, Atar D, Liu Y, et al. Role of troponin I proteolysis in the pathogenesis of stunned myocardium. Circ Res 1997;80:393–9.

67. McDonough JL, Arrell DK, Van Eyk JE. Troponin I degradation and covalent complex formation accompanies myocardial ischemia/reperfusion injury. Circ Res 1999;84:9 –20

68. Feng J, Schaus BJ, Fallavollita JA, et al. Preload induces troponin I degradation independently of myocardial ischemia. Circulation 2001;103:2035–7.

69. Hessel MH, Atsma DE, van der Valk EJ, et al. Release of cardiac troponin I from viable cardiomyocytes is mediated by integrin stimulation. Pflugers Arch 2008;455:979–86.

70. Sakai K, Gebhard MM, Spieckermann PG, Bretschneider HJ. Enzyme release resulting from total ischemia and reperfusion in the isolated, perfused guinea pig heart. J Mol Cell Cardiol 1975;7:827–40.

71. Schwartz P, Piper HM, Spahr R, Spieckermann PG. Ultrastructure of cultured adult myocardial cells during anoxia and reoxygenation. Am J Pathol 1984;115:349–61.

72. Piper HM, Schwartz P, Spahr R, Hutter JF, Spieckermann PG. Early enzyme release

from myocardial cells is not due to irreversible cell damage. J Mol Cell Cardiol 1984;16:385–8.

73. Larsen AK, Lametsch R, Elce JS, et al. Genetic disruption of calpain correlates with loss of membrane blebbing and differential expression of RhoGDI-1, cofilin and tropomyosin. Biochem J 2008;411:657–66.

74. Lemasters JJ, Ji S, Thurman RG. Centrilobular injury following hypoxia in isolated perfused rat liver. Science 1981;213 (4508):661-3.

75. Jewell SA, Bellomo G, Thor H et al. Bleb formation in hepatocytes during drug metabolism is caused by disturbances in thiol and calcium ion homeostasis. Science 1982; 217(4566):1257-9.

76. Gores GJ, Herman B, Lemasters JJ. Plasma membrane bleb formation and rupture: a common feature of hepatocellular injury. Hepatology 1990;11:690-8

77. Kamiike W, Fujikawa M, Koseki M, et al. Different patterns of leakage of cytosolic and mitochondrial enzymes. Clin Chim Acta 1989;185:265–70.

78. Hickman P, Potter J, Aroney C. Cardiac troponin may be released by ischemia alone, without necrosis. Clin Chim Acta 2010;411:318–323.

79. Katus HA, Remppis A, Scheffold T, et al. Intracellular compartmentation of cardiac troponin T and its release kinetics in patients with reperfused and nonreperfused myocardial infarction. Am J Cardiol 1991;67:1360–7.

80. Sage MD, Jennings RB. Cytoskeletal injury and subsarcolemmal bleb formation in dog heart during in vitro total ischemia. Am J Pathol 1988;133:327-37.

81. Maxwell L, Gavin J. Anti-oxidant therapy improves microvascular ultrastructure

and perfusion in postischemic myocardium. Microvasc Res 1992;43:255–66.

82. Armstrong SC, Latham CA, Shivell CL, Ganote CE. Ischemic loss of sarcolemmal dystrophin and spectrin: correlation with myocardial injury. J Mol Cell Cardiol 2001;33:1165–79.

83. Morrow D, Cannon C, Jesse R, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: clinica characteristics and utilization of biochemical markers in acute coronary síndromes. Clinical Chemistry 2007;53(4):552-574.

84. Hamm CW, Ravkilde J, Gerhardt W, et al. The prognostic value of serum troponin T in unstable angina. N Engl J Med 1992;327:146-50.

85. Apple FS, Sharkey SW, Falahati A, et al. Assessment of left ventricular function using serum cardiac troponin I measurements following myocardial infarction. Clin Chim Acta 1998;272:59–67.

86. Bukkapatnam R, Robinson M, Turnipseed S, et al. Relationship of Myocardial Ischemia and Injury to Coronary Artery Disease in Patients With Supraventricular Tachycardia. Am J Cardiol 2010;106:374 –377.

87. Turer A, Addo T, MD, Martin J, et al. Myocardial Ischemia Induced by Rapid Atrial Pacing Causes Troponin T Release Detectable by a Highly Sensitive Assay Insights From a Coronary Sinus Sampling Study. J Am Coll Cardiol 2011;57:2398–405.

88. Sabatine M, Morrow D, de Lemos J, et al. Detection of acute changes in circulating troponin in the setting of transient stress test-induced myocardial ischaemia using an ultrasensitive assay: results from TIMI 35. Eur Heart J 2009;30: 162–169.

89. Shave R, George KP, Atkinson G, et al. Exercise-induced cardiac troponin T release: a meta-analysis. Med Sci Sports Exerc 2007;39:2099–106.

90. Neumayr G, Pfister R, Mitterbauer G, et al. Effect of competitive marathon cycling on plasma N-terminal pro-brain natriuretic peptide and cardiac troponin T in healthy recreational cyclists. Am J Cardiol 2005;96:732–5.

91. Middleton N, Shave R, George K, et al. Novel application of flow propagation velocity and ischaemia-modified albumin in analysis of post-exercise cardiac function. Exp Physiol 2006;91:511–9.

92. Tulloh L, Robinson D, Patel A, et al. Raised troponin T and echocardiographic abnormalities after prolonged strenuous exercise - the Australian Ironman Triathlon. Br J Sports Med 2006;40:605–9.

93. Ramaraj R, Sorrell VL, Movahed MR. Levels of troponin release can aid in the early exclusion of stress-induced (takotsubo) cardiomyopathy. Exp Clin Cardiol 2009;14:6–8.

94. Sharkey SW, Lesser JR, Menon M, et al. Spectrum and significance of electrocardiographic patterns, troponin levels, and thrombolysis in myocardial infarction frame count in patients with stress (tako-tsubo) cardiomyopathy
and comparison to those in patients with ST-elevation anterior wall myocardial infarction. Am J Cardiol 2008;101:1723–1728.

95. Gupta R, Sech C, Lazzara R. Transient Cardiac Ballooning—The Syndrome. Clin. Cardiol 2009;32 (11), 614–620.

96. Nef H, Möllmann H, Akashi Y and Hamm C. Mechanisms of stress (Takotsubo) cardiomyopathy. Nat. Rev. Cardiol. 2010;**7**, 187–193.

Figure 1. Potential triggers of states associated with perioperative elevations in troponin levels, arterial thrombosis and myocardial infarction (adapted from ref 12)

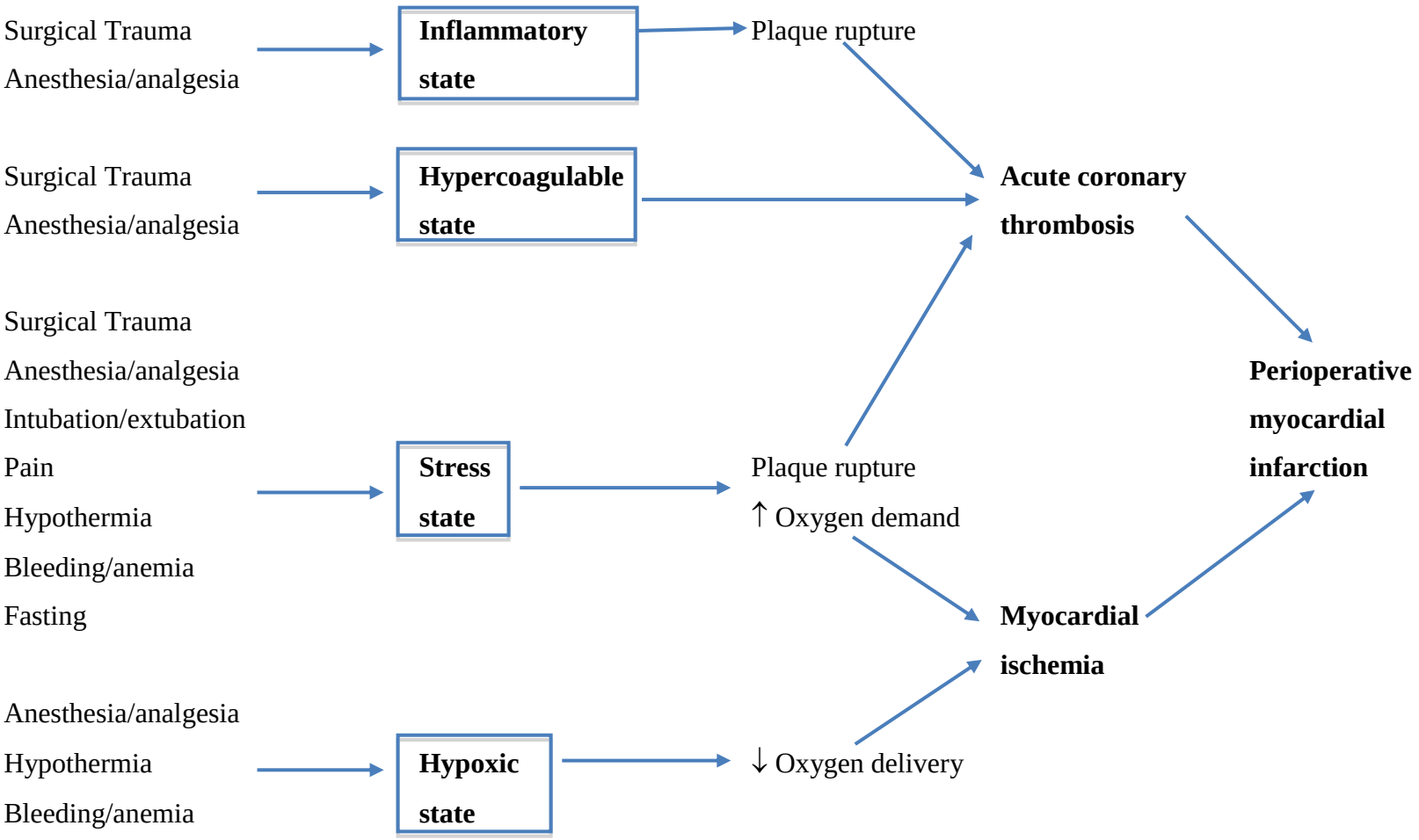

Figure 2. Prophylactic coronary revascularization. Pooled results of the composite of mortality and myocardial infarction at 30 days). Random-effects model.

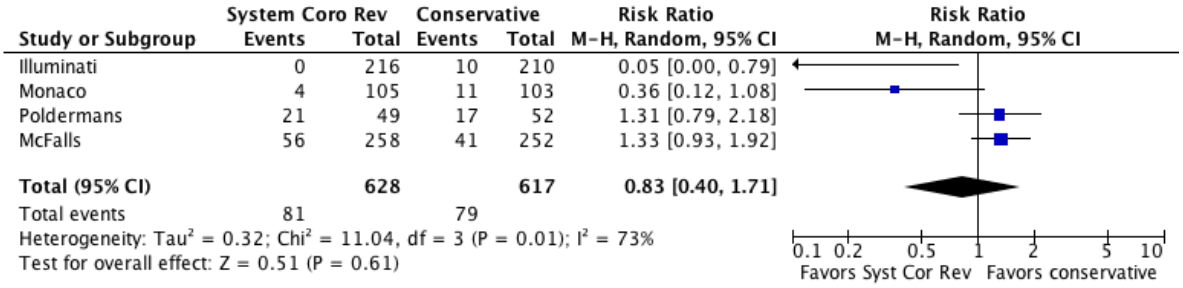

Figure 3. Prophylactic coronary revascularization. Pooled results of myocardial infarction at 30 days

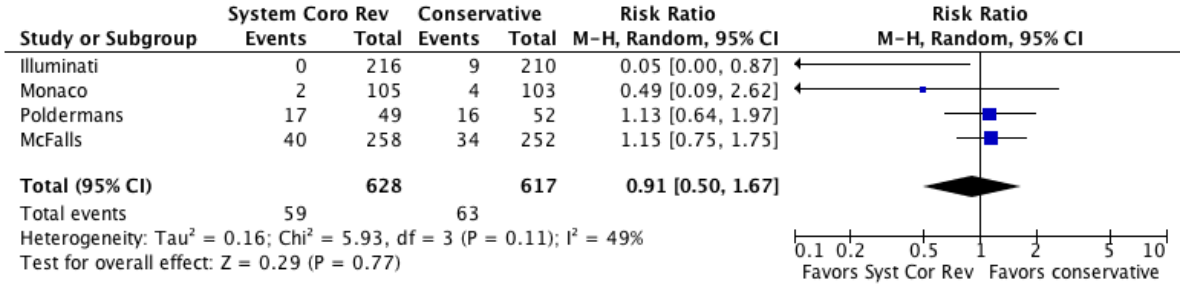

Table 1. Pathologic characteristics of coronary arteries in patients with fatal peri-operative myocardial infarction (from references 14 and 15)

	Dawood et al [15]	**Cohen and Aretz [14]**
	(n=42)	**(n=26)**
Left main disease	8 (19%)	6 (23%)
Three-vessel disease	25 (59%)	14 (54%)
Two-vessel disease	12 (29%)	8 (31%)
One-vessel disease	1 (2.4%)	1 (4%)
Plaque disruption	23 (55%)	12 (46%)
Intracoronary thrombus	12 (28%)	9 (35%)

Table 2. Incidence of myocardial infarction (MI) and presence of signs or symptoms among patients undergoing non-cardiac surgery (adapted from reference 44)

Study	No. of patients	Incidence of MI; no. (%) of patients			Study definition of MI
		Total	With chest pain	With any sign or symptom	
Mangano et al 26	474	12 (3)	1 (8)	8 (67)	Elevated CK-MB value and 1 of the following: • new Q-wave changes • persistent ST-segment and T-wave changes • autopsy evidence
Ashton et al 45	512	8 (2)	2 (25)	5 (62)	2 of the following: • new Q-wave changes • elevated CK-MB value • positive pyrophosphate scan
Badner et al 24	323	18 (6)	3 (17)	7 (39)	Elevated CK level and 2 of the following: • elevated CK-MB/CKratio • new Q-wave changes • elevated troponin level • positive pyrophosphate scan
Total (pooled result)*	**1309**	**38 (3)**	**6 (14)**	**20 (53)**	–

Note: CK-MB = creatine kinase MB isoenzyme. *The results were pooled with the use of a fixed-effects model. The pooled results did not show significant heterogeneity (MI with chest pain, p = 0.57 for heterogeneity; MI with any sign or symptom, p = 0.24 for heterogeneity).

Chapter 3

METHODOLOGICAL DESIGN

3.0 OBJECTIVES

Among patients undergoing non-cardiac surgery, we sought to:

3.1 Establish a definition of Myocardial Injury after Noncardiac Surgery (MINS) based upon a belief in a common ischemic pathophysiology and an important change in prognosis.

3.2 Describe the current characteristics of patients suffering MINS.

3.3 Determine the preoperative independent predictors of MINS.

3.4 Develop a scoring system to predict mortality risk at 30 days among patients suffering MINS.

3.1 STUDY DESIGN

The Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Study is a large ongoing multicentre, international, prospective cohort study in patients undergoing noncardiac surgery. VISION was designed to recruit 40,000 patients around the world, and has currently recruited more than 31,000 patients. After recruiting 15,000 patients the event rates were approximately three times higher than expected. Since this number assured the sample size requirements for the fourth-generation TnT analyses, the

Operations Committee decided to change the previous biomarker to the new fifth-generation high-sensitivity TnT.

Notable design and organizational aspects of VISION include: 1) the simplicity of the study design with simple entry criteria and a plan to record only essential baseline and outcome data ensures feasibility and facilitates rapid recruitment and completion; 2) our multicentre international study (including both university and non-university hospitals) broad eligibility criteria (including all noncardiac surgeries requiring hospital admission) ensure widely applicable results; and 3) the study's large sample size ensure an adequate number of events to provide precise estimates and avoid overfitting in our models.

3.2 JUSTIFICATION FOR STUDY DESIGN

Data emerged from the largest randomized trial performed in perioperative medicine, the POISE Trial [1], or another randomized controlled trial, cannot address our objectives because of their restrictive eligibility criteria that target high or moderate to high-risk patients, and biomarker measurements with different TnT or I asssays using different cut-off points. Further, studies have shown limited performance of prediction models developed from randomized controlled trial data when applied to general populations. [2, 3]

On the other hand, an administrative database study is a suboptimal design to address our objectives for the following reasons: the lack of details on important prognostic factors; [4] the inaccuracy of comorbidity data; [5, 6] the data distinguish only between events that happened pre and post admission but not pre and post surgery; the

data do not capture whether patients experienced symptoms or signs of a myocardial infarction; the data do not capture which patients had troponins after surgery; and if monitoring troponins after surgery facilitates diagnosing myocardial infarctions, and given that troponin screening is unusual, [7] then the administrative data are very likely to underestimate the incidence of perioperative myocardial injury.

Therefore, a multicenter, international, prospective cohort study is the best design to address our study objectives, as it allow us to prospectively collect complete and accurate risk factor data, ensure patients have troponins measured, closely monitor patients for perioperative events, ensure unbiased and comprehensive ascertainment of events, and include a heterogeneous group of patients who are ≥45 years of age undergoing a broad spectrum of noncardiac surgeries in both university and non-university hospitals.

3.3 ELEGIBILITY CRITERIA

3.3.1 Inclusion criteria

All patients who undergo noncardiac surgery are eligible if they are ≥45 years of age and receive a general or regional anesthetic (i.e., plexus block, spinal, or epidural).

3.3.2 Exclusion criteria

Patients undergoing noncardiac surgery who do not require at least an overnight hospital admission after surgery, or those who only receive infiltrative (i.e., local) or topical

anesthesia are excluded. Patients previously enrolled in the VISION Study and patients who do not consent to participate are also excluded.

3.4 SCREENING AND ENROLMENT OF PATIENTS

Through simple eligibility criteria, screening and enrolment procedures, we have ensured that investigators require minimal effort to recruit patients. In all centers, research personnel screen the patient list in the preoperative assessment clinic and use a variety of methods to capture those admitted through the emergency department and patients who do not attend the preoperative assessment clinic. These methods include screening the daily surgical list for eligible patients and the surgical list from the previous day to ensure no patients were missed, patients in the preoperative holding area, and the patient list on surgical wards and intensive care units.

Research personnel approach all patients (or patient families) who fulfill the eligibility criteria to obtain informed consent. Once a patient has consented and undergone surgery they are considered enrolled in the VISION study.

Centers recruit consecutive patients including patients undergoing surgery at night and on the weekends. The study protocol facilitates recruitment of these patients through the policy of allowing research personnel to obtain consent within the first 24 hours after surgery for patients in whom they cannot obtain consent prior to surgery. Further, if research personnel are not available to recruit consecutive patients week after week because a centre's surgical volumes are too high, then the project office assign randomly selected weeks for the centre to recruit patients.

3.5 VARIABLES COLLECTED

After obtaining written informed consent, research personnel interview and examine patients and review their charts to obtain information on patient characteristics that are potential predictors of major perioperative vascular events. This pre-operative patient characteristics are: age, coronary artery disease, recent high-risk coronary artery disease, recent coronary artery revascularization, atrial fibrillation, cerebrovascular disease, peripheral vascular disease, congestive heart failure, diabetes, hypertension, hypercholesterolemia treated with drug therapy, smoking history, history of cardiac arrest, renal insufficiency, chronic obstructive pulmonary disease, and obstructive sleep apnea. **Appendix I** reports the definitions of these variables. We also collect the following baseline descriptive data: ethnicity, active cancer, and chronic pain.

3.6 MONITORING, FOLLOW-UP, AND DATA COLLECTION

We have kept the follow-up procedures simple and to a minimum. Patients have blood drawn sometime between 6 to 12 hours postoperatively and on the 1st, 2nd, and 3rd day after surgery to measure troponin. Roche fourth-generation Elecsys TnT was the assay chosen for the VISION Study. Standard orders ensured these tests were undertaken, and also ensure that an ECG is undertaken immediately after an elevated troponin measurement is detected. If a troponin measurement is elevated but the patient has no ECG changes, ischemic symptoms, or pulmonary edema to fulfill the diagnostic criteria for MI, then the patient will undergo an echocardiographic study. Research personnel follow patients throughout their time in hospital and personally evaluate

patients and review patients' medical records ensuring study orders have been followed and noting any primary or secondary outcomes. The research personnel contact patients by phone at 30 days and 1 year after surgery. If patients indicate that they have experienced an outcome, the research personnel contact their physicians to obtain the appropriate documentation.

3.7 STATISTICAL AND ANALYTICAL METHODS

3.7.1 Analysis population

Analyses included all patients enrolled in VISION Study who had at least one fourth-generation TnT measurement after noncardiac surgery. We report how many patients were excluded from the analyses and the corresponding reasons. We report the median number (and intequartile range)) of troponins measured per patient. We consider TnT elevation as the presence of one or more measurements during the first 30 postoperative days after non-cardiac surgery that exceeded the proposed threshold according to the different phases of analyses. We use the peak TnT measurements that were obtained and assume these peak values represent the true peak value. Patients who had a documented pre-operative TnT value that exceeded the determined threshold in MINS analyses were not counted as having suffered MINS unless they suffered a separate event with a TnT elevation after their noncardiac surgery.

Follow-up was until day-30 after surgery. We report how many patients either die before 30 days or completed the 30-day follow-up. We censored patients at the time of

their last assessment if they did not complete the 30-day follow-up. We analyzed data generated by the VISION Adjudication Committee. We excluded patients from Italy because they did not include a representative sample at their centre.

3.7.2 Statistical analyses plan

As a general concept, VISION Study protocol used TnT ≥0.04 ng/mL as the threshold for assessing patients (i.e., inquiring about ischemic symptoms, obtaining ECGs - see Myocardial Infarction definition [8] in **Appendix II** for complete list), and study personnel reported on a case report form whether a patient had any of these defining clinical features of myocardial injury. This was based upon the guideline recommendations that suggested a TnT ≥0.04 ng/mL was the threshold defining abnormal. Because we did not inquire about ischemic symptoms and we did not obtain ECGs in patients with TnT values <0.04 ng/mL, we did not know whether patients with these lower values had clinical features of myocardial injury. Therefore, every time that we describe characteristics or prognosis of defining features we refer to a patients with TnT ≥0.04 ng/mL, even though our definition from the first objective may include lower values.

3.7.2.1 First objective: *"To establish a definition of Myocardial Injury after Non-cardiac Surgery (MINS) based upon a belief in a common ischemic pathophysiology and an important change in prognosis"*

For our first approach to define MINS, we included in the analysis patients with TnT ≥0.04 ng/mL based upon the blinded adjudicators decision of an assumed ischemic pathophysiology. Therefore, we excluded those who had a peak TnT ≥0.04 ng/mL due to a non-ischemic etiology (i.e., myocardial injury that was due to pulmonary embolism [PE], sepsis, cardioversion, a known TnT antibody or chronically elevated TnT measurements). The resulting population was divided into two subgroups: one with ≥1 clinical feature of MINS (see Myocardial Infarction definition in **Appendix II**), and the other without any clinical feature of MINS.

A prior VISION analysis demonstrated that TnT peak measurements of 0.02 and 0.03 ng/mL during the first 3 days after surgery were independent predictors of 30-day mortality.[9] Based on these findings, we also excluded those patients in this first step, because we did not know whether they had clinical features of MINS. We included patients with TnT peak ≤0.01 ng/mL as the reference group.

We undertook a Cox proportional hazards model in which the dependent variable was the time to 30-day mortality after noncardiac surgery. Independent variables included the independent predictors of 30-day mortality previously demonstrated in VISION analyses [9] (i.e., age 65-75 vs 45-65, and age ≥75 vs 45-65; recent high risk coronary artery disease, history of stroke, peripheral vascular disease, COPD, urgent or emergent surgery; active cancer; general surgery vs other surgery; and neurosurgery vs other surgery). We also added time-dependent post-operative significant clinical events as independent variables (i.e., stroke, arm or leg deep venous thrombosis [DVT], pneumonia, and infection), and we further added sepsis or PE that were not related to the

troponin elevation (as above, patients with sepsis or PE that were associated with a troponin elevation were excluded from these analyses). Finally, this model included TnT ≥0.04 ng/mL with and, separately, without clinical features of myocardial injury as independent variables.

The proposed MINS definition was established prior to the analyses according to 2 potential scenarios:

1- *Both TnT ≥0.04 ng/mL with and without clinical features independently predicts mortality at 30 days*; therefore MINS definition requires only a TnT ≥0.04 ng/mL, without accounting for the clinical features. In the next step, we would explore whether a lower TnT cut-off value (i.e. 0.02 or 0.03 ng/mL) independently predicts death in the model above, without knowledge of whether the patients did or did not experience clinical features of myocardial injury. We would exclude from this analysis patients with a peak TnT= 0.02 or 0.03 ng/mL and with a potential non-ischemic etiology detected within the 48 hours before the troponin measurement (i.e., PE, sepsis, cardioversion, a known TnT antibody or chronically elevated TnT).

2- *Only TnT ≥0.04 ng/mL with any clinical features but not without clinical features independently predicts mortality at 30 days;* therefore MINS definition requires TnT ≥0.04 ng/mL plus any clinical feature. In the next step, we would explore which clinical features should be included in the definition of MINS through a Cox proportional regression analysis including ischemic symptoms, and ECG changes (i.e., new Q waves, ST elevation, ST depression, T wave inversion, new LBBB).

We calculated the population attributable risk (PAR) and its 95% CI for each independent predictor of 30-day mortality [10, 11].

Whatever the proposed definition of MINS, we also determined in patients with TnT ≥0.04 ng/mL the prevalence of each clinical feature and the prognostic impact of each one on the 30-day mortality.

3.7.2.2 Second objective: *"To describe the current characteristics of patients suffering MINS"*

We described the baseline and surgical characteristics of patients with and without MINS. We also reported the hemodynamics from the adjudication form for systolic blood pressure and heart rate at the time of MINS. Proportions across the groups were compared using Fisher's exact test and continuous variables using the student's T or Mann-Whitney U test as appropriate.

Furthermore, we reported the prevalence and prognostic impact of clinical features in MINS patients with a peak TnT ≥0.04, even though our definition from objective 1 included lower troponin values. For those patients with more than one episode of MINS with TnT ≥0.04, we only considered the first episode.

We determined the proportion of MINS with TnT ≥0.04 that "probably would have gone undetected without monitoring of troponin after surgery", defined as a MINS without chest discomfort, other possible symptoms (i.e., arm, neck, or jaw discomfort, shortness of breath), or pulmonary edema.

Depending on our determined definition of MINS, we reported the outcomes (i.e., 30-day mortality, non-fatal cardiac arrest, congestive heart failure, cardiac catheterization, stroke) for patients with MINS who did and did not experience clinical features and the timing of patients suffering MINS. We informed odds ratios (OR) and 95% confidence intervals (CI).

3.7.2.3 Third objective: *"To determine the preoperative independent predictors of MINS"*

We performed a Cox proportional regression analysis among the complete set of patients undergoing noncardiac surgery (with and without TnT elevation) to develop a generic model. The dependent variable was the occurrence of MINS (as far as it was defined in the first objective) at 30 days. The independent variables were 17 baseline clinical variables and 7 types of surgeries. We included age and estimated glomerular filtration rate (eGFR) as categorical variables, based on a previous VISION analysis; age was divided in 45-64, 65-74 and ≥75 years, and eGFR in > 60, 45-60, 30-44, and <30 ml/min (we included in this group patients on dialysis). [9] eGFR was only included in a sensitivity analysis due to the fact that creatinine was not measured in all patients prior to surgery.

For all Cox regression analyses we used forced simultaneous entry (all candidate variables remained in the model) as opposed to automated stepwise selection, because simulation studies have demonstrated a higher risk of overfitting with the latter approach.

[12, 13] To assess the reliability of our models we undertook bootstrapping, [14] because this technique is superior to cross-validation and jack-knife techniques. [15]

3.7.2.4 Fourth objective: *"To develop a risk score to predict short-term mortality among patients suffering MINS"*

We performed a logistic regression analysis to develop a clinical scoring system for predicting mortality in patients suffering MINS. The dependent variable was mortality at 30 days. The independent variables were the preoperative variables (i.e. age, sex). Furthermore, we included characteristics of the index episode of MINS: chest discomfort, neck/jaw/or arm pain, dyspnea, pulmonary edema, ECG abnormalities (i.e., new Q wave, ST elevation or new LBBB, ST depression, T wave inversion), ECG location (i.e., anterior, lateral, inferior, septal, other reference). Based on our prior data, we also included a TnT elevation variable in this model defined as ≥0.30 ng/mL versus <0.30 ng/mL.[9] Logistic regression analyses included only patients with a peak TnT ≥0.04 ng/mL. For those patients with more than one episode of MINS with TnT ≥0.04 ng/mL, we only considered the first episode.

To validate the identified independent predictors, we performed bootstrapping based on 10,000 samples, and we further included the identified significant predictors alone in a model to determine their adjusted ORs. Then, a scoring system was achieved by assigning integer points to each independent predictor based on the obtained ORs. Finally, we predicted risk by summing integer points and observing a risk reference table. [16]

For all regression models, we reported the ORs (for logistic regression) or hazard ratio [HR] (for Cox proportional hazard regression), corresponding standard error, 95% CI and associated p-values. We reported P-values to 3 decimal places with p-values less than 0.001 reported as $p<0.001$. For all tests, we used alpha = 0.05 level of significance.

Goodness-of-fit for the models were performed using appropriate tests. For multivariable regression analysis, we anticipated multicolinearity (correlations among predictor variables). [17] We assessed colinearity using the variance inflation factor (VIF) which measures the extent to which the variance of the model coefficients was inflated (because of the correlation of the variable with other predictor variables) if that variable was included in the model. We considered variables with VIF>10 colinear. We performed all analyses using SAS version 9.2 (Cary, North Carolina).

3.7.3 Sample Size

Our adjusted Cox regression model to explore the association between MINS and 30-day mortality included 17 predictor variables. Simulation studies demonstrated that logistic models require 12 to 15 events per predictor to produce stable estimates.[19,20] Therefore, with the available 262 deaths we had sufficient events to avoid overfitting the model for our main objective.

Regarding our fourth objective, to determine the independent predictors of death at 30 days in patients suffering MINS, we analysed 15 variables in the model, including clinical features (e.g., chest discomfort, dyspnea, ST depression, etc). The available number of MINS was 944 and the number of deaths was 95. We performed

bootstrapping to test the stability of adjusted ORs, and we dropped from the model those variables with non-significant results.

3.8 PARTICIPATING COUNTRIES AND HOSPITALS

Twelve hospitals from eight countries (Brazil, Canada, USA, China, Colombia, Ausralia, India, Spain) participated in this first VISION Study phase. Every center recruited between 1000 – 4000 patients.

3.9 STUDY ORGANIZATION

The VISION coordinating centre responsible for the day-to-day study monitoring and management is located in McMaster University. It reports directly to the Operations Committee, and the Operations Committee reports directly to the Steering Committee.

3.10 ENSURING DATA QUALITY

Several procedures ensured data quality including: 1) all research personnel underwent a 1 day training session prior to study initiation to ensure consistency in study procedures including data collection and reporting; 2) all centres had a detailed study operations manual that outlined each step of the protocol; 3) investigators used a toll-free phone number to call a help line at the project office to resolve any problems or questions; 4) the project office personnel evaluated all data as soon as it is received and quality control checks identified any errors or omissions and notified the sender of any such issues via secure internet, FAX, telephone, or visit if necessary; 5) the project office

personnel reviewed detailed monthly reports on screening, enrollment, patients follow-up, data transmission, consistency of data collection, and event rates, and they immediately addressed any identified issues with the appropriate sites.

3.11 ETHICS

All centre principal investigators submitted this protocol to their Ethics Review Board. Research personnel approached all potentially eligible patients who fulfil eligibility criteria for consent. All patients signed a consent form to participate in VISION Study.

Confidentiality of patient data was maintained at local hospitals and the project office. Research personnel stored paper copies of case report forms (CRFs) in locked cabinets at their hospitals. The project office stored the electronic files of CRFs on a high-security computer system that has password protection. All study personnel ensured no patient identifiers were present on any files transmitted to any committee or clinical centre. We also ensured anonymization of all data in final reports.

3.12 REFERENCES

1. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008;371(9627):1839-47.

2. Rathore SS, Weinfurt KP, Gross CP, Krumholz HM. Validity of a simple ST-elevation acute myocardial infarction risk index: are randomized trial prognostic estimates generalizable to elderly patients? Circulation 2003;107(6):811-6.

3. Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. JAMA 2004;291(22):2727-33.

4. Norris CM, Ghali WA, Knudtson ML, Naylor CD, Saunders LD. Dealing with missing data in observational health care outcome analyses. J Clin Epidemiol 2000;53(4):377-83.

5. Discharge abstract database data quality re-abstraction study: Combined findings for fiscal years 1999/2000 and 2000/2001: Canadian Institute for Health Information, 2002.

6. Williams J, Young W. A summary of studies on the quality of health care administrative databases in Canada. In: Goel V, Williams J, Anderson G, Blackstien-Hirsch P, Fooks C, Naylor C, eds. Patterns of health care in Ontario: The ICES practice atlas. 2nd ed. Ottawa: Canadian Medical Association, 1996: 339-345.

7. Devereaux PJ, Ghali WA, Gibson NE, et al. Physicians' recommendations for patients who undergo noncardiac surgery. Clin Invest Med 2000;23(2):116-23.

8. Devereaux PJ, Goldman L, Yusuf S, Gilbert K, Leslie K, Guyatt GH. Surveillance and prevention of major perioperative ischemic cardiac events in patients undergoing

noncardiac surgery: a review. CMAJ 2005;173(7):779-88.

9. Devereaux PJ, Chan M, Alonso-Coello P, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. The Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Study Investigators. JAMA 2012;307(21):2295-2304.

10. Engel LS, Chow WH, Vaughan TL, et al. Population attributable risks of esophageal and gastric cancers. J Natl Cancer Inst. 2003;95(18):1404-1413.

11. Bruzzi P, Green SB, Byar DP, et al. Estimating the population attributable risk for multiple risk factors using case-control data. Am J Epidemiol. 1985;122(5):904-914.

12. Derksen S, Keselman H. Backward, forward and stepwise automated subset selection algorithms: frequency of obtaining authentic and noise variables. Br J Math Stat Psychol 1992;45:265-282.

13. Steyerberg EW, Eijkemans MJ, Harrell FE, Jr., Habbema JD. Prognostic modeling with logistic regression analysis: in search of a sensible strategy in small data sets. Med Decis Making 2001;21(1):45-56.

14. Efron B, Tibshirani R. An introduction to the bootstrap. London: Chapman & Hall, 2003.

15. Gong G. Cross-validation, the jackknife and the bootstrap: excess error estimation in forward logistic regression. J Am Stat Assoc 1986;81:108-113.

16. Sullivan L, Massaro J, D'Agostino R. Tutorial in biostatistics. Presentation of multivariate data for clinical use: The Framingham Study risk score functions. Statist. Med. 2004; 23:1631–1660.

17. Wax Y. Collinearity diagnosis for a relative risk regression analysis: an application to assessment of diet-cancer relationship in epidemiological studies. Stat Med 1992;11(10):1273-87.

18. Kline R. Data preparation and screening. In: Kline R, ed. Principles and Practice of Structural Equation Modeling. New York: The Guilford Press, 1998: 67-94.

19. Babyak MA. What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. Psychosom Med 2004;66(3):411-21.

20. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996;49(12):1373-9.

Appendix I. Study Definitions of Preoperative Patient Characteristics

1. Age – Patient age in years was recorded and subsequently categorized as 45-64 years of age, 65-74 years of age, and >75 years of age.

2. Sex – Male or female.

3. History of coronary artery disease – A current or prior history of any one of the following: i.angina; ii. myocardial infarction or acute coronary syndrome; iii. a segmental cardiac wall motion abnormality on echocardiography or a segmental fixed defect on radionuclide imaging; iv. a positive radionuclide exercise, echocardiographic exercise, or pharmacological cardiovascular stress test demonstrating cardiac ischemia; v. coronary angiographic or computer tomography (CT) coronary angiographic evidence of atherosclerotic stenosis ≥50% of the diameter of any coronary artery; vi. ECG with pathological Q waves in two contiguous leads.

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

5. History of cardiac arrest – A patient with a prior history of a cardiac arrest.

6. History of congestive heart failure – A physician diagnosis of a current or prior episode ofcongestive heart failure or prior radiographic evidence of vascular redistribution, interstitialpulmonary edema, or frank alveolar pulmonary edema.

7. History of peripheral vascular disease – A physician diagnosis of a current or prior history of: intermittent claudication, vascular surgery for atherosclerotic disease, an ankle/arm systolic blood pressure ratio <0.90 in either leg at rest, or angiographic or doppler study demonstrating >70% stenosis in a noncardiac artery.

8. History of stroke – A physician diagnosis of a current or prior stroke, or CT or magnetic
resonance (MR) evidence of a stroke.

9. History of deep venous thrombosis (DVT) or pulmonary embolus (PE) – A patient with a current or prior history of a DVT or PE.

10. Diabetes – Patient stated that they have a diagnosis of diabetes or a physician has previously recorded that the patient has diabetes. This included gestational diabetes at the time of noncardiac surgery, but not past gestational diabetes that had resolved.

11. Hypertension – A physician diagnosis of hypertension.

12. Hypercholesterolemia treated with drug therapy – patients taking drug therapy (e.g., statin, fibrate) for hypercholesterolemia in the week prior to surgery.

13. Smoking history – a patient with a current history of smoking.

14. Current atrial fibrillation – A patient with a current history of atrial fibrillation.

15. Obstructive sleep apnea – A physician or sleep study diagnosis of obstructive sleep apnea.

16. Chronic obstructive pulmonary disease (COPD) – A physician current or prior

diagnosis ofchronic bronchitis, emphysema, or COPD, or a patient provided a history of daily production of sputum for at least 3 months in 2 consecutive years.

17. Active cancer – A patient was designated as having active cancer if they fulfilled any of the following criteria: i. undergoing surgery for cancer; ii. known metastatic disease; or iii. patient had received active treatment for their cancer (e.g., chemotherapy, radiation, or surgery) within the 6 months prior to their surgery, but this did not apply to patients with non-melanoma skin cancers or surgery for a biopsy.

18. Urgent/Emergency surgery – Emergency surgery was surgery that occurred <24 hours after a patient developed an acute surgical condition, and urgent surgery was surgery that occurred 24-72 hours after a patient developed an acute surgical condition.

19. Major orthopedic surgery – A patient undergoing one or more of the following orthopedicsurgeries: major hip or pelvis surgery, internal fixation of femur, knee arthroplasty, above knee amputations, or lower leg amputation (amputation below knee but above foot).

20. Major general surgery – A patient undergoing one or more of the following general surgeries: complex visceral resection, partial or total colectomy or stomach surgery, other intra-abdominal surgery, or major head and neck resection for non-thyroid tumor.

21. Major urology or gynecology surgery – A patient undergoing one or more of the following major urology or gynecology surgeries: nephrectomy, ureterectomy, bladder resection, retroperitoneal tumor resection, exenteration, cytoreduction surgery, hysterectomy, radical prostatectomy, or transurethral prostatectomy.

22. Major neurosurgery – A patient undergoing one or more of the following neurosurgeries: craniotomy or major spine surgery (i.e., surgery involving multiple levels

of the spine).

23. Major vascular surgery – A patient undergoing one or more of the following vascular
surgeries: thoracic aorta reconstructive vascular surgery, aorto-iliac reconstructive vascular
surgery, peripheral vascular reconstruction without aortic cross-clamping, extracranial cerebrovascular surgery, or endovascular abdominal aortic aneurysm repair.

24. Major thoracic surgery – A patient undergoing one or more of the following thoracic
surgeries: pneumonectomy, lobectomy, wedge resection of lung, resection of mediastinal tumor, or major chest wall resection.

25. Low-risk surgeries – A patient undergoing one or more of the following surgeries: parathyroid, thyroid, breast, hernia, local anorectal procedure, oopherectomy, salpingectomy, endometrial ablation, peripheral nerve surgery, ophthalmology, ears/nose/throat surgery, vertebral disc surgery, hand surgery, cosmetic surgery, arterio-venous access surgery for dialysis, or any other surgery not mentioned above.

Appendix II. Study outcome definitions

1. Sub Classification of Death

Judicial outcome assessors will classify all deaths as either vascular or non-vascular. Vascular death is defined as any death with a vascular cause and includes those deaths following a myocardial infarction, cardiac arrest, stroke, cardiac revascularization procedure (i.e., percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery), pulmonary embolus, hemorrhage, or deaths due to an unknown cause. Non-vascular death is defined as any death due to a clearly documented non-vascular cause (e.g. trauma, infection, malignancy).

2. Myocardial Infarction [8]

The diagnosis of myocardial infarction requires any one of the following criterion:

1. A typical rise of troponin or a typical fall of an elevated troponin detected at its peak post surgery in a patient without a documented alternative explanation for an elevated troponin (e.g., pulmonary embolism). This criterion also requires that 1 of the following must also exist:

A. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema)

B. development of pathologic Q waves present in any two contiguous leads that are $\geq$ 30 milliseconds

C. ECG changes indicative of ischemia (i.e., ST segment elevation [$\geq$ 2 mm in leads V_1, V_2, or V_3 OR $\geq$ 1 mm in the other leads], ST segment depression [$\geq$ 1 mm], or symmetric inversion of T waves $\geq$ 1 mm) in at least two contiguous leads

D. coronary artery intervention (i.e., PCI or CABG surgery)

E. new or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging

2. Pathologic findings of an acute or healing myocardial infarction.

3. Development of new pathological Q waves on an ECG if troponin levels were not obtained or were obtained at times that could have missed the clinical event.

3. Nonfatal Cardiac Arrest

Nonfatal cardiac arrest is defined as successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy, or cardiac defibrillation.

4. Stroke

Stroke is defined as a new focal neurological deficit thought to be vascular in origin with signs and symptoms lasting more than 24 hours.

5. Leg or arm DVT/PE

Deep Venous Thrombosis of Leg or Arm: the diagnosis of DVT requires any one of the following:

1. A persistent intraluminal filling defect on contrast venography
2. Noncompressibility of one or more venous segments on B mode compression ultrasonography
3. A clearly defined intraluminal filling defect on contrast enhanced computed tomography

Pulmonary Embolus: The diagnosis of PE requires any one of the following:

1. A high probability ventilation/perfusion lung scan
2. An intraluminal filling defect of segmental or larger artery on a helical CT scan
3. An intraluminal filling defect on pulmonary angiography

4. A positive diagnostic test for DVT (e.g., positive compression ultrasound) and one of the following:
   A. non-diagnostic (i.e., low or intermediate probability) ventilation/perfusion lung scan.
   B. non-diagnostic (subsegmental deffects or technically inadequate study) helical CT scan.

6. Bleeding:

Bleeding is defined as bleeding which results in a drop in hemoglobin of 3g/dL (or 30 g/L), or leads to a transfusion, reoperation, or is thought to be the cause of death

7. New Acute Renal Failure Requiring Dialysis

Dialysis is defined as the use of a hemodialysis machine or peritoneal dialysis apparatus.

8. Sepsis/Infection.

Infection is defined as a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic organisms. Sepsis is a clinical syndrome defined by the presence of both infection and a systemic inflammatory response. Systemic inflammatory response requires 2 or more of the following factors: core temperature > 38 ºC or < 36 ºC; heart rate > 90 bpm; respiratory rate > 20 breaths/min; white blood cell count > 12 x 10^9/L or < 4 x 10^9/L.

9. Pneumonia

The diagnosis of postoperative pneumonia requires any one of the following:[56]
1. Rales or dullness to percussion on physical examinations of chest AND any of the following:
   A. New onset of purulent sputum or change in character of sputum
   B. Isolation of organism from blood culture

C. Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy

2. Chest radiography showing new or progressive infiltrate, consolidation, cavitation, or pleural effusion AND any of the following:

A. New onset of purulent sputum or change in character of sputum

B. Isolation of organism from blood culture

C. Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy

D. Isolation of virus or detection of viral antigen in respiratory secretions

E. Diagnostic single antibody titer (IgM) or fourfold increase in paired serum samples (IgG) for pathogen

F. Histopathologic evidence of pneumonia

10. New Clinically Important Atrial Fibrillation

New clinically important atrial fibrillation is defined as new atrial fibrillation that results in angina, congestive heart failure, symptomatic hypotension, or that requires treatment with a rate controlling drug, antiarrhythmic drug, or electrical cardioversion.

11. Congestive Heart Failure

The definition of congestive heart failure requires at least one of the following clinical signs (i.e. any of the following signs: elevated jugular venous pressure, respiratory rales/crackles, crepitations, or presence of S3) **and** at least one of the following radiographic findings (i.e., vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema).

12. Cardiac Revascularization Procedures

Cardiac revascularization procedures include PCI and CABG surgery.

Chapter 4

RESULTS AND DISCUSSION

4.1 RESULTS

From August 2007 to January 2011, 11 hospitals from 8 countries recruited 16,087 patients in VISION Study. After excluding 914 patients who did not have a troponin measurement or the absolute value was not reported, and 6 patients with missing variables assessed in model, 15,167 patients were included who had at least one fourth-generation TnT measurement after noncardiac surgery. The median number of troponins obtained during the first 3 days after surgery was 3 (interquartile range [IQR] 2-4).

In the following sections we describe the results according to the outlined four objectives, methodology and statistical analysis plan described in Chapter 3.

4.1.0 First objective: Definition of Myocardial Injury after Noncardiac Surgery (MINS)

After excluding patients with a peak TnT ≥0.04 ng/mL due to a non-ischemic etiology, those with a TnT value of 0.02 or 0.03 ng/mL and those with missing predictors, 14,314 patients and 228 deaths were available for this first analysis. A Cox proportional hazards model including time to 30-day mortality as the dependent variable, baseline independent predictors obtained from first VISION Study report (i.e., age, recent high

risk CAD, history of stroke, PVD and COPD, cancer, urgent/emergent surgery, general surgery and neurosurgery) [1], time-dependent postoperative significant clinical events (i.e., stroke, pneumonia, PE, DVT, sepsis) and the proposed MINS variable categorized in three groups (i.e., postoperative peak TnT ≥0.04 ng/mL with ≥1 clinical feature, postoperarative peak TnT ≥0.04 ng/mL with no clinical feature and postoperative peak TnT ≤0.01 ng/mL as reference variable) showed that postoperative peak TnT ≥0.04 ng/mL with ≥1 clinical feature (adjusted HR [aHR] 4.61, CI 95% 3.26-6.52, p<0.001) and postoperative peak TnT ≥0.04 ng/mL with no clinical feature (aHR 3.52, CI 95% 2.41-5.14, p<0.001) were independent predictors of 30-day mortality (**Table 1**).

Since peak TnT ≥0.04 ng/mL independently predicted death both with and without clinical defining features, we added back into the model, 640 patients with a peak TnT of 0.02 and 0.03 ng/mL, and excluded 96 patients with peak TnT *≥0.02 ng/mL* due to a non-ischemic etiology (89 for sepsis, 5 for pulmonary embolism and 2 for cardioversion). Of the resulting 15,071 patients, 15,049 with no missing predictors and 262 deaths were available for this second analysis. Both postoperative peak TnT ≥0.04 ng/mL with ≥1 clinical feature (aHR 4.47, CI 95% 3.18-6.28, p<0.001) and with no clinical features (aHR 3.43, CI 95% 2.35-5.00, p<0.001), and also postoperative peak TnT =0.03 ng/mL (aHR 4.24, CI 95% 2.62-6.87, p<0.001) were independent predictors of 30-day mortality. A postoperative peak TnT =0.02 ng/mL (aHR 1.62, CI 95% 0.91-2.85, p=0.099) was not a significant predictor. (**Table 2**)

Based on these data our diagnostic criteria for MINS is "*a post-operative peak TnT ≥0.03 ng/mL.*" According to this definition, MINS incidence was 7.96% (1,200 out

of 15,071 patients) in the whole population, and the median time of occurrence was day 1 (IQR 0-2) after surgery.

Table 3 shows the final Cox proportional hazards model including 15,049 patients with no missing predictors, 262 deaths and the binary definition of MINS based on TnT ≥0.03 ng/mL entered as a time-dependent covariate. Simultaneously, known baseline independent predictors from VISION Study [1] and time-dependent postoperative significant clinical events were included in the model. MINS showed a bootstrapped aHR of 3.82, CI 95% 2.84-5.10, p<0.001. Other post-operative independent prognostic factors were sepsis (aHR 6.95, CI 95% 4.74-9.73, p<0.001), PE (aHR 6.35, CI 95% 2.15-14.63, p<0.001) and stroke (aHR 3.24, CI 95% 1.54-6.52, p<0.001). The preoperative independent predictors were older age, recent high-risk CAD, history of stroke, history of PVD, COPD, active cancer, urgent or emergent procedures, general surgery, and neurosurgery. The model showed a good discrimination, with a C index= 0.89 (CI 95% 0.87-0.91). All the identified independent predictors potentially explain the majority of deaths that occurred at 30 days after noncardiac surgery (i.e., the total population attributable risk [PAR] was 91.9%, CI 95% 88.7- 94.6). Of the potentially modifiable risk factors, MINS demonstrated the largest PAR (33.7%).

4.1.1 Second objective: Characteristics of patients suffering MINS

4.1.1.2 Baseline characteristics

Table 4 shows that among VISION Study overall population (N=15,071), 24% of patients were ≥75 years old, 51% were women, 19% diabetics, and 51% hypertensives. Prevalence of CAD was 12%, active cancer 26 % and impaired estimated glomerular filtration rate [eGFR] (<60 mL/min per 1.73 m^2) 19.7%. More frequent types of surgeries were general (20%), orthopedic (18.4%), and low risk procedures (39.5%). Urgent or emergent surgery occurred in 14% of the patients. Finally, more frequent types of anesthesia were general (50.2%) and neuroaxial (i.e., spinal or epidural) (25.7%).

Regarding patients who suffered MINS, they were significantly older, and had significantly more risk factors, such as hypertension and diabetes, history of other cardiovascular disorders (i.e., CAD, congestive heart failure, PVD, stroke, renal failure), current atrial fibrillation, and COPD. Similarly, both major orthopedic and vascular surgery were significantly associated to MINS, as well as urgent or emergent procedures. On the contrary, low risk category of surgery was less frequently associated; however, a MINS incidence of 5% was observed among this subgroup of patients (**Table 4**).

4.1.1.3 Outcomes at 30 days

Overall, follow-up at 30 days after surgery was completed in 99.7% of patients. The total mortality rate was 1.74% (262/15,071).

Based on our proposed definition, MINS patients showed a significantly higher 30-day mortality rate of 9.6% (CI 95% 8.0-11.4%) when compared with 1.1% (CI 95% 0.9-1.2%) in patients without MINS, showing an unadjusted OR of 9.9 (CI 95% 7.69-

12.73%). The timing of death of MINS patients showed a median of 12 (IQR 5-18) days after surgery and 9 (IQR 3-16) days after MINS diagnosis.

Other important individual outcomes, such as non-fatal cardiac arrest, congestive heart failure, stroke, cardiac catheterization and coronary revascularization were also significantly increased in patients who suffered MINS. The incidence of a composite cardiovascular outcome (i.e., non-fatal cardiac arrest, congestive heart failure, stroke, and mortality) at 30 days was 18.7% in MINS patients versus 2.4% in those without MINS (unadjusted OR 9.48, CI 95% 7.90-11.37) (**Tables 5 and 6**).

4.1.1.4 Prevalence and prognostic impact of clinical features

Aiming to analyze the prevalence and prognostic impact of clinical features in MINS patients, we considered the available information from 944 patients with peak TnT ≥0.04 ng/mL, instead TnT ≥0.03 ng/mL, and 95 deaths.

Ischemic symptoms (e.g, chest pain) were experienced in 16.2% of patients suffering MINS. Therefore, 83.8% (791 of 944) probably would have gone undetected without monitoring of troponin after surgery.

Ischemic ECG abnormalities (e.g., ST depression) were observed in 34.9% of patients suffering MINS. The most common ECG abnormalities were ST segment depression (16.3 %) and T wave inversion (23.3%). Findings such as new Q waves, ST segment elevation or LBBB were infrequent (**Table 7**).

MINS without clinical features showed a 30-day mortality of 7.7% and MINS with one or more clinical feature 12.9%, unadjusted ORs of 7.81 (CI 95% 5.44-11.21%)

and 13.84 (CI 95% 9.99-19.18 %) respectively, when both were compared to patients without MINS (30-day mortality of 1.1 %). Other important outcomes (i.e, stroke, heart failure) were also significantly increased by MINS with and without clinical features (**Tables 5 and 6**).

A further analysis determined that MINS with no ischemic symptoms had a 30-day mortality of 9.0% and MINS with one or more ischemic symptom (i.e., chest/neck/jaw/arm discomfort, dyspnea, pulmonary edema) 15.7% (**Tables 5, 6 and 7**).

4.1.2 Third objective: Pre-operative independent predictors of MINS

Table 8 shows a Cox proportional hazards model including 13,820 patients with no missing predictors and 1137 cases with MINS (peak TnT ≥0.03 ng/mL). The dependent variable was time to MINS within 30 days and the independent variables were those previously explored as baseline characteristics in the objective 2 (item 4.1.1).

The observed preoperative independent predictors of MINS were age ≥75 years old (aHR 1.76, CI 95% 1.49-2.09, p<0.001), gender (aHR for female gender 0.71, CI 95% 0.62-0.80, p<0.001), current atrial fibrillation (aHR 1.39, CI 95% 1.10-1.75, p=0.006), history of diabetes (aHR 1.32, CI 95% 1.15-1.51, p<0.001), history of hypertension (aHR 1.33, CI 95% 1.14-1.55, p<0.001), history of congestive heart failure (aHR 1.40, CI 95% 1.13-1.73, p=0.002), history of CAD (aHR 1.38, CI 95% 1.15-1.65, p<0.001), history of high risk CAD (aHR 1.67, CI 95% 1.15-2.38, p=0.007), history of PVD (aHR 1.90, CI 95% 1.56-2.29, p<0.001), history of stroke (aHR 1.31, CI 95% 1.06-1.60, p=0.013),

cancer (aHR 1.17, CI 95% 1.00-1.37, p=0.047), increased heart rate (every 10 beats per mimute increase, aHR 1.10, CI 95% 1.06-1.15, p<0.001), preoperative eGFR (ml/min per 1.73 m^2 body surface) <30 ml/min (aHR 7.70, CI 95% 6.41-9.22, p<0.001), 30-44 ml/min (aHR 2.37, CI 95% 1.92-2.89, p<0.001) and 45-59 ml/min (aHR 1.70, CI 95% 1.41-2.03, p<0.001), and urgent or emergent surgery (aHR 1.69, CI 95% 1.44-1.99, p<0.001).

A sensitivity analysis excluding the preoperative eGFR from the previous model was performed. The available number of patients for this analysis was 14,932 and number of MINS was 1183. Independent predictors of MINS were similar, with the exception of atrial fibrillation and cancer that were no longer independent predictors (**Table 9**).

4.1.3 Fourth objective: Predictors of 30-day mortality in patients suffering MINS. Development of a scoring system.

A multiple logistic regression analysis including 944 MINS patients with peak TnT ≥0.04 ng/mL with no missing data and 95 deaths, determined that age ≥75 years old (adjusted OR [aOR] 2.59, CI 95% 1.41-4.76, p<0.002), the presence of ischemic chest discomfort (aOR 1.94, CI 95% 1.01-3.71, p<0.046), ST elevation or new LBBB (aOR 4.06, CI 95% 1.45-11.34, p=0.008), and the anterior location of ECG changes (aOR 2.22, CI 95% 1.14-4.34, p=0.020) were independent predictors of mortality at 30 days (**Table 10**). The model had a good calibration (Hosmer-Lemeshow goodness-of-fit test, p=0.727). Bootstrapping based on 10,000 samples validated than age ≥75 years old, ST elevation or new LBBB and anterior location of ECG changes were significant

independent predictors, but not ischemic chest discomfort which showed a bootstrapped aOR of 1.98, CI 95% 0.96-3.77.

A final model including only the significant variables is displayed in **Table 11**. Adjusted OR for age ≥75 years old was 2.08 (CI 95% 1.33-3.25, p=0.001), for ST elevation or new LBBB 3.61 (CI 95% 1.51-8.63, p=0.004), and for the anterior location of ECG changes 2.36 (CI 95% 1.49-3.75, p<0.001). Therefore, we assigned 2 points to age ≥75 years, 2 points to the anterior location of ECG changes, and 3 points to new ST elevation or LBBB according to the weighted aOR (**Table 12**). The scoring system ranged from 0 to 7 points.

Table 13 shows the estimated risk of death at 30 days in patients with a diagnosis of MINS: 0 points, 5.21%; 2 points 10.84%; 3 points, 15.31%; 4 points 21.20%; 5 points 28.58% and 7 points 46.96%. **Table 14** shows the risk estimate using the logistic formula directly.

4.2 DISCUSSION

4.2.1 Principal findings

In this prospective international cohort study with more than 15,000 patients ≥45 years old undergoing noncardiac surgery under a general or regional anesthetic, and requiring at least an overnight hospital admission after surgery, we developed and validated diagnostic criteria for a new diagnosis **"Myocardial Injury after Noncardiac Surgery" (MINS)**.

We found that peak TnT ≥0.03 ng-mL due to a perceived ischemic pathophysiology was an independent and strong predictor for 30-day mortality after noncardiac surgery, increasing the risk almost four times (aHR 3.82, CI 95% 2.84-5.10). A Cox proportional hazards model determined that the prognostic impact was independent of the association with ischemic symptoms and new ECG abnormalities, that are usually required for the universal definition of MI.[2]

Therefore, our definition for MINS is "myocardial cell injury caused by ischemia, characterized by a TnT value ≥0.03 ng/mL, which occurs during surgery or within 30 days after noncardiac surgery and has prognostic relevance at a short term"

According to this definition, the observed post-operative 30-day incidence of MINS was 8% and its mortality at 30 days was 9.6%. The population attributable risk analysis determined that MINS accounted for 33.7% of the total number of deaths. Given that 83.8% of MINS events would probably have gone undetected without postoperative troponin monitoring, this strongly suggests the need of its implementation during the first few days after surgery.

Additionally, we developed a seven point scoring system to estimate the mortality risk at 30 days in those patients with diagnose of MINS allocating points to the following 3 independent clinical predictors: age ≥75 years old, ECG with new ST elevation or left bundle branch block, and anterior location of any ischemic ECG abnormality (i.e., ST elevation or depression, T wave inversion, new Q wave development). By applying the score to patients suffering MINS, the estimation of mortality risk at 30 days showed a gradient from 5.2% (zero points) to 47% (7 points).

4.2.2 Strengths and limitations

Strengths of our study include the broad and heterogeneous prospective selection criteria that reduce bias and allows for generalizability, including urgent/emergent surgeries and all types of noncardiac surgeries requiring hospital admission; an international participation including both university and non-university hospitals; and patients recruitment during day and night, and also week-ends. All patients were closely monitored after surgery for troponin elevation during several days with the same assay, thus avoiding misinterpretation of different cut-off points. Furthermore, ECG evaluation was routinely required when troponin was elevated, and an echocardiogram was recommended. More than 99% of patients completed the follow-up at 30-days, and troponin elevations were centrally adjudicated using standardized definitions by independent physicians with expertise in perioperative medicine. Finally, the large sample size ensured an appropriate number of events to provide precise estimates and avoid overfitting in our models.

Our analysis has also limitations. Since we measured exclusively fourth-generation TnT, we cannot extend our conclusions to other commercially available assays. Furthermore, based upon guideline recommendations, by protocol we required the investigators to only assess (e.g., inquiring about ischemic symptoms, obtaining ECGs) a patient exceeding a threshold of TnT $\geq$0.04 ng/mL. Therefore, in patients suffering MINS with peak TnT =0.03 ng/mL we did not have data about clinical features. Consequently, the description of ischemic symptoms and ECG changes, and their association to risk prediction, outcomes and scoring system came from the analyses based

on TnT ≥0.04 ng/mL. The clinical expression of MINS based on a lower threshold (i.e., ≥0.03 ng/mL) might be more silent than our observed results, thus supporting our conclusions. Further, given the risk association for a TnT =0.03 ng/mL versus ≥0.04 ng/mL, we believe that it is unlikely that patients with peak TnT =0.03 ng/mL would require clinical features to impact mortality.

Since we excluded patients with peak TnT ≥0.03 ng/mL with sepsis and PE that occurred during the previous 48 hours to the biomarker elevation, we cannot extrapolate MINS results to these subgroups.

4.2.3 Comparison to other studies

Two meta-analyses addressed the independent prognostic value of troponin measurements after non-cardiac surgery regarding mortality at 30-days (8 studies, 1873 patients, 63 deaths),[3] and at 1 year and beyond 1 year of follow-up (14 studies, 3318 patients, 459 deaths).[4] Troponin elevation significantly predicted mortality at 30 days (OR 5.03, CI 95% 2.88-8.79),[3] at 1 year (OR 6.7, CI 95% 4.1-10.9),[4] and beyond 1 year of follow-up (OR 1.8, CI 95% 1.4-2.3).[4] However, both meta-analyses have several limitations: 1) the low number of events that prevents stable and reliable estimations; 2) the utilization of diverse troponin assays (mostly TnI) with different cut-off points across the hospitals that prevents extrapolation to the clinical practice; 3) the vast majority of studies were restricted to vascular surgery patients, thus preventing generalizability; 4) no individual study comprehensively explored troponin results in association to ischemic

clinical findings (i.e., chest pain, ECG abnormalities); and 5) no study was focused on the ischemic etiology as the cause of biomarker elevation.

Recently, the first VISION Study analysis evaluating the prognostic value of post-operative TnT level was published.[1] Among 15,133 patients undergoing noncardiac surgery, multivariable analyses demonstrated that a peak of TnT ≥0.02 ng/mL within the first 72 hours after noncardiac surgery independently predicted death at 30 days when compared with a reference value (TnT ≤0.01 μg/L) regardless of the cause of the elevation.

4.2.4. Interpretation

The aforementioned VISION analysis supported a prognostic message demonstrating that postoperative monitoring of TnT can enhance risk stratification after noncardiac surgery. [1] In the present analyses we developed and validated a new term, "Myocardial Injury after Non-cardiac Surgery" (MINS), based on postoperative TnT elevation resulting from an ischemic myocardial injury, not necessarily irreversible, capturing even small but prognostically relevant TnT values.

Clinical guidelines have suggested a fourth-generation TnT cut-off point of 0.04 ng/mL or more, including a coefficient of variation less than 10%.[2, 5] Our analysis confirmed the prognostic value of this troponin level recommendation, but we have also expanded it even to a lower value of TnT ≥0.03 ng/mL, which independently predicted almost a four-fold increase in the mortality risk at 30 days after noncardiac surgery.

We demonstrated that MINS represents a strong independent predictor of short-term mortality, as do a number of baseline conditions (i.e., older age, prior cardiovascular disorders, urgent/emergent surgery),[1, 6-8] or serious postoperative complications (i.e., sepsis, PE, stroke).[9, 10] However, analysis of population attributable risk determined that MINS (PAR=33.7%) and sepsis (PAR=28.9%) were the most frequent independent risk factors which may be treated if they are timely diagnosed, or even prevented.

Furthermore, supporting a simple clinical concept, our analysis determined that MINS criteria does not require any additional clinical feature, such as those stated in the universal definition of MI.[2] Our results demostrated a four-fold increase in its independent association with the risk of dying at 30 days. This finding is consistent with POISE Trial results, which showed that either symptomatic or asymptomatic perioperative MIs were independent predictors of death at 30 days. [11]

Previous reports have emphasized the subclinical nature of perioperative MI and ischemia [12-14]. POISE Trial substudy, which evaluated the highest number of perioperative MIs in a trial using a mandatory biomarker and ECG monitoring after surgery, determined than 65.3% of them were asymptomatic [11]. Based on peak TnT $\geq$0.04 ng/mL data, we also found that ischemic symptoms (1 of 6 patients, 16.2 %) and ECG changes (1 of 3 patients, 34.9 %) were an infrequent expression of MINS in our large unselected population. A possible explanation is related to residual anesthesia and indication of analgesics during the early hours after surgery.

MINS includes small peak TnT elevation due to myocardial ischemia that progress to irreversible necrosis, but also, that returns to normality. Troponin elevation

has long been considered synonymous with myocardial necrosis. [2] However, many authors have reported a cytosolic release from myocytes triggered by ischemia in different experimental and clinical conditions where no myocardial necrosis was ascertained (i.e, tachyarrhythmias, strong exercise, unstable angina, stress-induced cardiomyopathy).[15-26]

Histopathologically, there are several proposed mechanisms justifying troponin elevation without evidence of myocardial necrosis.[26,27] The first, resembles hepatocytes deprived from oxygen (e.g., ischemic hepatitis), which develop membrane blebs that are reabsorbed or shed into the circulation after reoxygenation without irreversible cellular damage.[26-30] This process has been replicated for troponin release in cultured cardiac myocytes.[31-33]. Another 2 proposed mechanisms involve release of small fragments of troponin without membranes disruption after proteolytic degradation by calpains, and an increased permeability of sarcolemma by stimulation of stretch-responsive integrins.[34-37]

Regarding prognostic relevance, unadjusted analyses showed that MINS increased nearly 10 times the risk of death or cardiovascular complications at 30 days (composite of non-fatal cardiac arrest, congestive heart failure, stroke, or mortality). Worldwide, more than 100 million adults over 45 years old undergo non-cardiac surgery per year [38]; consequently, nearly 8 million suffer MINS. Interestingly, based on our results, 84% of these patients, accounting for more than 6 million, are currently undetected without a systematic troponin monitoring. We may estimate that 1.5 million of MINS patients suffer a major vascular event and 800,000 die by day 30 because of this reason.

Evidence emerged from more than 100 randomized trials that recruited high-risk patients demonstrated that aspirin reduces vascular death by approximately 15% and nonfatal vascular events by 30%. Therefore, merely aspirin administration to every patient with MINS may avoid approximately 500,000 major vascular events, and 120,000 deaths per year.

To our knowledge, this is the first study evaluating the relationships between troponin levels, clinical features and short-term mortality after noncardiac surgery in patients with a suspected ischemic etiology. We believe that this evidence strongly supports the implementation of a systematic troponin monitoring, mainly during the first 48 hours, when most cases of MINS occur.

Regarding pre-operative prediction of MINS, as expected from prior evidence,[6, 10, 40, 41] several vascular conditions (i.e., diabetes, hypertension, congestive heart failure, coronary artery disease, high risk coronary artery disease, peripheral vascular disease and stroke) were independent predictors. Likewise, older age, male gender and urgent or emergent surgery increased the risk of MINS. Interestingly, heart rate (i.e., every 10 bpm increase) was an independent predictor but not systolic blood pressure. These finding may support research with pharmacologic perioperative reduction of heart rate with agents that minimize or not affect blood pressure, such as ivabradine or low-dose clonidine (the ongoing POISE-2 trial is testing this hypothesis). Beta-blockers have demonstrated to reduce perioperative MI, however, they increase the stroke and may increase mortality.

No individual type of surgery was found as independent predictor of MINS. This finding challenges the information from our first VISION analysis [1] where major general surgery and neurosurgery were independent predictors of mortality at 30 days. A possible explanation may underline non-ischemic etiologies, such as sepsis, PE or major bleeding.

Several widely applied scores have been developed for predicting risk in patients with non-operative acute coronary syndromes, such as GRACE and TIMI Scores.[43, 44] Since patients profile and physiopathology during the perioperative period are different, its application is unlikely optimal. Therefore, we developed a scoring system for predicting mortality risk at 30 days in patients suffering MINS. We found that age ≥75 years, new ST segment elevation or LBBB, and the anterior location of any ECG abnormality (i.e., ST elevation or depression, T wave inversion, new Q wave) were independent predictors of death at 30 days. The resulting score showed a gradient for 30-day mortality ranging from 5.2% (zero points) to 47% (7 points). For example, a 78 years old man, with MINS (TnT ≥0.03 ng/mL) diagnosed at 48 hours after a hip replacement surgery and an ECG showing T wave inversion from V1 to V4 has 4 points according to our MINS Score; the estimated risk of mortality at 30 days is 1 out of 5 patients (21.2%).

The universal definition of MI [2] has explicit diagnostic criteria for MI after PCI and CABG, however no specific criteria has been established after non-cardiac surgery. Although continuous debate about whether troponin release should be considered a marker of myocardial necrosis or occasionally ischemia without necrosis, does not refute our MINS definition proposal. In fact, we are not intending to fill the gap of a MI definition after noncardiac surgery. Our proposed concept is broader, aiming to predict,

diagnose, provide a prognostic message and inform therapeutic options. However, the complete spectrum of these objectives should be addressed in the near future by trial designs focused on MINS prevention and treatment.

Finally, as more sensitive troponin assays become commercially available, the proposed threshold defining MINS based on the fourth-generation TnT test will have to be reevaluated. The second part of our ongoing VISION Study (currently there are more than 32,000 patients recruited) will answer this question based on the fifth-generation TnT High Sensitivity assay.

4.3 REFERENCES

1. Devereaux PJ, Chan M, Alonso-Coello P, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. The Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Study Investigators. JAMA 2012;307(21):2295-2304.

2. Thygesen K, Alpert J, White H, on behalf of the joint ESC/ACCF/AHA/WHF task force for the Redefinition of Myocardial Infarction. Universal Definition of Myocardial Infarction. JACC 2007, 50(22): 2173-95.

3. Redfern G, Rodseth R and Biccard B. Outcomes in vascular surgical patients with isolated postoperative troponin leak: a meta-analysis. Anaesthesia, 2011, 66: 604–610.

4. Levy M, Heels-Ansdell D, Hiralal R et al. Prognostic value of troponin and creatine kinase muscle and brain isoenzyme measurement after noncardiac surgery: a systematic review and meta-analysis. Anesthesiology 2011;114(4):796-806.

5. Panteghini M, Pagani F, Yeo K, et al. Committee of Standardization of Markers of Cardiac Damage of the IFCC. Evaluation of imprecision for cardiac troponin assays at low-range concentrations. Clin Chem 2004;50(2):327-332.

6. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999;100 (10):1043-9.

7. 2009 ACCF/AHA Focused Update on Perioperative Beta Blockade Incorporated Into the ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery A Report of the American College of Cardiology

Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2009;54;e13-e118.

8. Poldermans D; Bax J, Boersma E. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery. The Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). Eur Heart J (2009) 30, 2769-2812.

9. Qaseem A, Snow V, Fitterman N, Hornbake ER, Lawrence VA, Smetana GW, et al. Risk assessment for and strategies to reduce perioperative pulmonary complications for patients undergoing noncardiothoracic surgery: a guideline from the American College of Physicians. Ann Intern Med 2006;144(8):575-80.

10. Davenport D, Ferraris V, Hosokawa P, et al. Multivariable Predictors of Postoperative Cardiac Adverse Events after General and Vascular Surgery: Results from the Patient Safety in Surgery Study. J Am Coll Surg 2007;204:1199–1210.

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

12. Mangano DT, Browner WS, Hollenberg M, et al. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. N Engl J Med. 1990; 323:1781-8.

13. Ashton CM, Petersen NJ, Wray NP, et al. The incidence of perioperative myocardial

infarction in men undergoing noncardiac surgery. Ann Intern Med. 1993;118:504-10.

14. Badner NH, Knill RL, Brown JE, et al. Myocardial infarction after noncardiac surgery. Anesthesiology. 1998;88:572-8.

15. Bukkapatnam R, Robinson M, Turnipseed S, et al. Relationship of Myocardial Ischemia and Injury to Coronary Artery Disease in Patients With Supraventricular Tachycardia. Am J Cardiol 2010;106:374 –377.

16. Turer A, Addo T, MD, Martin J, et al. Myocardial Ischemia Induced by Rapid Atrial Pacing Causes Troponin T Release Detectable by a Highly Sensitive Assay Insights From a Coronary Sinus Sampling Study. J Am Coll Cardiol 2011;57:2398–405.

17. Sabatine M, Morrow D, de Lemos J, et al. Detection of acute changes in circulating troponin in the setting of transient stress test-induced myocardial ischaemia using an ultrasensitive assay: results from TIMI 35. Eur Heart J 2009;30: 162–169.

18. Shave R, George KP, Atkinson G, et al. Exercise-induced cardiac troponin T release: a meta-analysis. Med Sci Sports Exerc 2007;39:2099–106.

19. Neumayr G, Pfister R, Mitterbauer G, et al. Effect of competitive marathon cycling on plasma N-terminal pro-brain natriuretic peptide and cardiac troponin T in healthy recreational cyclists. Am J Cardiol 2005;96:732–5.

20. Middleton N, Shave R, George K, et al. Novel application of flow propagation velocity and ischaemia-modified albumin in analysis of post-exercise cardiac function. Exp Physiol 2006;91:511–9.

21. Tulloh L, Robinson D, Patel A, et al. Raised troponin T and echocardiographic abnormalities after prolonged strenuous exercise - the Australian Ironman

Triathlon. Br J Sports Med 2006;40:605–9.

22. Ramaraj R, Sorrell VL, Movahed MR. Levels of troponin release can aid in the early exclusion of stress-induced (takotsubo) cardiomyopathy. Exp Clin Cardiol 2009;14:6–8.

23. Gupta R, Sech C, Lazzara R. Transient Cardiac Ballooning—The Syndrome. Clin. Cardiol 2009;32 (11), 614–620.

24. Nef H, Möllmann H, Akashi Y and Hamm C. Mechanisms of stress (Takotsubo) cardiomyopathy. Nat. Rev. Cardiol. 2010;**7**, 187–193.

25. Hamm CW, Ravkilde J, Gerhardt W, et al. The prognostic value of serum troponin T in unstable angina. N Engl J Med 1992;327:146–50.

26. Hickman P, Potter J, Aroney C. Cardiac troponin may be released by ischemia alone, without necrosis. Clin Chim Acta 2010;411:318–323.

27. White H. Pathobiology of Troponin Elevations. Do Elevations Occur With Myocardial Ischemia as Well as Necrosis?. JACC 2011, 57(24): 2406-8.

28. Lemasters JJ, Ji S, Thurman RG. Centrilobular injury following hypoxia in isolated, perfused rat liver. Science 1981;213(4508):661-3.

29. Gores GJ, Herman B, Lemasters JJ. Plasma membrane bleb formation and rupture: a common feature of hepatocellular injury. Hepatology 1990;11:690–8.

30. Jewell SA, Bellomo G, Thor H, et al. Bleb formation in hepatocytes during drug metabolism is caused by disturbances in thiol and calcium ion homeostasis. Science 1982;217(4566):1257-9.

31. Sakai K, Gebhard MM, Spieckermann PG, Bretschneider HJ. Enzyme release

resulting from total ischemia and reperfusion in the isolated, perfused guinea pig heart. J Mol Cell Cardiol 1975;7:827–40.

32. Piper HM, Schwartz P, Spahr R, Hutter JF, Spieckermann PG. Early enzyme release from myocardial cells is not due to irreversible cell damage. J Mol Cell Cardiol 1984;16:385–8.

33. Schwartz P, Piper HM, Spahr R, Spieckermann PG. Ultrastructure of cultured adult myocardial cells during anoxia and reoxygenation. Am J Pathol 1984;115:349–61.

34. Gao WD, Atar D, Liu Y, et al. Role of troponin I proteolysis in the pathogenesis of stunned myocardium. Circ Res 1997;80:393–9.

35. McDonough JL, Arrell DK, Van Eyk JE. Troponin I degradation and covalent complex formation accompanies myocardial ischemia/reperfusion injury. Circ Res 1999;84:9 –20

36. Feng J, Schaus BJ, Fallavollita JA, et al. Preload induces troponin I degradation independently of myocardial ischemia. Circulation 2001;103:2035–7.

37. Hessel MH, Atsma DE, van der Valk EJ, et al. Release of cardiac troponin I from viable cardiomyocytes is mediated by integrin stimulation. Pflugers Arch 2008;455:979–86.

38. Devereaux PJ, Chan M, Eikelboom J. Major vascular complications in patients undergoing noncardiac surgery: The magnitude of the problem, risk prediction, surveillance, and prevention. In: Yusuf S, Cairns JA, Camm AJ, Fallen EL, Gersh BJ, editors. *Evidence based Cardiology*. 3rd ed. London, England: BMJ Books, 2009:47-62.

39. Eikelboom J, Hirsh J, Spencer F, et al. Antiplatelet Drugs: Antithrombotic Therapy

and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141;e89S-e119S.

40. Gupta P, Gupta H, Sundaram A, et al. Development and Validation of a Risk Calculator for Prediction of Cardiac Risk After Surgery. Circulation. 2011;124:381-387.

41. Bertges D, Goodney P, Zhao Y, et al. The Vascular Study Group of New England Cardiac Risk Index (VSG-CRI) predicts cardiac complications more accurately than the Revised Cardiac Risk Index in vascular surgery patients. J Vasc Surg 2010;52:674-83.

42. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008;371(9627):1839-47.

43. Granger C, Goldberg R, Dabbous O, et al. Predictors of Hospital Mortality in the Global Registry of Acute Coronary Events. Arch Intern Med. 2003;163:2345-2353.

44. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA 2000; 16;284(7):835-42.

Table 1. MINS development. First Cox regression model to explore the association between postoperative peak TnT ≥0.04 ng/mL with and without clinical features and 30-day mortality

n=14314 with no missing predictors and 228 deaths.

	Adjusted HR (95% CI)	**p-value**
Peak TnT ≥0.04 ng/mL with clinical features	4.61 (3.26 - 6.52)	<0.001
Peak TnT ≥0.04 ng/mL with no clinical features	3.52 (2.41 - 5.14)	<0.001
Peak TnT ≤0.01 ng/mL	1.00	-

Table 2. MINS development. Second Cox regression model to explore the association between postoperative peak TnT ≥0.04 ng/mL with and without clinical features and 30-day mortality, including patients with peak TnT =0.02 and 0.03 ng/mL

n=15049 with no missing predictors and 262 deaths

	Adjusted HR (95% CI)	**p-value**
Peak TnT ≥0.04 ng/mL with clinical features	4.47 (3.18 - 6.28)	<0.001
Peak TnT ≥0.04 ng/mL with no clinical features	3.43 (2.35 - 5.00)	<0.001
Peak TnT = 0.03 ng/mL	4.24 (2.62 - 6.87)	<0.001
Peak TnT = 0.02 ng/mL	1.62 (0.91 - 2.85)	0.099
Peak TnT ≤0.01 ng/mL	1.00	-

Table 3. Final adjusted Cox regression model to explore the association between MINS (postoperative peak TnT ≥0.03 ng/mL) and 30-day mortality

n=15049 with no missing predictors and 262 deaths

		Model Derivation		Model Validation	
	Incidence of Predictors (%)	**Adjusted HR (95% CI)**	**p-value**	**Bootstrapped Adjusted HR* (95% CI)**	**PAR (95% CI**)**
Age (years)					42.2% (28.3, 55.0)
45-64	7677 (51.0)	1.00	-	1.00	
65-74	3751 (24.9)	1.53 (1.07, 2.19)	0.019	1.53 (1.05, 2.27)	
≥75	3621 (24.1)	2.79 (2.05, 3.80)	<0.001	2.83 (2.04, 3.99)	
Recent high risk CAD	170 (1.1)	2.80 (1.66, 4.71)	<0.001	2.79 (1.53, 4.59)	4.1% (1.1, 7.2)
History of stroke	692 (4.6)	1.64 (1.15, 2.34)	0.006	1.64 (1.06, 2.37)	7.2% (1.8, 12.5)
History of PVD	795 (5.3)	1.97 (1.39, 2.81)	<0.001	1.97 (1.31, 2.84)	8.1% (2.8, 13.2)
History of COPD	1261 (8.4)	1.75 (1.29, 2.36)	<0.001	1.73 (1.24, 2.38)	10.3% (3.9, 16.6)
Urgent/Emergent surgery	2115 (14.1)	3.39 (2.59, 4.43)	<0.001	3.44 (2.53, 4.60)	31.5% (24.0, 39.1)
Cancer	3992 (26.5)	2.03 (1.52, 2.70)	<0.001	2.04 (1.47, 2.83)	21.1% (12.3, 29.8)
General surgery	3033 (20.2)	1.63 (1.23, 2.17)	<0.001	1.63 (1.19, 2.18)	16.1% (6.5, 25.0)
Neurosurgery	887 (5.9)	2.04 (1.32, 3.16)	0.001	2.08 (1.22, 3.24)	5.5% (1.4, 9.7)
Post-op stroke	79 (0.5)	3.14 (1.81, 5.45)	<0.001	3.24 (1.54, 6.52)	4.2% (1.0, 7.4)
Post-op pneumonia	338 (2.2)	1.44 (0.98, 2.10)	0.062	1.44 (0.94, 2.23)	-
Post-op PE	95 (0.6)	6.12 (3.15, 11.88)	<0.001	6.35 (2.15, 14.63)	3.4% (0.9, 6.1)
Post-op DVT	86 (0.6)	1.57 (0.72, 3.43)	0.260	1.66 (0.48, 5.22)	-
Post-op Sepsis/infection					28.9% (22.3, 35.4)†
Sepsis	783 (5.2)	6.81 (4.92, 9.44)	<0.001	6.95 (4.74, 9.73)	
Infection, not sepsis	940 (6.2)	1.23 (0.73, 2.09)	0.436	1.23 (0.64, 2.12)	
Neither	13326 (88.6)	1.00	-	1.00	
MINS (peak TnT ≥0.03 ng/mL)	**1196 (7.9)**	**3.83 (2.93, 5.00)**	**<0.001**	**3.82 (2.84, 5.10)**	**33.7% (26.6, 41.2)**

* Obtained from 1,000 bootstrap samples: median, 2.5 and 97.5 percentiles.
** Only variables that are significant predictors in the Cox model are included in the model for PAR. 95% CIs for PAR are from 10,000 bootstrap samples. Overall PAR is 91.9% (88.7, 94.6).
† PAR for sepsis vs no sepsis.
Incidence of MINS and post-op events are reported as ever within 30 days post-op.

Table 4. Baseline characteristics of patients who did and did not suffer MINS (peak TnT ≥0.03 ng/mL).

n=15071. n (%) unless otherwise stated.

	Total (n=15071	No MINS (n=13871)	MINS (n=1200)	p-value
Age (years)				<0.001
45-64	7685 (50.9)	7347 (53.0)	338 (28.2)	
65-74	3758 (24.9)	3489 (25.2)	269 (22.4)	
≥ 75	3628 (24.0)	3035 (21.9)	593 (49.4)	
Gender, females	7777 (51.6)	7240 (52.2)	537 (44.8)	<0.001
Current Atrial Fibrillation	496 (3.29)	385 (2.8)	111 (9.3)	<0.001
History of				
Diabetes	2935 (19.4)	2534 (18.3)	401 (33.4)	<0.001
Hypertension	6949 (46.1)	6802 (49.0)	867 (72.3)	<0.001
CHF	694 (4.6)	517 (3.7)	177 (14.8)	<0.001
CAD	1818 (12.0)	1486 (10.7)	332 (27.7)	<0.001
High risk CAD	170 (1.1)	117 (0.8)	53 (4.4)	<0.001
Cor Revasc, anytime*	773 (5.1)	634 (4.6)	139 (11.6)	<0.001
Cor Revasc, ≤ 6 months**	54 (0.3)	44 (0.3)	10 (0.8)	0.009
Cardiac arrest	68 (0.4)	57 (0.4)	11 (0.9)	0.021
PVD***	797 (5.2)	591 (4.3)	206 (17.2)	<0.001
Stroke†	693 (4.6)	554 (4.0)	139 (11.6)	<0.001
COPD	1263 (8.3)	1086 (7.8)	177 (14.8)	<0.001
Cancer yes to any of: active Ca, Sx for Ca, mets††	3994 (26.5)	3691 (26.6)	303 (25.3)	0.323
Preop clinical examination				
HR, mean ± SD†††		76.4 ± 14.4	79.9 ± 17.2	<0.001
Systolic BP, mean ± SD‡		139.1 ± 23.3	144.0 ± 26.7	<0.001
Preop eGFR (ml/min)‡‡				<0.001
<30	508 (3.6)	263 (2.1)	245 (21.3)	
30-44	752 (5.4)	592 (4.6)	160 (13.9)	
45-59	1485 (10.6)	1304 (10.2)	181 (15.7)	
> 60	11207 (80.3)	10641 (83.1)	566 (49.1)	
Type of Surgery				
Vascular	499 (3.3)	404 (2.9)	95 (7.9)	<0.001
General	3038 (20.1)	2782 (20.1)	256 (21.3)	0.294
Thoracic	372 (2.4)	340 (2.5)	32 (2.7)	0.628
Major Urologic/Gynecologic	1888 (12.5)	1758 (12.7)	130 (10.8)	0.069
Major Orthopaedia	2783 (18.4)	2415 (19.6)	368 (30.7)	<0.001
Major Neurology	888 (5.9)	828 (6.0)	60 (5.0)	0.180
Low risk surgeries	5956 (39.5)	5657 (40.8)	299 (24.9)	<0.001
Urgent/emergent surgery	2118 (14)	1811 (13.1)	307 (25.6)	<0.001

* n=15061, ** n=15068, *** n=15070, † n=15064, †† n=15057, ††† n=14965, ‡ n=14993, ‡‡ n=13952, ‡‡‡ n=15067

Cor revasc: coronary revascularization, CHF: congestive heart failure, CAD: coronary artery disease, PVD: peripheral vascular disease, COPD: chronic obstructive pulmonary disease, Ca: cancer, HR: heart rate, BP: blood pressure, eGFR: estimated glomerular filtration rate

Table 5. Outcomes at 30 days of follow-up

Outcome	Patients without MINS n=13871	All patients with MINS n=1200		MINS with peak TnT ≥0.04 and clinical features* n=426		MINS with peak TnT ≥0.04 and without clinical features* n=518	
	n (%)	n (%)	Unadjusted OR (95% CI), vs no MINS	n (%)	Unadjusted OR (95% CI), vs no MINS	n (%)	Unadjusted OR (95% CI), vs no MINS
Non-fatal cardiac arrest	8 (0.06)	8 (0.7)	11.63 (4.36 - 31.04)	7 (1.6)	28.95 (10.45 - 80.21)	1 (0.2)	3.35 (0.42 - 26.84)
CHF	138 (1.0)	115 (9.6)	10.55 (8.17 - 13.61)	74 (17.4)	20.92 (15.47 - 28.28)	32 (6.2)	6.55 (4.41 - 9.73)
Stroke	58 (0.4)	21 (1.8)	4.24 (2.57 - 7.01)	10 (2.3)	5.72 (2.91 - 1.28)	6 (1.2)	2.79 (1.20 - 6.50)
Cardiac cath	8 (0.06)	47 (3.9)	70.64 (33.30 - 149.84)	41 (9.6)	184.54 (85.93 - 396.29)	4 (0.8)	13.49 (4.05 - 44.93)
PCI or CABG	4 (0.03)	23 (1.9)	67.74 (23.39 - 196.21)	22 (5.2)	188.78 (64.76 - 550.34)	1 (0.2)	6.71 (0.75 - 60.10)
Mortality	147 (1.1)	115 (9.6)	9.90 (7.69 - 12.73)	55 (12.9)	13.84 (9.99 - 19.18)	40 (7.7)	7.81 (5.44 - 11.21)
Composite of Nonfatal Cardiac arrest, CHF, stroke, or mortality	328 (2.4)	224 (18.7)	9.48 (7.90, 11.37)	121 (28.4)	16.38 (12.92, 20.77)	74 (14.3)	6.88 (5.26, 9.01)

* For patients with multiple episodes of MINS with peak troponin ≥0.04, we have used the first episode.

CHF: congestive heart failure, Cath: catheterization, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting

Table 6. Mortality at 30 days of patients with and without MINS, and subgroups defined by clinical features (i.e., ischemic symptoms, ECG abnormalities).

	Mortality at 30 days	
	count/n	**% (95% CI)**
No MINS, all	147/13871	1.1 (0.9, 1.2)
MINS, all	115/1200	9.6 (8.0, 11.4)
In those with peak TnT ≥0.04*		
Isolated TnT elevation **	40/518	7.7 (5.7, 10.3)
With ≥ 1 clinical feature	55/426	12.9 (10.1, 16.4)
In those with peak TnT ≥0.04*		
No ischemic symptoms	71/791	9.0 (7.2, 11.2)
At least one ischemic symptom	24/153	15.7 (10.8, 22.3)

* For patients with multiple episodes of MINS with peak TnT ≥0.04, we have used the first episode
** Without clinical features

Table 7. Clinical features of MINS: prevalence and 30-day mortality rate.

n=944 patients with peak troponin ≥0.04 and 95 deaths.

Defining feature	Prevalence of defining feature, (%)	Mortality at 30 days,	
		n	% (95% CI)
Ischemic symptoms			
- chest discomfort	86 (9.1)	18	20.9 (13.7, 30.7)
- neck/jaw/arm discomfort	5 (0.5)	0	0.0 (0.0, 43.4)
- dyspnea	68 (7.2)	11	16.2 (9.3, 26.7)
- pulmonary edema	48 (5.1)	9	18.8 (10.2, 31.9)
Any ischemic symptom	153 (16.2)	24	15.7 (10.8, 22.3)
ECG abnormality			
- New Q waves	13 (1.4)	1	7.7 (1.4, 33.3)
- ST elevation	21 (2.2)	6	28.6 (13.8, 50.0)
- ST depression	154 (16.3)	21	13.6 (9.1, 19.9)
- T wave inversion	220 (23.3)	31	14.1 (10.1, 19.3)
- New LBBB	5 (0.5)	3	60.0 (23.1, 88.2)
Any ECG abnormality	329 (34.9)	47	14.3 (10.9, 18.5)
New WMA on Echo	21 (2.2)	3	14.3 (5.0, 34.6)
Presumed new WMA on Echo	86 (9.1)	4	4.7 (1.8, 11.4)
New FD on Nuclear imaging	1 (0.1)	0	0.0 (0.0, 79.3)
Presumed new FD on Nuclear imaging	5 (0.5)	0	0.0 (0.0, 43.4)
SBP at time of MINS (N=272), mean (SD)	124.2 (28.0)	-	-
HR at time of MINS (N=459), mean (SD)	90.0 (23.2)	-	-

LBBB: left bundle branch block
WMA: wall motion abnormality
FD: fix defect

Table 8. Pre-operative predictors of MINS (peak TnT ≥0.03) at 30 days

n=13820, 1137 with MINS.

	Model Derivation		Model Validation
	Adjusted HR (95% CI)	**p-value**	**Bootstrapped Adjusted HRs* (95% CI)**
Age (years)			
45-64	1.00	-	1.00
65-74	1.05 (0.89, 1.25)	0.554	1.05 (0.88, 1.25)
≥ 75	1.76 (1.50, 2.06)	<0.001	1.76 (1.49, 2.09)
Gender, females	0.71 (0.62, 0.80)	<0.001	0.71 (0.62, 0.80)
Current atrial fibrillation	1.39 (1.13, 1.72)	0.002	1.39 (1.10, 1.75)
History of			
Diabetes	1.32 (1.16, 1.50)	<0.001	1.32 (1.15, 1.51)
Hypertension	1.33 (1.15, 1.54)	<0.001	1.33 (1.14, 1.55)
CHF	1.39 (1.16, 1.68)	<0.001	1.40 (1.13, 1.73)
CAD	1.38 (1.17, 1.64)	<0.001	1.38 (1.15, 1.65)
High risk CAD	1.66 (1.20, 2.29)	0.02	1.67 (1.15, 2.38)
Cor Revasc, anytime	0.98 (0.78, 1.23)	0/842	0.98 (0.76 (1.24)
Cor Revasc, ≤ 6 months	0.57 (0.28, 1.16)	0.122	0.56 (0.22, 1.16)
Cardiac arrest	1.76 (0.96, 3.21)	0.067	1.76 (0.81, 3.14)
PVD	1.89 (1.58, 2.26)	<0.001	1.90 (1.56, 2.29)
Stroke	1.30 (1.08, 1.57)	0.006	1.31 (1.06, 1.60)
COPD	1.14 (0.96, 1.35)	0.145	1.14 (0.94, 1.35)
Cancer yes to any of: active Ca, surgery for Ca, mets	1.17 (1.004, 1.37)	0.044	1.17 (1.001, 1.37)
Preop clinical examination			
HR, every 10 bpm increase	1.10 (1.06, 1.14)	<0.001	1.10 (1.06, 1.15)
Systolic BP, every 10 mm Hg increase	1.01 (0.99, 1.03)	0.406	1.01 (0.98, 1.04)
Preop eGFR (ml/min)			
<30	7.62 (6.46, 8.98)	<0.001	7.70 (6.41, 9.22)
30-44	2.37 (1.96, 2.86)	<0.001	2.37 (1.92, 2.89)
45-59	1.70 (1.42, 2.02)	<0.001	1.70 (1.41, 2.03)
> 60	1.00	-	1.00
Type of Surgery			
Vascular	1.23 (0.82, 1.84)	0.315	1.23 (0.77, 1.86)
General	0.90 (0.63, 1.27)	0.541	0.90 (0.59, 1.29)
Thoracic	1.30 (0.80, 2.12)	0.289	1.30 (0.74, 2.10)
Major Uro/Gyn	1.03 (0.73, 1.46)	0.849	1.03 (0.69, 1.47)
Major Ortho	1.17 (0.82, 1.68)	0.381	1.18 (0.77, 1.69)
Major Neuro	1.23 (0.80, 1.89)	0.337	1.23 (0.75, 1.87)
Low risk surgeries	0.70 (0.50, 0.97)	0.032	0.70 (0.47, 0.98)
Urgent/emergent surgery	1.69 (1.46, 1.96)	<0.001	1.69 (1.44, 1.99)

* Obtained from 1,000 bootstrap samples: median, 2.5 and 97.5 percentiles.
Cor revasc: coronary revascularization, CHF: congestive heart failure, CAD: coronary artery disease, PVD: peripheral vascular disease, COPD: chronic obstructive pulmonary disease, Ca: cancer, HR: heart rate, BP: blood pressure, Ca: cancer, Mets: metastasis

Table 9. Sensitivity analyses of pre-operative predictors of MINS (peak TnT ≥0.03) at 30 days excluding eGFR from the model in Table 9.

n=14932 with no missing predictors, 1183 with MINS

	Model Derivation		Model Validation
	Adjusted HR (95% CI)	**p-value**	**Bootstrapped Adjusted HRs* (95% CI)**
Age (years)			
45-64	1.00	-	1.00
65-74	1.16 (0.98, 1.37)	0.078	1.16 (0.98, 1.37)
≥ 75	2.29 (1.97, 2.66)	<0.001	2.28 (1.97, 2.68)
Gender, females	0.73 (0.65, 0.83)	<0.001	0.73 (0.65, 0.83)
Current atrial fibrillation	1.24 (0.998, 1.53)	0.053	1.25 (0.96, 1.58)
History of			
Diabetes	1.44 (1.27, 1.64)	<0.001	1.44 (1.26, 1.64)
Hypertension	1.54 (1.34, 1.78)	<0.001	1.54 (1.33, 1.79)
CHF	1.89 (1.58, 2.27)	<0.001	1.90 (1.55, 2.30)
CAD	1.42 (1.19, 1.68)	<0.001	1.41 (1.18, 1.68)
High risk CAD	1.72 (1.25, 2.36)	<0.001	1.74 (1.20, 2.43)
Cor Revasc, anytime	1.06 (0.84, 1.32)	0.630	1.06 (0.83, 1.34)
Cor Revasc, ≤ 6 months	0.68 (0.34, 1.34)	0.263	0.67 (0.27, 1.42)
Cardiac arrest	1.56 (0.86, 2.85)	0.145	1.57 (0.70, 2.90)
PVD	2.15 (1.80, 2.57)	<0.001	2.17 (1.78, 2.62)
Stroke	1.36 (1.13, 1.64)	0.001	1.36 (1.11, 1.65)
COPD	1.11 (0.94, 1.31)	0.229	1.11 (0.93, 1.31)
Cancer yes to any of: active Ca, surgery for Ca, mets	1.15 (0.98, 1.34)	0.083	1.14 (0.98, 1.33)
Preop clinical examination			
HR, every 10 bpm increase	1.12 (1.08, 1.17)	<0.001	1.13 (1.08, 1.17)
Systolic BP, every 10 mmHg increase	1.00 (0.98, 1.03)	0.709	1.00 (0.98, 1.03)
Type of Surgery			
Vascular	1.24 (0.83, 1.85)	0.292	1.23 (0.79, 1.83)
General	1.08 (0.76, 1.52)	0.663	1.07 (0.74, 1.47)
Thoracic	1.31 (0.81, 2.10)	0.272	1.29 (0.76, 2.03)
Major	1.22 (0.87, 1.69)	0.246	1.21 (0.84, 1.64)
Urologic/Gynecologic	1.30 (0.91, 1.85)	0.151	1.29 (0.87, 1.79)
Major Orthopaedia	1.13 (0.74, 1.72)	0.568	1.12 (0.71, 1.65)
Major Neurology	0.76 (0.55, 1.05)	0.097	0.75 (0.52, 1.02)
Low risk surgeries			
Urgent/emergent surgery	1.79 (1.55, 2.07)	<0.001	1.80 (1.55, 2.09)

* Obtained from 10,000 bootstrap samples: median, 2.5 and 97.5 percentiles.

Cor revasc: coronary revascularization, CHF: congestive heart failure, CAD: coronary artery disease, PVD: peripheral vascular disease, COPD: chronic obstructive pulmonary disease, Ca: cancer, HR: heart rate, BP: blood pressure, Ca: cancer, Mets: metastasis

Table 10. Predictors of 30-day mortality in patients with MINS (peak TnT ≥0.04).

n=944 with 95 deaths.

	Patients n (%)	Adjusted OR (95% CI)	p-value	Bootstrapped Adjusted OR (95% CI)
Age (years)				
45-64 years	273 (28.9)	1.00	-	-
65-74 years	215 (22.8)	1.59 (0.77, 3.28)	0.214	1.61 (0.74, 3.59)
≥ 75 years	456 (48.3)	2.59 (1.41, 4.76)	0.002	2.64 (1.48, 5.41)
Gender, female	434 (46.0)	0.82 (0.51, 1.30)	0.387	0.82 (0.51, 1.32)
Peak TnT ≥0.30	156 (16.5)	1.50 (0.86, 2.62)	0.151	1.54 (0.82, 2.72)
Ischemic symptoms				
- chest discomfort	86 (9.1)	1.94 (1.01, 3.71)	0.046	1.98 (0.96, 3.77)
- neck/jaw/arm discomfort*	5 (0.5)	-	-	-
- dyspnea	68 (7.2)	0.98 (0.44, 2.19)	0.957	0.97 (0.38, 2.05)
- pulmonary edema	48 (5.1)	1.49 (0.62, 3.57)	0.374	1.44 (0.56, 3.17)
New Q waves	13 (1.3)	0.37 (0.04, 3.61)	0.393	0.29 (0.000, 2.21)
ST elevation	21 (2.2)	-	-	-
ST depression	154 (16.3)	0.72 (0.33, 1.61)	0.428	0.71 (0.27, 1.71)
T wave inversion	220 (23.3)	1.12 (0.54, 2.31)	0.768	1.11 (0.49, 2.26)
New LBBB	5 (0.5)	-	-	-
ST elevation and/or New LBBB	26 (2.8)	4.06 (1.45, 11.34)	0.008	4.21 (1.34, 12.50)
ECG Location				
- Anterior vs not	202 (21.4)	2.22 (1.14, 4.34)	0.020	2.23 (1.20, 4.30)
- Lateral vs not	186 (19.7)	1.59 (0.76, 3.34)	0.219	1.61 (0.71, 3.76)
- Inferior vs not	75 (7.9)	0.47 (0.17, 1.29)	0.141	0.44 (0.09, 1.22)
- Septal vs not	76 (8.1)	0.42 (0.16, 1.11)	0.081	0.40 (0.10, 1.05)
- Other* vs not	5 (0.5)	-	-	-

* No deaths occurred in patients with neck/jaw/arm discomfort and other ECG location. Therefore these variables have not been included in the logistic model.
Based on 10,000 bootstrap samples.
LBBB: left bundle branch block

Table 11. Model including only significant variables for developing the scoring system

	Number of Patients (%)	Adjusted OR (95% CI)	p-value
Age ≥ 75 years	456 (48.3)	2.08 (1.33 - 3.25)	0.001
ST elevation and/or new LBBB	26 (2.8)	3.61 (1.51, 8.63)	0.004
Anterior ECG change (vs not anterior)	202 (21.4)	2.36 (1.49 - 3.75)	<0.001

Hosmer-Lemeshow goodness-of-fit test, p=0.482 indicating no evidence of a lack of fit.

Table 12. Scoring System

Risk factor	Points
Age ≥ 75 years	2
ST elevation and/or new LBBB	3
Anterior ECG change	2

LBBB: left bundle branch block

Table 13. Total points determined by score and estimate of risk of 30-day mortality after non-cardiac surgery

Total Points	Estimate of risk of 30-day death, %
0	5.21
2	10.84
3	15.31
4	21.20
5	28.58
7	46.96

Table 14. Risk estimate using logistic formula directly

Risk factors	Points	Estimate of risk of 30-day death, %
None	0	5.21
Age ≥ 75	2	10.23
Anterior ECG change	2	11.48
ST elevation and/or new LBBB	3	16.53
Age ≥ 75 and Anterior ECG change	4	21.20
Age ≥ 75 and ST elevation and/or new LBBB	5	29.12
Anterior ECG change and ST elevation and/or new LBBB	5	31.86
Age ≥ 75, Anterior ECG change and ST elevation and/or new LBBB	7	49.24

Chapter 5

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

Perioperative myocardial ischemia is the most frequent perioperative cardiovascular complication. Unfortunately, most of these patients do not experience the typical symptoms or ECG abnormalities. Further, biochemical markers of cardiac damage are not routinely measured. Therefore, these ischemic syndromes are usually ignored, resulting in a short-term poor prognosis for many patients after surgery.

We developed and validated a new diagnosis with independent prognostic value at 30 days after surgery entitled **"Myocardial Injury after Non-cardiac Surgery" (MINS)**, based on the monitoring of a biochemical marker, i.e., TnT, after surgery.

We defined MINS as "myocardial cell injury caused by ischemia, which is the result of a perfusion imbalance between supply and demand, and has prognostic relevance and occurs during noncardiac surgery or within 30 days after noncardiac surgery." Our analyses established the diagnostic criteria for MINS as a TnT value ≥0.03 ng/mL.

MINS occured in 1 every 13 patients ≥45 years of age undergoing noncardiac surgery, and explained 1 of 3 deaths within 30 days after surgery. This suggest that for every 1000 adults undergoing noncardiac surgery, 80 will suffer MINS and of these patients, 8 will die within 30 days after the procedure.

We additionally developed a 7 points scoring system to predict mortality risk at 30 days in patients suffering MINS, through a simple ascertainment of only 3 clinical

variables (i.e., age and 2 ECG attributes).

The implications of these findings are extremely important and strongly support a routine monitoring of cardiac TnT during the early hours after noncardiac surgery.

Patients suffering MINS deserve consideration of more intensive monitoring and correction of abnormalities such as hypoxia, anemia, volume overload, tachycardia, and hypotension. Through these and other medical indications, postoperative complications of millions of patients will be reduced.

Clinical trials are, however, needed to address therapeutic interventions with more specific pharmacologic agents, (i.e., angiotensin-converting enzyme inhibitors, statins, beta-blockers, platelet $P2Y_{12}$ receptor inhibitors, and anticoagulants). In this regard, the upcoming MANAGE Trial will be the first attempt to recruit patients suffering MINS to address the indication of the direct thrombin inhibitor dabigatran versus placebo in addition to aspirin treatment.

Finally, my thesis work has laid the foundation for a new diagnostic entity that has potential to bring focus to this common problem with prognostic relevance. The identification of patients suffering MINS has enormous potential to help millions of patients worldwide on an anual basis.