VASCULAR EVENTS IN PATIENTS UNDERGOING NONCARDIAC SURGERY

By

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VASCULAR EVENTS IN PATIENTS UNDERGOING NONCARDIAC SURGERY

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ABSTRACT

For patients undergoing noncardiac surgery uncertainty exists about the current number of adult patients undergoing noncardiac surgery and their mortality rate, the current incidence of major vascular events, the optimal clinical risk estimation model for predicting major vascular events, whether screening troponin measurements after surgery can avoid underdiagnosing myocardial infarctions, and whether perioperative beta-blocker therapy can prevent major cardiovascular events. The original studies and the systematic review and meta-analysis in this thesis address these issues. Chapters 2 and 3 are narrative reviews of major cardiovascular events in patients undergoing noncardiac surgery, and these reviews provide an overview of the magnitude of the problem, the pathophysiology, methods to estimate and communicate risk, surveillance, and prevention. Chapter 4 uses data from the Canadian Institute for Health Information to inform the number of adult Canadians undergoing noncardiac surgery annually and the associated mortality. Chapter 5 reports data from a prospective cohort pilot study and offers insights into the current incidence of major vascular events and whether monitoring troponins after noncardiac surgery can assist physicians to avoid missing myocardial infarctions. Chapter 6 is a systematic review and meta-analysis that provides insights into whether perioperative beta-blockers can prevent major cardiovascular events in patients undergoing noncardiac surgery. Chapter 7 describes the rationale, design, and organization of an international randomized controlled trial we have initiated that is evaluating metoprolol versus placebo in patients undergoing noncardiac surgery.

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CONTRIBUTIONS BY OTHERS

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

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LIST OF ABBREVIATIONS

ACC/AHA	American College of Cardiology/American Heart Association
ACP	American College of Physicians
ASA	acetyl-salicylic acid
BPM	beats per minute
CABG	coronary artery bypass graft
CCP	Canadian Classification of Procedures
CK	creatine kinase
CI	confidence interval
CIHI	Canadian Institute for Health Information
CR	controlled release
DAD	Discharge Abstract Database
DIPOM	Diabetic Postoperative Mortality and Morbidity
ECG	electrocardiogram
ESEMC	External Safety and Efficacy and Monitoring Committee
ESC	European Society of Cardiology
MaVS	Metoprolol after Vascular Surgery
OR	odds ratio
PCI	percutaneous coronary intervention
RCT	randomized controlled trial
SBP	systolic blood pressure
VISION	Vascular events In noncardiac Surgery patIents cOhort evaluation

CHAPTER 1

Introduction

1.1 BACKGROUND

Throughout the last few decades, noncardiac surgery has made substantial advances in treating diseases (e.g., cancer) and improving patient quality of life (e.g., arthroplasty). As a result, the number of patients undergoing noncardiac surgery is growing worldwide,[1] and noncardiac surgery accounts for greater than 95% of all adult surgeries requiring hospital admission.[2]

Although 4 decades ago researchers identified perioperative vascular events in patients undergoing noncardiac surgery as a major population health issue, fundamental questions remain unanswered. For example, uncertainty exists about the current number of adult patients undergoing noncardiac surgery and their mortality rate, the current incidence of major perioperative vascular events, the optimal clinical risk estimation model for predicting major perioperative vascular events, whether screening troponin measurements after noncardiac surgery can avoid underdiagnosing myocardial infarctions, and whether perioperative beta-blocker therapy can prevent major cardiovascular events. My thesis provides insights into these issues.

1.2 OVERVIEW OF PERIOPERATIVE CARDIOVASCULAR MEDICINE

Chapters 2 and 3 provide an overview of perioperative cardiovascular medicine in patients undergoing noncardiac surgery. Chapter 2 reviews the magnitude of the

problem, the pathophysiology of these events, approaches to risk assessment, and communication of risk. Chapter 3 summarizes the evidence regarding monitoring strategies for perioperative myocardial infarction, proposes diagnostic criteria for perioperative myocardial infarction, and reviews the evidence for perioperative prophylactic cardiac interventions.

1.3 NONCARDIAC SURGERY IN CANADA: NATIONAL MORTALITY RATES

Little is known about the number of patients undergoing noncardiac surgery in Canada, their characteristics, and their in-hospital mortality rates. Chapter 4 informs these issues through use of hospital discharge data from the Canadian Institute for Health Information on all admissions of patients $\geq$ 18 years old who underwent noncardiac surgery with a length of stay $\geq$ 24 hours from April 1, 2000 until March 31, 2001 in all Canadian provinces except Quebec.

1.4 VASCULAR EVENTS IN PATIENTS UNDERGOING NONCARDIAC SURGERY

The increase in elderly patients undergoing noncardiac surgery, the change in the invasiveness of some surgical interventions, and the limitations of previous research (e.g., dated information, focus on select high-risk groups, small sample sizes),[3-9] contribute to uncertainty about the current incidence of major vascular events in patients undergoing noncardiac surgery. Further, uncertainty exists regarding the optimal clinical risk estimation model for predicting major perioperative vascular events. Previous risk

modeling studies were underpowered, the composite outcome in most studies did not include similarly important components, and most studies were conducted in a single university hospital.[3 5 9 10] There is promising but inconclusive evidence that troponin measurements after surgery may allow physicians to avoid missing myocardial infarctions and predict total mortality in the first year after surgery.[11] Chapter 5 is a prospective pilot study that provides insights into these issues and evaluates the feasibility of conducting a large definitive study.

1.5 PERIOPERATIVE BETA-BLOCKER THERAPY

Several authors and guideline committees have advocated the use of beta-blockers for patients undergoing noncardiac surgery.[12-15] However, other authors have questioned the robustness of the perioperative beta-blocker evidence and have advocated the need for a large definitive randomized controlled trial (RCT).[16 17] Accurate understanding of the strength of the perioperative beta-blocker evidence requires a systematic, comprehensive, and unbiased accumulation of the available evidence. Chapter 6 reports a systematic review and meta-analysis of the perioperative beta-blocker evidence in patients undergoing noncardiac surgery. Chapter 7 reports the rationale, design, and organization of an international RCT we have initiated that is evaluating metoprolol versus placebo in patients undergoing noncardiac surgery.

1.6 CONCLUSIONS AND FUTURE DIRECTIONS

Chapter 8 provides conclusions regarding my thesis work and outlines my research program based on this work.

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CHAPTER 2

Devereaux, PJ, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH. 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: 627-634.

PERIOPERATIVE CARDIAC EVENTS IN PATIENTS UNDERGOING NONCARDIAC SURGERY – THE MAGNITUDE OF THE PROBLEM, THE PATHOPHYSIOLOGY, AND METHODS TO ESTIMATE AND COMMUNICATE RISK: A REVIEW

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ABSTRACT

This is the first of 2 articles evaluating cardiac events in patients undergoing noncardiac surgery. In this article, we review the magnitude of the problem, the pathophysiology of these events, approaches to risk assessment, and communication of risk.

The number of patients undergoing noncardiac surgery worldwide is growing and annually 500,000 to 900,000 of these patients suffer a perioperative cardiac death, nonfatal myocardial infarction, or nonfatal cardiac arrest. Although the evidence is limited, a substantial proportion of fatal perioperative myocardial infarctions may not share the same pathophysiology as non-operative myocardial infarctions. A clearer understanding of the pathophysiology is needed to direct future research evaluating prophylactic, acute, and long-term interventions.

Researchers have developed tools to facilitate perioperative cardiac risk estimation. Studies suggest that the Lee index is the most accurate generic perioperative cardiac risk index. The limitations of the studies evaluating the ability of noninvasive cardiac tests to predict perioperative cardiac risk reveals considerable uncertainty as to the role of these popular tests. Similarly, there is uncertainty as to the predictive accuracy of the American College of Cardiology / American Heart Association algorithm for cardiac risk assessment.

Patients are likely to benefit from improved estimation and communication of cardiac risk because the majority of noncardiac surgeries are elective and accurate risk estimation is important to allow informed patient and physician decision-making.

INTRODUCTION

Throughout the last few decades, noncardiac surgery has made substantial advances in treating diseases (e.g., cancer) and improving patient quality of life (e.g., arthroplasty). As a result, the number of patients undergoing noncardiac surgery is growing worldwide.[1] However, such surgery is associated with significant cardiac morbidity, mortality, and consequent cost.

This is the first of 2 articles evaluating perioperative cardiac events in patients undergoing noncardiac surgery. In this article, we review the magnitude of the problem, the pathophysiology of these events, approaches to perioperative risk assessment, and the communication of risk. In the second article, we will present evidence regarding monitoring strategies for perioperative myocardial infarction, propose diagnostic criteria for perioperative myocardial infarction, and review the evidence for perioperative prophylactic cardiac interventions.

The breadth of these topics covered in this article prohibited a fully systematic approach to this review. Although this is a narrative review, we did conduct thorough literature searches in each area and contacted the authors of relevant articles when necessary. We sought relevant systematic reviews and have highlighted their findings in our discussion. Our methods and attempt to focus on systematic reviews distinguishes our review from several others,[2-4] which may explain why we often reached different conclusions

MAJOR PERIOPERATIVE CARDIAC EVENTS

Patients undergoing noncardiac surgery are at risk of major perioperative cardiac events (i.e., cardiac death, nonfatal myocardial infarction, and nonfatal cardiac arrest). Patients suffering a myocardial infarction after noncardiac surgery have a hospital mortality rate of 15-25%,[5-8] and nonfatal perioperative myocardial infarction is an independent risk factor for cardiovascular death and nonfatal myocardial infarction during the 6 months following surgery (hazard ratio = 18; 95% CI 6 to 57).[9] Patients suffering a cardiac arrest after noncardiac surgery have a hospital mortality rate of 65%,[10] and nonfatal perioperative cardiac arrest is a risk factor for cardiac death during the 5 years following surgery.[11]

What is the Magnitude of Risk of Major Perioperative Cardiac Events?

Table 1 presents the proportion of patients undergoing noncardiac surgery suffering a cardiac death, nonfatal myocardial infarction, and nonfatal cardiac arrest in prospective cohort studies with sample sizes greater than 300 patients that were not restricted to a specific type of surgery (e.g., vascular surgery), and that required patients to have at least one measurement of a cardiac enzyme or biomarkers after surgery.[5-8 12-14] We included only studies that required such measurement after surgery because perioperative myocardial infarctions occur primarily during the first 3 days after surgery,[7 15] a period when the majority of patients are receiving narcotic therapy and therefore may not experience cardiac signs or symptoms during their myocardial infarction.[6 7 16]

The pooled results from the studies evaluating noncardiac surgery patients who had or were at risk of cardiac disease suggest that 3.9% (95% CI 3.3 - 4.6%) of these patients suffer major perioperative cardiac events. The study by Lee and colleagues is the only study in Table 1 that included relatively unselected patients (i.e., it was not limited to patients referred to a medical consult service or to patients with or at risk of coronary artery disease).[14] This study suggests that major perioperative cardiac events occur in 1.4% (95% CI 1.0-1.8%) of adults $\geq$ 50 years of age undergoing elective noncardiac surgery requiring hospital admission.

There are a number of reasons why the time frame of the studies reported in Table 1 – most were conducted over one decade ago - limit their ability to inform us about the current incidence of major perioperative cardiac events. First, patients with coronary artery disease are living longer as a result of major medical advances.[17] Therefore, patients with high burdens of coronary artery disease are now surviving long enough for other conditions to develop that require surgical consideration, including cancer and severe osteoarthritis of the hip and knee. Second, there has been a shift in practice patterns toward advanced medical care (including surgery) for elderly patients. Third, some surgical interventions have become less invasive.

Despite these limitations, results from the study by Lee and colleagues likely represent a conservative estimate of the current incidence of major perioperative cardiac events among unselected adults undergoing noncardiac surgery that requires hospital admission. We say conservative estimate because of the authors' exclusion of emergent surgical cases and the increasing numbers of elderly patients undergoing noncardiac surgery

today. Emergency cases represent about 10% of noncardiac surgeries,[18] and patients undergoing emergent surgeries are at higher risk of major perioperative cardiac events than patients undergoing elective surgery (OR=2.6, 95% CI 1.2 to 5.6).[8]

Approximately 100 million adults worldwide undergo noncardiac surgery annually.[1] Conservative assumptions suggest that half of these patients are in an at-risk age group and that the results from the study by Lee and colleagues reflects their cardiac risk. Therefore, each year it is likely that 500,000 to 900,000 patients worldwide suffer a perioperative cardiac death, nonfatal myocardial infarction, or nonfatal primary cardiac arrest. This problem is important because of the burden of illness it represents and the health resources it consumes; perioperative cardiac complications prolong hospital stays by a mean of 11 days (95% CI 9-12 days).[15]

PATHOPHYSIOLOGY OF PERIOPERATIVE CARDIAC OUTCOMES

Perioperative Cardiac Death

The 5 studies in Table 1 reported 41 cardiac deaths. The authors attributed the etiology of cardiac death to myocardial infarction in 66% of the cases and arrhythmia or heart failure in 34% of the cases. However, none of these studies reported formal criteria to establish the underlying causes of cardiac death or determined intra-rater reliability.[5-8] [13] In addition, it is unclear whether ischemia, arrhythmia, or a preexisting cardiomyopathy caused heart failure that resulted in death. Further well-designed studies

are needed to determine accurately the frequency with which these events cause perioperative cardiac death and to elucidate other etiologies.

Perioperative Cardiac Arrest

We identified only 1 study that has evaluated the etiology of cardiac arrest in patients undergoing noncardiac surgery.[10] This study by Sprung and colleagues evaluated 223 perioperative cardiac arrests that occurred between the start of anesthesia and discharge from the recovery room in patients undergoing noncardiac surgery at a single centre from 1990 to 2000. A committee of staff anesthesiologists, anesthesia chief residents, certified nurse anesthetists, and recovery room nurses reviewed all cases and judged the probable cause of each cardiac arrest. The dominant etiologies of perioperative cardiac arrest were cardiac causes (e.g., myocardial infarction) and bleeding (Table 2). Confidence in these conclusions will require a multicentre study including all cardiac arrests that occur in the postoperative period (i.e., from the start of surgery to 30 days post surgery).

Perioperative Myocardial Infarction

Arterial thrombosis constitutes the underlying pathophysiology in the majority of non-operative myocardial infarctions.[19] Between 64-100% of patients with non-operative myocardial infarctions have coronary artery plaque fissuring [20,21] and 65-95% have an acute luminal thrombus.[21-25] The pathophysiology underlying myocardial infarctions in the operative setting is less clear.

Coronary Pathology of Patients with Fatal Perioperative Myocardial Infarctions

Two retrospective autopsy studies have evaluated the coronary arteries of patients who have undergone noncardiac surgery and suffered a fatal myocardial infarction.[26 27] The first study evaluated 42 patients,[26] and the second study evaluated 26 patients.[27] Approximately 66% of the patients in each of these studies had left main (defined as a > 50% cross sectional narrowing) or three vessel coronary artery disease. In contrast to the non-operative infarction, the first operative study demonstrated that only 7% of the patients had coronary artery plaque fissuring and 28% (study one)[26] and 35% (study two)[27] of the patients had an acute luminal thrombus.

Preoperative Coronary Angiography and Perioperative Myocardial Infarction

Ellis and colleagues used a prospective angiographic database at the Cleveland Clinic to identify 1242 patients who, between 1984 and 1991, underwent preoperative coronary angiography within 6 months – but in a mean of 5 days - of vascular surgery.[28] Personnel blinded to the clinical status analyzed the angiograms. Of 21 patients who suffered a perioperative myocardial infarction, 6 were fatal. In 38% of the patients suffering a myocardial infarction, this event was possibly related to suboptimal collaterals beyond a total occlusion. Not a single event was related to a previously noted high-grade subtotal stenosis.[28]

Interpretation of the Coronary Pathology and Angiography Data

The two coronary pathology studies suggest that a majority of patients who suffer a fatal perioperative myocardial infarction have significant left main or 3 vessel coronary artery disease.[26 27] These data also suggest a substantial proportion of fatal perioperative myocardial infarctions are not associated with plaque fissuring or acute coronary artery thrombosis, but rather these events may result from an increase in oxygen demand in the setting of fixed coronary artery stenoses.[29] The results of the coronary angiography study, however, suggest that a majority of nonfatal perioperative myocardial infarctions occur in arteries without high grade stenoses suggesting that these events may result from plaque fissuring and acute coronary artery thrombosis.[28] Future therapeutic trials would benefit from further research to establish clearly the pathophysiology of fatal and nonfatal perioperative myocardial infarctions. As was the case with non-operative myocardial infarctions,[30 31] this area of investigation would gain important insights from a study in which all patients suffering a perioperative myocardial infarction underwent acute coronary angiography.

Triggers of Perioperative Myocardial Infarction

Surgery, with its associated trauma, anesthesia and analgesia, intubation and extubation, pain, hypothermia, bleeding and anemia, and fasting is analogous to an extreme stress test. Figure 1 demonstrates how these factors initiate inflammatory, hypercoagulable, hypoxic, and stress states that are associated with perioperative elevations in troponin levels, arterial thrombosis, and mortality.[32-37]

The stress state involves increased levels of catecholamines (i.e., epinephrine and norepinephrine) and cortisol. Perioperative catecholamine and cortisol levels increase with general anesthesia, anesthetic reversal, extubation, increasing pain scores, increasing grades of surgical trauma, anemia, fasting, and hypothermia.[38-43] Increased stress hormone levels result in an increase in blood pressure, heart rate, coronary sheer stress, relative insulin resistance, and free fatty acid levels.[35 43 44] These factors increase oxygen demand and can result in perioperative myocardial ischemia, which is strongly associated with perioperative myocardial infarction.[13 45 46] Coronary sheer stress may trigger plaque fissuring and acute coronary thrombosis.[43]

Factors that can initiate an hypoxic state include anemia, hypothermia (through shivering), and anesthesia and analgesia (through suppression of breathing).[47-49] Perioperative hypoxia can result in myocardial ischemia in the setting of a hemodynamically significant coronary stenosis. Increasing grades of surgical trauma and general anesthesia can initiate a hypercoagulable and inflammatory state.[33 50-53] The hypercoagulable state involves increases in plasminogen activator inhibitor -1 (PAI-1), factor VIII, and platelet reactivity, as well as decreases in antithrombin – III; all these factors can lead to acute coronary thrombosis.[33 54 55] The inflammatory state involves increases in tumor necrosis factor α (TNF-α), interleukin (IL)-1, IL-6, and C-reactive protein (CRP), and these factors may have a direct role in initiating plaque fissuring and acute coronary thrombosis.[52 56-58]

Further research is needed to evaluate the independence of these potential triggers and to assess other potential triggers. To determine if suppression of these triggers will prevent perioperative myocardial infarctions will require large randomized trials.

PREOPERATIVE CARDIAC RISK ASSESSMENT

Is There a Need for Preoperative Cardiac Risk Assessment?

Although no research has documented its benefits, preoperative cardiac risk assessment may serve an important function. The majority of noncardiac surgeries are elective procedures, and an accurate estimate of risk facilitates informed patient and physician decision-making. For example, if an elderly female with multiple risk factors undergoing hip arthroplasty for osteoarthritis was accurately informed that her risk of a major perioperative cardiac event was 10-12%, she might decide to live with her suboptimal quality of life until her grand-daughter graduates in 1 year, and then undergo surgery. Further, accurate risk estimates provide guidance for perioperative management, including the choice of surgical techniques and the location and intensity of post-operative care.

Clinical Risk Indices to Predict Perioperative Cardiac Risk

Two types of clinical indices- generic and Bayesian – exist to estimate the risk of a perioperative cardiac event in patients undergoing noncardiac surgery. The various published generic risk indices (Goldman, Larsen, Lee, and Gilbert Indices) estimate a patient's risk through determination of how many predictors of risk (e.g., history of angina, diabetes, emergent surgery) an individual patient has.[14 59-61] The published Bayesian risk indices (Detsky and Kumar Indices) modify the hospital's average cardiac

event rate for a specific surgery (pretest probability) through use of a patient's individual index score (likelihood ratio), which is based upon how many predictors of risk (e.g., history of angina, diabetes) an individual patient has; this results in an estimate of the patient's risk of a perioperative cardiac event (posttest probability).[8 12]

Although several studies have compared the predictive accuracy of the generic and Bayesian risk indices[8 12 14 61 62] only 2 have used contemporary pretest probabilities based on data from the hospitals studied at that time.[8 12] These 2 studies demonstrated superior prediction capabilities of the Bayesian risk indices.[8 12] While these studies fulfill the methodological criteria of a clinical prediction rule study[63] it is only the Detsky index that has shown consistent results in a separate setting, although this validation is limited to one high quality single centre study.[8] Despite this research, the current predictive accuracy of the Detsky index is uncertain because there is no high quality study that has established contemporary complication rates for individual surgeries, and it is unknown if contemporary complication rates at one institution are applicable to another institution. Because of the limitations of the available data (e.g., most studies have occurred in single university hospitals, most have not focused on composite outcomes with more-or-less equally important components), determining the optimal risk index to predict major perioperative cardiac events will require a multicenter study including a large number of university and non-university hospitals.

Until more definitive research becomes available, clinicians require a practical clinical risk index to facilitate perioperative cardiac risk estimation. The Lee index is the best validated and most accurate predictive generic risk index, and it is simple to use in

clinical practice.[14] It consists of 6 equally weighted cardiovascular risk factors: high-risk surgery (intraperitoneal, intrathoracic, or suprainguinal vascular surgery), history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease (i.e., stroke or transient ischemic attack), use of insulin therapy for diabetes, and a preoperative serum creatinine > 175 μmol/L (> 2.0 mg/dl). Table 3 presents the estimated risk of a major perioperative cardiac event (i.e., cardiac death, nonfatal myocardial infarction, and nonfatal cardiac arrest) and the corresponding 95% confidence intervals, based on the number of risk factors met. Although there are many positive aspects of the Lee index, the study that derived and validated it had limitations (it excluded emergent surgeries and surgical cases with an expected length of stay < 2 days during the years 1989 to 1994).

Noninvasive Cardiac Testing to Predict Perioperative Cardiac Risk

Table 4 presents the results from a recent meta-analysis that evaluated the prognostic accuracy of 6 noninvasive cardiac tests for predicting perioperative cardiac death or nonfatal myocardial infarction in patients undergoing vascular surgery.[64] The results suggested a trend towards superior prognostic accuracy with dobutamine stress echocardiography compared to the other tests, but this trend was statistically significant only in comparison with myocardial perfusion scintigraphy. These results warrant cautious interpretation for the following reasons: a majority of studies used weak methods (e.g., retrospective design, failure to blind individuals interpreting the test results to the clinical predictors of risk, and failure to blind the outcome assessors to the test results); the cumulative event

rate for most noninvasive cardiac tests was low; there was significant heterogeneity across study results for individual tests; and test results were analyzed using a single threshold (i.e., results were dichotomized as test positive or test negative).

The relevance of this last limitation is highlighted in another recent meta-analysis that evaluated semiquantitative dipyridamole myocardial stress perfusion imaging for predicting perioperative cardiac death or nonfatal myocardial infarction in patients undergoing vascular surgery.[65] This meta-analysis included 9 studies evaluating 1179 patients, of whom 82 suffered a cardiac death or nonfatal myocardial infarction. Rather than considering test results as positive or negative, variation in the likelihood ratios were demonstrated based on the extent of reversible myocardial defects (Table 5). In the setting of a diagnostic study, many individuals would not consider variations in likelihood ratios from 0.42 to 2.9 of much relevance. In evaluating prognostic information, however, a patient or physician may value the ability to distinguish between a perioperative risk of a major cardiovascular outcome of 3%, 7%, or 18%, so to them the test and its results are relevant (Table 5). Narrowing the confidence intervals for these results, and determining more precisely the number of patients who are likely to have the various proportions of reversible myocardial defects, will require further high-quality research.

The limitations of the studies evaluating the ability of noninvasive cardiac tests to predict perioperative cardiac risk leaves considerable uncertainty concerning the role of these popular tests prior to noncardiac surgery. Until investigators undertake further research, some physicians may want to consider noninvasive cardiac testing in patients

who have severe exercise restrictions (e.g., patients with severe claudication) that limit the clinical assessment of symptoms suggestive of coronary artery disease.

When considering what noninvasive cardiac test to recommend, physicians may want to consider the following: the results of the relevant meta-analyses, and their limitations; the uncertain utility of noninvasive tests in patients undergoing nonvascular noncardiac surgery; what tests and expertise are available at their hospital; what test a patient can undertake (e.g., patients with severe claudication are unlikely to complete an exercise electrocardiographic stress test); and the likelihood of an important change in risk estimation (e.g., physicians using the Lee index should use a noninvasive test to refine the risk estimate only if the refined risk estimate, based on the potential test results, would be interpreted by the patient or physician as important). To illustrate the last point, if the results of the meta-analysis evaluating semiquantitative dipyridamole myocardial stress perfusion imaging in vascular surgery patients (Table 5) are applicable to other types of surgery, use of this test in patients undergoing nonvascular noncardiac surgery with no risk factors on the Lee index (i.e., a risk estimate of 0.4% [Table 3]) may result in a refined risk estimate <0.01 or 5%; for patients with 3 risk factors on the Lee index (i.e., a risk estimate of 5.4% [Table 3]), the refined risk estimate may be 2% or 14%.

The American College of Cardiology/American Heart Association (ACC/AHA) Preoperative Cardiac Assessment Algorithm

Some authors have advocated physicians use the ACC/AHA cardiac assessment algorithm to risk stratify patients undergoing noncardiac surgery.[66 67] This algorithm was

not derived from a prospective study; rather, it was derived from the interpretation of data from various studies and the judgements of the committee members.[68] The few studies that have evaluated the reliability of the ACC/AHA risk stratifying algorithm are limited for the following reasons: these studies have had few events; they have failed to demonstrate that the algorithm is effective in stratifying cardiac risk across the three strata proposed in the algorithm; and they did not compare the predictive accuracy of the ACC/AHA algorithm with the most accurate clinical risk indices (i.e., the Lee and Detsky indices) .[69 70] The recommendations regarding noninvasive testing in the ACC/AHA algorithm ignore the issue of patient and physician values. Noninvasive testing is relevant only if patients or physicians would value the potential magnitude of changes in predicted risk.

How do Clinicians Define and Communicate Perioperative Cardiac Risk?

A recent survey of 104 general internists who completed an average of 17 preoperative consults a month provides insights into how physicians communicate and define perioperative cardiac risk.[71] Of the respondents, 96% indicated that they informed patients of their perioperative cardiac risk, but 77% of these respondents indicated that they communicated the risk subjectively (i.e., simply telling patients that they were at low, moderate, or high risk). When asked what they meant by low, moderate, and high perioperative cardiac risk respondents provided 8, 27, and 12 different definitions, respectively. The range of definitions demonstrated marked variability from <1% to <20%

for low risk, 1% to 50% for moderate risk, and >2% to >50% for high risk of a perioperative cardiac event.

Given the marked variability in definitions of low, moderate, and high risk among general internists who perform a high volume of preoperative consultations, physicians should avoid these terms to prevent misunderstandings. Options for physicians include telling patients and surgeons the percentage risk of cardiac death, nonfatal myocardial infarction, or nonfatal cardiac arrest or the expected event rate among 100 or 1000 similar patients. Given the uncertainty around the risk estimation data, physicians may also want to present the range of risk consistent with the 95% confidence interval. For example, a 50 year old man receiving insulin therapy undergoing a bowel resection would have 2 risk factors according to the Lee index (Table 3); a consultant could convey to the patient and surgeon that the patient's risk of cardiac death, nonfatal myocardial infarction, or nonfatal cardiac arrest is in the range of 1.5 to 3.5%.

CONCLUSION

Noncardiac surgery is associated with substantial cardiac mortality, morbidity, and consequent cost. Perioperative myocardial infarctions likely result from triggers that initiate inflammatory, hypercoagulable, hypoxic, and stress states. Because the majority of noncardiac surgeries are elective, accurate perioperative cardiac risk estimation is important to allow informed patient and physician decision-making. The Lee index is a practical clinical risk index that physicians can use to facilitate perioperative cardiac risk estimation. There is significant uncertainty regarding the predictive accuracy of preoperative

noninvasive cardiac tests and the ACC/AHA cardiac assessment algorithm. Physicians informing patients or surgeons about a patient's perioperative cardiac risk should provide specific risk estimates and avoid assumptions associated with subjective classifications of risk.

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CONTRIBUTORSHIP STATEMENT

P.J. Devereaux originated the idea for this paper and brought together all the authors to formulate and debate the points included in the text. He contributed significantly to the design of this manuscript. He undertook data acquisition, data analysis, interpretation of the data, wrote the first draft of the manuscript, and provided critical revisions to the manuscript.

Lee Goldman contributed significantly to the manuscript's design, data acquisition, interpretation of the data, and provided critical revisions to the manuscript.

Deborah Cook contributed significantly to the manuscript's design, interpretation of the data, and provided critical revisions to the manuscript.

Ken Gilbert contributed significantly to the manuscript's design, interpretation of the data, and provided critical revisions to the manuscript.

Kate Leslie contributed significantly to the manuscript's design, interpretation of the data, and provided critical revisions to the manuscript.

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Table 1: Major Perioperative Cardiac Outcomes

Study	Country	Patient population	Enrolment years	N	Cardiac death	Myocardial infarction*	Cardiac arrest	Major cardiac outcome
Studies evaluating noncardiac surgery patients with or at risk of cardiac disease								
Detsky[12]	Canada	Consecutive patients age > 40 who were evaluated by a general medical service for perioperative cardiac risk	1983-1985	455	11 (2.4%)	14 (3.1%)	0	25 (5.5%)
Shah[5]	US	Consecutive patients age > 70 who had cardiac disease	1986-1987	688	15 (2.2%)	32 (4.7%)	NA	40 (5.8%)
Mangano[13]	US	Consecutive men with CAD or 2 risk factors for CAD, patients undergoing non-elective surgery were excluded	1987-1988	474	6 (1.3%)	12 (2.5%)	NR	13 (2.7%)
Ashton[6]	US	Consecutive men age ≥ 40 with CAD, cerebral or peripheral atherosclerosis, or risk factors for CAD, patients undergoing emergent surgery were excluded	1987-1989	835	9 (1.1%)	15 (1.8%)	NA	20 (2.4%)
Badner[7]	Canada	Consecutive patients age ≥ 50 with CAD	1993-1996	323	3 (0.9%)	18 (5.6%)	0	18 (5.6%)
Kumar[8]	US	Patients with known or suspected CAD	1992-1995	1121	8 (0.7%)	31 (2.8%)	7 (0.6%)	36 (3.2%)
Totals (mean)				3896	52 (1.3%)	122 (3.1%)	7 (0.2%)	152 (3.9%)

Study	Country	Patient population	Enrolment years	N	Cardiac death	Myocardial infarction*	Cardiac arrest	Major cardiac outcome
Study evaluating relatively unselected noncardiac surgery patients								
Lee[14]	US	Patients age $\geq$ 50 with an expected postoperative length of stay $\geq$ 48 hrs, patients undergoing emergent surgery were excluded	1989-1994	4315	12 (0.3%)	46 (1.1%)	16 (0.4%)	59 (1.4%)

*** - various definitions of myocardial infarction were used across studies and this may account for some of the variation in event rates**

Major cardiac outcomes = composite of cardiac death, nonfatal myocardial infarction, and nonfatal cardiac arrest
US = United States
CAD = coronary artery disease
NA = Author contacted but unable to provide data
NR = Not reported

Table 2: Probable Causes of Perioperative Cardiac Arrest

Probable Cause	N	% (95% CI)
Bleeding	78	35% (29-42%)
Cardiac	98	44% (37-51%)
Other	47	21% (16-27%)

Cardiac = myocardial infarction, high-degree block, or dysrhythmias due to any etiology such as electrolyte abnormalities and medication related asystole

Other = pulmonary emboli (thromboembolism, air, fat, or carbon dioxide embolism), anaphylactic drug reactions, and hypoxia (e.g., upper airway obstruction, unrecognized tracheal extubation)

Table 3: Perioperative Cardiac Risk Estimation

Number of risk factors	Percentage risk of patients suffering a major perioperative cardiac event	95% CI
0	0.4%	0.1-0.8%
1	1.0%	0.5-1.4%
2	2.4%	1.3-3.5%
>3	5.4%	2.8%-7.9%

Risk factors = high-risk surgery (intraperitoneal, intrathoracic, or suprainguinal vascular surgery), history of ischemic heart disease (defined as a history of myocardial infarction, positive exercise test, current complaint of ischemic chest pain or nitrate use, or ECG with pathological Q waves; patients with prior coronary bypass surgery or angioplasty were included only if they had such findings after their procedure), history of congestive heart failure (defined as a history of heart failure, pulmonary edema, or paroxysmal nocturnal dyspnea; an S3 gallop or bilateral rales on physical examination; or a chest radiograph showing pulmonary vascular resistance), history of cerebrovascular disease (i.e, stroke or transient ischemic attack), use of insulin therapy for diabetes, and a preoperative serum creatinine > 175 μmol/L (> 2.0 mg/dl)

Major perioperative cardiac event = cardiac death, nonfatal myocardial infarction, or nonfatal cardiac arrest; note that this table does not include postoperative cardiogenic pulmonary edema and complete heart block, which were included as outcomes in the Lee index

Table 4: Predictive Capabilities of Noninvasive Cardiac Tests in Patients Undergoing Noncardiac Surgery

Test	No. of studies	No. of patients	No. of events	Sensitivity (95% CI)	Specificity (95% CI)
radionuclide ventriculography	8	532	54	50% (32-69%)	91% (87-96%)
ambulatory electrocardiography	8	893	52	52% (21-84%)	70% (57-83%)
exercise electrocardiography	7	685	25	74% (60-88%)	69% (60-78%)
myocardial perfusion scintigraphy	23	3119	207	83% (77-89%)	49% (41-57%)
dobutamine stress echocardiography	8	1877	82	85% (74-97%)	70% (62-79%)
dipyridamole stress echocardiography	4	850	33	74% (53-94%)	86% (80-93%)

This table has been modified, with permission, from the original, which appeared in reference 64 (Kertai MD, Boersma E, Bax JJ, Heijenbrok-Kal MH, Hunink MG, L'Talien G J, et al. A meta-analysis comparing the prognostic accuracy of six diagnostic tests for predicting perioperative cardiac risk in patients undergoing major vascular surgery. *Heart* 2003;89(11):1327-34.) © BMJ Publishing Group Ltd. And British Cardiac Society.

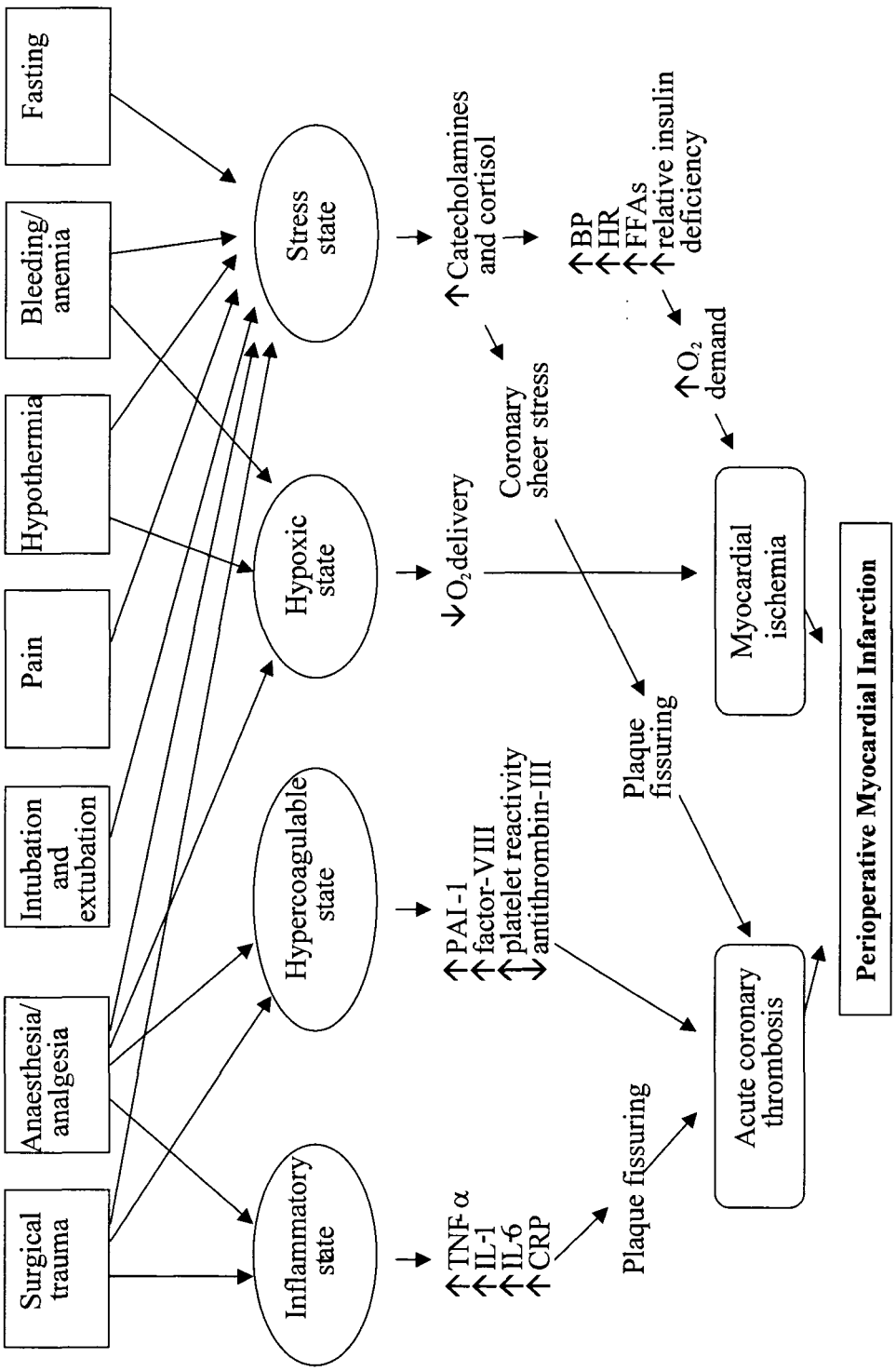
Table 5: Likelihood Ratios Associated with Dipyridamole Myocardial Stress Perfusion Imaging for Perioperative Cardiac Risk Assessment

Extent of reversibility	Likelihood ratio (95% CI)	Posttest probability* of event (95% CI)	Percentage of scans with this result
No defects	0.42 (0.20-0.88)	3 (1-6)	30%
Fixed defects only	0.51 (0.24-1.1)	4 (2-8)	30%
Reversibility < 20%	1.3 (0.88-1.9)	9 (6-13)	17%
Reversibility 20-29%	1.6 (1.0-2.6)	11 (7-16)	11%
Reversibility 30-39%	2.9 (1.6-5.1)	18 (11-28)	6%
Reversibility 40-49%	2.9 (1.4-6.2)	18 (10-32)	3%
Reversibility ≥ 50%	11 (5.8-20)	45 (30-60)	3%

This table has been modified, with permission, from the original, which appeared in reference 65 (Etchells E, Meade M, Tomlinson G, Cook D. Semiquantitative dipyridamole myocardial stress perfusion imaging for cardiac risk assessment before noncardiac vascular surgery: a meta-analysis. *J Vasc Surg* 2002;36(3):534-40.) © 2002, with permission from The Society of Vascular Surgery.

* = Assumption of pretest probability of 7% based on mean event rate across all studies in the meta-analysis

Event = cardiac death or nonfatal myocardial infarction



Legend

Figure 1: Potential Triggers and States Leading to Perioperative Myocardial Infarction

TNF-α = tumor necrosis factor α, IL-1 = interleukin-1, IL-6 = interleukin-6, CRP = C-reactive protein, PAI-1 = plasminogen activator inhibitor -1, O_2 = oxygen, BP = blood pressure, HR = heart rate, FFAs = free fatty acids

CHAPTER 3

Devereaux PJ, Goldman L, Yusuf S, Gilbert K, Leslie K, Guyatt GH. Surveillance and prevention of major perioperative ischemic cardiac events in patients undergoing noncardiac surgery: A review. CMAJ. 2005; 173: 779-788.

SURVEILLANCE AND PREVENTION OF MAJOR PERIOPERATIVE ISCHEMIC CARDIAC EVENTS IN PATIENTS UNDERGOING NONCARDIAC SURGERY: A REVIEW

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ABSTRACT

This is the second of 2 articles evaluating cardiac events in patients undergoing noncardiac surgery. Unrecognized myocardial infarctions are common, and up to 50% of perioperative myocardial infarctions may go unrecognized if physicians rely only on clinical symptoms and signs. In this article, we summarize the evidence regarding monitoring strategies for perioperative myocardial infarction in patients undergoing noncardiac surgery. Perioperative troponin measurements and 12 lead electrocardiograms can detect clinically silent myocardial infarctions and provide independent prognostic information.

Currently, there are no standard diagnostic criteria for perioperative myocardial infarction in patients undergoing noncardiac surgery. We propose diagnostic criteria that reflect the unique features of perioperative myocardial infarctions.

Finally, we review the evidence for perioperative prophylactic cardiac interventions. There is encouraging evidence that some perioperative interventions (e.g., beta-blockers, alpha-2 agonists, statins) may prevent major cardiac ischemic events, but firm conclusions await the results of large definitive trials. The best evidence does not support a management strategy of preoperative coronary revascularization prior to noncardiac surgery.

INTRODUCTION

This is the second of 2 articles in which we evaluate cardiac events in patients undergoing noncardiac surgery. In the first article, we established that patients undergoing noncardiac surgery frequently suffer major perioperative cardiac events (i.e., cardiac death, nonfatal myocardial infarction, and nonfatal cardiac arrest).[1] We discussed the still unresolved pathophysiology of these events and suggested strategies for preoperative cardiac risk assessment and communication of risk. In this article, we summarize the evidence regarding monitoring strategies for perioperative myocardial infarction, propose diagnostic criteria for perioperative myocardial infarction, and review the evidence for perioperative prophylactic cardiac interventions.

The breadth of the topics covered in this article prohibits a fully systematic approach to this review. Although this is a narrative review, we did conduct thorough literature searches in each area and contacted the authors of relevant studies when necessary. We sought relevant systematic reviews and have highlighted their findings in our discussion.

THE DIFFICULTY IN DETECTING PERIOPERATIVE MYOCARDIAL INFARCTIONS

Unrecognized myocardial infarction is not restricted to the perioperative setting.[2] Eight large (i.e., sample sizes over 1000 patients) cohort studies, which were not confined to patients undergoing surgery (e.g., Framingham Study), have evaluated the frequency of unrecognized myocardial infarction in more than 65,000 people,[3-10] based upon the

new appearance of diagnostic Q waves (typically ≥ 30 milliseconds in 2 or more anatomically adjacent leads). In these studies 3237 myocardial infarctions occurred, of which 945 (29%; 95% CI 28-31%) were not detected at the time of the event. These myocardial infarctions were not benign; patients suffering an unrecognized myocardial infarction have a similar prognosis to patients suffering a recognized myocardial infarction.[11]

To estimate the frequency of perioperative clinically-unrecognized myocardial infarction, we evaluated all prospective noncardiac surgery cohort studies that fulfilled the following criteria: sample size greater than 300 patients; not restricted to a specific type of surgery (e.g., vascular surgery); at least one measurement of a cardiac enzyme or biomarker after surgery; and an accounting of the patients suffering a perioperative myocardial infarction who had no clinical symptoms or signs suggestive of a myocardial infarction (Table 1).[12-14] The pooled results from the 3 eligible studies suggest that only 14% (95% CI 3-25%) of patients suffering a perioperative myocardial infarction will experience chest pain and only 53% (95% CI 38-68%) will experience a clinical symptom or sign that may trigger a physician to consider a myocardial infarction.

Although the number of events is small, the large proportion of clinically unrecognized myocardial infarcts is plausible. First, the majority of perioperative myocardial infarctions occur during the first 3 days post surgery,[14 15] a period when most patients receive analgesics (e.g., narcotics), which can blunt cardiac pain perception. Second, a small but high-risk group of surgical patients will remain intubated and sedated during the highest risk period, limiting their ability to communicate symptoms. Third,

surgical patients experiencing potential symptoms (e.g., shortness of breath, nausea) or signs (e.g., hypotension, tachycardia) of myocardial infarction have a host of more common potential explanations (e.g., atelectasis, pneumonia, hypovolemia, bleeding, medication side effect), and physicians may therefore not consider myocardial infarction.

DIAGNOSING MYOCARDIAL INFARCTION IN PATIENTS UNDERGOING NONCARDIAC SURGERY

Currently, there are no standard diagnostic criteria for myocardial infarction in patients undergoing noncardiac surgery. Optimal diagnostic criteria must consider the unique features of perioperative myocardial infarctions, in particular that a large proportion are clinically silent. We propose diagnostic criteria for perioperative myocardial infarction based upon an adaptation of the recent joint European Society of Cardiology (ESC) / American College of Cardiology (ACC) consensus for the redefinition of non-perioperative myocardial infarction (Table 4).[16]

The first of our criteria requires 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 level (e.g., pulmonary embolism) or – only if troponin measurement is unavailable – a rapid rise and fall of CK-MB. We encourage physicians to use troponin measurement, because perioperative CK-MB measurements are prone to false-positive and false-negative values. Surgical trauma can result in the release of CK-MB from skeletal muscle and a false-positive CK-MB value for myocardial infarction.[17-19] A substantial proportion of perioperative myocardial

infarctions occur in the first 2 days after surgery when serum CK values are high secondary to surgical trauma. These high CK values can result in a low, and thus false-negative, ratio of CK-MB to total CK.[19 20] Given the limitations of CK-MB in the perioperative setting, physicians should only use CK-MB if troponin is unavailable at their centre.

As troponin values rise, their variability, as measured by the coefficient of variation, decreases. The ESC/ACC guidelines define an increased troponin level as, "a measurement exceeding the 99th percentile of a reference control group." At the same time, however, they specify that the coefficient of variation at the 99th percentile should be $\leq$ 10%. Unfortunately, no available troponin assay meets the 10% coefficient of variation criterion at the 99th percentile – higher levels (above the 99th percentile) are required to meet this criterion.[21 22] In keeping with previous suggestions,[21 23] until the assays are improved to meet the ESC/ACC recommendation, we define an increased troponin level as the lowest value that has a coefficient of variation equal to 10% (Appendix I).[21]

New Q wave changes ($\geq$ 30 milliseconds) present in any 2 contiguous leads fulfill the definition for the development of pathologic Q waves. We define electrocardiogram (ECG) changes indicative of ischemia as ST segment elevation ($\geq$ 2 mm in leads V_1, V_2, or V_3 and $\geq$ 1 mm in the other leads) or ST segment depression ($\geq$ 1 mm) in at least 2 contiguous leads, or symmetric inversion of T waves $\geq$ 1 mm in at least 2 contiguous leads. Coronary artery intervention includes percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery.

Because many patients will not experience symptoms, clinicians may still miss the correct diagnosis in patients with an elevated troponin after surgery who have suffered a myocardial infarction. Some of these patients will have an uninterpretable ECG (e.g., paced, left bundle-branch block, chronic ST segment changes); some will have an infarct in a territory (e.g. posterior) where the conventional ECG lacks sensitivity;[24] and some will have significant ST changes that resolve by the time the ECG is repeated the following day. To avoid missing the diagnosis of myocardial infarction, we have added to the first criterion a new or presumed new cardiac wall motion abnormality on echocardiography or a new or presumed new fixed defect on radionuclide imaging.

When physicians encounter a patient who has an elevated troponin level after surgery without either ischemic symptoms or a diagnostic ECG, the differential diagnosis includes myocardial infarction and noncardiac causes (e.g., pulmonary embolism). Because myocardial infarction is a probable cause of an elevated troponin in this situation, physicians should consider obtaining an echocardiogram or radionuclide imaging.

While physiological studies suggest that an imaging study may be insensitive (an injury involving > 20% of myocardial wall thickness may be required to detect a wall motion abnormality on echocardiography, and an injury of myocardial tissue > 10 grams may be required to detect a radionuclide perfusion defect),[16] at least 1 clinical study has suggested that echocardiography has a high sensitivity: 108 patients had troponin measurements before surgery and every 6 hours for the first 36 hours after surgery, as

well as an echocardiogram prior to surgery and 3 to 5 days after surgery.[19] Echocardiography demonstrated a new wall motion abnormality in all but 1 of the 9 patients who suffered a myocardial infarction based upon the diagnostic criteria of an elevated troponin level and significant ECG changes.

This study also suggested excellent specificity for the echocardiogram. None of the remaining 99 patients had a new cardiac wall motion abnormality. These results suggest that a wall motion abnormality detected on an imaging study in the absence of a prior study suggests the diagnosis of perioperative infarction, and a demonstrably new abnormality increases the likelihood further and thus support our definition of a perioperative myocardial infarction. Further research is needed to evaluate the diagnostic criteria we propose.

PROGNOSTIC FACTORS

Cardiac Biomarkers

Perioperative measurement of cardiac enzymes or biomarkers not only can help to identify otherwise silent myocardial infarctions but may also contribute important prognostic information. To assess the prognostic value of perioperative troponin and CK-MB measurements, we evaluated all noncardiac surgery studies that fulfilled the following criteria: at least 1 troponin or CK-MB measurement after surgery; reporting short-term (i.e., within 30 days of surgery) cardiac or total mortality, or intermediate (i.e., $\leq$ 1 year after surgery) or long-term (i.e., > 1 year after surgery) mortality or major

cardiac events; and assessment of the prognostic value of perioperative troponin and CK-MB measurements through multivariable analysis.

The 6 eligible studies,[25-30] which included a total of 2175 patients and 249 events (Table 2), evaluated CK-MB,[26 27 29 30] troponin T,[28-30] troponin I,[25 27] or both troponin T and I.[26] In all 6 studies, troponin measurement proved a statistically significant independent predictor of intermediate and long-term outcomes (i.e., mortality and major cardiac events). This finding persisted even in the 2 studies that excluded patients who suffered a perioperative myocardial infarction.[29 30] Two studies evaluated and demonstrated a dose-response relationship – the higher the peak troponin value the higher the 1 year mortality.[25 28] In contrast, 3 of the 4 studies that assessed CK-MB failed to demonstrate an association between an elevated CK-MB value and intermediate or long-term outcomes.[26 27 29 30]

The authors of one study[27] published a second paper evaluating the same patients but excluding deaths in the first month post surgery and extending the follow-up period from 1 to 2 years.[31] In this second paper, an elevated perioperative troponin value did not significantly predict the few deaths between months 1 to 24 post surgery (OR=2.7 (95% CI 0.7-10),[31] suggesting that an elevated perioperative troponin value more strongly predicts mortality in the first 12 months post surgery.

We did not evaluate the short-term predictive power of the troponin or CK-MB for diagnosing myocardial infarction because they are now part of the diagnostic criteria. Troponin was not, however, part of the diagnostic criteria when one of the earlier studies showed its prognostic benefit.[29]

Electrocardiography

We used the same eligibility criteria for troponin and CK-MB, made specific for the ECG, to assess the prognostic value of ECG evidence of perioperative ischemia. Because of the consistency with which an elevated perioperative troponin value proved an independent predictor of major outcomes after surgery, we also required studies to include troponin in their multivariable analysis. Three studies met our criteria (Table 3).[26 27 30]

Filipovic and colleagues did not demonstrate a statistically significant association between 3 lead ECG evidence of perioperative ischemia and post surgical mortality,[27] likely because ECG monitoring with fewer leads has lower sensitivity.[32] The other 2 studies, one of which excluded patients who suffered a myocardial infarction within 30 days of surgery,[30] demonstrated a statistically significant association, independent of perioperative troponin values, between perioperative ischemia on a 12 lead ECG and long-term mortality.[26 30]

The ECG, like biomarkers, is part of the diagnostic criteria for myocardial infarction, but it also is often the sole criterion for myocardial ischemia in the absence of infarction. Even a single postoperative ECG demonstrating ischemia in the recovery room is predictive of a major cardiac complication later during the hospital stay.[33]

USE OF DIAGNOSTIC AND PROGNOSTIC DATA

If clinicians wish to avoid missing a significant proportion of perioperative myocardial infarctions and identify patients at high risk of intermediate or long-term major cardiac events, they should monitor troponin levels and ECGs daily during the first 3 days post surgery. Choosing whom to monitor presents a challenge. The risk of missing an asymptomatic infarct increases with increasing postoperative risk of major cardiac events. A reasonable threshold would be to obtain troponin levels and ECGs for patients with established atherosclerotic disease (i.e., coronary artery disease and peripheral vascular disease) who are undergoing surgery requiring hospital admission. An alternative threshold would include patients with other risk factors for perioperative cardiac events (e.g., diabetes mellitus, renal insufficiency, or a history of heart failure or cerebrovascular disease).[34] Definitive recommendations await the results of further studies.

INTERVENTIONS TO PREVENT PERIOPERATIVE CARDIAC EVENTS

The multiple triggers and states (i.e., inflammatory, hypercoagulable, hypoxic, and stress states) that may result in a myocardial infarction in patients undergoing noncardiac surgery, which we discussed in the first article in this series,[1] open the possibility for a variety of potential prophylactic interventions. We will review the evidence for perioperative prophylactic beta-blockers, calcium channel blockers, alpha-2 adrenergic agonists, coronary revascularization, 3-hydroxy-3-methyl-glutaryl (HMG) coenzyme A

reductase inhibitors (i.e., statins), and acetyl-salicylic acid (ASA) in patients undergoing noncardiac surgery (Table 5).

In considering the evidence for these interventions, readers should keep in mind 2 points. First, it is only realistic to expect moderate treatment effects (i.e., relative risk reductions of 20-35%). Even when an intervention effectively blocks one or more pathogenic mechanisms, there will remain a number of unaffected pathogenic mechanisms; thus, large treatment effects are unlikely. Second, even assuming a high perioperative cardiovascular event rate of 10%, trials need at least 350 and ideally 650 events to convincingly demonstrate a 25% relative risk reduction.[35]

Beta-blockers

Beta-blockers moderate the effects of increased catecholamines and therefore may prevent perioperative cardiac events.[36 37] Many authors and 2 guideline committees have recommended that patients with coronary artery disease or risk factors for coronary artery disease undergoing noncardiac surgery receive perioperative beta-blocker therapy.[38-41] Important developments have occurred since these recommendations have been published, and since reviews published after the recommendations.[42 43]

Proponents of beta-blocker prophylaxis have based their recommendations primarily upon the results of 2 randomized controlled trials (RCTs) (Table 5).[44 45] These 2 trials have limitations. Poldermans and colleagues stopped their unblinded trial after an interim analysis based on 20 outcomes, and they demonstrated an implausible relative risk reduction of 90% in the composite outcome of cardiac death and nonfatal myocardial

infarction. In a second trial, by Mangano and colleagues, the results were no longer statistically significant when patients who died while receiving the study drug were included in the intention-to-treat analysis.[46]

In contrast, the results from 2 recent trials did not demonstrate any benefit from beta blocker therapy.[47 48] Although these 2 recent trials had a greater number of cardiac events and enrolled more patients than the 2 previous trials, they were nonetheless underpowered to determine the impact of beta-blocker therapy on major cardiovascular outcomes. However, they indicate that the results from the earlier trials were overly optimistic. Ongoing trials[42] will help to resolve the inconsistency in the results of the current perioperative beta-blocker trials.

Calcium Channel Blockers and Alpha-2 Adrenergic Agonists

Calcium channel blockers dilate coronary arteries;[49] alpha-2 agonists suppress the release of catecholamines.[50 51] These effects may prevent perioperative cardiac events. In Table 5 we present the results from 2 recent systematic reviews and meta-analyses that evaluated the effects of perioperative calcium channel blockers and alpha-2 agonists in patients undergoing noncardiac surgery.[52 53] The calcium channel blocker meta-analysis results were not statistically significant; however, there were too few events to draw conclusions.[52] More research is needed to determine the effect of perioperative calcium channel blockers.

A meta-analysis of alpha-2 agonists demonstrated a statistically significant reduction in both mortality and myocardial infarction with alpha-2 agonist therapy among

the patients who underwent vascular surgery.[53] The investigators, however, found no effect on mortality and myocardial infarction among the patients who underwent nonvascular noncardiac surgery.

Although there were 12 RCTs included in the alpha-2 agonist meta-analysis, a single study accounted for most of the events.[54] While this trial randomized 2854 patients, the published report excludes 957 of these patients at high risk of coronary artery disease in whom an interim analysis demonstrated a lower than expected event rate. The investigators then focused on the remaining 1897 randomized patients with established coronary artery disease, 52% of who underwent thoracic, abdominal, or orthopedic surgery. Mivazerol resulted in a statistically significant reduction in the composite outcome of total mortality and nonfatal myocardial infarction only for the subgroup of vascular surgery patients.

An RCT completed since the publication of the alpha-2 agonist meta-analysis evaluated the long term effects of perioperative clonidine in patients undergoing noncardiac surgery.[51] Clonidine had no effect on myocardial infarctions (4 events) during the original hospital admission but the trial suggested a mortality benefit at 2 years post surgery.

While the results of the alpha-2 agonist meta-analysis are encouraging, they warrant a cautious interpretation. The most recent clonidine trial is also encouraging, but given there were few events, unrealistic relative risk reductions, and borderline statistical significance, the results may represent a chance finding. Overall, the results from these

alpha-2 agonist trials are promising and require confirmation in a large, well-designed trial.

Coronary Revascularization

Coronary revascularization before noncardiac surgery is based on the assumption that perioperative myocardial infarctions primarily occur in coronary arteries with hemodynamically significant stenoses and that revascularization may therefore prevent infarction. As we discussed in the first article in this series,[1] this assumption may be erroneous.

Although some observational studies suggested a benefit to coronary revascularization before noncardiac surgery,[55 56] a recent RCT has revealed that coronary revascularization performed in patients with chronic stable angina had no effect on outcomes after elective vascular surgery for abdominal aortic aneurysm or severe leg claudication (Table 5).

This trial excluded patients with unstable angina, some of whom may benefit from undergoing coronary revascularization before noncardiac surgery. Small observational studies suggest that patients should have their noncardiac surgery delayed for at least 1 month following coronary artery bypass surgery and 6 weeks following coronary artery bare metal stenting.[57-60] The optimal period to delay noncardiac surgery following coronary artery drug-eluting stenting is unknown.[61] It is probable, however, that the optimal period of delay is substantially longer than 6 weeks, because drug-eluting

stenting delays endothelialization relative to bare metal stenting and likely prolongs the period of risk for late stent thrombosis.[62]

Statins

Statins have plaque stabilizing properties and therefore may prevent perioperative cardiac events.[63] Three observational studies suggest that statin therapy reduces the risk of perioperative death in patients undergoing noncardiac surgery.[64-66] The 1 RCT that evaluated the effects of perioperative statin therapy in patients undergoing vascular surgery demonstrated a statistically significant benefit but there were few events (Table 5).[67]

Given the limited current evidence (i.e., 17 events in the only RCT, implausibly large relative risk reduction, borderline statistically significant result for a broad composite outcome) the effectiveness of perioperative statin therapy remains uncertain. The evidence does, however, provide the impetus for an adequately powered RCT to determine whether perioperative statin therapy prevents major perioperative cardiac events.

ASA

ASA suppresses platelet aggregation and therefore may prevent perioperative cardiac events.[68] A systematic review of antiplatelet therapy versus placebo in patients undergoing infra-inguinal bypass surgery offers encouraging evidence that antiplatelet therapies prevent vascular events (Table 5).[69] In contrast, the Pulmonary Embolism

Prevention (PEP) trial suggested worse cardiac ischemic outcomes with ASA therapy in patients undergoing surgery for a hip fracture.[70] Although PEP suggests ASA therapy can prevent pulmonary emboli (HR=0.43; 95% CI 0.18 to 0.60), this result has failed to impact clinical practice because only 25% of patients in the placebo group were receiving a low molecular weight heparin. The American College of Chest Physicians' evidence-based guidelines recommend low molecular weight heparin, not ASA, as the venous thromboembolism prophylactic intervention for patients undergoing hip fracture surgery.[71]

ASA therapy in patients undergoing noncardiac surgery is associated with a higher risk of bleeding. In the PEP trial there were 197 postoperative bleeding episodes requiring a transfusion among the 6679 patients randomized to ASA compared to 157 postoperative bleeding episodes requiring a transfusion among the 6677 patients randomized to placebo (RRI=24%; 95% CI 1 to 53%).[70] In the antiplatelet trialists' overview of RCTs of antiplatelet therapy (ASA was the intervention in 1/3 of these trials) in surgical patients there were 28 nonfatal bleeding episodes requiring a transfusion among the 3798 patients randomized to antiplatelet therapy compared to 15 nonfatal bleeding episodes requiring a transfusion among the 3808 patients randomized to control (p=0.04).[72]

Given the evidence that ASA prevents cardiovascular events in the non-perioperative setting,[73] the conflicting RCT evidence surrounding the impact of ASA on perioperative cardiovascular events, and the likelihood of increased risk of bleeding associated with perioperative ASA, determining the balance of benefits and risk of ASA in patients undergoing noncardiac surgery will require a large definitive RCT. Until

such a trial is completed physicians must weigh the increased risk of bleeding against yet unproven cardiovascular benefits.

ACUTE AND LONG TERM MANAGEMENT OF MAJOR PERIOPERATIVE ISCHEMIC CARDIAC EVENTS

Unfortunately, there are no RCTs informing us how to manage perioperative ischemic cardiac events acutely or in the long-term. Identifying and treating correctable causes of perioperative ischemic events (e.g., anemia, hypoxia) seems advisable. Although thrombolytic, antiplatelet, and anticoagulant therapy is beneficial in the management of acute non-operative myocardial infarctions,[74] these therapies in the acute perioperative setting are likely to have a different risk benefit ratio. Drugs that are efficacious in the long-term management of patients surviving a non-operative myocardial infarction (e.g., ASA, ACE inhibitor, beta-blocker, statin) may not have the same impact in survivors of a perioperative myocardial infarction.[75] Only RCTs specific to the perioperative period will leave us confident of generalizing from other settings.

CONCLUSIONS

Unrecognized myocardial infarctions are common, and about half of all perioperative myocardial infarctions may go unrecognized if physicians solely rely upon clinical symptoms and signs. Perioperative troponin measurements and 12 lead ECGs can facilitate detection of clinically silent myocardial infarctions, and these tests provide long-term prognostic information. While several perioperative prophylactic interventions

(alpha-2 agonists, beta-blockers, statin therapy, ASA, calcium channel blockers) may prevent major perioperative cardiac events, definitively establishing or refuting their benefit will require large, well-designed and conducted trials. Current evidence does not support a management strategy of preoperative coronary revascularization before noncardiac surgery.

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CONTRIBUTORSHIP STATEMENT

P.J. Devereaux originated the idea for this paper and brought together all the authors to formulate and debate the points included in the text. He contributed significantly to the design of this manuscript. He undertook data acquisition, data analysis, interpretation of the data, wrote the first draft of the manuscript, and provided critical revisions to the manuscript.

Lee Goldman contributed significantly to the manuscript's design, interpretation of the data, and provided critical revisions to the manuscript.

Salim Yusuf contributed significantly to the manuscript's design, interpretation of the data, and provided critical revisions to the manuscript.

Ken Gilbert contributed significantly to the manuscript's design, interpretation of the data, and provided critical revisions to the manuscript.

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Table 1: Myocardial Infarction and Presence of Signs or Symptoms in Patients Undergoing Noncardiac Surgery

Study	N	Myocardial infarction	Myocardial infarction with chest pain	Myocardial infarction with any sign or symptom	Study definition of myocardial infarction
Mangano[12]	474	12 (2.5%)	1 (8%)	8 (67%)	elevated CKMB and 1 of the following: new Q waves, persistent ST-T wave changes, or autopsy evidence
Ashton[13]	512	8 (1.6%)	2 (25%)	5 (62%)	2 of the following: new Q waves, elevated CKMB, positive pyrophosphate scan
Badner[14]	323	18 (5.6%)	3 (17%)	7 (39%)	elevated CK and 2 of the following: elevated CKMB/CK, new Q waves, elevated troponin, positive pyrophosphate scan
Total (Pooled result)	1,309	38 (2.9%)	6 (14%)	20 (53%)	

We pooled results using a fixed effects model. The pooled results did not demonstrate significant heterogeneity (myocardial infarction with chest pain P=0.57 for heterogeneity, myocardial infarction with any sign or symptom P=0.24 for heterogeneity)

Table 2: The Prognostic Value of Perioperative Troponin and CK-MB Measurements in Patients Undergoing Noncardiac Surgery

Study	N	Variables adjusted for	Primary outcome (number of events)	Association of an elevated troponin to the outcome (95% CI)	Association of an elevated CK-MB to the outcome (95% CI)
Kim[25]	229	age, CHF, TAA surgery, perioperative beta-blockade	6 month total mortality (18)	OR = 5.9 (1.6-22)	NA
Landesberg[26]	447	age, MI, renal failure, type of vascular surgery	32 month total mortality (82)	OR = 2.15 (1.4-3.4)	OR = 2.71 (1.5-5)
Filipovic[27]	173	age, renal failure, CHF, hypertension, diabetes, anesthetic, heart rate variability, ECG ischemia, elevated CK-MB	12 month mortality (28)	OR = 10.2 (2.8-37)	OR = 6.9 (0.8-56)
Oscarsson[28]	161	BMI, ASA score, perioperative beta-blocker and diuretic therapy, perioperative tachycardia	12 month mortality (22)	HR = 15 (4-60)	NA
Studies that excluded patients who suffered an MI before hospital discharge or within 30 days of surgery					
Lopez-Jimenez[29]	772	age, sex, cardiac history, diabetes, smoking, type of surgery, CK-MB	6 month composite outcome (19) consisting of cardiac death (14), nonfatal MI (3), unstable angina (2)	OR = 4.6 ($p < 0.05$)	RR = 1.2 (0.5-3.2)
Kertai[30]	393	clinical risk score, ECG ischemia	48 month mortality (80)	HR = 1.9 (1.1-3.1)	HR = 1.6 (0.7-3.4)

CHF = congestive heart failure, TAA surgery = thoracoabdominal aneurysm surgery, OR = odds ratio, NS = not significant, NA = not assessed, MI = myocardial infarction, ECG = electrocardiogram, ASA score = American Society of Anesthesiologists score, HR = hazard ratio, RR = relative risk

Table 3: The Prognostic Value of ECG Evidence of Perioperative Ischemia in Patients Undergoing Noncardiac Surgery

Study	ECG monitoring method	Association of ECG evidence of perioperative ischemia with post surgical mortality
Landesberg[26]	continuous 12 lead ECG monitoring for 48-72 hours post surgery	OR = 2.20 (P = 0.03)
Filipovic[27]	continuous 3 lead ECG monitoring for 48 hours post surgery	OR = 2.0 (95% CI 0.3-12)
Kertai[30]	12 lead ECG on days 2, 3, and 7 post surgery	HR = 1.8 (95% CI 1.0-3.1)

OR = odds ratio, NS = not significant, HR = hazard ratio

Table 4: Diagnostic Criteria for Myocardial Infarction

I. ESC / ACC Diagnostic Criteria for Non-Perioperative Myocardial Infarction

A. The diagnosis of acute, evolving, or recent MI requires either one of the following criterion	
criterion 1	A typical rise and gradual fall (troponin) or a more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
	1. ischemic symptoms
	2. development of pathologic Q waves on an ECG
	3. ECG changes indicative of ischemia
	4. coronary artery intervention
criterion 2	Pathologic findings of an acute myocardial infarction
B. The diagnosis of established MI requires either one of the following criterion	
criterion 1	Development of new pathological Q waves on serial ECGs
criterion 2	Pathological findings of a healed or healing MI

II. Our Proposed Diagnostic Criteria for Perioperative Myocardial Infarction in Patients Undergoing Noncardiac Surgery

The diagnosis of perioperative MI requires any one of the following criterion	
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), or a rapid rise and fall of CK-MB only if troponin is unavailable.* This criterion also requires that 1 of the following criteria must also exist:
	1. ischemic signs or symptoms (e.g., chest, arm, or jaw discomfort; shortness of breath, pulmonary edema)
	2. development of pathologic Q waves on an ECG
	3. ECG changes indicative of ischemia
	4. coronary artery intervention
	5. new or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging
criterion 2	Pathologic findings of an acute or healing myocardial infarction
criterion 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

MI = myocardial infarction, ECG = electrocardiogram

* Because CK-MB is both less sensitive and less specific in the perioperative setting compared with other settings and compared with troponin levels, it should be used for diagnostic purposes only when troponins are not obtainable

Table 5: Perioperative Prophylactic Cardiac Interventions

Author (publication date)	Study design	Outcome	Treatment group (#/N)	Control group (#/N)	RR (95% CI)	Comment
Beta-blocker trials with short term follow-up (30 days post surgery)						
Poldermans[44] (1999)	RCT	Cardiac death or nonfatal MI	2/59	18/53	0.10 (0.02-0.41)	Unblinded trial stopped early after first interim analysis
Yang[47] (2004)	RCT	Cardiac death or nonfatal MI	19/246	22/250	0.88 (0.49-1.58)	Blinded trial not stopped after interim analysis
Beta-blocker trials with long term follow-up						
Mangano[45] (1996)	RCT	Total mortality (2 year)	13/99	23/101	0.58 (0.31-1.07)	Trial reported statistically significant result but excluded deaths that occurred while patients were taking the study drug. We include all deaths in an intention-to-treat analysis and the result is not significant.
Juul[48] (2004)	RCT	Total mortality, MI, UA, or CHF (18 months)	99/462	93/459	1.06 (0.82-1.36)	This trial included all events. There was also no difference in total mortality between the two groups (i.e., 16% in each group died).
Calcium Channel Blocker trial data based on short term follow-up						
Wijeysundera[52] (2003)	M-A of RCTs	Total mortality	5/358	12/334	0.40 (0.14-1.16)	Results based on 11 RCTs (8 trials evaluated diltiazem, 2 evaluated verapamil, and 2 evaluated dihydropyridines).
		MI	0/252	5/234	0.25 (0.05-1.18)	

Author (publication date)	Study design	Outcome	Treatment group (#/N)	Control group (#/N)	RR (95% CI)	Comment
Alpha-2 Agonist trial data based on short term follow-up						
Wijeysundera[53] (2003)	M-A of RCTs	Total mortality (vascular surgery)	13/877	26/771	0.47 (0.25-0.90)	The authors of the M-A decided to report separately the results of the patients who underwent vascular surgery and the patients who underwent nonvascular noncardiac surgery. The M-A includes 12 noncardiac surgery RCTs of which 8 included vascular surgery.
		MI (vascular surgery)	45/859	65/757	0.66 (0.46-0.94)	
		Total mortality (nonvascular noncardiac surgery)	16/512	15/501	1.09 (0.52-2.09)	
		MI (nonvascular noncardiac surgery)	36/502	26/491	1.35 (0.83-2.21)	
Oliver[54] (1999)	RCT	Total mortality	91/946	100/941	0.89 (0.67-1.18)	This trial was included in Wijeysundera's M-A. We report it separately as it accounts for 56 of the 70 deaths and 157 of the 172 MIs in the M-A.
		Total mortality or nonfatal MI	22/946	34/941	0.61 (0.35-1.03)	
Alpha-2 Agonist trial data based on long term follow-up (2 years)						
Wallace[51] (2004)	RCT	Total mortality	19/125	19/65	0.43 (0.21-0.89)	These results are based on a trial that evaluated the effect of 4 days of perioperative clonidine.
Preoperative coronary artery revascularization trial with long term follow-up (2.7 years)						
McFalls[76] (2004)	RCT	Total mortality	70/258	67/252	0.98 (0.70-1.37)	Among the patients assigned to coronary artery revascularization 38% underwent CABG surgery, 55% underwent PCI, and 7%

Author (publication date)	Study design	Outcome	Treatment group (#/N)	Control group (#/N)	RR (95% CI)	Comment
						did not receive coronary revascularization.
Statin trial with 6 month follow-up post surgery						
Durazzo[67] (2004)	RCT	Cardiac death, nonfatal MI, ischemic stroke, or UA	4/50	13/50	0.31 (0.11-0.88)	None of the individual outcomes demonstrated statistically significant results.
Antiplatelet therapy trial data based on short term follow-up						
Robless[69] (2001)	M-A of RCTs	Vascular death, nonfatal MI, or nonfatal stroke	76/893	92/872	odds ratio 0.76 (0.54-1.05)	Patients underwent infra-inguinal bypass surgery. M-A based upon 10 RCTs of which 6 evaluated the effects of ASA.
PEP investigators[70] (2000)	RCT	Death due to ischemic heart disease or nonfatal MI	105/6679	79/6677	hazard ratio 1.33 (1.00-1.78)	The Pulmonary Embolism Prevention (PEP) trial evaluated ASA therapy in patients undergoing hip fracture surgery.

#/N = number of events / number of patients randomized; RCT = randomized controlled trial; MI = myocardial infarction; UA = unstable angina; CHF = congestive heart failure; M-A = meta-analysis; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention

Appendix I: Recommended Troponin* Threshold for Myocardial Infarction Based Upon Concentrations Corresponding to a Coefficient of Variation Equal to 10%

Manufacturer	Platform	Troponin	Concentration corresponding to 10% CV impression (ug/L)
Abbott Diagnostics, Inc.	AxSYM	I	1.22
Bayer Diagnostics	ACS:180	I	0.37
	Centaur	I	0.33
	Immuno 1	I	0.34
Beckman Coulter, Inc.	Access, second generation	I	0.06
	Access, 2. second generation	I	0.09
BioMerieux	Vidas	I	0.36
Byk-Sangtec Diagnostica	Liaison	I	0.065
Dade Behring, Inc.	Dimension RxL, second generation	I	0.26
	Opus, second generation	I	0.90
	Stratus CS	I	0.10
Diagnostic Products Corp.	Immulite One	I	0.32
Ortho Clinical Diagnostics	Vitros ECi	I	0.44
Roche Diagnostics	E170	T	0.04
	Elecsys 1010, third generation	T	0.04
Tosoh Corp.	AIA 21, second generation	I	0.09

CV= coefficient of variation, Inc = Incorporated, Corp. = Corporation

* If troponin levels are not obtainable, no CK-MB threshold is of equivalent diagnostic accuracy. A CK-MB threshold physicians may want to use, when troponin is unavailable, is a CK-MB value at the 99th percentile of a reference control group.[16]

This table has been modified, with permission, from the original, which appeared in reference 21 (Panteghini M, Pagani F, Yeo KT, Apple FS, Christenson RH, Dati F, et al. Evaluation of imprecision for cardiac troponin assays at low-range concentrations. *Clin Chem* 2004;50(2):327-32.) © 2004 American Association for Clinical Chemistry.

CHAPTER 4

Devereaux PJ, Julian JA, Cook DJ, Yusuf S, Bhandari M, Cinà CS, Villar JC, Heels-Ansdell D, Haynes RB, DeBeer J, Paul J, McAlister FA, Buckley N, Marcaccio M, Guyatt GH. Noncardiac surgery in Canada: National mortality rates. (Submitted for Publication)

NONCARDIAC SURGERY IN CANADA: NATIONAL MORTALITY RATES

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ABSTRACT

Background: Little is known about national in-hospital mortality rates associated with noncardiac surgery.

Methods: The Canadian Institute for Health Information provided hospital discharge data on all admissions of patients ≥ 18 years old who underwent noncardiac surgery with a length of stay ≥ 24 hours from April 1, 2000 until March 31, 2001 in all Canadian provinces except Quebec. We evaluated the association between age, sex, admission category, preadmission comorbidities, the top 10 common major surgeries with the highest death rates, and in-hospital mortality using logistic regression modeling.

Results: A total of 383,478 admissions underwent noncardiac surgery at 319 hospitals, of which 39 were teaching hospitals performing 50% of the operations. A total of 2772 patients died (mortality rate 0.7%), and 97% of the deaths occurred after patients left the recovery room. The top 10 common major surgeries with the highest death rates (all orthopedic, intra-abdominal, or vascular) accounted for 40% of all deaths. Significant predictors of in-hospital mortality included for every year increase in age (odds ratio 1.06, 95% confidence interval 1.06-1.07), female sex (0.80, 0.74-0.87), urgent admission category (5.83, 5.15-6.59), emergent admission category (10.92, 9.64-12.37) [reference category was elective admissions for both urgent and emergent admissions], 15 of 17 preadmission comorbidities, and 9 of the top 10 common major surgeries with the highest death rates.

Conclusions: Noncardiac surgery is common and a substantial number of noncardiac surgery patients die in-hospital annually. We have identified predictors of in-hospital

death. Prospective cohort studies are needed to evaluate these patient groups (e.g., patients undergoing top 10 surgeries with highest death rates) to establish the mechanisms of death, which will inform future clinical trials to test interventions to improve outcomes.

INTRODUCTION

While investigators have addressed national mortality rates associated with coronary artery bypass grafting surgery,(1, 2) National mortality rates associated with noncardiac surgery remain largely unexplored. This has remained so despite the fact that noncardiac surgery accounts for greater than 95% of all adult surgeries requiring hospital admission.(3)

Limitations of studies evaluating the risk of death in patients undergoing noncardiac surgery include dated information, relatively small sample sizes, focus on selected high-risk groups (e.g., patients referred for a preoperative consult), and exclusion of community hospitals.(4-7) Understanding the national burden of disease will inform clinicians, managers, and investigators, as well as allocation decisions of granting agencies.

To address this knowledge deficit, we undertook a study to determine the following: the annual number of adult hospital admissions in Canada, excluding Quebec, undergoing noncardiac surgery requiring hospital admission $\geq$ 24 hours; the characteristics of these admissions; the mortality rates; the association between age, sex, admission category (i.e., elective, urgent, and emergent), 17 preadmission comorbidities, the top 10 common major surgeries with the highest death rates, and hospital mortality; the timing of death post surgery; and, as a marker of cost, the hospital length of stay among those who died and survived.

METHODS

Data Source

The Discharge Abstract Database (DAD) of the Canadian Institute for Health Information (CIHI), which includes data on all hospital admissions in all Canadian provinces and territories except Quebec, provided the data for our analyses. All hospitals employ health records staff to abstract and code standard demographic, clinical, and administrative data for services provided for each hospital admission, based upon the discharge summary and patient chart.(8) We studied all acute care hospital admissions for patients $\geq$ 18 years of age who underwent noncardiac surgery with a length of stay $\geq$ 24 hours during the period of April 1, 2000 until March 31, 2001. Appendix I reports data items CIHI provided for this study.

Case Identification

We identified noncardiac surgery cases through eliminating all hospital discharges who underwent cardiac surgery as identified through the Canadian Classification of Procedures (CCP) codes 47.0 through 49.99.(9) We excluded 2 cases who underwent noncardiac surgery during the fiscal year 2000 but were admitted to hospital prior to 1999. We also excluded all cases from hospitals that performed fewer than 10 noncardiac surgeries during the fiscal year 2000 because these may represent patients discharged from a small hospital after transfer from a large hospital where they underwent noncardiac surgery.

Preadmission Comorbidities

We evaluated 17 comorbidities (i.e., Charlson Index comorbidities)(10) through use of an ICD-9 coding scheme.(11) We used the diagnosis-type designator to determine if a variable was a preadmission comorbidity. In many cases (e.g., dementia, chronic pulmonary disease, metastatic solid tumor) we judged comorbidities as existing prior to admission even if the diagnosis-type designator indicated the diagnosis arose after hospital admission.

Surgical Procedures

We identified 10 common major surgeries with the highest death rates; henceforth referred to as top 10 surgeries. We defined common surgeries as surgeries for which there were > 750 cases as identified through CCP codes. These surgeries were then ordered based upon their death rates and we removed surgeries that resulted from a clear complication of a preceding surgery (e.g., repeat laparotomy for bleeding) and surgeries that were clearly not a major surgery (e.g., anal sutures). After identifying the top 10 surgeries, we looked at their individual CCP codes and assessed if there were similar CCP codes that were appropriate to combine based upon the similarity of the surgeries and death rates. For example, left hemicolectomy (CCP code 57.55) was one of the 10 surgeries identified; we combined this surgery with partial excision of large intestine (CCP codes 57.51 – 57.54, 57.56 and 57.59) and total colectomy (CCP code 57.6) to

create the surgical category of partial or total colectomy. Appendix II reports the CCP codes used for the top 10 surgeries.

Statistical Analysis

We evaluated the age, sex, admission category (elective - admission that is planned or expected; urgent - admission that requires immediate assessment, but for whom delayed action would not be threatening to life; emergent - admission for a life threatening condition requiring immediate assessment and treatment)(12), 17 individual preadmission comorbidities (each recorded as present or absent), and the individual top 10 surgeries and determined the associated mortality rates and 99% confidence intervals. We also determined the timing of death.

We conducted a multivariable logistic regression analysis in which the dependent variable was mortality and the independent variables were age (continuous), sex, admission category, 17 individual preadmission comorbidities, and individual top 10 surgeries. We repeated this multivariable logistic regression analysis and added interaction terms to determine the simultaneous influence of individual variables (i.e., age, sex, and admission category) on death among patients undergoing individual top 10 surgeries. For patients who underwent more than one top 10 surgery we attributed the case to the higher risk surgery in our regression analyses.

We computed the c index (the probability of concordance) as a measure of the model's discrimination and predictive ability. We also conducted a residual analysis to detect influential and extreme observations by (1) plotting the predicted values against

the change in the Pearson chi-square, deviance and beta coefficients due to subject deletions, and (2) inspecting the leverage values (i.e., the hat matrix diagonals) and residuals.(13, 14)

Because our data were restricted to the hospital admission period, it is possible that spurious associations could occur in our multivariable analyses secondary to increased length of stay associated with some variables (e.g., it is possible that older patients stay in hospital longer than younger patients due to impaired mobility, and an association between age and death may result from longer follow-up). To address this possibility we conducted sensitivity analyses in which for each top 10 surgery we removed all admissions above the 75^{th} percentile for total length of stay from the multivariable analyses. We also conducted a sensitivity analysis in which we only included cases in which patient's underwent one of the top 10 surgeries to determine if this influenced the results of our multivariable analyses.

For the top 10 surgeries we compared the hospital length of stay among admissions associated with death versus those associated with survival using the Mann-Whitney U test. Admissions undergoing multiple noncardiac surgeries during a single admission were counted only once for these analyses.

All analyses were undertaken using SPSS version 11.0 except for the analyses involving the interaction terms and residuals which were undertaken using SAS version 9.1.

RESULTS

A total of 383,478 admissions who underwent noncardiac surgery were evaluated. Table 1 reports the characteristics and location of these admissions. A total of 319 hospitals performed these surgeries; 39 teaching hospitals accounted for 50% of the cases. Patients most commonly received care in Ontario (48%). Approximately half of the admissions were age 50 years or greater and over 30,000 admissions involved patients $\geq$ 80 years of age. Urgent and emergent hospital admissions accounted for over a third of all admissions. The most common preadmission comorbidities were malignancy (11.0%), diabetes (5.8%), and chronic pulmonary disease (4.5%). The hospital length of stay for all admissions was right-skewed with a median of 3 days (figure).

A total of 2772 patients died (overall mortality rate 0.7%) (Table 2). Of admissions in patients aged 30 to 39, one in 1489 ended in death; whereas one in 29 admissions who were age 80-89 years died and one in 11 admissions who were $\geq$ 90 years of age died (these numbers are based upon the absolute event rates, not the rounded percentages in Table 2). One in 676 admissions associated with elective surgery resulted in death; the comparable rate for emergent surgery was one in 40. Of the patients who died, 75 (3%) died in the operating or recovery room; 551 (20%) died within 2 days of leaving the recovery room; 916 (33%) died $\geq$ 2 days and $\leq$10 days post surgery; and 921 (33%) died > 10 days post surgery. In 309 (11%) admissions, hospital discharge data did not include the timing of their death.

A total of 35,975 admissions underwent one or more of the top 10 surgeries and 1116 (3%) of these admissions died in hospital. These top 10 surgeries are used to treat

orthopedic, intra-abdominal, and vascular conditions and account for 40% of all admission deaths. Table 3 reports the hospital death rates for the top 10 surgeries. The top 10 surgeries included above knee amputation (1 in 8 patients having this procedure died), colostomy (1 in 13 patients having this procedure died), lower leg amputation (1 in 14 patients having this procedure died), and reduction of femur fracture with internal fixation (1 in 21 patients having this procedures died). The three most common of these top 10 surgeries (i.e., hip arthroplasty, reduction of femur fracture with internal fixation, and partial or total colectomy) accounted for 768 deaths.

Table 4 reports the unadjusted and adjusted associations between the independent variables age, sex, admission category, 17 individual preadmission comorbidities, and individual top 10 surgeries and the dependent variable mortality, among 383,472 admissions (6 admissions were excluded because of missing data). The differences between the unadjusted and adjusted associations were quantitative and some were large (e.g., congestive heart failure unadjusted and adjusted odds ratios 18.35 and 2.80, respectively; above knee amputation unadjusted and adjusted odds ratios 30.38 and 4.25, respectively). Significant predictors of in-hospital mortality in our multivariable analysis included for every year increase in age (odds ratio 1.06, 95% confidence interval 1.06-1.07), female sex (0.80, 0.74-0.87), urgent admission category (5.83, 5.15-6.59), emergent admission category (10.92, 9.64-12.37), 15 of 17 preadmission comorbidities, and 9 of the top surgeries.

Table 5 reports the results from our multivariable analysis that included interaction terms to determine the simultaneous influence of individual variables (i.e.,

age, sex, and admission category) on death among patients undergoing individual top 10 surgeries. This analysis included 383,472 admissions (6 admissions were excluded because of missing data). Most of the differences between the results of the multivariable analyses that did and did not include interaction terms were quantitative and some were large (e.g., overall urgent admission odds ratio 5.83, 95% confidence interval 5.15-6.59 compared to the odds ratio 0.71, [0.34-1.45] for urgent admission among patients undergoing lower leg amputation; overall emergent admission odds ratio 10.92, [9.64-12.37] compared to the odds ratio 1.00 [0.52-1.91] for emergent admission among patients undergoing reduction of femur fracture with internal fixation). One qualitative difference existed between the results of the multivariable analyses that did and did not include interaction terms. The overall odds ratio for female sex was 0.80, 95% confidence interval 0.74-0.87 whereas the odds ratio for female sex among patients undergoing resection of aorta with replacement or anastomosis was 2.44 (1.29-4.63). The c statistic was 0.93 for both models suggesting good predictive ability.

In the sensitivity analysis in which, for each top 10 surgery, we removed all admissions above the 75th percentile for total length of stay, we only observed quantitative changes in our results. Likewise, in our sensitivity analysis that only included patients who underwent one of the top 10 surgeries we only observed quantitative changes in our results. When we removed 4 cases because they were identified as outliers in our residual analysis once again we only witnessed quantitative changes in our results.

Table 6 reports the hospital length of stay among admissions discharged alive and dead who underwent the top 10 surgeries. Of the 6 surgeries with statistically significant results 4 demonstrated longer lengths of stay among patients who died. The 2 surgeries that demonstrated statistically significant shorter lengths of stay among patients who died were vascular surgeries. Overall for the 10 common major surgeries with the highest death rates the median hospital length of stay among admissions associated with death versus survival was 11 and 8 days, respectively ($P<0.01$).

DISCUSSION

Principal Findings

A total of 383,478 adult admissions underwent noncardiac surgery requiring hospital admission $\geq$ 24 hours in Canada, excluding Quebec, during the fiscal year 2000. Admissions undergoing noncardiac surgery occur often in non-teaching hospitals (50% of the surgeries), frequently in the elderly, and over a third of the time in urgent or emergent circumstances. Noncardiac surgery is associated with substantial hospital mortality (i.e., 1 in 142 cases die), and a minority of deaths (3%) occur in the operating or recovery room. Ten common major surgeries account for 40% of all the noncardiac surgery admission deaths and the three most common of these surgeries (i.e., hip arthroplasty, reduction of femur fracture with internal fixation, and partial or total colectomy) account for 27,894 admissions and 768 deaths, annually. Independent predictors of in-hospital

death included: age, female sex, urgent and emergent admission category, 15 of 17 preadmission comorbidities, and 9 of the top 10 surgeries. Considering the top 10 surgeries with the highest death rates, median length of hospital stay was 3 days longer among patients who died.

Strengths and Weaknesses of Our Study

Strengths of our study include: current data; large sample size, resulting in precise estimates; and inclusion of non-teaching hospitals. Several of the variables (i.e., age, sex, admission category, death) included in our multivariable models are mandatory elements that hospitals must report in hospital discharge submissions to CIHI. As a result there were no admissions with missing data on vital status at discharge or age and only 3 admissions were missing data on sex and admission category. Our model suggested good predictive ability according to the c index and there were no qualitative changes on our sensitivity analyses.

Our study has several limitations. We excluded patients who underwent noncardiac day surgery. This is a minor concern, however, because noncardiac day surgery has a very low mortality rate (i.e., approximately one in 11,000 patients die within 30 days of day surgery).(15) Our study does not include data from Quebec. Quebec hospitals do not submit discharge data to CIHI; however, it is unlikely that noncardiac surgery in Quebec differs substantially from the rest of the country.

Although administrative databases may contain errors and omissions, CIHI produces reports so that hospitals can analyze and correct erroneous data as a method of

quality control.(8) A CIHI re-abstraction study, conducted during the year that hospitals collected the data included in our study, suggests these measures ensured the accuracy of demographic (e.g., age, sex), major procedural (e.g., hip arthroplasty), and death codes; agreement on blinded re-abstraction was $\geq$ 99%.(8) Although this investigation demonstrated a 15% discrepancy rate on blinded re-abstraction of admission categories, most of these discrepancies arose from some hospitals recording all cases admitted from the emergency room as emergent admissions. It is unlikely that these discrepancies had a major impact on our findings as most of these discrepancies would have related to the distinction between urgent and emergent admissions and our reference group was elective admissions. The results of prospective studies that have demonstrated that urgency of surgery is an independent predictor of major post surgical outcomes support our findings regarding the association between the urgency of admission and mortality.(4, 16)

The accuracy of blinded re-abstraction of comorbidities in the CIHI re-abstraction study was only 77%. Further, a systematic review of studies evaluating the quality of Canadian hospital discharge data suggests suboptimal accuracy of comorbidity data with several studies demonstrating accuracy rates < 50%.(17) Given this research, readers should view our results related to comorbidities with caution.

A total of 2212 (0.6%) admissions were missing data on province and 309 (11%) of the admissions who died were missing data on the timing of death. The small percentage of admissions with missing provincial data is not relevant, because we only report provincial data to provide a broad perspective of where surgeries occurred. The percentage of missing data regarding the timing of death weakens our confidence that

only 3% of the deaths occurred in the operating or recovery room. Our conclusion, however, that only a minority of deaths occurred in the operating or recovery room remains true, as even assuming the unlikely scenario that all patients with missing data died within the operating or recovery room this would still mean an overall minority of the patients (14%) died in these locations.

We focused on death but did not examine important morbid outcomes (e.g., myocardial infarction) in patients undergoing noncardiac surgery. Further research is needed to gain a national perspective on major morbid events in patients undergoing noncardiac surgery. The accuracy of major morbid postoperative outcomes in the Discharge Abstract Database of CIHI is unknown, but other administrative databases have demonstrated poor capture of severe postoperative complications.(18)

Implications of Our Study

Our study demonstrates that noncardiac surgery is common, occurs frequently in the elderly, and a substantial number of patients undergoing noncardiac surgery die in-hospital annually. If Quebec is similar to the rest of Canada in the proportion of patients undergoing noncardiac surgery and the surgical mortality rate, over 500,000 Canadians undergo noncardiac surgery requiring hospital admission $\geq$ 24 hours annually and over 3500 of these patients die in hospital. If assumptions about Quebec are correct, annually > 40,000 admissions for noncardiac surgery in Canada are $\geq$80 years of age.

Limited research exists regarding the cause of death among patients who have undergone noncardiac surgery. The timing of death in our study suggests that few deaths

are due to acute surgical or anesthetic complications. Two prospective studies in adults undergoing noncardiac surgery requiring hospital admission suggest that approximately one third of the deaths are due to major cardiac events.(4, 6) These studies are, however, limited because there were only 102 deaths in total. The major events resulting in death may stem from many triggers including: 1. the underlying condition (e.g., hip fractures cause great physiological stress that may predispose to a major perioperative event such as a myocardial infarction);(19, 20) 2. the surgical procedure itself (i.e., surgery can produce extreme physiologic stress due to its inherent trauma and also as a result of anesthesia and analgesia, intubation and extubation, pain, hypothermia, bleeding and anemia, and fasting);(21) and 3. the underlying comorbidities (e.g., patients with severe coronary artery disease are more vulnerable to the physiological stress of the condition requiring operative intervention and the surgery itself).(22, 23)

Considering the magnitude of this problem and the likely substantial economic costs (i.e., the median hospital length of stay was three days longer among patients who died) further research is needed to understand the mechanisms of death and to establish interventions to improve outcomes. Given that the top 10 surgeries with the highest death rates accounted for 40% of all the noncardiac surgery deaths and the 3 most common of these surgeries (i.e., > 27,000 cases) accounted for 768 deaths identifies these surgeries as an appropriate focus for such research. Our multivariable analyses suggest that targeted investigation should include urgent and emergent surgery and surgery in the growing elderly population.

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CONTRIBUTORSHIP STATEMENT

Dr. P.J. Devereaux contributed significantly to the study's concept and design, data acquisition, data analysis, and interpretation of the data. He wrote the first draft of the manuscript, provided critical revisions to the manuscript, and gave final approval of the submitted manuscript.

Dr. Jim Julian contributed significantly to the study's concept and design, data analysis, interpretation of the data, and provided critical revisions to the manuscript. He also gave final approval of the submitted manuscript.

Dr. Deborah Cook contributed significantly to the study's concept and design, interpretation of the data, and provided critical revisions to the manuscript. She also gave final approval of the submitted manuscript.

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FIGURE LEGEND

Figure – Total Length of Hospital Stay for all Patients who Underwent Noncardiac Surgery

Table 1: Characteristics and Location of Admissions Who Underwent Noncardiac Surgery

Characteristics	Admissions who underwent noncardiac surgery (N=383,478)
Age category:	
18-29	54,284 (14.2%)
30-39	70,002 (18.3%)
40-49	60,817 (15.8%)
50-59	54,719 (14.3%)
60-69	55,386 (14.4%)
70-79	57,928 (15.1%)
80-89	26,365 (6.9%)
≥90	3,977 (1.0%)
Sex:	
female	235,586 (61.4%)
male	147,889 (38.6%)
Admission category:	
elective	246,549 (64.3%)
urgent	84,326 (22.0%)
emergent	52,600 (13.7%)
Charlson preadmission comorbidities:	
Myocardial infarction	6,822 (1.8%)
Congestive heart failure	4,281 (1.1%)
Peripheral vascular disease	6,002 (1.6%)
Cerebrovascular disease	7,732 (2.0%)
Dementia	1,291 (0.3%)
Chronic pulmonary disease	17,278 (4.5%)
Rheumatologic disease	4127 (1.1%)
Peptic ulcer disease	1213 (0.3%)
Mild liver disease	944 (0.2%)
Diabetes	22,147 (5.8%)
Diabetes with chronic complications	4,307 (1.1%)
Hemiplegia or paraplegia	1,088 (0.3%)
Renal disease	4,333 (1.1%)
Any malignancy, including leukemia and lymphoma	42,316 (11.0%)
Moderate or severe liver disease	431 (0.1%)
Metastatic solid tumor	11,438 (3.0%)
AIDS	369 (0.1%)

Characteristics	Admissions who underwent noncardiac surgery (N=383,478)
Province:	
Alberta	65,572 (17.2%)
British Columbia	44,373 (11.6%)
Ontario	182,628 (47.9%)
Other provinces	88,693 (23.3%)
Type of hospital:	
75 hospitals with 1-49 beds	6,174 (1.6%)
85 hospitals with 50-99 beds	20,134 (5.3%)
55 hospitals with 100-199 beds	26,323 (6.9%)
49 hospitals with 200-399 beds	84,378 (22.0%)
14 hospitals with $\geq$ 400 beds	54,593 (14.2%)
39 teaching hospitals	191,804 (50.0%)
2 pediatric hospitals	72 (0.02%)

Number of admissions with missing data: age (0), sex (3), admission category (3), comorbidities (0), province (2212), type of hospital (0)

Table 2: Hospital Deaths in Admissions Who Underwent Noncardiac Surgery

Category	Number of deaths	Percentage death rates (99% CI)
All admissions	2,772	0.7% (0.7-0.8)
Age category:		
18-29	35	0.06% (0.04-0.09)
30-39	47	0.07% (0.05-0.1)
40-49	90	0.1% (0.1-0.2)
50-59	181	0.3% (0.3-0.4)
60-69	371	0.7% (0.6-0.8)
70-79	771	1.3% (1.2-1.5)
80-89	916	3.5% (3.2-3.8)
≥90	361	9.1% (8.2-10.0)
Sex:		
female	1,367	0.6% (0.5-0.6)
male	1,405	1.0% (0.9-1.0)
Admission category:		
elective	357	0.1% (0.1-0.2)
urgent	1,107	1.3% (1.2-1.4)
emergent	1,306	2.5% (2.3-2.7)
Charlson preadmission comorbidities:		
Myocardial infarction	255	3.7% (3.2-4.4)
Congestive heart failure	437	10.2% (9.1-11.5)
Peripheral vascular disease	308	5.1% (4.4-5.9)
Cerebrovascular disease	305	3.9% (3.4-4.6)
Dementia	129	10.0% (8.0-12.4)
Chronic pulmonary disease	403	2.3% (2.1-2.6)
Rheumatologic disease	42	1.0% (0.7-1.5)
Peptic ulcer disease	68	5.6% (4.1-7.6)
Mild liver disease	63	6.7% (4.9-9.1)
Diabetes	439	2.0% (1.8-2.2)
Diabetes with chronic complications	132	3.1% (2.5-3.8)
Hemiplegia or paraplegia	53	4.9% (3.4-6.8)
Renal disease	268	6.2 % (5.3-7.2)
Any malignancy, including leukemia and lymphoma	728	1.7% (1.6-1.9)
Moderate or severe liver disease	60	13.9% (10.2-18.8)
Metastatic solid tumor	498	4.4% (3.9-4.9)
AIDS	11	3.0% (1.4-6.2)

Table 3: Hospital Deaths in Admissions Who Underwent Top 10 Surgeries and Other Surgeries

Surgery	Number of admissions	Number of deaths	Percentage (99% confidence interval)
Above knee amputation	756	96	12.7% (9.9-16.1%)
Colostomy	1,190	90	7.6% (5.8-9.8%)
Lower leg amputation	970	69	7.1% (5.3-9.5%)
Reduction of femur fracture with internal fixation	7,724	364	4.7% (4.1-5.4%)
Resection of aorta with replacement or anastomosis	1,341	53	3.9% (2.8-5.6%)
Internal fixation of femur without fracture reduction	1,302	47	3.6% (2.5-5.2%)
Partial or total colectomy	7,312	189	2.6% (2.1-3.1%)
Aorta-iliac-femoral bypass	887	20	2.3% (1.3-3.9%)
Non aortic peripheral vascular bypass or shunt	2,859	64	2.2% (1.6-3.1%)
Hip arthroplasty	12,983	222	1.7% (1.4-2.0%)
Other surgeries	347,501	1,656	0.5% (0.4-0.5%)

If an admission underwent more than one of these top 10 surgeries they were counted as an admission for each surgery.

Table 4: Predictors of Hospital Death among 383,472 Admissions

Variables included in model	Association with mortality Unadjusted Odds Ratio (95% confidence interval)	Association with mortality Adjusted Odds Ratio (95% confidence interval)
Age	1.09 (1.08-1.09)	1.06 (1.06-1.07)
Female	0.61 (0.56-0.66)	0.80 (0.74-0.87)
Admission category:		
urgent	9.17 (8.14-10.3)	5.83 (5.15-6.59)
emergent	17.6 (15.6-19.8)	10.9 (9.64-12.4)
Charlson preadmission comorbidities:		
Myocardial infarction	5.77 (5.06-6.58)	1.46 (1.26-1.69)
Congestive heart failure	18.4 (16.5-20.4)	2.80 (2.48-3.17)
Peripheral vascular disease	8.23 (7.29-9.29)	2.13 (1.80-2.51)
Cerebrovascular disease	6.21 (5.50-7.01)	2.32 (2.01-2.66)
Dementia	15.9 (13.2-19.2)	1.81 (1.48-2.22)
Chronic pulmonary disease	3.67 (3.30-4.08)	1.46 (1.30-1.64)
Rheumatologic disease	1.42 (1.04-1.93)	1.04 (0.75-1.43)
Peptic ulcer disease	8.34 (6.51-10.7)	3.16 (2.40-4.16)
Mild liver disease	10.0 (7.74-13.0)	2.75 (1.89-3.98)
Diabetes	3.11 (2.81-3.45)	1.14 (1.01-1.27)
Diabetes with chronic complications	4.51 (3.78-5.38)	1.05 (0.84-1.32)
Hemiplegia or paraplegia	7.15 (5.41-9.45)	1.91 (1.39-2.64)
Renal disease	9.92 (8.71-11.3)	3.76 (3.24-4.38)
Any malignancy, including leukemia and lymphoma	2.90 (2.67-3.16)	1.62 (1.44-1.82)
Moderate or severe liver disease	22.7 (17.2-29.9)	11.4 (7.68-16.9)
Metastatic solid tumor	7.40 (6.71-8.17)	4.87 (4.27-5.57)
AIDS	4.23 (2.32-7.72)	16.5 (8.63-31.4)

Variables included in model	Association with mortality Unadjusted Odds Ratio (95% confidence interval)	Association with mortality Adjusted Odds Ratio (95% confidence interval)
Top 10 surgeries:		
Above knee amputation	30.4 (24.4-37.8)	4.25 (3.28-5.50)
Colostomy	16.9 (13.5-21.1)	3.24 (2.53-4.15)
Lower leg amputation	15.8 (12.2-20.4)	2.67 (1.96-3.65)
Reduction of femur fracture with internal fixation	10.3 (9.18-11.6)	1.35 (1.18-1.54)
Resection of aorta with replacement or anastomosis	8.61 (6.51-11.4)	2.61 (1.86-3.65)
Internal fixation of femur without fracture reduction	7.77 (5.77-10.5)	1.28 (0.94-1.76)
Partial or total colectomy	4.16 (3.47-4.99)	1.27 (1.04-1.55)
Aorta-iliac-femoral bypass	3.46 (1.90-6.29)	2.20 (1.16-4.18)
Non aortic peripheral vascular bypass or shunt	3.96 (2.98-5.27)	1.49 (1.10-2.02)
Hip Arthroplasty	3.55 (3.07-4.10)	1.17 (1.00-1.37)

The reference category for sex was male, admission category was elective, and top 10 surgeries was all other surgeries. The odds ratios for age represent the association for every year increase in age.

Table 5: Results of Multivariable Analysis Assessing Interactions

Surgery	Variables in models	Adjusted Odds Ratio (95% confidence interval)
Above knee amputation	Age	1.02 (1.00-1.04)
	Female	1.05 (0.66-1.68)
	Urgent admission	1.94 (0.98-3.87)
	Emergent admission	4.64 (2.37-9.05)
Colostomy	Age	1.08 (1.06-1.11)
	Female	1.11 (0.68-1.83)
	Urgent admission	5.30 (2.31-12.1)
	Emergent admission	6.80 (2.94-15.7)
Lower leg amputation	Age	1.06 (1.04-1.09)
	Female	1.70 (0.98-2.95)
	Urgent admission	0.71 (0.34-1.45)
	Emergency admission	4.33 (1.91-9.83)
Reduction of femur fracture with internal fixation	Age	1.09 (1.08-1.11)
	Female	0.51 (0.40-0.64)
	Urgent admission	1.50 (0.74-3.03)
	Emergent admission	1.00 (0.52-1.91)
Resection of aorta with replacement or anastomosis	Age	1.07 (1.03-1.11)
	Female	2.44 (1.29-4.63)
	Urgent admission	2.51 (1.05-6.02)
	Emergent admission	14.5 (7.22-29.3)
Internal fixation of femur without fracture reduction	Age	1.08 (1.04-1.12)
	Female	0.71 (0.36-1.42)
	Urgent admission	1.85 (0.41-8.41)
	Emergent admission	3.49 (0.79-15.4)

Surgery	Variables in models	Adjusted Odds Ratio (95% confidence interval)
Partial or total colectomy	Age	1.10 (1.08-1.12)
	Female	0.67 (0.45-0.98)
	Urgent admission	3.06 (1.87-5.02)
	Emergent admission	10.4 (6.41-16.9)
Aorta-iliac-femoral bypass	Age	1.09 (1.02-1.18)
	Female	1.80 (0.45-7.24)
	Urgent admission	11.3 (1.20-107)
	Emergent admission	36.7 (4.03-335)
Non aortic peripheral vascular bypass or shunt	Age	1.08 (1.04-1.11)
	Female	0.66 (0.35-1.24)
	Urgent admission	2.30 (1.12-4.74)
	Emergent admission	5.02 (2.42-10.4)
Hip arthroplasty	Age	1.12 (1.10-1.14)
	Female	0.47 (0.35-0.64)
	Urgent admission	5.55 (3.25-9.48)
	Emergent admission	5.79 (3.40-9.85)

The reference category for sex was male, admission category was elective, and top 10 surgeries was all other surgeries. The odds ratios for age represent the association for every year increase in age.

Table 6: Comparison of Hospital Length of Stay (HLS) Among Patients Discharged Alive or Dead Who Underwent Top 10 Surgeries

Surgery	Survivors median HLS (days)	Patients who died median HLS (days)	P value
Above knee amputation	13	19	0.05
Colostomy	11	12	0.4
Lower leg amputation	16	32	<0.01
Reduction of femur fracture with internal fixation	9	10	0.2
Resection of aorta with replacement or anastomosis	8	1	<0.01
Internal fixation of femur without fracture reduction	8	11	0.06
Partial or total colectomy	9	10	0.5
Aorta-iliac-femoral bypass	8	2	<0.01
Non aortic peripheral vascular bypass or shunt	7	13	<0.01
Hip arthroplasty	7	11	<0.01
All 10 surgeries	8	11	<0.01

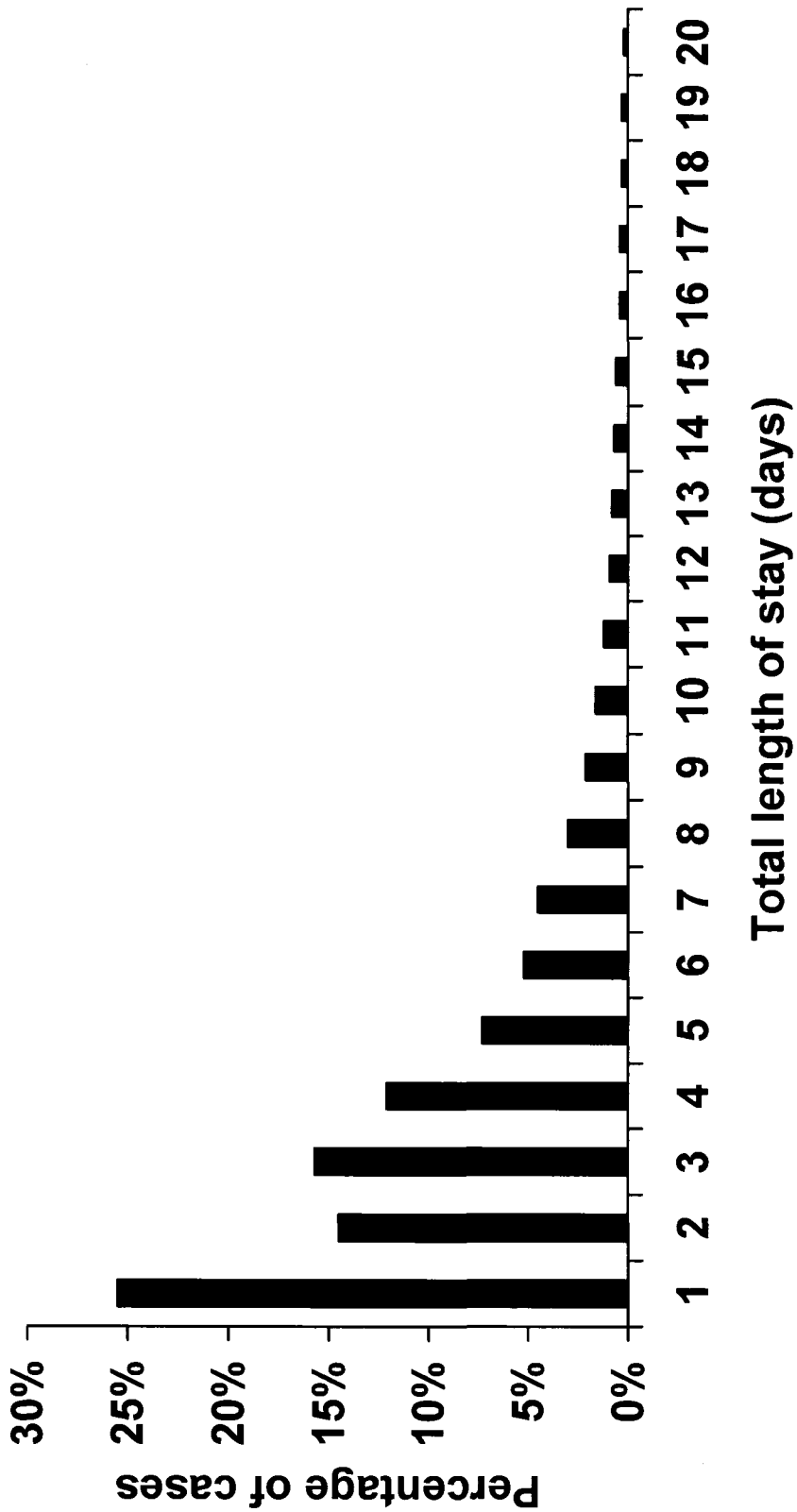

Figure - 2.8% of patients had a total length of stay ≥ 21 days

Appendix I: Data items CIHI provided for this study

Health care number (encrypted)
Institution number (encrypted)
Exit alive
Operative death code
Supplemental death code
Age units
Sex
Admission category
Admission day
Admission month
Admission year
Total length of stay
Acute length of stay
Alternate level of care length of stay
Diagnosis 1-16 code
Diagnosis 1-16 type
Diagnosis 1-16 suffix
Diagnosis 1-16 prefix
Procedure 1-10 year
Procedure 1-10 month
Procedure 1-10 day
Procedure 1-10 code
Procedure 1-10 suffix
Procedure 1-10 anaesthetic technique
Procedure 1-10 operative status
Procedure 1-10 time
Province Group
Peer group

Appendix II: Procedural Codes for top 10 Surgeries

Surgery	CCP codes
Above knee amputation	96.15
Colostomy	58.11-58.14
Lower leg amputation	96.14
Reduction of femur fracture with internal fixation	91.14, 91.34
Resection of aorta with replacement or anastomosis	50.24, 50.34, 50.54
Internal fixation of femur without fracture reduction	90.54
Partial or total colectomy	57.51 – 57.56, 57.59, 57.6
Aorta-iliac-femoral bypass	51.25
Non aortic peripheral vascular bypass or shunt	51.29
Hip arthroplasty	93.51, 93.59, 93.61-93.64, 93.69

CCP = Canadian Classification of Procedures

CHAPTER 5

Devereaux PJ, Bhandari M, Guyatt GH, Haynes RB, Heels-Ansdell D, Julian JA, Buckley N, Cinà CS, De Beer J, Worster A, Marcaccio M, Villar JC, Paul J, Cook DJ. Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Pilot Study. (Submitted for Publication)

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

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ABSTRACT

Background: For patients undergoing noncardiac surgery uncertainty exists about the current incidence of major vascular events, the optimal clinical risk estimation model for predicting major vascular events, and whether screening troponin measurements after surgery can avoid underdiagnosing myocardial infarctions.

Methods: In this prospective cohort pilot study we included patients undergoing noncardiac surgery who were $\geq$ 45 years of age and receiving a general or regional anesthetic. Patients had a troponin T measurement drawn 6 to 12 hours postoperatively and on the first, second, and third day after surgery.

Results: We recruited 99 patients at the Hamilton Health Sciences McMaster University Medical Centre. During the first 30 days after surgery 8% (95% CI 3-15) of the patients suffered a major vascular event (2 vascular deaths and 6 nonfatal myocardial infarctions). The observed event rate was significantly increased 6 fold compared to the expected event rate according to the Revised Cardiac Risk Index. Of the 6 patients who suffered a myocardial infarction only 1 patient experienced chest discomfort and 3 had no symptoms or signs to suggest myocardial infarction.

Conclusions: This study suggests that major perioperative vascular events are common, that the Revised Cardiac Risk Index underestimates risk, and that monitoring troponins after surgery can assist physicians to avoid missing myocardial infarctions. These results underscore the need for a large multicentre prospective cohort study to confirm or refute these findings.

INTRODUCTION

Because noncardiac surgery continues to make important advances in treating diseases and improving quality of life, more patients are undergoing noncardiac surgery.[1] Currently, approximately 100 million adults worldwide undergo noncardiac surgery requiring hospital admission annually.[1] Despite its benefits, noncardiac surgery is associated with adverse vascular events (including vascular death, nonfatal myocardial infarction, nonfatal cardiac arrest, and nonfatal stroke).

The increase in elderly patients undergoing surgery, the change in the invasiveness of some surgical interventions, and the limitations of previous research (e.g., dated information, focus on select high-risk groups, relatively small sample sizes), highlight uncertainty about the current incidence of major vascular events in patients undergoing noncardiac surgery.[2] Accurate information about major vascular events associated with noncardiac surgery is necessary to inform clinicians, administrators, and granting agencies about resources required to confront the problem.

Further, uncertainty exists regarding the optimal clinical risk estimation model for predicting major vascular events in patients undergoing noncardiac surgery. Previous risk modeling studies have been underpowered, the composite outcome in most studies did not include similarly important components, and stroke was not incorporated; moreover, most studies were conducted in a single centre university hospital.[2] Accurate risk estimation is essential to facilitate informed patient and physician decision-making regarding the appropriateness of noncardiac surgery.

There is promising but inconclusive preliminary evidence that troponin measurements after surgery can assist physicians to avoid missing perioperative myocardial infarctions.[3] If monitoring troponins after noncardiac surgery assists physicians to detect perioperative myocardial infarctions that would otherwise go undetected, troponin screening will facilitate appropriate timely interventions.

Given these uncertainties, we undertook a pilot study with the following objectives: 1) to determine the feasibility of conducting a large prospective cohort study to address these uncertainties; 2) to estimate the current incidence of major vascular events in patients undergoing noncardiac surgery; 3) to compare the observed event rates to the expected event rates according to the Revised Cardiac Risk Index;[4] and 4) to provide an estimate of the proportion of perioperative myocardial infarctions that may go undetected without troponin monitoring after surgery.

METHODS

Study Design and Eligibility Criteria

We conducted a prospective cohort study of patients undergoing noncardiac surgery. The Vascular events In noncardiac Surgery patIents cOhort evaluation (VISION) Pilot Study was performed at the Hamilton Health Sciences McMaster University Medical Centre (a 365 bed teaching hospital). Patients who underwent noncardiac surgery, were $\geq$ 45 years of age, and received a general or regional anesthetic (plexus block, spinal, or

epidural) met inclusion criteria. Patients for whom we could not obtain consent preoperatively (e.g., some emergent surgical cases) were included if research personnel obtained consent within the first 24 hours after their surgery. We excluded patients receiving only local or topical anesthesia, those not requiring at least an overnight hospital admission postoperatively, patients previously enrolled in the VISION Pilot Study, and patients who did not consent to participate.

Patient Recruitment

Research personnel screened the daily patient list in the preoperative assessment clinic to identify eligible patients undergoing elective surgery. To identify eligible patients admitted through the emergency department and those who did not attend the preoperative assessment clinic, research personnel screened daily surgical lists, surgical lists from the previous day, patient lists on surgical wards and in intensive care units, and patients in the preoperative holding area. Research personnel approached patients (or their families) who fulfilled the eligibility criteria to obtain written informed consent.

Data Collection, Monitoring, and Follow-up

Research personnel interviewed and examined patients and reviewed their charts to obtain information on potential predictors of major perioperative vascular events, including risk factors from the Revised Cardiac Risk Index.[4] Patients had an electrocardiogram recorded and a troponin T drawn 6 to 12 hours postoperatively and on the first, second, and third day after surgery. Patients enrolled between 12 and 24 hours

after surgery had an ECG and troponin T drawn right away and continued testing as outlined above.

Research personnel followed patients throughout their hospital stay, clinically evaluating them and examining their medical records to ensure caregivers followed study orders and to identify primary and secondary outcomes. We contacted patients by phone at 30 days after surgery; if patients (or their families) indicated that they had experienced an outcome, we contacted their physicians to obtain documentation.

Outcomes

Appendix I provides definitions for the outcomes. For our first objective (to determine the feasibility of conducting a large cohort study) our primary outcome was achieving $\geq$ 95% follow-up. For our second and third objectives (to estimate the current incidence of major vascular events and to compare the observed event rates to the expected event rates according to the Revised Cardiac Risk Index) our primary outcome was major vascular events (a composite of vascular death, nonfatal myocardial infarction, nonfatal cardiac arrest, and nonfatal stroke) at 30 days post surgery. Secondary outcomes for our second objective included vascular mortality, myocardial infarction, cardiac arrest, stroke, congestive heart failure, new clinically important atrial fibrillation, and re-hospitalization for vascular reasons at 30 days after surgery.

For our fourth objective (to provide an estimate of the proportion of perioperative myocardial infarctions that may go undetected without perioperative troponin monitoring) our primary outcome at 30 days after surgery was myocardial infarction that

probably would have gone undetected without perioperative troponin monitoring (myocardial infarction without chest discomfort or other symptoms or signs suggesting myocardial infarction), and our secondary outcome was myocardial infarction that possibly would have gone undetected without perioperative troponin monitoring (myocardial infarction without chest discomfort but with possible symptoms or signs of myocardial infarction).

Two outcome adjudicators independently adjudicated all major vascular events without knowledge of the patient's vascular risk factors. All disagreements were resolved by consensus except one disagreement that required a third adjudicator.

Analysis

We determined the proportion of patients suffering a major vascular event and the associated 95% confidence interval. For all patients and patients with 0, 1, 2, and ≥ 3 risk factors from the Revised Cardiac Risk Index, we determined the ratio of the observed number of major vascular events to the expected number of events according to the Revised Cardiac Risk Index and the associated 95% confidence interval. We also used Fisher's exact test to compare the proportion of urgent or emergent patients who underwent surgery on a weekend to the proportion who underwent surgery on a weekday. We used generalized estimating equations for repeated measures to determine if there were statistically significant variations in the usage of various cardiovascular drugs across any of the 4 time periods we evaluated (the week before surgery, within 24 hours prior to surgery, during the first 72 hours after surgery, and at discharge).

Ethics

All patients or their families provided written informed consent. The Hamilton Health Sciences Research Ethics Board in Hamilton, Ontario approved the protocol.

RESULTS

During a 10 week period starting in March 2005, we recruited 99 consecutive patients fulfilling eligibility criteria into the VISION Pilot Study, 6 of whom consented during the first 24 hours after surgery (on average, 10 hours post operatively). Figure 1 reports a patient flow chart for recruitment. A comparison of the study log with operating room surgical records and the hospital computer system demonstrated that study personnel did not approach 31 potentially eligible patients to participate (we approached 79% of the potentially eligible patients). Missed patients were primarily elective patients who were rescheduled on short notice, elective patients with the same booking time as many other elective cases, and some patients who underwent weekend surgery. Seventeen patients refused to participate (15% refusal rate).

Table 1 presents the patient characteristics. The most common surgery was intra-abdominal (50 patients) and 17 patients underwent surgery within 72 hours of an acute event (i.e., urgent/emergent surgery). Six of the 16 patients (37%) who underwent surgery on a weekend met our definition for urgent/emergent surgery whereas only 11 of the 83 patients (13%) who underwent surgery on a weekday were in this category ($p = 0.03$).

Eighteen patients had a history of coronary artery disease, and 36 patients had a history of hypertension. Before surgery the mean heart rate was 81 beats per minute (standard deviation [SD] 13) and the mean systolic blood pressure was 138 mm Hg (SD 20).

Table 2 reports the proportion of patients taking various cardiovascular drugs regularly in the week before surgery, within 24 hours of surgery, during the first 72 hours after surgery, and at hospital discharge. Aspirin and statin therapy demonstrated the greatest decrease in usage during the first 72 hours after surgery. Twenty patients received a beta-blocker within 24 hours prior to surgery and 23 patients received a beta-blocker at least once during the first 72 hours after surgery. Six patients in the VISION Pilot Study also participated in the POISE Trial (a perioperative beta-blocker randomized controlled trial)[5] and received either a beta-blocker or placebo. Anesthesia used included general (65 patients), spinal (7 patients), and combined general and thoracic epidural (27 patients). Patients underwent surgery for a median of 98 minutes (interquartile range [IQR] 69-157).

Patient follow-up was 100% complete at 30 days after surgery. The median length of hospital stay was 6 days (IQR 3-10). During the first 30 days after surgery 8% (95% CI 4-15) of the patients suffered a major vascular event (2 vascular deaths [1 due to stroke and 1 sudden death thought due to arrhythmia] and 6 nonfatal myocardial infarctions). Secondary outcomes included 4 patients who developed congestive heart failure and 2 patients who developed new clinically important atrial fibrillation.

Table 3 reports the observed major vascular event rates and the expected major vascular event rates according to the Revised Cardiac Risk Index. For patients with 1, 2,

or ≥ 3 risk factors, the observed event rates were approximately 7 fold higher than the expected event rates according to the Revised Cardiac Risk Index.

The median number of protocol troponins drawn per patient (maximum of 4 per patient) was 3 (IQR 2-4). Six patients suffered a myocardial infarction of whom only 1 experienced chest discomfort and 3 had no symptoms or signs to suggest myocardial infarction. Therefore, probably 3 and possibly another 2 of these myocardial infarctions would have gone undetected without perioperative troponin monitoring.

DISCUSSION

Principal Findings

Among patients ≥ 45 years of age undergoing noncardiac surgery requiring hospital admission, we demonstrated an 8% (95% CI 4-15) event rate for major vascular events during the first 30 days after surgery. In our study the Revised Cardiac Risk Index substantially underestimated the risk of major perioperative vascular events. Monitoring troponin levels after surgery detected 3 (and potentially 5) of 6 myocardial infarctions that physicians likely would have missed.

Strengths and Weaknesses of Our Study

Strengths of our study include its reflection of current practice, and the inclusion of patients who underwent surgery during weekends and urgent and emergent surgery.

Research personnel used a wide variety of approaches to identify eligible patients, who therefore approximate a consecutive and thus representative sample. We recorded stroke and new clinically important atrial fibrillation as outcomes. Two independent outcome adjudicators, blinded to patients' vascular risk factors, evaluated all major vascular events. We achieved 100% follow-up.

Our study has several limitations. We enrolled only 99 patients; therefore the findings of this pilot study warrant cautious interpretation. We evaluated the accuracy of the Revised Cardiac Risk Index but were unable to conduct similar analyses according to other risk indices (e.g., Veterans Affairs Model, Modified Cardiac Risk Index)[6 7] because the original publications did not report the precision of their estimates. Our study was conducted at a single university hospital.

Our Study in Relation to Other Studies

Considering prior research, the study by Lee and colleagues[4] provides the best estimate of the incidence of major vascular events in unselected adults undergoing noncardiac surgery requiring hospital admission.[2] This study suggests that major perioperative vascular events occur in 1.4% (95% CI 1.0-1.8%) of adults.[2]

Several potential explanations exist for the higher event rate (8%) in the VISION Pilot Study. First, the patient population may have changed in the decade between the study by Lee et al. and our study. Since then patients with coronary artery disease are living longer and developing conditions that require noncardiac surgery, a higher proportion of elderly patients are now undergoing noncardiac surgery, and some surgical interventions

have become less invasive,[2] raising questions regarding the applicability of Lee's results from the late 1980's and early 1990's. Second, we used troponin whereas Lee et al. used CK-MB in the diagnostic criteria for myocardial infarction. CK-MB is prone to false-positive and false-negative values for perioperative myocardial infarction.[3] Third, we included emergent surgical cases (2 events occurred in emergent patients), and we considered stroke a major adverse outcome whereas the study by Lee et al. excluded emergent surgical cases, and stroke was not considered as a major vascular event.[4] Finally, our results may represent a chance finding as a consequence of the small sample size.

We are unaware of any prior studies that have compared observed event rates to the expected event rates according to the Revised Cardiac Risk Index. Three prior prospective cohort studies of patients undergoing various noncardiac surgeries who had at least 1 post surgical measurement of a cardiac enzyme or biomarker have evaluated the proportion of perioperative myocardial infarctions with and without symptoms or signs suggestive of myocardial infarction.[8-10] The pooled results from these 3 studies demonstrated that only 16% (95% CI 6-31) of patients who suffered a perioperative myocardial infarction experienced chest discomfort and approximately half (45%, 95% CI 29-62%) had neither chest pain nor any other symptoms or signs to suggest myocardial infarction.[3]

Although these studies demonstrated similar results to the VISION Pilot Study they are limited in that there were only a total of 38 myocardial infarctions and they were restricted to patients with, or at high-risk for, coronary artery disease. These studies are also limited because they used CK-MB in their diagnostic criteria for myocardial

infarction, and there were variations across studies regarding monitoring (e.g., 2 studies monitored CK-MB[8 9] and 1 study started monitoring troponin T[10] after enrolling 28% of the patients).

Implications of Our Study

Our results suggest that major perioperative vascular events are more common than previously reported, that the Revised Cardiac Risk Index underestimates risk, and that monitoring troponins after surgery will allow physicians to avoid missing myocardial infarctions. Our study, however, is a pilot with a modest sample size and it identifies the need and provides the impetus for a large multicentre prospective cohort study to determine the current incidence of major perioperative vascular events and the optimal clinical estimation model to predict these events, and to determine whether troponin monitoring would allow better detection, and thus management, of perioperative myocardial infarctions.

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CONTRIBUTORSHIP STATEMENT

Dr. P.J. Devereaux contributed significantly to the study's concept and design, data acquisition, data analysis, and interpretation of the data. He wrote the first draft of the manuscript, provided critical revisions to the manuscript, and gave final approval of the submitted manuscript.

Dr. Mohit Bhandari contributed significantly to the study's concept and design, interpretation of the data, and provided critical revisions to the manuscript. He also gave final approval of the submitted manuscript.

Dr. Gordon Guyatt contributed significantly to the study's concept and design, interpretation of the data, and provided critical revisions to the manuscript. He also gave final approval of the submitted manuscript.

Dr. Brian Haynes contributed significantly to the study's concept and design, interpretation of the data, and provided critical revisions to the manuscript. He also gave final approval of the submitted manuscript.

Diane Heels-Ansdell contributed significantly to the study's concept and design, data analysis, interpretation of the data, and provided critical revisions to the manuscript. She also gave final approval of the submitted manuscript.

Dr. Jim Julian contributed significantly to the study's concept and design, data analysis, interpretation of the data, and provided critical revisions to the manuscript. He also gave final approval of the submitted manuscript.

Dr. Norman Buckley contributed significantly to the study's concept and design, interpretation of the data, and provided critical revisions to the manuscript. He also gave final approval of the submitted manuscript.

Dr. Claudio Cina contributed significantly to the study's concept and design, interpretation of the data, and provided critical revisions to the manuscript. He also gave final approval of the submitted manuscript.

Dr. Justin de Beer contributed significantly to the study's concept and design, data analysis, interpretation of the data, and provided critical revisions to the manuscript. He also gave final approval of the submitted manuscript.

Dr. Andrew Worster contributed significantly to the study's concept and design, interpretation of the data, and provided critical revisions to the manuscript. He also gave final approval of the submitted manuscript.

Dr. Michael Marcaccio contributed significantly to the study's concept and design, interpretation of the data, and provided critical revisions to the manuscript. He also gave final approval of the submitted manuscript.

Dr. Juan Carlos Villar contributed significantly to the study's concept and design, interpretation of the data, and provided critical revisions to the manuscript. He also gave final approval of the submitted manuscript.

Dr. James Paul contributed significantly to the study's concept and design, interpretation of the data, and provided critical revisions to the manuscript. He also gave final approval of the submitted manuscript.

Dr. Deborah Cook contributed significantly to the study's concept and design, interpretation of the data, and provided critical revisions to the manuscript. She also gave final approval of the submitted manuscript.

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Dr. Deborah Cook holds a Canada Research Chair

Table 1: Patient Characteristics

Characteristics	Patients (N=99)
Mean +/- SD age, years	64 +/- 11
Female sex, n	60
Type of surgery, n	
Intra-abdominal	50
Gynecology	30
Orthopedics	15
Ears/Nose/Throat	2
Hernia/breast	2
Vascular	0
Thoracic	0
Urology	0
Neurology	0
Plastics	0
Timing of surgery, n	
< 24 hours after an acute event	3
24-72 hours after an acute event	14
other	82
History of coronary artery disease, n	18
History of peripheral vascular disease, n	2
History of cerebrovascular event, n	6
History of congestive heart failure, n	4
Use of insulin or an oral hypoglycemic, n	13
Hypertension, n	36
Smoking status, n	
Never	68
Current	15
Former	16
Creatinine level > 175 μmol/L	0

Table 2: Perioperative Cardiovascular Drug Usage Among the 99 Participants

Drug	Regular use in week prior to surgery N	Taken within 24 hours prior to surgery n	Taken at least once during the 1st three days after surgery n	Discharged on medication n	P value
Aspirin	16	5	3	10	<0.01
Long-acting nitrate	4	5	1	1	0.14
Oral anticoagulant	5	1	2	6	0.15
Statin	26	26	9	26	<0.01
ACEI or ARB	24	26	28	28	0.24
Beta-blocker*	20	20	23	27	0.02
Alpha-2 agonist	1	1	0	2	N.S.^
Rate controlling CCB	9	8	8	10	0.34
Dihydropyridine CCB	2	2	2	4	0.16
Unfractionated IV heparin or LMWH	0	0	17	1	<0.01

n = number of patients taking the drug, % = percentage, ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, N.S.^ = non statistically significant result but unable to provide an accurate p value because of failure of convergence of the model due to minimal data, CCB = calcium channel blocker, IV = intravenous, LMWH = low molecular weight heparin, * = an additional 6 patients participated in a perioperative beta-blocker trial and received either a beta-blocker or placebo

Table 3: Observed and Expected Event Rates (according to the Revised Cardiac Risk Index) by Number of Risk Factors

Number of risk factors[†]	Number of patients	Observed (O) events[‡]	Observed event rate	Expected event rate[§]	Expected (E) events	O/E ratio (95% CI*)
0	35	0	0%	0.4%	0.16	0 (0-23.5)
1	44	3	6.8%	1.0%	0.42	7.1 (1.5-20.8)
2	12	2	16.7%	2.4%	0.28	7.1 (0.9-25.5)
≥3	8	3	37.5%	5.3%	0.43	7.0 (1.5-20.6)
All	99	8	8.1%	1.3%	1.29	6.2 (2.7-12.2)

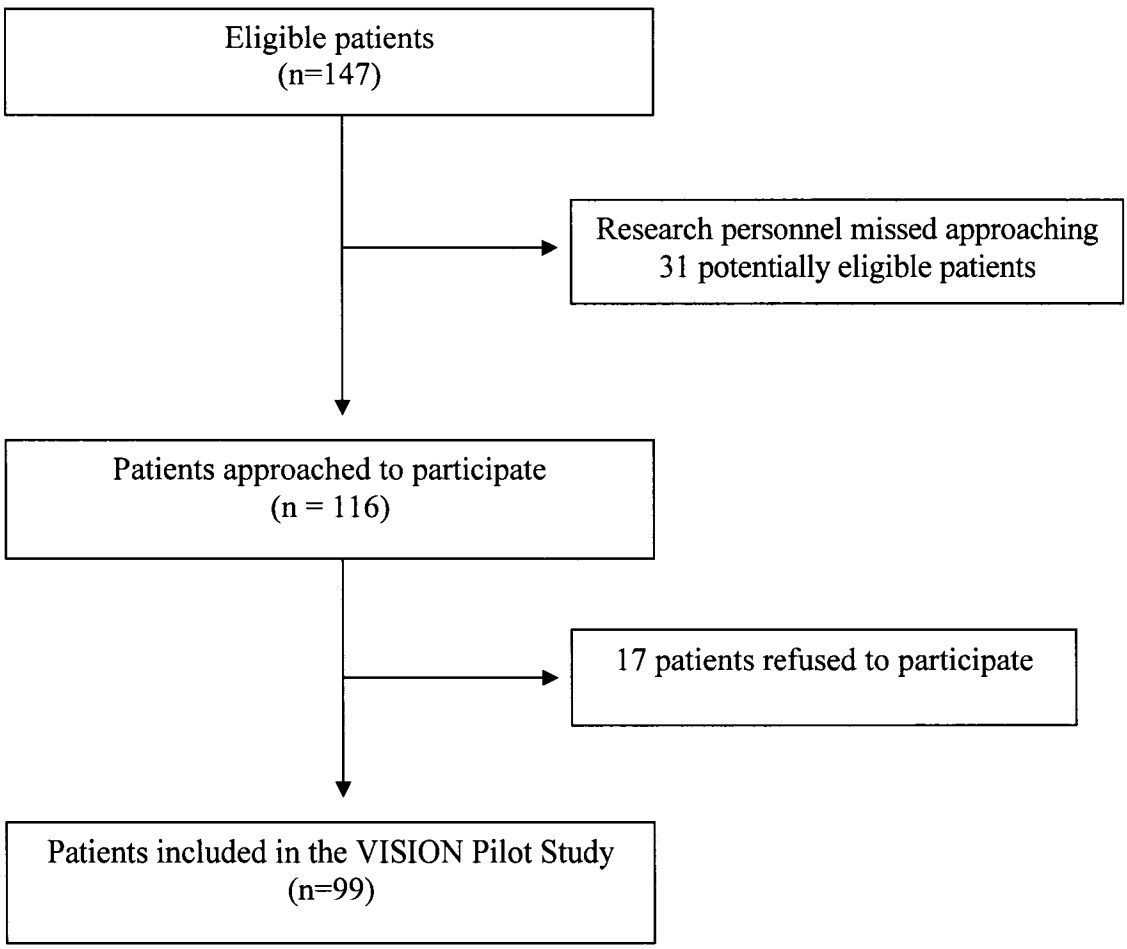
[†] risk factors = ischemic heart disease, cerebrovascular event, congestive heart failure, diabetes, creatinine > 175 μmol/L, and high risk surgery (i.e., vascular, intraperitoneal, or intrathoracic); [‡] events = cardiovascular death, nonfatal myocardial infarction, nonfatal cardiac arrest, or nonfatal stroke; [§] expected event rates = rates based on the Revised Cardiac Risk Index[2]; * CI = confidence interval

Appendix I: Outcome Definitions

Outcome	Definition
Sub classification of death	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).
Myocardial infarction	The diagnosis requires either one of the following: 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, 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 and $\geq$ 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

Outcome	Definition
Nonfatal cardiac arrest	The diagnosis requires a successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical alternans.
Congestive heart failure	The diagnosis requires both clinical (i.e. any of the following signs: elevated jugular venous pressure, respiratory rales, crepitations, or presence of S3) and radiographic evidence (e.g. vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema).
Clinically important atrial fibrillation	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.
Rehospitalization for vascular reasons	Rehospitalization for congestive heart failure, ischemic symptoms with ST or T wave changes on an ECG, arrhythmia, or stroke.
Stroke	A new focal neurological deficit thought to be vascular in origin with signs and symptoms lasting more than 24 hours.

Figure 1: Patient Flow Chart



CHAPTER 6

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HOW STRONG IS THE EVIDENCE FOR THE USE OF PERIOPERATIVE BETA-BLOCKERS IN NONCARDIAC SURGERY? SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS

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ABSTRACT

Objective: To determine the effect of beta-blocker therapy in patients undergoing noncardiac surgery.

Design: Systematic review and meta-analysis

Data Sources: We used seven search strategies including searching two bibliographic databases and hand searching seven medical journals.

Review Methods: We included randomised controlled trials (RCTs) that evaluated beta-blocker therapy in patients undergoing noncardiac surgery. Perioperative outcomes within 30 days of surgery included: total mortality, cardiovascular mortality, nonfatal myocardial infarction, nonfatal cardiac arrest, nonfatal stroke, congestive heart failure, hypotension requiring treatment, bradycardia requiring treatment, and bronchospasm.

Results: Twenty-two RCTs that randomised a total of 2437 patients met eligibility criteria. Perioperative beta-blockers did not demonstrate any statistically significant beneficial effects on any of the individual outcomes and the only nominally statistically significant beneficial relative risk was 0.44 (95% CI 0.20 to 0.97, 99% CI 0.16 to 1.24) for the composite outcome of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal cardiac arrest. To assess the strength of this finding we used methods adapted from formal interim monitoring boundaries applied to cumulative meta-analysis that demonstrated that the evidence fails, by a considerable degree, to meet standards for foregoing additional studies. The individual safety outcomes in patients treated with perioperative beta-blockers demonstrated a relative risk for bradycardia requiring treatment of 2.27 (95% CI 1.53 to 3.36, 99% CI 1.36 to 3.80) and the nominally

statistically significant relative risk for hypotension requiring treatment of 1.27 (95% CI 1.04 to 1.56, 99% CI 0.97 to 1.66).

Conclusion: The current evidence that perioperative beta-blockers reduce major cardiovascular events is encouraging but too unreliable to allow definitive conclusions.

INTRODUCTION

Noncardiac surgery is associated with an increase in catecholamines,[1] which result in an increase in blood pressure, heart rate, and free fatty acid levels.[2-4] Beta-blockers suppress the effects of increased catecholamines and as a result may prevent perioperative cardiovascular events.

Several authors and guideline committees have advocated the use of beta-blockers for patients undergoing noncardiac surgery.[5-8] The two authors of the American College of Physicians (ACP) noncardiac surgery perioperative guidelines inserted an addendum, after the ACP had approved the guidelines, advocating the use of perioperative atenolol in patients with coronary artery disease.[7] More recently, the American College of Cardiology/American Heart Association (ACC/AHA) task force on guidelines for noncardiac surgery recommended perioperative beta-blockers for the following patients: class I recommendation for patients undergoing vascular surgery with preoperative stress test ischemia; class IIa recommendation for patients undergoing noncardiac surgery with established or risk factors for coronary artery disease or untreated hypertension.[8] Other authors have questioned the robustness of the perioperative beta-blocker evidence and have advocated the need for a large definitive randomised controlled trial (RCT).[9 10]

Accurate understanding of the strength of the perioperative beta-blocker evidence requires a systematic, comprehensive, and unbiased accumulation of the available evidence and methods adapted from formal interim monitoring boundaries applied to cumulative meta-analysis.[11] We therefore undertook a systematic review and meta-

analysis to evaluate the effect of beta-blockers on cardiovascular events in patients undergoing noncardiac surgery.

METHODS

Eligibility Criteria

We included RCTs that evaluated the effect of beta-blocker therapy in patients undergoing noncardiac surgery. RCTs were eligible regardless of their publication status, language, or primary objectives. We excluded: RCTs in which there was no control group receiving a placebo or standard care; and RCTs in which there were no relevant events in both the treatment and control groups because these trials provide no information on the magnitude of the treatment effects.[12]

Study Identification

Strategies to identify studies included: electronic search of two bibliographical databases (Appendix 1); a hand search of seven anesthesia journals (Appendix 1); consultation with experts; our own files; review of reference lists from eligible RCTs; PubMed (April 2003), using the "see related articles" feature for key publications; and SciSearch (April 2003) for publications that cited key publications.

Assessment of Study Eligibility

Two individuals independently evaluated study eligibility (kappa = 0.96). The consensus process to resolve disagreements required individuals to discuss the reasoning for their decisions; in all cases, one individual recognized an error.

Data Collection and Quality Assessment

We abstracted descriptive data (e.g., type of surgery, patient population) and markers of validity (e.g., concealment, blinding) from all RCTs. We abstracted data on our perioperative outcomes: total mortality, cardiovascular mortality, nonfatal myocardial infarction, nonfatal cardiac arrest, nonfatal stroke, congestive heart failure, hypotension requiring treatment, bradycardia requiring treatment, bronchospasm, and the composite outcome of major perioperative cardiovascular events (i.e., cardiovascular death, nonfatal myocardial infarction, or nonfatal cardiac arrest). We defined perioperative outcomes as outcomes that occurred within 30 days of surgery.

The definitions of outcomes were those used in the original RCTs, except when an RCT did not define or report one of our main outcomes. We anticipated that three of our main outcomes would not be defined or reported in all RCTs. We therefore defined, a priori, cardiovascular death, bradycardia requiring treatment, and hypotension requiring treatment (Appendix 2).

Teams of two individuals independently abstracted data from all RCTs (kappas were 0.69 to 1.0). Disagreements were resolved by consensus using the process discussed above.

Statistical Analysis

For each RCT we calculated the relative risks of the outcomes for patients receiving perioperative beta-blocker therapy compared with patients receiving placebo or standard care. For each relative risk we determined the conventional 95% confidence limit and the 99% confidence limit. When – as it is true with small trials with few or a moderate number of events – statistical significance depends on a difference of only a handful of events, the 99% confidence interval may better convey our confidence in the estimate of the treatment effect.

Analyses were carried out on an intention to treat basis. Relative risks were pooled using Dersimonian and Laird random effects model.[13] We calculated an I^2 as a measure of heterogeneity for each outcome analysis. An I^2 value represents the percentage of total variation across trials that is due to heterogeneity rather than chance, and we considered an I^2 value $\leq 25\%$ as low and an I^2 value $\geq 75\%$ as high.[14] Prior to the analyses, we specified several hypotheses related to the markers of trial validity, treatment interventions, and duration of follow-up to explain potential heterogeneity (i.e., I^2 value $> 25\%$). We evaluated the ratio of relative risks across subgroups in an attempt to explain heterogeneity using a test of interaction.[15] We entered data in duplicate and conducted analyses using RevMan 4.2 (Cochrane Collaboration, Oxford, UK).

Because there is no reason to believe that the standards for a meta-analysis should be less rigorous than those of a good single RCT, we used methods adapted from formal interim monitoring boundaries applied to cumulative meta-analysis to assess the

reliability and conclusiveness of the available perioperative beta-blocker evidence,[16] focusing on the composite outcome of major perioperative cardiovascular events. The sample size required for a reliable and conclusive meta-analysis is at least as large as that of a single optimally-powered RCT. Therefore, we calculated the sample size (i.e., the optimal information size) requirement for our meta-analysis. We conducted formal interim monitoring for meta-analyses using the optimal information size to help construct a Lan DeMets sequential monitoring boundary for our meta-analysis,[16] analogous to interim monitoring in an RCT. We used this monitoring boundary as a means to determine whether the evidence in our meta-analysis was reliable and conclusive.

RESULTS

Included RCTs

We identified 22 RCTs published between 1980 and 2004 that fulfilled our eligibility criteria (Figure 1).[17-38] We obtained or confirmed data with trialists from all included trials. Table 1 summarizes the design characteristics of the included RCTs. [17-38] The 22 RCTs randomised a total of 2437 patients and the median sample size was 61 patients. The type of noncardiac surgery was unrestricted in 8 RCTs. Treatment interventions varied from brief intravenous beta-blocker interventions just prior to surgery to 30 day postoperative beta-blocker interventions. The duration of patient follow-up was limited to the end of surgery in 1 RCT and until discharge from the recovery room in 5 RCTs.

Quality Assessment

Most RCTs fulfilled our quality measures (e.g., all RCTs had complete patient follow-up). Table 2 reports the quality measures of the RCTs that failed to fulfill at least one of our markers of validity.[20 23 34 36 37]

Effect of Perioperative Beta-Blockers

Table 3 presents the results of the meta-analyses. Overall there were only a moderate number of major perioperative cardiovascular events (i.e., 18 cardiovascular deaths, 58 nonfatal myocardial infarctions, and 7 nonfatal cardiac arrests).

Perioperative beta-blockers did not demonstrate any statistically significant beneficial effects on any of the individual outcomes. Patients in 4 trials suffered fatal events.[32-34 38] There were 9 deaths (5 cardiovascular) among the 453 patients randomised to beta-blocker therapy compared with 19 deaths (13 cardiovascular) among the 454 patients randomised to placebo or standard care (RR=0.56; 95% CI 0.14 to 2.31, 99% CI 0.09 to 3.60 for total mortality) (RR=0.40; 95% CI 0.14 to 1.15, 99% CI 0.10 to 1.60 for cardiovascular mortality).

The individual safety outcomes in patients treated with perioperative beta-blockers demonstrated a relative risk of 2.27 (95% CI 1.53 to 3.36, 99% CI 1.36 to 3.80) for bradycardia requiring treatment (Figure 2) and 1.27 (95% CI 1.04 to 1.56, 99% CI 0.97 to 1.66) for hypotension requiring treatment. Both these analyses demonstrated low

heterogeneity (i.e., I^2 of 3% for bradycardia requiring treatment and 6% for hypotension requiring treatment).

Eight trials had patients who suffered a major perioperative cardiovascular event (i.e., cardiovascular death, nonfatal myocardial infarction, or nonfatal cardiac arrest) (Figure 3).[31-38] There were 28 major perioperative cardiovascular events among the 589 patients randomised to beta-blocker therapy compared with 55 among the 563 patients randomised to placebo or standard care (RR=0.44; 95% CI 0.20 to 0.97, 99% CI 0.16 to 1.24). There was moderate heterogeneity across the trial results (I^2 = 42%).

Exploring Heterogeneity

Our a priori hypothesis related to trial validity helped explain this heterogeneity. The 3 trials by Poldermans,[34] Zaug,[36] and Urban[37] did not fulfill all our quality measures (i.e., these trials were stopped early after an interim analysis suggested a much larger than originally predicted treatment effect or there was no blinding of patients, health care providers, or data collectors) and their pooled relative risk for major perioperative cardiovascular events was 0.13 (95% CI 0.04 to 0.38, 99% CI 0.03 to 0.54) with an I^2 =0%. The remaining 5 high-quality trials had a pooled relative risk for major perioperative cardiovascular events of 0.82 (95% CI 0.49 to 1.36, 99% CI 0.42 to 1.59) with an I^2 = 0%.[31-33 35 38] The test of interaction across these subgroups of high quality and lower quality RCTs was significant ($p<0.01$), and the corresponding ratio of relative risks was 6.3 (95% CI 1.8 to 22) indicating that the lower quality RCTs relative risk estimate was 6 fold lower than that of the higher quality RCTs.

Reliability and Conclusiveness of Composite Outcome Result

To determine the optimal information size we assumed a 10% control event rate (i.e., the control event rate in our meta-analysis for the composite outcome) and a 25% relative risk reduction (the average relative risk reduction among the beta-blocker myocardial infarction RCTs)[39] with 80% power and a 0.01 two-sided alpha. Our calculations indicated that the optimal information size required to reliably detect a plausible treatment effect, for the composite outcome of major perioperative cardiovascular events, is 6124 patients. Currently there have been 1152 patients randomised in the beta-blocker RCTs with patients who have suffered a major perioperative cardiovascular event. We used the optimal information size to help construct the Lan-DeMets sequential monitoring boundary, Figure 4. The sequential monitoring boundary has not been crossed indicating that the cumulative evidence is unreliable and inconclusive.

DISCUSSION

Statement of Principal Findings

Our results suggest that perioperative beta-blockers may decrease the risk of major perioperative cardiovascular events, but increase the risk of bradycardia and hypotension requiring treatment. These results, however, are based upon only a moderate number of major perioperative cardiovascular events and bradycardic patients requiring

treatment. A total of 1152 patients were randomised in the 8 trials that had patients who suffered a major perioperative cardiovascular event. This number of patients randomised is much smaller than our calculated optimal information size (6124 patients, based upon the 10% event rate in current trials) required to reliably detect a plausible treatment effect of beta-blocker therapy in patients undergoing noncardiac surgery. Our use of methods adapted from formal interim monitoring boundaries applied to cumulative meta-analysis demonstrated that the current perioperative beta-blocker evidence is insufficient and inconclusive.

Strengths and Weaknesses of Our Systematic Review

Our systematic review has several strengths. We undertook a comprehensive search using 7 strategies to identify RCTs, conducted eligibility decisions and data abstraction in duplicate and demonstrated a high degree of agreement, obtained or confirmed data with all trialists, and evaluated the reliability and conclusiveness of the available perioperative beta-blocker evidence through a method adapted from formal interim monitoring boundaries applied to cumulative meta-analysis.

Our systematic review only focuses on short term outcomes (i.e., outcomes within 30 days of surgery). It is possible that perioperative beta-blockers affect long term cardiovascular outcomes. Of all the RCTs we identified only the RCT by Mangano and colleagues evaluated the effect of perioperative beta-blocker therapy on long term outcomes.[40] This RCT is the long term follow-up component of the RCT by Wallace and colleagues that is included in our review. The authors reported 30 deaths during the two

year follow-up among the 200 patients randomized to atenolol or placebo for a maximum duration of 7 postoperative days, and a > 50% reduction in the relative risk of death among patients who received atenolol.[40] These results, however, did not include the 6 deaths that occurred during the period when patients were receiving the study drug. When these events are appropriately included in the intention to treat analysis the reduction in the risk of death with atenolol is no longer statistically significant.[10]

Our Systematic Review in Relation to Other Systematic Reviews

A systematic review by Auerbach and Goldman[41] and a systematic review and meta-analysis by Stevens and colleagues[42] have evaluated the effects of perioperative beta-blockers. The main difference between our systematic reviews is that we included a lot more RCTs and we used methods adapted from formal interim monitoring boundaries applied to cumulative meta-analysis to determine if the current evidence is reliable and conclusive.

Implications of Our Systematic Review

Our systematic review provides encouraging evidence that perioperative beta-blockers may reduce the risk of major perioperative cardiovascular events but increase the risk of bradycardia and hypotension requiring treatment in patients undergoing noncardiac surgery. Using a subset of the evidence we identified, several authors and the ACC/AHA perioperative guidelines have recommended perioperative beta-blocker

therapy to varying groups of patients undergoing noncardiac surgery.[5-8 43] These recommendations warrant cautious interpretation.

First, there were only a moderate number of events in the perioperative beta-blocker RCTs (e.g., 83 major perioperative cardiovascular events). Second, the perioperative beta-blocker evidence from our meta-analyses suggests a large treatment effect (i.e., a 56% relative risk reduction in major perioperative cardiovascular events). This treatment effect, however, is inconsistent with the results of the beta-blocker RCTs in myocardial infarction and congestive heart failure that have randomized > 50,000 patients and have demonstrated moderate treatment effects (i.e., relative risk reductions of 15-35%).[39 44-47] If perioperative beta-blockers prevent major perioperative cardiovascular events they probably do so through suppressing adrenergic activity. Therefore, large perioperative beta-blocker treatment effects are unlikely, because there remains a substantial number of perioperative cardiovascular pathogenic mechanisms that beta-blockers do not affect (i.e., increased platelet reactivity, plasminogen activator inhibitor I (PAI-I), factor VIII-related antigen levels, and inflammation, and decreased in antithrombin III levels).[48-51]

Third, the nominally statistically significant beneficial result of decreased major perioperative cardiovascular events with beta-blocker therapy demonstrated moderate heterogeneity ($I^2 = 42\%$), which weakens the reliability of this finding. Further, the relative risk estimate from the 3 trials with methodological limitations (i.e., stopped early for unexpected large treatment effects or failure to blind) was 6 fold lower than that of the high-quality RCTs that failed to demonstrate a statistically significant result. This

finding is in contrast to the outcomes of bradycardia and hypotension requiring treatment that demonstrated low heterogeneity, which strengthens the reliability of these findings.

Fourth, for a meta-analysis to provide definitive evidence it should fulfill at least the minimum standards expected of a well-designed, adequately powered, and rigorously conducted single RCT. In fact, the potential for additional biases (e.g. publication bias), heterogeneity in various features of the design and conduct of the included RCTs, and an inflated type I error rate (due to multiple looks at the data as trials are added) suggest the appropriateness of a higher level of skepticism in interpreting a meta-analysis than a single RCT. One can address the issue of whether a meta-analysis is definitive using the logic of early stopping for an RCT. The analogy to early stopping of a single trial would be a recommendation, on the basis of a meta-analysis, to cease conducting further trials. Using this logic, one can adduce criteria for concluding that evidence is adequate to recommend that no further studies are needed.

Our calculated optimal information size required to reliably detect a plausible treatment effect was 6124 patients assuming a 10% event rate – with a lower event rate, which is more probable, a higher optimal information size is required. Our meta-analysis, however, demonstrated that the 8 trials that had patients who suffered a major perioperative cardiovascular event included only 20% of this minimal sample size. Using the optimal information size we constructed a sequential monitoring boundary, and the cumulative meta-analysis has not crossed this monitoring boundary. If the data included in our meta-analysis were from a single RCT at an interim analysis, insufficient evidence

would exist to justify stopping the trial. Therefore, the monitoring boundary indicates that the cumulative evidence is inconclusive and further research is needed.

The RCT evidence in our systematic review identifies the need and provides the impetus for a large adequately powered perioperative beta-blocker RCT to definitively establish the benefits and risks of beta-blocker therapy. Such a trial, the PeriOperative ISchemic Evaluation (POISE) trial that plans to recruit 10,000 patients, was recently initiated and has recruited over 3400 patients in 17 countries to date. Clear evidence establishing the role of beta-blockers in patients undergoing noncardiac surgery awaits the results of such trials.

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CONTRIBUTORSHIP STATEMENT

Dr. P.J. Devereaux contributed significantly to the systematic review's concept and design, data acquisition, data analysis, and interpretation of the data. He wrote the first draft of the manuscript, provided critical revisions to the manuscript, and gave final approval of the submitted manuscript.

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Dr. Devereaux will act as the guarantor.

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FIGURE LEGENDS

Figure 1 - Flowchart of Systematic Review

Figure 2 – Bradycardia requiring treatment

Figure 3 - Major perioperative cardiovascular events

Figure 4 - Cumulative meta-analysis with Lan-DeMets sequential monitoring boundary

Table 1. Design characteristics of randomised controlled trials included in systematic review

Trials	Year of publication	Number randomised	Type of surgery and patient population	Intervention	Duration of follow-up
Coleman[17]	1980	42	inpatient elective general noncardiac surgery	metoprolol 2 mg, 4 mg, or placebo injection just before anesthesia	hospital discharge
Cucchiara[18]	1986	74	inpatient carotid endarterectomy, patients with a MI the preceding 6 months and CHF were excluded	esmolol 500ug/kg/min for 4 minutes then 300ug/kg/min for 8 minutes or placebo infusion starting 5 minutes prior to anesthesia	end of surgery
Jakobsen[19]	1986	20	inpatient middle ear or nasal septum surgery, patients with evidence of cardiopulmonary disease were excluded	oral metoprolol 50 mg or placebo the day before surgery and metoprolol 100mg or placebo 1.5-3 hours before anaesthesia	discharged from recovery room
Liu[20]	1986	30	noncardiac surgery (primarily gynaecological), unclear if restricted to inpatient surgery, patients were ASA class I	esmolol 500ug/kg/min for 4 minutes then 300ug/kg/min for 8 minutes or placebo infusion starting 5 minutes prior to anesthesia	discharged from recovery room
Magnusson[21]	1986	30	inpatient cholecystectomy or hernia repair, patients had untreated hypertension but no prior MI or CHF	oral metoprolol 200 mg or placebo daily for at least 2 weeks prior to surgery, the morning of surgery, and metoprolol 15 mg or placebo injection just before anesthesia	hospital discharge
Gibson[22]	1988	40	inpatient neurosurgery, patients had a $\geq$ 20% increase in systolic blood pressure above ward pressure on emergence from anesthesia	esmolol 40 mg/min or placebo infusion for 4 minutes just prior to extubation and then esmolol 24 mg/min or placebo infusion for 10 minutes	discharged from recovery room
Stone[23]	1988	128	inpatient major noncardiac surgery, patients had untreated hypertension but no	oral labetalol 100mg, atenolol 50 mg, oxprenolol 20 mg, or usual care 2 hours prior to surgery	hospital discharge

Trials	Year of publication	Number randomised	Type of surgery and patient population CAD or CHF	Intervention	Duration of follow-up
MacKenzie[24]	1989	100	outpatient gynaecological surgery or dental extractions	oral timolol 10 mg or placebo 72 minutes prior to anesthesia	hospital discharge
Inada[25]	1989	30	inpatient elective noncardiac surgery, patients with CHF, unstable angina, or ASA class IV were excluded	labetalol 5 mg, 10 mg or placebo injection 2 minutes prior to anesthesia	discharged from recovery room
Leslie[26]	1989	60	inpatient elective noncardiac surgery, patients were ASA class I or II but no prior MI or CHF	labetalol 0.25, 0.5, 0.75, or 1 mg/kg or placebo injection just prior to surgery	hospital discharge
Jakobsen[27]	1990	98	inpatient elective hysterectomy or lower extremity orthopaedic surgery, patients were ASA class I or II	oral metoprolol (slow release) 100 mg or placebo 1-3 hours prior to surgery	hospital discharge
Miller[28]	1990	45	inpatient elective peripheral vascular surgery, patients had known CAD or $\geq$ 2 risk factors but no history of CHF or MI within 6 months of surgery	esmolol 1.5mg/kg, 3.0 mg/kg, or placebo injection just before anesthesia	hospital discharge
Miller[29]	1991	548	inpatient elective noncardiac surgery, patients had no history of CHF or MI within 6 months of surgery	esmolol 100mg, 200mg, or placebo injection just before anesthesia	discharged from recovery room
Davies[30]	1992	40	inpatient carotid endarterectomy	oral atenolol 50 mg or placebo 2 hours prior to surgery	day 4 post surgery

Trials	Year of publication	Number randomised	Type of surgery and patient population	Intervention	Duration of follow-up
Jakobsen[31]	1997	36	inpatient elective thoracotomy for lung resection, patients without cardiovascular problems	oral metoprolol 100 mg or placebo 90 minutes prior to surgery and once daily thereafter until day 11 post surgery or hospital discharge if sooner	day 11 post surgery or hospital discharge if sooner
Wallace[32]	1998	200	inpatient elective noncardiac surgery, patients with or at risk for CAD	atenolol 5 mg (for a HR $\geq$ 55 bpm and a SBP $\geq$ 100 mm Hg) or placebo injection twice 30 minutes prior to surgery, repeat dosing immediately after surgery, daily thereafter the study drug was given the same way twice a day, or oral atenolol 100 mg (for a HR > 65 bpm and a SBP $\geq$ 100 mm Hg) or 50 mg (for a HR 55-65 bpm and a SBP $\geq$ 100 mm Hg) or placebo on the first postoperative morning and each day until day 7 post surgery or hospital discharge if sooner	Hospital discharge
Bayliff[33]	1999	99	inpatient major (noncardiac) thoracic surgery	oral propranolol 10 mg or placebo every 6 hours, starting before surgery and continuing for 5 days post surgery	Hospital discharge
Poldermans[34]	1999	112	inpatient elective abdominal aortic or infrainguinal arterial surgery, patients had a cardiac risk factor and a positive dobutamine echocardiography study	oral bisoprolol 5 mg daily for a least a week prior to surgery and then 10mg daily if the HR was > 60 bpm, post surgery the study drug was continued for 30 days, patients who were unable to take drugs orally were given metoprolol infusions to keep the HR below 80 bpm, the control group received standard perioperative care	day 30 post surgery

Trials	Year of publication	Number randomised	Type of surgery and patient population	Intervention	Duration of follow-up
Raby[35]	1999	26	inpatient elective vascular surgery, patients had ischemia during preoperative holter monitor testing	esmolol or placebo infusion adjusted every hour to reduce the HR below a predetermined ischemic threshold starting immediately post surgery and continuing for 48 hours	hour 49 post surgery
Zaugg[36]	1999	63	inpatient elective major noncardiac surgery, patients with CHF were excluded	group 1. the control group received standard perioperative care group 2: atenolol 5 mg (for a HR > 54 bpm and a SBP > 99 mm Hg) injection twice 30 minutes prior to surgery, repeat dosing immediately after surgery and twice daily thereafter for 72 hours group 3: atenolol 5 mg injections every 5 minutes during surgery to maintain a HR < 80 bpm and a MAP ≤ 20% of preoperative MAP	hospital discharge
Urban[37]	2000	120	inpatient elective total knee arthroplasty, patients had known or probably CAD	esmolol infusion started within the first hour after surgery and titrated to keep the HR < 80 bpm until the next morning, then metoprolol 25 mg BID with titration to keep the HR < 80 bpm, the study drug continued until discharge from hospital, the control group received standard perioperative care	hospital discharge
Yang[38]	2004	496	inpatient elective vascular surgery (i.e., abdominal aortic, infrainguinal, or extra-anatomical), patients were ASA III or less and had no history of CHF	oral metoprolol (50 mg for a weight < 75 kg or 100 mg for a weight ≥ 100 mg) or placebo 2 hours prior to surgery, repeat dosing 2 hours after surgery, daily thereafter the study drug was given the same way twice a day until	day 30 post surgery

Trials	Year of publication	Number randomised	Type of surgery and patient population	Intervention	Duration of follow-up
				day 5 post surgery or hospital discharge if sooner, patients who were unable to take drugs orally were given metoprolol infusions of 0.2mg/kg (15 mg maximum) or placebo Q 6 hrs	

MI = Myocardial infarction
CHF = Congestive heart failure
ASA = American Surgical Association Classification
CAD = Coronary artery disease
HR = heart rate
SBP = systolic blood pressure
bpm = beats per minute
MAP = mean arterial pressure

Table 2. Quality measures of the RCTs that failed to fulfill any one of our markers of validity

Trials	Concealment of randomisation	RCT stopped early	Patients blinded	Health care providers blinded	Data collectors blinded	Outcome assessors blinded
Liu[20]	No	No	Yes	Yes	Yes	Yes
Stone[23]	Yes	No	No	Yes	Yes	Yes
Poldermans[34]	Yes	Yes	No	No	No	Yes
Zaugg[36]	Yes	No	No	No	Yes	Yes
Urban[37]	Yes	Yes	No	No except Anesthesiologists	Yes	Yes

RCT = randomised controlled trial
NR = Not reported

Table 3: The effect of perioperative beta-blockers within the first 30 days of noncardiac surgery

Outcome and trials	Beta-blocker groups n/N	Control groups n/N	RR	95% CI	99% CI	I^2
Total Mortality						
Wallace[32]	4/99	2/101	2.04	0.38 to 10.89	0.23 to 18.43	
Bayliff[33]	2/49	1/50	2.04	0.19 to 21.79	0.09 to 45.85	
Poldermans[34]	2/59	9/53	0.20	0.05 to 0.88	0.03 to 1.41	
Yang[38]	1/246	7/250	0.15	0.02 to 1.17	0.01 to 2.26	
Total	**9/453**	**19/454**	**0.56**	**0.14 to 2.31**	**0.09 to 3.60**	**57%**
Cardiovascular Mortality						
Wallace[32]	1/99	2/101	0.51	0.05 to 5.54	0.02 to 11.71	
Bayliff[33]	2/49	1/50	2.04	0.19 to 21.79	0.09 to 45.85	
Poldermans[34]	2/59	9/53	0.20	0.05 to 0.88	0.03 to 1.41	
Yang[38]	0/246	1/250	0.34	0.01 to 8.27	0.01 to 22.59	
Total	**5/453**	**13/454**	**0.40**	**0.14 to 1.15**	**0.10 to 1.60**	**0%**
Nonfatal Myocardial Infarction						
Jakobsen[31]	1/18	0/18	3.00	0.13 to 69.09	0.05 to 185.13	
Poldermans[34]	0/59	9/53	0.05	0.00 to 0.79	0.00 to 1.93	
Raby[35]	0/15	1/11	0.25	0.01 to 5.62	0.00 to 14.93	
Zaugg[36]	0/43	3/20	0.07	0.00 to 1.26	0.00 to 3.15	
Urban[37]	1/60	3/60	0.33	0.04 to 3.11	0.02 to 6.29	
Yang[38]	19/246	21/250	0.92	0.51 to 1.67	0.42 to 2.01	
Total	**21/441**	**37/412**	**0.38**	**0.11 to 1.29**	**0.08 to 1.88**	**45%**
Nonfatal Cardiac Arrest						
Wallace[32]	2/99	3/101	0.68	0.12 to 3.98	0.07 to 6.94	
Bayliff[33]	0/49	2/50	0.20	0.01 to 4.14	0.00 to 10.67	
Total	**2/148**	**5/151**	**0.50**	**0.11 to 2.29**	**0.07 to 3.70**	**0%**
Major Perioperative Cardiovascular Events						
Jakobsen[31]	1/18	0/18	3.00	0.13 to 69.09	0.05 to 185.13	
Wallace[32]	3/99	5/101	0.61	0.15 to 2.49	0.10 to 3.88	
Bayliff[33]	2/49	3/50	0.68	0.12 to 3.90	0.07 to 6.74	

Outcome and trials	Beta-blocker groups n/N	Control groups n/N	RR	95% CI	99% CI	I^2
Poldermans[34]	2/59	18/53	0.10	0.02 to 0.41	0.02 to 0.64	
Raby[35]	0/15	1/11	0.25	0.01 to 5.62	0.00 to 14.93	
Zaugg[36]	0/43	3/20	0.07	0.00 to 1.26	0.00 to 3.15	
Urban[37]	1/60	3/60	0.33	0.04 to 3.11	0.02 to 6.29	
Yang[38]	19/246	22/250	0.88	0.49 to 1.58	0.41 to 1.90	
Total	**28/589**	**55/563**	**0.44**	**0.20 to 0.97**	**0.16 to 1.24**	**42%**
Nonfatal Stroke						
Wallace[32]	4/99	1/101	4.08	0.46 to 35.87	0.23 to 71.02	NA
Congestive Heart Failure						
Magnusson[21]	0/15	1/15	0.33	0.01 to 7.58	0.01 to 20.25	
Jakobsen[31]	1/18	0/18	3.00	0.13 to 69.09	0.05 to 185.13	
Wallace[32]	9/99	7/101	1.31	0.51 to 3.38	0.38 to 4.56	
Bayliff[33]	8/49	4/50	2.04	0.66 to 6.34	0.46 to 9.05	
Yang[38]	5/246	3/250	1.69	0.41 to 7.01	0.26 to 10.96	
Total	**23/427**	**15/434**	**1.54**	**0.83 to 2.87**	**0.68 to 3.48**	**0%**
Hypotension Requiring Treatment						
Colman[17]	1/27	0/15	1.71	0.07 to 39.65	0.03 to 106.39	
Cucchiara[18]	5/37	5/37	1.00	0.32 to 3.17	0.22 to 4.55	
Gibson[22]	1/21	0/19	2.73	0.12 to 63.19	0.04 to 169.63	
Stone[23]	12/89	2/39	2.63	0.62 to 11.20	0.39 to 17.65	
Miller[28]	1/30	0/15	1.55	0.07 to 35.89	0.02 to 96.36	
Miller[29]	39/368	19/180	1.00	0.60 to 1.69	0.51 to 1.98	
Davies[30]	6/20	11/20	0.55	0.25 to 1.19	0.20 to 1.52	
Wallace[32]	13/99	13/101	1.02	0.50 to 2.09	0.40 to 2.62	
Bayliff[33]	24/49	13/50	1.88	1.09 to 3.26	0.92 to 3.87	
Yang[38]	114/246	84/250	1.38	1.11 to 1.72	1.03 to 1.84	
Total	**216/986**	**147/726**	**1.27**	**1.04 to 1.56**	**0.97 to 1.66**	**6%**
Bradycardia Requiring Treatment						
Cucchiara[18]	0/37	1/37	0.33	0.01 to 7.93	0.01 to 21.46	
Liu[20]	0/16	1/14	0.29	0.01 to 6.69	0.00 to 17.86	
Magnusson[21]	4/15	0/15	9.00	0.53 to 153.79	0.22 to 375.21	

Outcome and trials	Beta-blocker groups n/N	Control groups n/N	RR	95% CI	99% CI	I^2
Stone[23]	10/89	0/39	9.33	0.56 to 155.41	0.23 to 376.09	
McKenzie[24]	1/50	0/50	3.00	0.13 to 71.92	0.05 to 195.17	
Jakobsen[27]	5/49	1/49	5.00	0.61 to 41.25	0.31 to 80.06	
Davies[30]	12/20	8/20	1.50	0.79 to 2.86	0.64 to 3.50	
Wallace[32]	2/99	1/101	2.04	0.19 to 22.14	0.09 to 46.84	
Yang[38]	53/246	19/250	2.83	1.73 to 4.64	1.48 to 5.42	
Total	**87/621**	**31/575**	**2.27**	**1.53 to 3.36**	**1.36 to 3.80**	**3%**
Bronchospasm						
Cucchiara[18]	1/37	0/37	3.00	0.13 to 71.34	0.05 to 193.10	
Jakobsen[19]	1/10	0/10	3.00	0.14 to 65.90	0.05 to 173.99	
MacKenzie[24]	0/50	1/50	0.33	0.01 to 7.99	0.01 to 21.69	
Inada[25]	1/20	1/10	0.50	0.03 to 7.19	0.02 to 16.62	
Leslie[26]	1/40	2/20	0.25	0.02 to 2.59	0.01 to 5.41	
Jakobsen[27]	1/49	1/49	1.00	0.06 to 15.54	0.03 to 36.80	
Miller[29]	4/368	2/180	0.98	0.18 to 5.29	0.11 to 8.99	
Jakobsen[31]	1/18	1/18	1.00	0.07 to 14.79	0.03 to 34.47	
Wallace[32]	3/99	0/101	7.14	0.37 to 136.46	0.15 to 344.84	
Bayliff[33]	12/49	16/50	0.77	0.41 to 1.45	0.33 to 1.77	
Yang[38]	4/246	1/250	4.07	0.46 to 36.11	0.23 to 71.74	
Total	**29/986**	**25/775**	**0.91**	**0.55 to 1.50**	**0.47 to 1.75**	**0%**

Major Perioperative Cardiovascular Events = Composite outcome of cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest

NA = Not applicable

Figure 1.

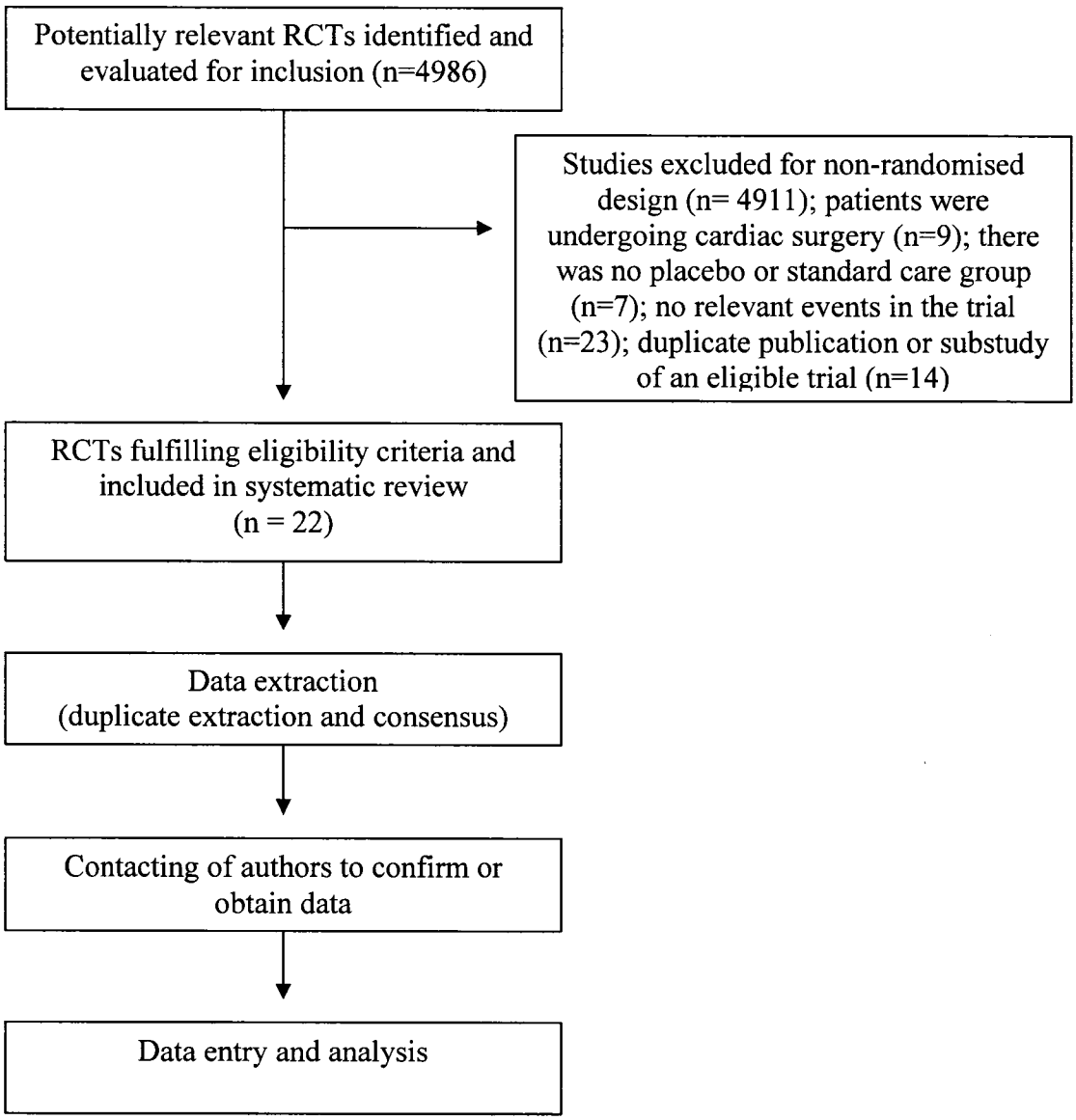


Figure 2. Bradycardia requiring treatment

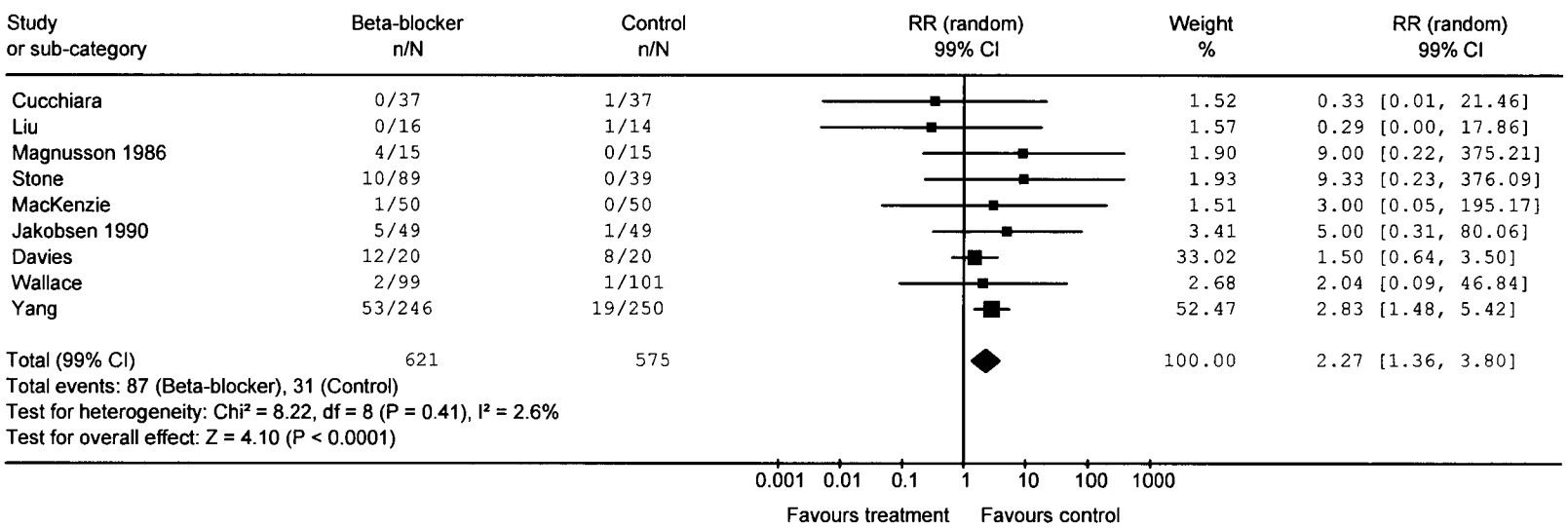
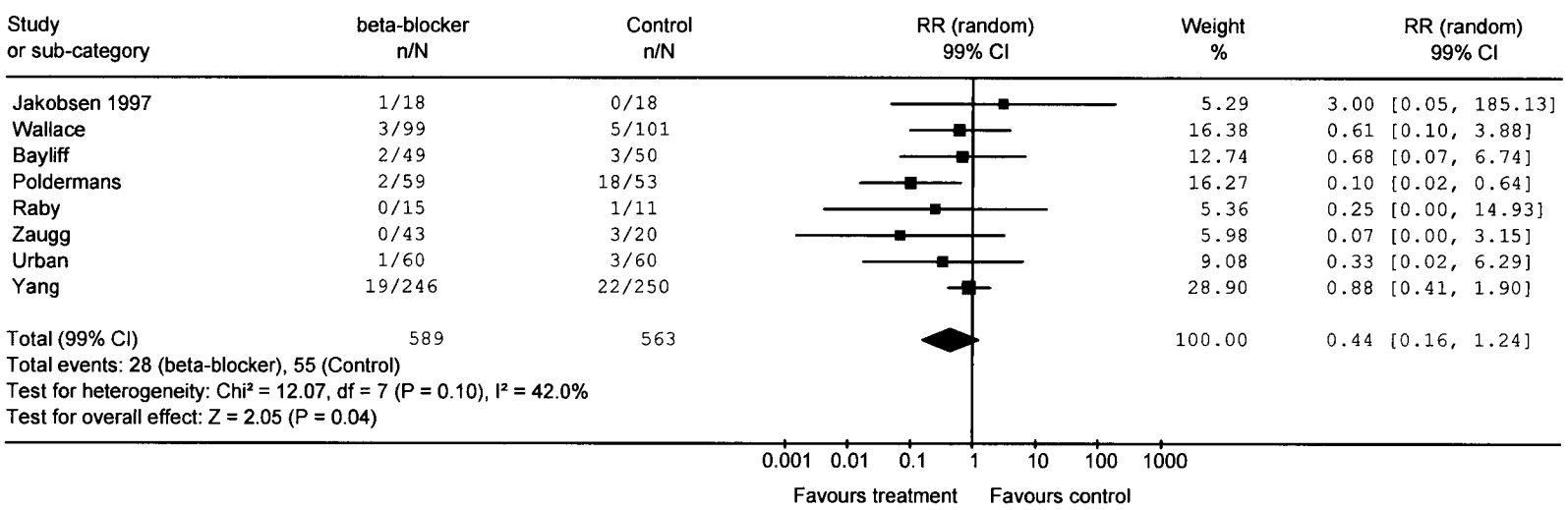


Figure 3. Major perioperative cardiovascular events



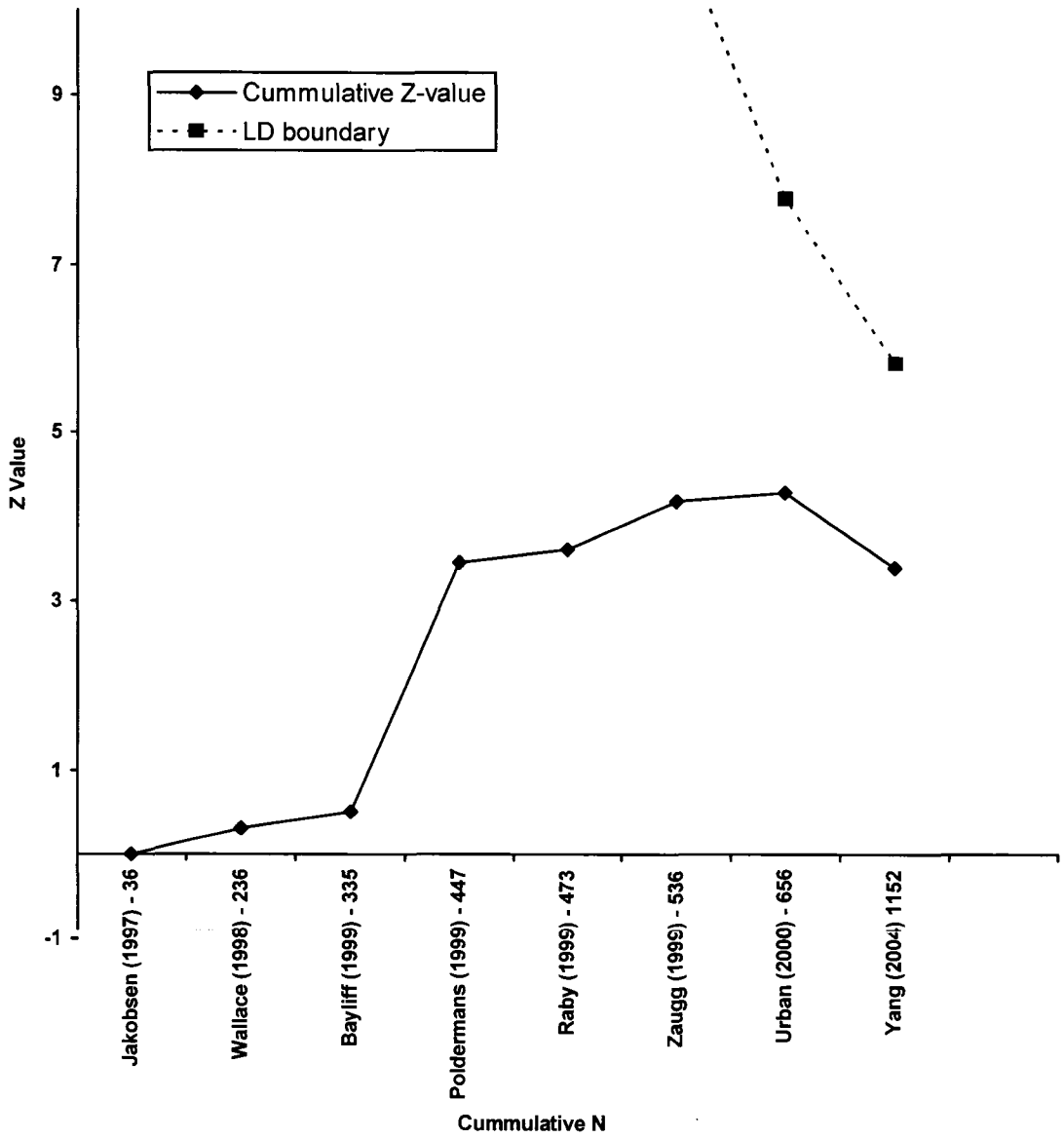


Figure 4. Cumulative meta-analysis assessing the effect of perioperative beta-blockers on the 30 day risk of major perioperative cardiovascular events (i.e. cardiovascular death, nonfatal myocardial infarction, or nonfatal cardiac arrest) in patients undergoing noncardiac surgery. The Lan-DeMets (LD) sequential monitoring boundary, that assumes 10% control event rate and a 25% relative risk reduction with 80% power and a two-sided alpha = 0.01, has not been crossed indicating that the cumulative evidence is inconclusive.

APPENDIX 1

Electronic Search of Bibliographical Databases

We searched EMBASE (1980-2002) and MEDLINE (1966-2002). Our EMBASE search strategy included: beta adrenergic antagonists AND postoperative complications OR postoperative period OR perioperative period OR Intraoperative period OR perioperative care. Our MEDLINE search strategy included: Beta adrenergic antagonist (exploded) or propranolol (exploded) or metoprolol (exploded) or atenolol (exploded) or esmolol (mp) or nadolol (exploded) and perioperative care (exploded) or postoperative complications (exploded) or surgery (exploded) or anesthesia (exploded).

Hand Searched Anesthesia Journals

We hand searched (1985-2002) the following journals: Acta Anaesthesiologica Scandinavica, Anaesthesia, Anesthesiology, Anesthesia & Analgesia, British Journal of Anaesthesia, Canadian Journal of Anesthesia, and Regional Anesthesia & Pain Medicine.

APPENDIX 2

Cardiovascular death - any death with a cardiovascular cause including those deaths following a cardiac arrest, myocardial infarction, pulmonary embolus, stroke, hemorrhage, or deaths due to an unknown cause

Bradycardia requiring treatment - bradycardia requiring a temporary pacemaker, sympathomimetic agent, or atropine

Hypotension requiring treatment - hypotension requiring a vasopressor agent, an inotropic agent, an intraaortic balloon pump, or fluid resuscitation

CHAPTER 7

The POISE Trial Investigators. Rationale, design, and organization of the PeriOperative ISchemic Evaluation (POISE) Trial: A randomized controlled trial of metoprolol versus placebo in patients undergoing noncardiac surgery. (Submitted for publication)

Trial Design

Rationale, design, and organization of the PeriOperative ISchemic Evaluation (POISE) Trial: A randomized controlled trial of metoprolol versus placebo in patients undergoing noncardiac surgery

The POISE Trial Investigators

Abbreviated Title: The POISE Trial Design Paper

ABTRACT

Background: Noncardiac surgery is associated with significant cardiovascular mortality, morbidity, and cost. Beta-blockers may prevent cardiovascular events in patients undergoing noncardiac surgery, but the trial results are contradictory. We have initiated the PeriOperative ISchemic Evaluation (POISE) trial to definitively establish the effects of beta-blocker therapy in patients undergoing noncardiac surgery.

Methods: The POISE trial is a blinded randomized controlled trial of metoprolol CR versus placebo in 10,000 patients at risk of a perioperative cardiovascular event (i.e. patients with atherosclerotic cardiovascular disease or with risk factors for atherosclerotic cardiovascular disease) who are undergoing noncardiac surgery. Patients receive study drug two to four hours prior to surgery and subsequently for 30 days. The primary outcome is a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest at 30 days. Patients are also followed for events at one year.

Results: To date the POISE trial has recruited over 5600 patients in more than 150 centers in 20 countries. Currently, patients' mean age is 70 years, 63% are males, 44% have a history of coronary artery disease, 43% have a history of peripheral arterial disease, 30% have diabetes, and 63% have a history of hypertension. The majority of participants have undergone vascular (41%), intra-abdominal (23%), or orthopedic (18%) surgery.

Conclusions: POISE is a large international trial that will resolve the uncertainty surrounding the effects of beta-blocker therapy in patients undergoing noncardiac surgery.

INTRODUCTION

Magnitude of the Problem

Approximately 2% of unselected consecutive adults ≥ 45 years of age undergoing noncardiac surgery requiring hospital admission will suffer a perioperative cardiovascular death or nonfatal myocardial infarction during the first 30 days after surgery.(1-5) Cardiac complications after noncadiac surgery result in substantial cost because these events prolong hospitalization by a mean of 11 days.(6) Further, perioperative ischemia is an independent predictor of cardiac death and myocardial infarction during the two years following surgery.(7, 8)

Rationale for a Perioperative Beta-blocker Trial

Perioperative cardiovascular events are likely mediated through a host of mechanisms including increases in adrenergic activity, free fatty acid levels, platelet reactivity, plasminogen activator inhibitor I (PAI-I), factor VIII-related antigen levels, and inflammation, and decreases in antithrombin III levels.(9-14) Beta-blockers reduce adrenergic activity and free fatty acid levels.(15) Therefore, beta-blockers may prevent perioperative cardiovascular events. At the same time, it is unlikely that beta-blockers would result in a large reduction in risk (i.e., a relative risk reduction > 35%) because of the number of important pathogenic mechanisms unaffected by beta-blockers.

Recently, the American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines for noncardiac surgery stated, "there are still very few

randomized trials of medical interventions before noncardiac surgery to prevent perioperative cardiac complications, and they do not provide enough data from which to draw firm conclusions or recommendations."(16) Despite this statement, these guidelines and several other authors have recommended that patients receive beta-blocker therapy around the time of noncardiac surgery.(16-19) The results of two small randomized controlled trials (RCTs), both with serious limitations, provide the basis for these recommendations.(20)

Mangano and colleagues randomized 200 patients to receive atenolol or placebo until hospital discharge (maximum seven days), and patients were followed for two years post hospital discharge.(20) They reported nine deaths in the atenolol group and 21 deaths in the placebo group during follow-up. They only included deaths after patients stopped taking the study medication and excluded the four deaths in the atenolol group and two deaths in the placebo group that occurred after randomization but during study treatment. An intention to treat analysis which includes all deaths after randomization (13 versus 23) is not statistically significant ($p = 0.1$).(21)

Poldermans and colleagues randomized 112 patients undergoing elective vascular surgery who had a positive dobutamine echocardiography study to receive bisoprolol or standard care.(22) The primary outcome was cardiovascular death or nonfatal myocardial infarction within 30 days of surgery. The authors reported two primary outcomes in the bisoprolol group and 18 primary outcomes in the standard care group and a 91% relative risk reduction. Although the result was statistically significant the trial was unblinded, there were very few events, and the treatment effect was implausibly

large. This trial was stopped early after the first interim analysis suggested a much larger than predicted treatment effect, circumstances that warrant skepticism about the effect.(23)

The results of these two trials, although promising, have demonstrated large treatment effects that are at variance with the trials in acute myocardial infarction and chronic congestive heart failure that have randomized > 50,000 patients and have demonstrated that beta-blockers reduce mortality by about a quarter.(15, 24-27) Furthermore, two recent blinded perioperative beta-blocker trials (MaVS in individuals undergoing vascular surgery [496 patients] and DIPOM in diabetic patients undergoing noncardiac surgery [921 patients]) demonstrated no benefit.(28, 29)

These mixed results warrant cautious interpretation. This evidence identifies the need and provides the impetus for a large adequately powered perioperative beta-blocker RCT that will provide a definitive answer. We have initiated the PeriOperative ISchemic Evaluation (POISE) trial to address this need.

POISE – an Overview

The POISE trial is a large RCT designed to determine the impact of perioperative administration of metoprolol on the 30 day risk of major cardiovascular events (defined as cardiovascular death, nonfatal myocardial infarction or nonfatal cardiac arrest) in at risk patients (i.e. patients with atherosclerotic cardiovascular disease or patients with risk factors for atherosclerotic cardiovascular disease) undergoing noncardiac surgery.

In the POISE trial we are evaluating oral metoprolol succinate controlled-release (CR) and intravenous metoprolol tartrate, which patients will receive when they are unable to take oral medications. Both of these drugs are cardioselective ß-1 adrenergic-receptor antagonist. The dissolution and absorption properties of metoprolol CR result in stable plasma concentrations with minimum fluctuations over a 24-hour period under fasting and nonfasting conditions.(30, 31)

METHODS

Trial Design

The POISE trial is an RCT of metoprolol versus placebo in patients at risk of a perioperative cardiovascular event who are undergoing noncardiac surgery. Participants, health care providers, data collectors, and outcome assessors are blinded to whether patients receive metoprolol or placebo.

Trial Population

Investigators will consider all patients undergoing elective and urgent/emergent noncardiac surgical procedures for enrollment. Table 1 and 2 present the POISE inclusion and exclusion criteria, respectively.

Randomization

Patients are randomized after consent via a 24 hour computerized randomization phone service at the Population Health Research Institute, Hamilton Health Sciences and McMaster University, Hamilton, Ontario, Canada. The computerized randomization process uses block randomization stratified by center. The block size is unknown to study center personnel. Patients are randomized in a 1 to 1 ratio to receive metoprolol or matching placebo.

Drug Administration

The oral study drug preparation consists of 200 mg tablets of metoprolol CR or matching placebo, and the intravenous study drug preparation consists of 5 mg ampoules of metoprolol tartrate or matching placebo. Administration of the study drug at each dosing time, except during the first 6 hours post surgery, requires a patient to have a heart rate $\geq$ 50 beats / minute (bpm) and a systolic blood pressure (SBP) $\geq$ 100 mm Hg.

Two to four hours prior to surgery patients take 100 mg (i.e., a half tablet) of the study drug orally. If during the first 6 hours post surgery a patient's heart rate is $\geq$ 80 bpm and their SBP $\geq$ 100 mm Hg the patient takes 100 mg of the study drug orally. Patients who do not receive a dose of the study drug during the first 6 hours post surgery take 100mg of the study drug orally at 6 hours post surgery. Starting 12 hours after patients receive their first post surgical study drug dose, and daily thereafter for 30 days, patients take 200 mg of the study drug orally. If a patient's heart rate is consistently below 45 bpm or their SBP < 100 mm Hg, caregivers hold the study drug until the

patient's heart rate or SBP recovers and then they will administer 100 mg of the study drug orally. If a patient's heart rate is consistently 45-49 bpm and their SBP > 100 mm Hg the patient delays taking their study drug for 12 hours.

Patients who are not able to take medications orally receive the study drug by slow or rapid intravenous infusion every 6 hours until they are able to receive the study drug orally. The slow intravenous infusion consists of 15 mg of the study drug in 25 ml of normal saline infused over a 60 minute period, and patients have their heart rate and blood pressure checked 10, 30, and 60 minutes after starting the infusion. If a patient's heart rate is < 50 bpm or SBP < 100 mm Hg the infusion is stopped and subsequent infusions consist of 10 mg of the study drug in 25 ml of normal saline infused over a 60 minute period.

The rapid intravenous infusion consists of 5 mg of the study drug infused over 2 minutes. Patients receive the rapid intravenous infusion every 5 minutes for a total of 15 mg as long as their vital signs fulfill the standard heart rate and SBP requirements prior to each dosing.

If a patient develops congestive heart failure, significant first degree heart block, second or third degree heart block, or bronchospasm, they have their study medication held until the attending physician decides it is safe to restart the study drug. Patients restarting the study drug after one of these problems restart the study drug dosage at 100 mg orally.

Patient Follow-up

Short Term Follow-up

Patients have an ECG recorded 6 to 12 hours postoperatively and on the 1st, 2nd and 30th day after surgery. Patients have a troponin or CK-MB measurement, when troponin is not available, drawn 6 to 12 hours postoperatively and on the 1st, 2nd, and 3rd day after surgery. Research personnel follow patients in hospital and record the occurrence of any primary or secondary outcomes. Research personnel contact patients at 30 days and record the occurrence of any primary or secondary outcomes.

Long Term Follow-up

We will undertake a long term follow-up (minimum of 1 year) for all patients. In Canada, the Canadian Institute for Health Information (CIHI) and Statistics Canada will provide the long term follow-up data on nonfatal outcomes and mortality, respectively. In other countries without a national health administrative database, study personnel are contacting patients by phone at 1 year post surgery.

Trial Outcomes

The primary outcome of the POISE trial is a composite outcome of cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest at 30 days. Secondary outcomes at 30 days include: total mortality, cardiovascular death, myocardial infarction, nonfatal cardiac arrest, cardiac revascularization (i.e. coronary artery bypass surgery or percutaneous transluminal coronary angioplasty), congestive heart failure, clinically

significant atrial fibrillation, rehospitalization for cardiac reasons, clinically significant bradycardia, clinically significant hypotension, stroke, length of hospital stay, and length of intensive care unit / cardiac care unit (ICU/CCU) stay. For the long term follow-up we will evaluate total mortality, cardiovascular death, nonfatal myocardial infarction, nonfatal cardiac arrest, cardiac revascularization, and stroke. Appendix 1 presents our outcome definitions.

Outcome Adjudication

A committee of clinicians who are blinded to the treatment allocation will adjudicate the following outcomes: sub-classification of death, myocardial infarction, nonfatal cardiac arrest, and stroke. We will use the decisions from the adjudication committee for all statistical analyses involving these outcomes.

STATISTICAL CONSIDERATIONS

Sample Size

Using published data from existing risk indices for predicting perioperative cardiovascular events,(1, 3, 5, 32) we anticipate that patients with any three of seven risk factors (high-risk type of surgery [i.e. intrathoracic or intraperitoneal], emergency/urgent surgery, any history of congestive heart failure, history of a transient ischemic attack (TIA), diabetes and currently on an oral hypoglycemic agent or insulin therapy, preoperative serum creatinine >175 μmol/L (> 2.0 mg/dl), or age > 70 years) will have a

perioperative rate of cardiac death, nonfatal myocardial infarction, or nonfatal cardiac arrest of at least 5.3% during their hospitalization.

We expect that 6% of the control group in the POISE trial will suffer the primary outcome within 30 days, based on a screening study and the eligibility criteria that the patients randomized to date have fulfilled. Table 3 presents the power to detect relative risk reductions of 25 and 30% based on sample sizes of 6000, 8000, and 10,000 patients with an $\alpha = 0.05$ (two-sided). Our goal is to randomize 10,000 patients but even with smaller sample sizes we may have adequate power.

Data Analysis

Main Analysis

We will tabulate the number of primary outcomes by treatment group using the intention to treat principle. We will present the time-to-the first occurrence of one of the components of the primary outcome using the Kaplan-Meier estimator. We will use a log-rank statistic to compare the rate of occurrence of the primary outcome between the two groups. Employing Cox proportional hazards model, we will calculate the hazard ratio and its associated 95% confidence interval. We will infer statistical significance if the computed p-value is ≤ 0.05.

Secondary Analyses

We will tabulate the number of secondary outcomes by treatment group. We will use the log-rank statistic to compare the occurrence rate of each binary secondary

outcome. We will compare the length of hospital stay and length of ICU/CCU stay using an unpaired t-test or a non-parametric test if the data are far from normally distributed. The Cox proportional hazards model will provide the basis for subgroup analyses (i.e. patients with diabetes, renal failure, coronary artery disease, hypertension, congestive heart failure, cerebrovascular disease, peripheral vascular disease, patients who receive an epidural or spinal anesthesia, men and women, types of surgeries, and effects among patients at different ages); and we will infer a subgroup effect if the interaction term of treatment and subgroup is statistically significant.

Interim Analyses

The independent External Safety and Efficacy and Monitoring Committee (ESEMC) will ensure patient safety, review interim analyses, provide feedback to the Operations Committee and ensure the study adheres to the highest standards of ethical standards. Three interim efficacy analyses will occur when 25%, 50% and 75% of the 30-day primary outcome data are available. The ESEMC will employ the modified Haybittle-Peto rule of four standard deviations for analyses in the first half of the study and three standard deviations for all analyses in the second half.(33, 34) The ESEMC will only consider a finding in favor of treatment significant if these predefined boundaries are exceeded in at least two consecutive analyses, three or more months apart. The corresponding critical Chi Squared values are 15.14 (i.e. $\alpha = 0.0001$) for the first two planned analyses and 12.25 ($\alpha = 0.00047$) for the third analysis. The α-level for the final analysis will remain the conventional $\alpha = 0.05$ given the infrequent interim analyses,

their extremely low α levels, and the requirement for confirmation with subsequent analyses.

If the intervention surpasses the modified Haybittle-Peto rule then the ESEMC will advise the Operations Committee of the finding. The ESEMC will also consider the consistency of the secondary endpoints and subgroups and any relevant external data when considering a recommendation to stop the trial.

The ESEMC will also monitor the study to assess if there is an adverse impact of metoprolol on mortality. For these analyses, an excess in mortality of 3 standard deviations in the first half and 2.6 standard deviations in the second half would trigger discussions about stopping the trial for harm.

TRIAL ORGANIZATION AND FUNDING

The Population Health Research Institute is the coordinating center for this study worldwide and is primarily responsible for the development of the trial protocol, organization of the trial, development of the randomization scheme, the study database, data analysis and data consistency checks, and coordination of the study centers. The trial structure includes the following groups: the operations committee, coordinating center, national coordinators, the adjudication committee, the ESEMC, and the investigators. Appendix 2 lists the group members.

Grants from the Canadian Institutes of Health Research, the Commonwealth Government of Australia's National Health and Medical Research Council, and the

British Heart Foundation provide the funds for the POISE trial. AstraZeneca has provided the study drug and funding for drug labeling, packaging, and shipping.

CURRENT STATUS OF THE TRIAL

The POISE trial is currently recruiting patients in over 150 centers within 20 countries and has randomized over 5600 patients as of January 2006. Tables 4 and 5 present baseline characteristics and type of surgery and anesthesia/analgesia. These data demonstrate that after randomizing over 1/2 of the sample size patients mean age is 70 years, 63% are males, 44% have a history of coronary artery disease, 43% have a history of peripheral vascular disease, 30% have diabetes, and 63% have a history of hypertension. The most common types of surgery are vascular 41%, intra-abdominal 23%, and orthopedic 18%, and over 2/3rds of patients have received a general anesthetic. The ESEMC was unanimous after the first two interim analyses in recommending that the POISE trial continue.

DISCUSSION

Patients undergoing noncardiac surgery frequently suffer major perioperative cardiovascular events. There exists encouraging but inconsistent preliminary evidence that suggests beta-blockers may prevent perioperative cardiovascular events. The POISE trial is an RCT designed to definitively determine if metoprolol can prevent major perioperative cardiovascular events in patients undergoing noncardiac surgery. The

POISE trial is currently randomizing patients in over 150 centers in 20 countries and over 5600 patients have been randomized to date.

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CONTRIBUTORSHIP STATEMENT

Dr. P.J. Devereaux contributed significantly to the study's concept and design, data acquisition, data analysis, and interpretation of the data. He wrote the first draft of the manuscript, provided critical revisions to the manuscript, and gave final approval of the submitted manuscript.

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Competing interests:

Dr. Salim Yusuf has received research grants and honoraria from Astra Zeneca the manufacturers of metoprolol CR.

Table 1: Inclusion criteria of the POISE trial

All patients undergoing noncardiac surgery are eligible if they:
1. are ≥ 45 years of age
2. have an expected postoperative length of stay ≥ 24 hours for surgical reasons; AND
3. fulfill any one of the following 6 criteria:
A. history of coronary artery disease as defined by any one of the following 6 criteria i. history of angina ii. prior myocardial infarction iii. prior positive exercise stress test iv. prior documentation of cardiac ischemia on nuclear or echocardiography stress testing v. prior coronary artery angiographic evidence of atherosclerotic stenosis >50% of vessel diameter vi. ECG with pathological Q waves in two contiguous leads
B. history of peripheral vascular disease as defined by any one of the following 3 criteria i. intermittent claudication that is known or likely to be due to atherosclerotic disease ii. an ankle/arm systolic blood pressure ratio ≤ 0.90 in either leg at rest iii. angiographic or doppler study demonstrating > 70% stenosis
C. history of stroke thought due to atherothrombotic disease
D. history of hospitalization for congestive heart failure within 3 years of randomization
E. undergoing major vascular surgery (i.e., vascular surgery excluding arteriovenous shunt, vein stripping procedures, and carotid endarterectomies); OR
F. any 3 of the following 7 risk factors i. high-risk type of surgery (i.e., intrathoracic or intraperitoneal) ii. any history of congestive heart failure iii. diabetes and currently taking an oral hypoglycemic agent or insulin therapy iv. preoperative serum creatinine >175 μmol/L (> 2.0 mg/dl) v. age > 70 years vi. history of a transient ischemic attack (TIA) vii. emergency/urgent surgery (i.e. surgery which must be undertaken within 24 hours of acute presentation to hospital)

ECG = electrocardiogram

Table 2: Exclusion criteria of the POISE trial

All patients are excluded if they:
1. have significant bradycardia (heart rate < 50 beats per minute) or second or third degree heart block without a pacemaker
2. have asthma that has been active within the last decade (i.e. a clinical diagnosis of asthma and use of regular inhaled steroids, or beta agonists at least once per week over the period of a month, any time in the last ten years)
3. have COPD with bronchospasm on pulmonary function tests (i.e. an increase in FEV1 ≥ 12% and of at least 200 ml, 15 minutes after inhalation of a beta 2 – agonist)
4. are currently taking a systemic beta-blocker or their physician plans to prescribe a systemic beta-blocker preoperatively or during the first 30 postoperative days
5. have had a prior adverse reaction to a beta-blocker
6. have had CABG surgery with complete revascularization in the preceding 5 years and no evidence of cardiac ischemia since the surgery
7. are undergoing a surgical procedure that the investigator deems low risk (e.g., cataract surgery)
8. are currently taking verapamil; OR
9. have previously enrolled in the POISE trial

COPD = chronic obstructive pulmonary disease, FEV1=forced expiratory volume in one second, CABG = coronary artery bypass graft

Table 3: Power calculations for 30-day follow-up

Primary Study Outcome: cardiac death, nonfatal MI, nonfatal cardiac arrest at 30 days			Power based on various sample sizes and (2-sided $\alpha = 0.05$)		
Control event rate	**Treatment event rate**	**RRR**	**N=6000**	**N=8000**	**N=10,000**
6%	4.5%	25%	74%	85%	92%
6%	4.2%	30%	89%	96%	98%
5.5%	4.1%	25%	72%	83%	91%
5.5%	3.9%	30%	83%	92%	97%

Table 4: Baseline characteristics (n= 5680)

Age [years, mean (+/-SD)]	70 (10)
Gender (% female)	37%
Preoperative heart rate [beats/minute, mean (+/-SD)]	78 (12)
Preoperative systolic blood pressure [mm HG, mean (+/- SD)]	138 (20)
Percentage of patients fulfilling eligibility criterion	
coronary artery disease	44%
peripheral vascular disease	43%
stroke thought due to atherothrombotic disease	15%
hospitalization for CHF within 3 years of randomization	3%
undergoing major vascular surgery	34%
3 of 7 risk factors	19%
intrathoracic or intraperitoneal surgery	29%
any history of congestive heart failure	6%
diabetes and currently on an oral hypoglycemic agent or insulin therapy	30%
preoperative serum creatinine >175 μmol/L (> 2.0 mg/dl)	5%
age > 70 years	50%
history of a transient ischemic attack	11%
emergent/urgent surgery	11%
Percentage of patients with other cardiovascular risk factors	
History of hypertension	63%
Current smoker	19%
Former smoker	37%

CHF = congestive heart failure

Table 5: Type of surgery and anesthesia/analgesia (n=5680)

Type of surgery	Percentage of patients
Vascular	41%
Intra-abdominal	23%
Orthopaedic	18%
Head and neck	3%
Thoracic	2%
Gynecologic	2%
Other	11%
Type of anesthesia/analgesia	
General	54%
Spinal	14%
General and thoracic epidural	10%
Lumbar epidural	8%
Spinal and lumbar epidural	3%
Nerve block	3%
Other combination	8%

Appendix 1: Outcome Definitions

Outcome	Definition
Sub classification of death	Cardiovascular death is defined as any death with a cardiovascular cause and includes those deaths following a cardiovascular procedure (e.g. percutaneous transluminal coronary angioplasty), cardiac arrest, myocardial infarction, pulmonary embolus, stroke, hemorrhage, or deaths due to an unknown cause. Non-cardiovascular death is defined as deaths due to a clearly documented non-cardiovascular cause (e.g. trauma, infection, malignancy).
Myocardial infarction	The diagnosis requires either one of the following: 1. A typical rise of troponin OR a typical fall of an elevated troponin OR a rapid rise and fall of CK-MB. An increased troponin value (i.e. above the decision limit for MI) is a measurement exceeding the threshold at which the coefficient of variation equals 10%. An increased CK MB value (i.e. above the decision limit for MI) is one that exceeds the 99th percentile for CK MB values in a reference control group. One of the following must also exist for the diagnosis of myocardial infarction: A. ischemic symptoms (e.g. chest, epigastric, arm, wrist, or jaw discomfort OR shortness of breath lasting at least 20 minutes) B. development of pathologic Q waves on the ECG (Q wave changes must be present in any two contiguous leads, and be $\geq$ 1 mm in depth, further Q waves in leads I, II, aVL, aVF, V4, V5, or V6 must be $\geq$ to 30 milliseconds C. ECG changes indicative of ischemia (new or presumed new ST segment elevation or depression in at least two contiguous leads OR new or presumed new symmetric inversion of T waves $\geq$ 1 mm in at least two contiguous leads) D. coronary artery intervention (e.g. coronary angioplasty) E. new or presumed new cardiac wall motion abnormality on echocardiographic or a new or presumed new fixed defect on radionuclide imaging 2. Pathologic findings of an acute MI

Outcome	Definition
Nonfatal cardiac arrest	The diagnosis requires a successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, or asystole.
Congestive heart failure	The diagnosis requires both clinical (i.e. any of the following signs: elevated jugular venous pressure, respiratory rales, crepitations, or presence of S3) and radiographic evidence (e.g. vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema).
Clinically significant atrial fibrillation	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.
Rehospitalization for cardiac reasons	Rehospitalization for congestive heart failure, ischemic symptoms with ST or T wave changes on an ECG, arrhythmia, or heart block.
Clinically significant bradycardia	Bradycardia requiring a temporary pacemaker, sympathomimetic agent, atropine, or study drug discontinuation.
Clinically significant hypotension	A systolic blood pressure < 90 mm Hg requiring fluid resuscitation, intraaortic balloon pump, an inotropic agent, or study drug discontinuation.
Stroke	A new focal neurological deficit thought to be vascular in origin with signs and symptoms lasting more than 24 hours.

Appendix 2: Trial Organization

Operations Committee: P.J. Devereaux (Co-Principal Investigator), H. Yang (Co-Principal Investigator), G. Guyatt, P. Choi, S. Yusuf (Chair)

Population Health Research Institute Coordinating Center: S. Chrolavicius (Trial Manager), L. Greenspan, J. Pogue (Statistician), P. Tait (Statistician), B. Cracknell (accountant), A. Mead, J. Finocchi, L. Gallacher

National Coordinators: **Argentina**, A. Ciapponi and M. Dieguez; **Australia/New Zealand/Hong Kong/Singapore/Malaysia**, K. Leslie; **Brazil**, A. Avezum and O. Berwanger; **Canada**, R. Hudson, M. Jacka, T. Schricker, B. Warriner; **China**, L.S. Liu and S.C. Xu; **Colombia**, J. Carlos Villar, L. Ximena Martinez; **Central America**, M. Tristan, Y. Baidel, A. Salazar; **Ecuador**, M. Espinel and J. Carlos Zevallos; **Egypt**, A. Ghali; **Finland**, K. Leino; **Hungary**, M. Keltai and J. Faller; **India**, P. Pais and D. Xavier; **Iran**, N. Sarrafzadegan; **Mexico**, S. Islas Andrade; **Norway**, J. Raeder; **Peru**, G. Málaga; **Sweden**, P. Gannedahl; **United Kingdom**, P. Foex, J. Giles, J. Sear

Adjudication Committee: G. Guyatt (Chair), P.J. Devereaux (Co-chair), D. Chauret, P. Choi, K. Gilbert, R. Hudson, P. Ibarra, L. Lanthier, V. Montori, A. Panju, O. Berwanger

External Safety and Efficacy Monitoring Committee: G. Dagenais (Chair), D. Cheng, E. Lowenstein, R. Roberts

Investigators: **Australia**, S. Barratt, D. Beilby, S. Bolsin, J. Grant, R. Kerridge, K. Leslie, J. Love, T. McCulloch, P. Myles, M. Paech, P. Peyton, M. Priestley, M. Reeves, D. Wolfers; **Brazil**, D. de Albuquerque, A.C. do Amaral Baruzzi, C. Blacher, L. Carlos Bodanese, J. Pericles Esteves, M. Lucio Alves Bapista Filho, L. Eduardo Guiselli

Gallina, N. Mitsuru Izukawa, L. Nigro Maia, J. Antonio Marin-Neto, O. Ribeiro Franca Neto, R. Rabello, P. Henrique Penha Rosateli, J. Francisco Kerr Saraiva; **Canada**, N. Ali, N. Badner, C. Baer, S. Beattie, H. Bertozzi, D. Brunet, G. Bryson, J. Campeau, D. Chauret, P. Choi, D. Cook, B. Davies, P.J. Devereaux, G. Doak, G. Doig, G. Dresser, P. Duffy, A. Findlayson, K. Gilbert, D. Hughes, M. Jacka, C. Kamra, M. Khurana, L. Lanthier, D. Lazaric, C. MacDonald, P. MacDonald, J. Marti, R. Martinek, R. Merchant, D. Miller, J. Misterski, R. Mizera, J. Morin, J. Parlow, J. Paul, M. O'Reilly, J. Ostrander, S. Rammohan, C. Rosen, T. Schricker, S. Sivakamaran, M. Turabian, D. Twist, J. VanVlymen, B. Warriner, D. Wong, K. Zarnke; **China**, W. Chen, W.Z. Chen, J.Y. Cui, L.L. Deng, W.J. Hu, W. Guan, H.Y. Li, J. Li, X. Li, H.L. Liu, J.H. Liu, L.H. Liu, S.P. Ma, F.X. Ren, L. Sun, C.P. Wang, R.S. Wang, X.M. Wu, Z.D. Wu, Q. Yuan, Z.X. Zhan, L. Zhang, M.Z. Zuo; **Colombia**, G. Torres, M. Arrieta, E. Barrera, J. Guillermo Barrera, H. Castellanos, A. Chavez, J. Chona, E. Duarte, H. Garcia, P. Ibarra, E. Javier Manrique, J. Montenegro, L.F. Pava, P. Perafan, R. Plata, G. William Rangel, M. Romero, T. Romero, J. Ruiz; **El Salvador,** V. Rodriguez; **Finland**, M. Hynynen, J. Jalonen, K. Leino, A.C Lindroos, T. Oksanen, S. Swanto; **Hong Kong**, M. Chan; **Hungary**, K. Darvas, L. Entz, Z. Hajdu, G. Keleti, A. Nagy, J. Regoly-Merei, P. Sapy, P. Sipos; **India**, A. Sigamani, F. Xavier, I. Afzal, C. Ashokan Nambiar, R. Babu Panwar, S. Bera, A. Bharani, A. Campus, H. Chandra, N. Chidambaram, T. Deb, H.R. Devendra, R. Gupta, K.K. Haridas, B.K. Jain, V. Jain, T.M. Jaison, N. Jothi, P.G. Kerkar, K. Kilpadi, L. Kumar, P.R. Kumar, N. Laiker, K. Madhava, L.N. Mohan, S.R. Naik, J. Narendra, P.Y. Nyayadhish, A. Patel, S.K. Paul, P. Rajendra Kumar, M. Ramanathan, T. Ramani Devi,

E.K. Ramdas, R.L. Ranka, D. Sahaj Anand, A. Shetty, G. Sidhu, R.S. Sidhu, H. Singh, O.P. Srivastava, A. Swami, R. Umarani, S. Varma, M. Vijayakumar, H.S. Wealthy; **Iran,** N. Ahmadi, A.A. Beigi Borojeni, A. Khosravi, S. Sadeghi, A.E. Shahidi, S. Shirani, A. Tavassoli; **Malaysia**, M. Yani Bahari, J. Hassan, K.T. Hooi; **New Zealand**, S. Walker, Y. Young; **Norway**, V. Aasboe, E. Lindholm, J. Mellin-Olsen, J. Raeder, K. Reite; **Peru**, M. Aphang, R. Botazzi, J. Escobedo, G. Malaga, D. Ponce de Leon, G. Rojas; **Singapore**, R. Kelly; **Sweden**, R. Hornquist, J. Malmstedt, P. Gannedahl, L. Vimlati; **United Kingdom**, F. Gamlin, J. Giles, S. Howell, C.S. Reilly, J. Ross, J. Sear; **United States**, L. Goldman.

CHAPTER 8

Conclusions and future directions

8.1 BACKGROUND

This doctoral thesis explored issues related to vascular events in patients undergoing noncardiac surgery. The original studies and the systematic review and meta-analysis in this thesis informed the current number of adult patients undergoing noncardiac surgery and their mortality rate, the current incidence of major vascular events, the optimal clinical risk estimation model for predicting major vascular events, whether screening troponin measurements after surgery can avoid underdiagnosing myocardial infarctions, and whether perioperative beta-blocker therapy can prevent major cardiovascular events.

8.2 NONCARDIAC SURGERY IN CANADA: NATIONAL MORTALITY RATES

In chapter 4 hospital discharge data from the Canadian Institute for Health Information (CIHI) was used to inform the number of patients undergoing noncardiac surgery in Canada, their characteristics, and their in-hospital mortality rates. A total of 383,478 adult admissions underwent noncardiac surgery requiring hospital admission $\geq$ 24 hours in Canada, excluding Quebec, during the fiscal year 2000. Admissions undergoing noncardiac surgery occur often in non-teaching hospitals (50% of the surgeries), frequently in the elderly, and over a third of the time in urgent or emergent circumstances. Noncardiac surgery is associated with substantial hospital mortality (i.e.,

0.7% - 1 in 142 cases die), and a minority of deaths (3%) occur in the operating or recovery room. Ten common major surgeries account for 40% of all the noncardiac surgery admission deaths and the three most common of these surgeries (i.e., hip arthroplasty, reduction of femur fracture with internal fixation, and partial or total colectomy) account for 27,894 admissions and 768 deaths, annually. Independent predictors of in-hospital death included: age, female sex, urgent and emergent admission category, 15 of 17 preadmission comorbidities, and 9 of the top 10 surgeries. Considering the top 10 surgeries with the highest death rates, median length of hospital stay was 3 days longer among patients who died.

If Quebec is similar to the rest of Canada in the proportion of patients undergoing noncardiac surgery and the surgical mortality rate, over 500,000 Canadians undergo noncardiac surgery requiring hospital admission $\geq$ 24 hours annually and over 3500 of these patients die in hospital.

These results establish that noncardiac surgery is common and a substantial number of noncardiac surgery patients die in-hospital annually. Considering the magnitude of this problem and the likely substantial economic costs (i.e., the median hospital length of stay was three days longer among patients who died), prospective studies are needed to understand the mechanisms of death and to establish interventions to improve outcomes.

8.3 VASCULAR EVENTS IN PATIENTS UNDERGOING NONCARDIAC SURGERY

In chapter 5 data from a prospective cohort pilot study of 99 patients ≥ 45 years of age undergoing noncardiac surgery and receiving a general or regional anesthetic provided insights into the current incidence of major vascular events and whether monitoring troponins after noncardiac surgery can assist physicians to avoid missing myocardial infarctions. During the first 30 days after surgery 8% (95% CI 3-15) of the patients suffered a major vascular event (2 vascular deaths and 6 nonfatal myocardial infarctions). The observed event rate was significantly increased 6 fold compared to the expected event rate according to the Revised Cardiac Risk Index (the best existing generic risk model). Monitoring troponin levels after surgery detected 3 (and potentially 5) of 6 myocardial infarctions that physicians likely would have missed.

This study suggests that major perioperative vascular events are common, that the Revised Cardiac Risk Index underestimates risk, and that monitoring troponins after surgery can assist physicians to avoid missing myocardial infarctions. Our study, however, is a pilot with a modest sample size and it identifies the need and provides the impetus for a large multicentre prospective cohort study to confirm or refute these findings.

8.4 PERIOPERATIVE BETA-BLOCKER THERAPY

In chapter 6 we reported data from a systematic review and meta-analysis that evaluated the effects of beta-blocker therapy in patients undergoing noncardiac surgery. Perioperative beta-blockers did not demonstrate any statistically significant beneficial

effects on any of the individual outcomes and the only nominally statistically significant beneficial relative risk was 0.44 (95% CI 0.20 to 0.97, 99% CI 0.16 to 1.24) for the composite outcome of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal cardiac arrest. To assess the strength of this finding we used methods adapted from formal interim monitoring boundaries applied to cumulative meta-analysis that demonstrated that the evidence fails, by a considerable degree, to meet standards for foregoing additional studies. The individual safety outcomes in patients treated with perioperative beta-blockers demonstrated a relative risk for bradycardia requiring treatment of 2.27 (95% CI 1.53 to 3.36, 99% CI 1.36 to 3.80) and the nominally statistically significant relative risk for hypotension requiring treatment of 1.27 (95% CI 1.04 to 1.56, 99% CI 0.97 to 1.66).

This systematic review suggests the current evidence that perioperative beta-blockers reduce major cardiovascular events is encouraging but too unreliable to allow definitive conclusions. Further this systematic review identifies the need and provides the impetus for a large adequately powered perioperative beta-blocker randomized controlled trial (RCT) to definitively establish the benefits and risks of beta-blocker therapy. We have initiated such a trial, the PeriOperative ISchemic Evaluation (POISE) Trial.

In chapter 7 we reported the rationale, design, organization, and progress of the POISE Trial. The POISE trial has recruited over 5600 patients in more than 150 centers in 19 countries. Currently, patients' mean age is 70 years, 63% are males, 44% have a history of coronary artery disease, 43% have a history of peripheral arterial disease, 30%

have diabetes, and 63% have a history of hypertension. The majority of participants have undergone vascular (41%), intra-abdominal (23%), or orthopedic (18%) surgery. The POISE Trial is a large international trial that will resolve the uncertainty surrounding the effects of beta-blocker therapy in patients undergoing noncardiac surgery and is scheduled to complete recruitment of 10,000 in early 2007.

8.5 FUTURE DIRECTIONS

Based on the results of the VISION Pilot Study I have submitted a grant application to the Canadian Institutes of Health Research (CIHR) for a 20,000 patient prospective cohort study. This study (the VISION Study) has 4 primary objectives. Among patients undergoing noncardiac surgery we will determine: (1) the incidence of major perioperative vascular events; (2) the optimal clinical model to predict major perioperative vascular events; (3) the proportion of patients with perioperative myocardial infarctions that may go undetected without perioperative troponin monitoring; and (4) the relationship between postoperative troponin measurements and the 1 year risk of total mortality and major vascular events. I have also submitted a grant to CIHR to obtain funding to conduct the VISION study in China. Further, Peru, Colombia, and Denmark are all starting VISION Pilot Studies.

The POISE Trial will finish in early 2007, and I am currently undertaking preliminary research to inform a perioperative ASA trial in patients undergoing noncardiac surgery. One of the studies is a survey of all Canadian vascular, general, and orthopedic surgeons evaluating their perioperative practice patterns regarding ASA

therapy and their willingness to have their patients participate in a perioperative ASA trial. A second study is a systematic review and meta-analysis evaluating the effects of perioperative ASA therapy on major vascular events. My goal for conducting a large ASA trial is to complete preliminary research, obtain full trial funding, and begin recruitment in the next 3 years.

As outlined in chapter 2 there is a need to establish the underlying pathophysiology of perioperative myocardial infarctions. I plan to determine the biochemical and anatomical processes underlying perioperative myocardial infarctions. I will evaluate what happens to the biomarkers of inflammation, coagulation, platelet function, and sympathetic activation during the perioperative period and determine if these markers are associated with perioperative myocardial infarctions. I also plan to intensely monitor patients post surgery and undertake coronary angiography on patients as soon as they demonstrate they are infarcting to determine if the underlying anatomy in the vessels causing these events has plaque fissuring with artery thrombosis or no thrombosis but hemodynamically significant coronary artery disease. I plan to initiate this study in the next 2 years.

I am currently conducting a systematic review and meta-analysis evaluating whether an elevated perioperative troponin measurement independently alter patients long term prognosis. If this systematic review or the VISION Study established this association this will identify the need for acute interventional trials to determine how to manage patients suffering a perioperative myocardial infarction acutely and long-term. I

plan to initiate a pilot trial evaluating a potential intervention for patients suffering a perioperative myocardial infarction in the next 4 years.

Although the VISION Study will determine the optimal clinical risk prediction model it is possible that noninvasive testing may enhance risk prediction in patients with severe exercise restrictions. I am currently conducting a pilot study to evaluate the feasibility of a large prospective cohort study to determine if preoperative noninvasive pharmacological cardiovascular stress testing (i.e., dipyridamole stress perfusion imaging or dobutamine stress echocardiography) has additional predictive value, beyond clinical variables, for the occurrence of major perioperative vascular events in patients undergoing major hip and knee surgery. I plan to initiate the full study in the next 2 years.

8.6 SUMMARY

The original studies in this thesis provide insights into many issues related to perioperative vascular medicine. My future research agenda, as outlined, will further elucidate our understanding of perioperative vascular medicine in patients undergoing noncardiac surgery.