

HIGH-RISK CAD & VASCULAR OUTCOMES WITH NON-CARDIAC SURGERY

The impact of recent high-risk coronary artery disease on major vascular complications after non-cardiac surgery

Sabu Thomas M.D.

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The Impact of Recent High-Risk Coronary Artery Disease on Major
Vascular Complications After Non-Cardiac Surgery

AUTHOR: Sabu Thomas B.Sc.(Hons.), M.D.

SUPERVISOR: P.J. Devereaux, M.D., Ph.D.

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ABSTRACT:

Recent high-risk coronary artery disease (CAD), defined as Canadian Cardiovascular Society (CCS) class III or IV angina or acute coronary syndromes (ACS) unstable angina, is independently associated with increased mortality and morbidity following non-cardiac surgery. It remains unclear how the components of high-risk CAD, use of stents and timing of surgery after a high-risk CAD event is associated with risk. This project will address these issues and how they affect current perioperative medicine.

Chapter 1 further introduces how this is an important problem in perioperative medicine and outlines the specific objectives of this thesis project. Chapter 2 comprises a theoretical framework in the form of a narrative review addressing studies of (a) how components of high-risk CAD affect risk (b) the effect of revascularization on perioperative outcomes particularly stents and (c) how timing of non-cardiac surgery after a high-risk CAD event and after stent placement affects risk. Chapter 3 outlines our research study on high-risk CAD patients within the VISION cohort. Finally, chapter 4 summarizes what is known on this topic and proposes future areas of research.

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DECLARATION OF ACADEMIC ACHIEVEMENT

I, Dr. Sabu Thomas, participated in various activities of the VISION Study as a member of the Operations/Executive Committee. I designed, together with my supervisor, Dr. P.J. Devereaux, the statistical analysis plan for analyzing the impact of recent high-risk coronary artery disease (CAD) on major vascular complications after non-cardiac surgery. Furthermore, I participated in the interpretation of results with Dr. Devereaux and Ms. Diane Heels-Ansdell, a statistician at McMaster University. Finally, I performed all the literature searches, drafted all the chapters and incorporated the suggestions of my thesis committee members.

Dr. P.J. Devereaux is the Principal Investigator of the VISION Study and contributed with the original concept and design of the main study, obtained funding to support it, conceived the idea of troponin monitoring during the perioperative period, coordinated the activities for the high-risk CAD analysis, and critically reviewed all chapters of the manuscript.

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

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LIST OF ABBREVIATIONS

ACS	Acute Coronary Syndrome
ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
AHA	American Heart Association
ANOVA	Analysis of Variance
aOR	Adjusted Odds Ratio
ASA	Acetylsalicylic Acid
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CARP	Coronary Artery Revascularization Prophylaxis Trial
CASS	Coronary Artery Surgery Study
CCS	Canadian Cardiovascular Society
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
DAPT	Dual Antiplatelet Therapy
DES	Drug Eluting Stent
ECG	Electrocardiogram
ESC	European Society of Cardiology
GFR	Glomerular Filtration Rate

LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiovascular Event
MI	Myocardial Infarction
MINS	Myocardial Injury in the setting of Non-Cardiac Surgery
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
PVD	Peripheral Vascular Disease
RR	Relative Risk/Risk Ratio
SD	Standard Deviation
TIA	Transient Ischemic Attack
VISION	Vascular Events in Non-Cardiac Surgery Patient Cohort Evaluation Study
WHF	World Heart Federation

1.0 INTRODUCTION:

1.1 The Problem:

Based on analyses of surgical data from 56 countries, it is estimated that more than 200 million major non-cardiac surgeries occur each year.¹ Despite the obvious benefits provided by surgery, contemporary studies indicate that >2 million people will die within 30 days with nearly 50 percent of deaths attributed to a cardiovascular cause.^{2,3} Furthermore, an estimated 6-10 million patients will suffer a myocardial infarction (MI) during the perioperative period.³ These statistics firmly establish perioperative cardiovascular events as a major public health issue. The incidence of these perioperative complications will likely rise as the number of surgeries increase and more patients with pre-existing cardiovascular disease or risk factors for cardiovascular disease undergo these procedures. Identifying those at risk for perioperative complications is a critical first step to addressing this problem.

Recent high-risk coronary artery disease (CAD), defined as Canadian Cardiovascular Society (CCS) class III or IV angina or acute coronary syndromes (ACS), which includes MI or unstable angina, is independently associated with increased mortality and morbidity following non-cardiac surgery.⁴ Given our aging population, the number of patients with a history of high-risk CAD undergoing non-cardiac surgery will likely increase.⁵⁻⁷ There is a need to better understand what constitutes recent high-risk CAD in patients undergoing non-cardiac surgery. Despite numerous studies and guideline directives⁷⁻⁹, it remains unclear what the perioperative risk is for these patients in the modern era. In particular it is not clear (1) how each

component of high-risk CAD contributes to risk, (2) what effect prior stenting has on risk and (3) when the optimal time is to operate on such patients.

While many studies have looked at perioperative risk for non-cardiac surgery in patients who have had a prior MI, there are very few studies that have looked at the risk of non-cardiac surgery among patients who have unstable angina or class III/IV angina. Guidelines have uniformly recommended delaying elective non-cardiac surgery in patients with severe anginal symptoms and to treat them according to established management guidelines for ACS or angina.⁷⁻⁹ These perioperative guidelines also recommend delaying non-emergent non-cardiac surgery until these symptoms have resolved. Many times, these syndromes resolve with a combination of aggressive medical and revascularization therapy which can further delay non-cardiac surgery. While delaying non-cardiac surgery for truly elective procedure may be prudent, some surgical procedures need to occur expeditiously due to time-sensitive serious conditions (e.g., cancer). Waiting 1 year for dual antiplatelet therapy (DAPT) to complete after a drug-eluting stent (DES) is placed may be risky depending on the indication for the non-cardiac surgery.

With respect to revascularization in particular, perioperative management of patients with prior high-risk cardiac events is further complicated by the widespread use of angioplasty and stenting. Angioplasty involves percutaneous balloon inflations across a stenosis to treat atheromatous plaque. While this minimized the degree of stenosis, this procedure was plagued by smooth muscle growth at the original site of stenosis resulting in restenosis rates as high as 20-30 percent.¹⁰ The use of stents, in which a metal matrix is placed in the coronary artery at the same time or soon after

balloon inflation, led to fewer cases of restenosis and ultimately less need for repeat revascularization. Stents can be bare metal (BMS) or DES in design. DES stents have a chemotherapeutic coating that further inhibits the growth of smooth muscle cells. Bare metal stents (BMS) have resulted in a 10-20% drop in clinically indicated target lesion revascularization compared with angioplasty alone. This has been reduced further with DES.¹¹

While DES prevents, or at least, attenuates smooth muscle cell growth, they also reduce endothelialization rates. Until stents endothelialize, they are at higher risk for thrombosis due to blood being in contact with exposed metal. While most BMS are significantly endothelialized by 1 month and completely endothelialized by 3-6 months, near complete endothelialization of DES occurs later (i.e., up to 1 year in some series).^{12,13} As a result, all stents require DAPT with aspirin and a second antiplatelet agent (thienopyridine/ P2Y₁₂ receptor blockers) for varying periods of time. DES require DAPT for longer periods of time (>1 year) since endothelialization is further delayed.¹⁴

Most intermediate to high-risk non-cardiac surgery requires cessation of DAPT given the higher risk of bleeding. Since some studies suggest incomplete endothelialization of DES as long as 5 years out, the optimal duration of DAPT remains unknown.¹³ Premature cessation of DAPT carries a significant risk of stent thrombosis and may contribute to an increased incidence of perioperative MI.

Finally, when to proceed after a high-risk CAD event is also unclear. Studies have suggested that patients who have had surgery within 3 months of an MI have postoperative MI and 30-day mortality rates as high as 36 and 27%, respectively.^{15,16}

Delaying non-cardiac surgery is generally thought to reduce these risks, however, many of the studies that form the basis of these recommendations are limited as they had small sample sizes, data that is more than 30 years old (1970's and 1980's), heterogeneous populations with varying complexities of surgeries and intervals from recent MI assessed in 3 month blocks only. In particular, many of these studies were done in an era when older patients were less likely to be operated on and less invasive surgical options were not available. Furthermore, during that era, medical therapies and revascularization options for high-risk CAD were also minimal. Given this, there is uncertainty regarding the appropriate time necessary to delay surgery to reduce risk or whether delaying surgery reduces risk at all.^{8,17,18}

The American College of Cardiology (ACC) and the American Heart Association (AHA) joint taskforce recommendations in 2009 suggest waiting approximately 4-6 weeks (30-45 days) after an MI before elective surgical procedures are performed if treated medically or if a BMS is implanted and ≥ 365 days if a DES is used (figure 1).^{7,9} These guidelines concede, however, that these timings are “. . . somewhat arbitrary [owing to] a lack of high-quality evidence” rendering this a class IIa recommendation with level of evidence C.⁷ Most recently in 2014, the ACC/AHA perioperative guidelines now recommend waiting ≥ 60 days after an MI in the absence of any intervention in light of data from recent observational studies.¹⁹ They continue to recommend waiting 30 days after a BMS is implanted—however if the BMS was implanted primarily for an MI, then the 60 day window would still apply. The new guidelines continue to recommend waiting ≥ 365 days if a DES is implanted (figure 1).¹⁹

Delaying surgery for up to 1 year may be unacceptable especially if a potentially life-saving surgery is required sooner. Based on this, the ACC/AHA guidelines proposed a class IIb recommendations for waiting only 180 days after a DES “if the risk of further delay is greater than the expected risks of ischemia and stent thrombosis.”¹⁹

To date, there have been no contemporary, prospective studies and very few retrospective studies exploring the risk and optimal timing of surgery for patients with a history of a recent high-risk CAD and current recommendations are therefore suboptimally informed.

The Vascular Events In Non-Cardiac Surgery Patients Cohort Evaluation (VISION) Study (clinicaltrials.gov identifier NCT 00512109) is an international multi-centre prospective cohort study that has evaluated major complications among a planned 40 000 patient cohort undergoing non-cardiac surgery—interim results for the first 15 000 patients have already been published.²⁰ Among the main objectives of the VISION Study, those that are particularly pertinent to this project include determining (1) the incidence of major perioperative vascular events; (2) the optimal clinical model to predict major perioperative vascular events; and (3) the relationship between postoperative troponin measurements and the 1 year risk of vascular death. Ischemic perioperative troponin elevation including perioperative myocardial infarction together referred to as Myocardial Injury in Non-cardiac Surgery (MINS) among patients who have had a preexisting high-risk CAD was ascertained in the VISION Study. These data will serve as the foundation from which the assessment of perioperative risk among high-risk CAD patient will be derived.

1.2 Thesis Objectives:

Please note that all of the research objectives in this thesis are exploratory and are as follows:

(1) to review the current state of the literature regarding perioperative risk assessment and management following a high-risk cardiac event; in particular, we will define the components of risk including, mortality, MI and the recently defined phenomenon of MINS. We will also review some of the literature on the use of stents as it relates to patients who have had a high-risk cardiac event. In particular we will look at what the literature says about timing of non-cardiac surgery after a stent and when to stop DAPT prior to non-cardiac surgery.

(2) to assess among VISION study participants, who have had a recent high-risk cardiac event, the risk of mortality at 30 days based upon the various components of how one defines a recent high-risk CAD event (ACS, class III/IV angina);

(3) to further assess among VISION study participants, who have had a recent high-risk cardiac event, the risk of MINS at 30 days based upon the various components of how one defines a recent high-risk CAD event (ACS, class III/IV angina);

(4) to assess among VISION study participants, who have had a recent high-risk CAD event, the risk of mortality at 30-days among those who received cardiac stent(s) versus those who did not receive a stent within the year prior to surgery;

(5) to assess among VISION study participants, who have had a recent high-risk CAD event, the risk of MINS at 30-days among those who received cardiac stent(s) versus those who did not receive a stent within the year prior to surgery;

(6) to determine if the associated increased risk of 30-day mortality with recent high-risk CAD varies throughout the first 6 months and to identify if there is an optimal time after which non-cardiac surgery should be performed;

(7) to determine if the associated increased risk of 30-day MINS with recent high-risk CAD varies throughout the first 6 months and to identify if there is an optimal time after which non-cardiac surgery should be performed;

Identifying the contemporary risk of mortality and MINS among patients with a recent high-risk cardiac event will better inform clinicians regarding this common clinical scenario. Furthermore, determining the effects of stents prior to non-cardiac surgery will allow clinicians to determine if these patients are at higher or lower risk for adverse events in the perioperative setting especially as it pertains to discontinuation of antiplatelet agents. Finally, determining whether risk varies throughout the first 6 months after a high-risk cardiac event will help determine if there is an optimal time for non-cardiac surgery after a high-risk cardiac event. This information may ultimately prove useful in reducing perioperative adverse events.

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30-day mortality among patients undergoing noncardiac surgery. JAMA : the journal of the American Medical Association 2012;307:2295-304.

2.0 THEORETICAL FRAMEWORK:

Although the VISION study clearly demonstrated an increased risk of perioperative events among patients with a prior high-risk CAD event, identifying how this risk varies with the type of high risk CAD, the effect of revascularization with stents and the duration of time from high risk CAD to subsequent non-cardiac surgery is not clear. Guidelines for instance have recommended delaying elective surgical procedures for prolonged periods of time after coronary stents due to the risk of stent thrombosis caused by premature cessation of DAPT. Although it is generally accepted that delaying non-cardiac surgery after a high-risk cardiac event is associated with decreased perioperative mortality, this recommendation is primarily based on relatively few, older studies with small sample sizes and heterogeneous patient populations. Furthermore, many of these studies were done in an era prior to optimal revascularization, advanced medical therapy and more modern anesthetic and monitoring techniques. These studies and the guideline directives they inform may not apply in the current era as risk has likely changed with many of these advances.

Perioperative risk today may be lower today for several reasons. Surgery itself has changed. Increasingly safer and less invasive techniques are being employed leading to better perioperative outcomes and in some cases obviating the absolute need for DAPT cessation. Although the evidence is limited, the anesthetic technique (i.e., regional versus general) ¹ as well as improved optimization of hemodynamics with invasive monitoring² may also reduce perioperative risk. Observational data and small randomized controlled trials suggest HMG-CoA reductase inhibitors may reduce both

morbidity and major adverse cardiovascular events (MACE) including mortality in patients with prior high-risk cardiac events.³⁻⁵

Conversely, it is also possible that the perioperative risk is actually higher today since older estimates of risk occurred in an era when high-risk patients including those with prior high-risk cardiac events were less likely to undergo surgery. Older studies generally excluded urgent and emergent procedures. Moreover, increasingly older patients are undergoing surgery. For instance, in the VISION cohort, nearly 1 in 4 patients (3657 patients or 24.2%) were ≥ 75 years of age representing a clear epidemiologic shift in those undergoing surgery.⁶

Based on this, it is unclear to what extent various components of the definition of a prior high-risk CAD event contributes to postoperative complications, when the optimal time is to send these patients for surgery and what effect stents have in these circumstances. Existing recommendations on when to operate on patients with prior high-risk CAD have substantial limitations. To date, there are no contemporary prospective studies that address this issue and there are only a few contemporary retrospective registry studies with somewhat conflicting results.

The purpose of this literature review was to critically assess the current evidence to further identify knowledge deficits and conflicts that will help guide the rationale for further analyses.

2.1 Studies Addressing Components of High-Risk CAD

There is a paucity of literature regarding how each component of high-risk CAD contributes to perioperative risk. Perhaps the most important attempt at addressing this issue derives from Detsky et al's study mentioned previously that looked at several components of high-risk CAD.^{7,8} Detsky et al scoring system extended Goldman's risk criteria⁹ by including a more granular assessment of high-risk CAD and how it contributes to the likelihood of perioperative cardiac events notably recurrent MI, HF and mortality. Where Goldman et al's study only assessed MI within 6 months as part of the high-risk CAD criteria, Detsky et al looked at MI within 6 months, MI more than 6 months, CCS class III and IV angina as well as unstable angina within 3 months. This scoring system was validated among 455 patients referred to the general medical consultation service for cardiac risk assessment prior to non-cardiac surgery. All components of high-risk CAD increased the likelihood of perioperative cardiac events (MI or death). All specified components of high-risk CAD increased the likelihood of perioperative cardiac events. MI within 6 months had a 10 fold increased likelihood of perioperative events, MI more than 6 months had a 5 fold increased likelihood of perioperative events. Unstable angina within 3 months of non-cardiac surgery increased the likelihood of a perioperative event 10 fold.^{7,8} These likelihood ratios are summarized in table 7.

The main limitations of this study were that it was not done in a contemporary setting and as such patients were not receiving what we would consider optimal medical therapy (no statins or DAPT) and patients did not have angioplasty or stents. Furthermore, risks of surgical procedures were likely different than they are today.

These all limit the usefulness of this study to inform the current risks of perioperative events among patients with prior high-risk CAD events.

Shah et al in 1990, assessed components of high-risk CAD among 688 consecutive patients with cardiac diseases who were older than 70 years of age—all of whom were undergoing non-cardiac surgery.¹⁰ Thirty-two patients (4.65%) developed a perioperative MI. Cardiac death occurred among 7/32 patients (21.9%) who suffered a perioperative MI and 8/656 patients who did not suffer a perioperative MI. Serious non-fatal complications occurred in 23% of the patients. Among the 24 preoperative risk factors analyzed for the outcome of perioperative MI or cardiac death, patients with chronic stable angina, previous myocardial infarction, and electrocardiographic signs of ischemia were found to be at increased risk of perioperative MI and cardiac death.¹⁰

The 2007, 2009 and 2014 ACC/AHA guidelines list recent MI, unstable and severe class III/IV angina as active cardiac conditions for which patients should undergo evaluation and treatment prior to non-cardiac surgery. The guidelines direct practitioners to follow the relevant guidelines for each of the active conditions.

2.2 Studies that have addressed role of revascularization including stents in high-risk patients:

Guidelines do not recommend routine revascularization prior to non-cardiac surgery to improve outcomes except in the case of significant left main disease or active symptoms with significant ischemia.^{11,56} The evidence is unclear supporting the role of routine revascularization in the perioperative setting. Thus, indication for revascularization in patients with ischemic heart disease is generally similar to those in the non-surgical setting with the intention of preventing perioperative ischemia that can lead to infarction and/or death. This is why the guidelines recommend treatment for these conditions irrespective of the surgical context.¹¹ The majority of fatal perioperative MIs were due to severe CAD disease (left main artery or three-vessel disease).¹² Pathology studies have shown that most of these patients did not have plaque fissuring/rupture and only 1 in 3 had coronary artery thrombus formation. This suggests that mortality may be reduced with revascularization in these settings. The majority of non-fatal perioperative MIs occurred due to plaque rupture in arteries without high-grade stenosis. Plaque rupture in these circumstances may be due to the stresses associated with surgery including trauma, bleeding, inflammation, intubation, anesthesia, pain and hypercoagulability.¹³ (We refer the reader to the schemata illustrated in reference 13: a review paper by Devereaux et al.). In these cases, routine revascularization with PCI or bypass would likely not prevent these events.

A retrospective review of the Coronary Artery Surgery Study (CASS) looked at >3000 patients who underwent non-cardiac surgery with known stable CAD who were allocated to either CABG and medical management or medical management alone with

more than 10 years of follow-up.¹⁴ No patients underwent PCI including stents or balloon angioplasty. This study found that non-revascularized patients who underwent higher risk procedures (vascular and neurosurgical procedures) were at a higher risk for perioperative MI and mortality. This study also showed that patients with three vessel disease and reduced ejection fraction undergoing high-risk procedures had more pronounced reduction in perioperative MI and mortality. The main weakness of this study was that it was performed at a time when medical therapy was limited and it did not include the role of percutaneous revascularization with stents or balloon angioplasty. This study also included MI only and not MINS—routine troponin monitoring was not done.

A landmark study looking at revascularization in the perioperative setting was the Coronary Artery Revascularization Prophylaxis Trial (CARP).¹⁵ This trial randomized patients scheduled for vascular surgery with stable ischemic heart disease to revascularization with PCI or CABG with optimal medical therapy or optimal medical therapy alone. Among 5989 patients screened, 1190 patients were considered to be at increased risk based on clinical assessment and non-invasive ischemic testing. 680 patients were excluded after coronary angiography revealed severe left ventricular dysfunction (LVEF \leq 20 percent), severe left main disease, severe aortic stenosis, or coronary anatomy not suitable for revascularization. 510 patients were then enrolled in the trial. Enrolled patients had an increased risk of perioperative complications as assessed by cardiovascular risk factors and ischemia detection on non-invasive testing. 49 percent of patients had two or more risk factors from the revised cardiac risk index. Of those assigned to revascularization, 38 percent underwent CABG, 55 percent

underwent PCI/stents, and 7 percent received no revascularization. After nearly 3 years of follow-up, no differences were detected in perioperative MI or mortality rate between the medical therapy group and the routine revascularization group groups (22 versus 23 percent, relative risk [RR] 0.98, 95% CI, 0.70-1.37). The 30-day perioperative MI rate among patients assigned to the revascularization group was 8.4 percent and it was also 8.4 percent in the no revascularization group.¹⁵ Weaknesses of this study as it relates to the objectives of this thesis are that routine troponin monitoring was not done therefore leading to lower event rates. Only vascular surgery was evaluated and we cannot necessarily rule out an interaction between revascularization and other surgery types. Finally, ACS patients were not included.

A smaller prospective RCT of 208 patients compared 2 different routine revascularization procedures before major vascular surgery: a 'selective' strategy or a 'systematic' strategy.¹⁶ The 'selective' strategy involved performing angiography only on those patients who had abnormal non-invasive testing (stress tests) that warranted angiography. The 'systematic' strategy involved routine angiography before non-cardiac surgery. Revascularization could include either bypass, stenting or balloon angioplasty. This study found that not surprisingly the rate of revascularization was higher in the 'systematic' strategy group (58 percent versus 40 percent). The outcome of interest included a composite of mortality, non-fatal MI, cerebrovascular accident, heart failure and need for repeat revascularization. Despite this, the perioperative (short-term) adverse cardiovascular event rate although higher was not statistically significant (11.7 percent versus 4.8 percent; $p=0.1$).¹⁶ Long-term outcomes (>58 months) were better with respect to survival and reduced adverse cardiac events in the 'systematic' strategy

which subsequently had higher rates of revascularization. The main weakness of this study with respect to applying it to our question is that it did not adequately answer the question of whether these results apply to patients who have had recent high-risk CAD. It is possible that patients may have ischemia on non-invasive testing but this alone does not fulfill our criteria for high-risk CAD. Other important weaknesses of this study were its small size, limited difference between the groups regarding the number of patients who received revascularization prior to non-cardiac surgery, and narrow indications for surgery (only vascular surgery patients with aorto-femoral and iliac disease).¹⁶

A more recent study looked at 426 patients scheduled to undergo carotid endarterectomy procedures.¹⁷ This study prospectively randomized patients to undergo either routine preoperative angiography and stenting or no coronary angiography. The primary end-point was the incidence of any post-operative myocardial ischemic event combined with the incidence of complications from angiography or stenting. In the angiography group, 31 percent of patients (68 patients) were noted to have a significant stenosis and 66/68 of these patients underwent stenting with the majority (87 percent) receiving a DES. Compared to this group, the non-angiography group 4.2 percent ($p=0.01$) experienced an ischemic event in the perioperative period suggesting a benefit of routine angiography and revascularization. Again, like the previous study, high-risk CAD patients were excluded from this study and routine troponin monitoring was not done.¹⁷

Finally, a meta-analysis that evaluated the value of preoperative revascularization prior to non-cardiac surgery looked at 9 observational studies and the

CARP trial.¹⁸ These studies were all performed between 1996 and 2006 and comprised nearly 4000 patients (3949 patients). Overall, the pooled estimates did not find a significant difference between coronary revascularization and medical management groups in terms of postoperative mortality and MI (odds ratio (OR) 0.85; 95 percent CI 0.48-1.50 for mortality and OR 0.95; 95 percent CI 0.44-2.08 for MI).¹⁸ Again the majority of these patients did not have a recent high-risk CAD event and so they do not necessarily apply to our question re: the role of revascularization in patients who have had a recent high-risk CAD event.

Overall, it appears that revascularization of stable patients prior to non-cardiac surgery is of limited benefit with respect to survival or reduction of perioperative ischemic events. It remains unclear what benefit revascularization with stents or bypass surgery will have in patients with recent high-risk CAD prior to non-cardiac surgery. Also, having had non-cardiac surgery does not necessarily mean that patients would not benefit beyond the immediate perioperative period. It is possible then that revascularization may be recommended in patients with recent high-risk CAD or other signs of extensive ischemia before elective non-cardiac surgery as recommended by cardiology guidelines.¹⁹⁻²¹ There have been no trials that have evaluated the role of prophylactic revascularization in patients with ACS or CCS III/IV and current guidelines recommend priority be given to managing cardiac disease over proceeding with non-cardiac surgery whenever possible. If the surgery is emergent, then patients should undergo non-cardiac surgery and patients be evaluated and treated for the high-risk CAD postoperatively. Again, if surgery needs to happen sooner, BMS is preferred or newer DES can be used if surgery can be delayed more than 1 year and/or data from

ongoing trials confirm equivalency.^{22,23} In rare cases, balloon angioplasty alone without a stent can be used as ASA is alone sufficient in this situation.

2.3 Studies that have addressed timing of surgery after high-risk CAD event:

The first observational studies to assess cardiac outcomes associated with non-cardiac surgery following MI were performed in the late 1960's. Tarhan et al. from the Mayo Clinic retrospectively evaluated 32,877 patients who underwent non-cardiac surgery with general anesthesia between 1967 -1968. 422 patients had a prior MI. Among these patients with a prior MI, 8 patients were operated on within 3 months of suffering an MI. They had a re-infarction rate of 37% (3 cases). 19 patients were operated on within 4-6 months of their prior MI and had a reinfarction rate of 16% (3 cases). Finally, the remaining 395 patients were operated on >6 months from their prior MI. Their recurrent MI rate was 5% (22 cases).²⁴ While this study did not perform tests to determine statistical significance, the absolute numbers suggest delaying surgery after an MI decreases a patient's risk of recurrent MI after surgery, these data should be cautiously interpreted given the small number of events. There was also no assessment of the effects of other high-risk CAD features such as angina and angioplasty and stenting were not used in this era nor did this study address surgical coronary revascularization.

In a repeated analysis conducted at the same institution from 1974-1975, 587 patients who had suffered a prior MI underwent non-cardiac surgery with general anesthesia.²⁵ Among these patients, 15 were operated on within 3 months of their prior MI and had a 27% (4 cases) re-infarction rate and all of those patients died in the

perioperative period. Among 18 patients who had an MI within 4-6 months of their prior MI, 11% (2 cases) had a recurrent MI and 1 of those patients died. Finally, among the 461 patient who had their prior MI >6 months from surgery, the reinfarction rate further declined to 4% (19 cases) and there were 9 deaths. Again these data suggested that delaying surgery reduced the risk of recurrent and fatal MI. Table 1 outlines the effects of the timing of surgery on the risk of mortality and recurrent MI in this study.

Other risk factors besides timing of surgery that were associated with significantly increased re-infarction rates included preoperative hypertension, intraoperative and perioperative hypotension, non-cardiac thoracic or upper abdominal operations and greater than 3 hours of anesthesia time. Postoperative intensive care unit admission did not significantly affect the reinfarction rate nor did diabetes, angina, patient age or sex.²⁵ While these investigators did explore other components of high-risk CAD particularly angina, the effects of angioplasty and/or stenting were not assessed because they were not available clinically during that time.

Rao et al evaluated patients with prior MIs scheduled to undergo routine or emergent non-cardiac surgeries.²⁶ They specifically looked at the incidence and factors related to recurrent perioperative MIs both retrospectively from 1973-1976 (group 1) and prospectively in a separate publication that included patients having surgery from 1977-1982 (group 2). Group 2 had routine intraoperative hemodynamics measured using a pulmonary artery catheter to help guide therapies such as fluids to control hypotension and tachycardia and inotropes to further mitigate hypotension. Overall, myocardial re-infarctions occurred in 28/364 patients in group 1 (7.7%) and 14/733 patients in group 2 (1.9%). Specifically looking at the timing of non-cardiac surgery demonstrated that re-

infarctions decreased from 36% in group 1 patients who had their surgeries from 0-3 months after their initial MI compared to 26% with a 4-6 month delay. For group 2 patients, the reinfarction rates also decreased depending on the timing of surgery from 5.7%(0-3 month delay) to 2.3%(4-6 month delay).²⁶ Therefore these data also suggested that reinfarction rates declined with the delaying of non-cardiac surgery after an MI. The authors attributed the dramatically lower event rates in group 2 compared with group 1 to better perioperative monitoring. Furthermore, there was also no assessment of the effects of other high-risk CAD features such as angina and angioplasty and stenting were not used in this era.

The same group of investigators in 1990 prospectively evaluated 275 patients with a prior myocardial infarction who underwent non-cardiac surgery.²⁷ Overall the perioperative myocardial reinfarction rate was 4.7% (13 patients). When the time interval between prior MI and non-cardiac surgery was analyzed, the perioperative reinfarction rate was 4.3% (12 patients) at 0-3 months, 0% (0 patients) at 4-6months and 5.7%(16 patients) incidence when the surgery was performed greater than 6 months after the initial MI (p-values not reported).²⁷ These data did not support the earlier studies suggesting delaying surgery was protective. These investigators did note that when patients had a recurrent MI, the mortality rate was as high as 57% which further emphasizes the importance of avoiding this complication in the perioperative period.²⁶ The effects of other high-risk CAD features were not looked at and angioplasty and stenting were not widely used during this era and were not evaluated in this study.

Goldman et al in 1977 prospectively evaluated 1001 patients who were >40 years of age and undergoing non-cardiac surgery. Using a multivariable analysis, the

investigators found that an MI in the preceding 6 months was an independent predictor of post-operative life-threatening and fatal cardiac complications (RR 15.9; $p < 0.01$ compared to control).⁹ They did not, however, look at the effect of the time of the non-cardiac surgery after an MI on mortality or recurrent MI within the 6 month period evaluated. Other markers for high-risk CAD were not looked at including angina. Again, angioplasty and stenting were not in use during this era.⁹

Detsky et al. in 1986 modified the Goldman index by including additional variables believed to be clinically important in predicting perioperative risk in particular more specific features of high-risk CAD including MI within 6 months, MI more than 6 months, CCS class III/IV angina, and unstable angina within 3 months.^{7,8} The authors also simplified the scoring system using a pretest probability determined by type of surgery and likelihood ratios based on the number of preoperative predictors. Their model was validated in 455 consecutive patients referred to the general medical consultation service for cardiac risk assessment prior to non-cardiac surgery. For patients undergoing major surgery, the modified index added predictive information to a statistically significant degree ($p < 0.05$). The modified index also added predictive information for patients undergoing both major and minor surgery, demonstrating an area under the Receiver Operating Characteristic curve of 0.75 (95% confidence interval of 0.70 to 0.80). This was ultimately found to be more predictive than the Goldman index.^{7,8}

All specified components of high-risk CAD increased the likelihood of perioperative cardiac events. MI within 6 months had a 10 fold increased

likelihood of perioperative events, MI more than 6 months had a 5 fold increased likelihood of perioperative events. Unstable angina within 3 months of non-cardiac surgery increased the likelihood of a perioperative event 10 fold.^{7,8} This study did look at most components of high-risk CAD, but timing was only addressed after MI and unstable angina and not after stable angina or after revascularization.

Since then, few studies have further explored the relationship between high-risk CAD and perioperative outcomes leaving guideline recommendations suboptimally informed especially in the modern era of optimal surgical, anesthetic, revascularization and medical therapy. The most recent study looking at this was done by Livhits et al utilizing the California Patient Discharge Database where they retrospectively analyzed 563,842 patients undergoing a variety of non-cardiac surgeries including hip surgery, cholecystectomy, colectomy, elective abdominal aortic aneurysm repair and lower extremity amputation from 1999 through 2004.²⁸ These procedures represented major inpatient operations from a wide variety of surgical specialties. Postoperative 30-day MI rates, 30-day mortality and 1-year mortality rates were compared for patients with and without a recent MI using multivariate logistic regression. A “recent” MI was defined as occurring within 1 year of the index surgery. Length of time from MI to non-cardiac surgery was included in the multivariable analysis.

Of the 563,842 patients, 16,242 had a recent MI (2.8%). The 30-day postoperative MI rate was 1.4% for patients without a history of recent MI. Among patients with a recent MI, the postoperative MI rate was 32.8% ($p < 0.001$). The

investigators found that postoperative MI rates among patients who had a recent MI decreased substantially as the length of time from preoperative MI to index surgery increased: 0-30 day delay had a 32.8% postoperative MI rate, 31-60 day delay had a 18.7% rate, 61-90 day delay had a 8.4% rate, and 91-180 day delay had a 5.9% rate ($p < 0.001$ compared with patients without a prior MI).

Thirty-day mortality was 3.9% for patients without a recent MI. Patients with a history of recent MI within 30 days before their operation had a 30-day mortality rate of 14.2%. They also found that 30 day mortality rates decreased substantially with increasing delay to non-cardiac surgery after a myocardial infarction: 0-30 day delay had a 14.2% mortality rate, 31-60 day delay had a 18.7% rate, 61-90 day delay had a 8.4% rate, and 91-180 day delay had a 9.9% rate ($p < 0.001$ compared with patients without a prior MI).

One-year mortality was 13.3% for patients without a history of recent MI. Patients with a recent MI within 30 days of surgery had an overall mortality rate of 41.2%. One-year mortality rates also decreased when greater time elapsed from recent MI (31–60 days 39.4%, 61–90 days 34.5% and 91–180 days 32.2%, $P < 0.001$ compared with patients without a prior MI). The results of this study are summarized in tables 2-4.

Based on these results, the investigators concluded that a recent MI even in a contemporary setting with optimal medical, anesthetic and surgical management with modern revascularization remains a significant risk factor for postoperative MI and both 30-day and 1-year mortality following surgery. Because of the significant risk of postoperative MI for patients undergoing surgery within 0 to 60 days of suffering an MI compared with >60 days (RR range, 9.98–44.29 or 4.53–21.95), the investigators

suggest that surgery should ideally be delayed for 8 weeks (the apparent inflexion point) when clinically possible to allow for medical optimization prior to non-cardiac surgery. This study went on to become the main justification for the 60-day waiting period in the 2014 iteration of the ACC/AHA guidelines. Table 6 summarizes all the studies that have looked at timing of non-cardiac surgery after an MI.

This study should be interpreted in the context of several limitations. Although coronary revascularization prior to surgery was included in their multivariate analysis, the impact of stents alone, stent type, use or discontinuation of antiplatelet agents and appropriateness of revascularization could not be ascertained since these data were not reported in the California database. Baseline medication use was not included in the multivariable model. While MI and mortality rates were evaluated, MINS rates were not evaluated and as demonstrated in VISION, MINS also independently impacts 30-day mortality rates.

2.4 Studies that have addressed timing of surgery after cardiac stents

As mentioned earlier, the literature reviewed thus far does not include the often-complicating factor of coronary stents. Stents have been widely used for the treatment of ACS including MI since the mid-1990s. This complicates the timing of non-cardiac surgery since having a stent requires dual anti-platelet therapy with ASA and a P2Y₁₂ inhibitor such as clopidogrel, ticagrelor or prasugrel especially during the time when stent endothelialization has not been completed. During this time, cessation of the P2Y₁₂ inhibitor antiplatelet agent, which is often a prerequisite to undergo non-cardiac surgery, can put a patient at risk of in stent thrombosis.²⁹ Endothelialization can take up to 30-45 days for a BMS and up to 1 year for a DES.³⁰⁻³³ There have been several recent investigations looking at the relationship between stents and non-cardiac surgery.

Wijeysundera et al in a 2012 publication, also used linked administrative databases from the Cardiac Care Network of Ontario, the Canadian Institute for Health Information, the Ontario Health Insurance Plan Database and the Registered Persons Database to conduct a retrospective cohort study in Ontario between 2003-2009 of 8116 patients ≥ 40 years of age who received a coronary stent within 10 years before elective non-cardiac surgery of which 34% (n=2725) underwent stent implantation within 2 years before surgery.³⁴ The primary outcome was a 30-day major adverse cardiac event, which was a composite outcome comprising mortality, readmission for acute coronary syndrome or repeat revascularization. The overall 30-day event rate was 2.1%. The earliest optimal time for performing elective non-cardiac surgery appeared to

be from 46 to 180 days after BMS implantation, or >180 days after DES implantation. This is further illustrated in table 5.

It is important to note that the optimal timings suggested by this study are not concordant with the 2009 ACC/AHA guidelines nor reflected in the updated 2014 guidelines. Strictly speaking, this study did not provide insight into optimal timing for non-cardiac surgery after a *high-risk cardiac event* since the reason for initial stent implantation was not available in the administrative database. That being said, it can be assumed that a substantial proportion of stents were placed for high-risk CAD compared to stable class I/II angina.³⁴ Furthermore, the lack of a non-stented arm precludes an analysis of the effect of stenting on important postoperative outcomes. Other important weaknesses of this study were that there were no data available on some key inpatient/hospital outcomes such as myocardial infarction, congestive heart failure and stent thrombosis. Information regarding perioperative management of antiplatelet therapy was incomplete. Also, information regarding clinical factors determining the urgency/emergency of surgery was unavailable. Postoperative adverse cardiac events were also infrequent (2.1% at 30 days) which further limited the power of this study to compare multiple time intervals. “Survivor bias” also may have affected the results of this study as the sicker patients would have been scheduled for surgery sooner than the current ACC/AHA guidelines would recommend (i.e. within the first 30-45 days). Finally, routine troponin monitoring was not done.

Hawn et al in 2013, looked at the risk of major adverse cardiac events following non-cardiac surgery in patients with coronary stents in general.³⁵ This was a retrospective cohort study of 28 029 patients undergoing non-cardiac surgeries within

the 24 month period after coronary stent implantation during the years 2000-2010. Of these patients, 4068 patients had suffered an MI in the 6 months prior to non-cardiac surgery. Infarct rate by stent type was 5.1% for BMS and 4.3% for DES ($P<0.001$). The time between the stent and surgery was associated with MACE (<6 week 11.6%; 6 weeks to <6mos, 6.4%; 6-12 months, 4.2%; >12-24 mos, 3.5%; $p<0.001$). Here, the rate of postoperative MIs in patients with prior MI was 19.1% if the surgery occurred within 6 weeks of the prior MI, 8.8% if the surgery occurred within 3 months, 5.7% between 3-6 months, 3.4% from 6-12 months and 2.4% from 12-24 months ($P<0.05$)³⁵. The increased risk associated with a DES was no longer evident around 60 days and after BMS it was no longer evident around 180 days.

In terms of explanatory variables, stent type ranked last, and DES was not significantly associated with MACE (aOR, 0.91; 95%CI, 0.83-1.01). After both BMS and DES placement, the risk of MACE was stable at 6 months. A case-control analysis of 284 matched pairs found no association between antiplatelet cessation and MACE (OR, 0.86; 95%CI, 0.57-1.29).

2.5 Contemporary Guideline Positions:

Based on some, but not all, of the studies discussed and the management guidelines for myocardial infarction in the non-operative setting³⁶, the 1996 ACC/AHA guidelines for perioperative cardiovascular evaluation were the first to suggest that surgery be delayed for 4-6 weeks after an MI^{37,38}. The more contemporary guidelines of 2002³⁹, 2007³⁸ as well as 2009⁴⁰ continued to adhere to the 4-6 week delay after MI. The guidelines have defined acute MI as ≤ 7 days and recent MI as 8-30 days before non-cardiac surgery. It appears that the decision to use the 4-6 week interval seems to have been extrapolated from the 1990 management guidelines for myocardial infarction.³⁶ These guidelines suggested that if there was no residual myocardium at risk of ischemia in 4-6 weeks, the reinfarction rate remained low. There was also a significant mortality benefit waiting following MI secondary to the initiation of medical therapy and further optimization of risk factors. This also resulted in improved blood pressure and heart rate control. There was also an ability to perform a stress test to further risk stratify patients based on their ability to achieve target heart rate and appropriate metabolic equivalency (METs) or demonstrate ischemia on non-invasive testing.^{36,55} With respect to stents, these guidelines recommend non-cardiac surgery after 30 days from a BMS and 365 days after DES. This was not supported by Hawn et al's study where the risks were stable after 6 months.³⁵

Most recently, based primarily on Livhits' study²⁸, the 2014 guidelines recommended a 60 day window after a recent MI.⁴¹ They continue to recommend waiting 30 days after a BMS is implanted—however if the BMS was implanted primarily for an MI, then the 60 day window would still apply. The new guidelines continue to

recommend waiting ≥ 365 days if a DES is implanted¹¹ however it is unclear why this recommendation persists in light of Hawn et al's findings.³⁵

2.6 Differences between operative and non-operative MIs. Defining MINS:

The 2007 Joint Task Force of the European Society of Cardiology, American College of Cardiology Foundation, the American Heart Association, and the World Health Federation (ESC/ACCF/AHA/WHF) defined acute myocardial infarction (MI) as a “clinical event consequent to the death of cardiac myocytes (myocardial necrosis) that is caused by ischemia.”⁴² This definition remained unchanged in the third universal definition of MI released in 2012 by the ESC/ACCF/AHA/WHF.⁴³ In non-cardiac surgery, the diagnosis of MI is confirmed with an elevated cardiac biomarker (usually troponin) with at least one of the following defining features: symptoms of ischemia, new ST or T wave changes or new left bundle branch block, development of significant Q waves on the electrocardiogram, imaging evidence of new loss of myocardium or new wall motion abnormality, or identification of an intracoronary thrombus by angiography or autopsy.⁴³

The pathophysiology of perioperative MI is highly debated. Although supply-demand mismatch has long been thought to result in perioperative MIs, the evidence to support this explanation is extremely weak. In general, arterial thrombotic events which include plaque fissuring and acute luminal thrombosis are now believed the dominant mechanism of non-operative ST and non-ST elevation MIs and these can occur in sites without significant angiographic stenosis.⁴⁴⁻⁴⁷ Less is known about the pathophysiology of perioperative MIs. Two small autopsy studies suggest that fatal perioperative MIs are commonly associated with left main or 3 vessel CAD^{12,48} and these events may have resulted from supply demand mismatch or a thrombotic event⁴⁹. Non-fatal operative MIs also occur in arteries without high-grade stenoses suggesting that these

events may also be due to plaque fissuring and acute luminal thrombosis⁵⁰. Most patients suffering a perioperative MI die from recurrent events and recurrent MIs may be related to recurrent plaque fissuring and luminal thrombotic events.

Based on the universal definition of MI, troponin elevations that are not associated with symptoms, ECG changes or imaging evidence of myocardial necrosis do not meet the strict criteria of MI. These troponin elevations are, however, predictive of increased mortality based on the original VISION study publication.⁶ Looking at all troponin elevations regardless of whether they met the strict criteria of MI, one finds that patients from VISION can be grouped into 4 risk criteria. Group 1 had a peak troponin of ≤ 0.01 $\mu\text{g/L}$ after surgery and this was associated with a 30-day mortality rate of 1%. Group 2 had a peak troponin of 0.02 $\mu\text{g/L}$ after surgery and this was associated with a 30-day mortality rate of 4%. Group 3 had a peak troponin of 0.03 - 0.29 $\mu\text{g/L}$ after surgery and this was associated with a 30-day mortality rate of 9.3%. Finally, Group 4 had a peak troponin of ≥ 0.30 $\mu\text{g/L}$ after surgery and this was associated with a 30-day mortality rate of 16.9%. What is important to note is that of the 1200 patients (8% of the cohort) that had an elevated troponin, 58.2% did not meet the strict criteria of MI. Regardless, these events portend a poor prognosis and were found to be an independent predictor of 30-day mortality (aHR 3.87; 95%CI, 2.96-5.08). The impact of these troponin elevations may also be reduced with appropriate interventions.⁵¹

Given the importance of troponin elevations, a new term was introduced that would encompass biomarker elevation that would otherwise not meet criteria for MI. Myocardial injury with noncardiac surgery (MINS) was proposed and described from the original VISION cohort.⁵² MINS is a broad term that includes MI (after noncardiac

surgery) and is defined as myocardial injury believed due to an ischemic process in patients who have undergone an operative procedure. These are patients with postoperative elevations in troponin who do not necessarily have symptoms, electrocardiographic abnormalities, or other criteria that meet the universal definition described earlier. In the VISION prospective cohort using 4th generation troponin-T, a troponin T level of 0.03ng/mL or greater occurred in 1200 patients (8%) but only 41.8% of these patients met strict criteria for an MI. The majority of troponin elevations occurred in the first 48 hours.⁵²

The VISION data demonstrated that troponin elevations after surgery that were not associated with ischemic symptoms or ECGs changes but had no evidence of a non-ischemic etiology were independent predictors of 30-day mortality. Hence troponin elevations after surgery that are believed due to ischemia but do not fulfill the Universal Definition of MI are prognostically relevant. Therefore MINS encompasses both perioperative MI and troponin elevations after surgery that are due to ischemia but do not fulfill the universal definition of MI.

Based on these data, the VISION investigators' diagnostic criteria of MINS was "a peak troponin T level of 0.03ng/mL or greater judged to be due to myocardial ischemia."⁵² It should be noted that the term MINS does not apply to patients in whom a non-ischemic etiology is responsible for the troponin elevation such as pulmonary embolism, sepsis, or cardioversion.

Looking at other studies including VISION subgroup analyses in patients with moderate to high perioperative risk and using this definition of MINS, the incidence of asymptomatic troponin elevations without any other defining feature for MI has been

reported to range between 5-45 percent.^{13,52-54} In a recent observation study of 2232 patients, the incidence of myocardial injury with an elevated troponin alone was 19% compare with an MI rate of 0.6%; however, not all patients had ECGs with elevated troponins.⁵⁴ It is also likely that as the sensitivity of troponin assays increase, as seen with the newer high-sensitive generation troponin assays, the frequency of MINS events will increase.

2.7 Conclusions:

Overall, with respect to timing of surgery, the dominant message from the literature suggests that waiting longer before proceeding with noncardiac surgery will likely reduce the risk of recurrent MI and mortality after a high-risk CAD event with only a few studies suggesting the possibility of ongoing risk beyond a 6 month delay. In particular, there are no studies that directly establish the 4-6 week time point as suggested by the ACC/AHA guidelines and this is largely translated from the non-operative MI guidelines. The 2014 guidelines suggest the 60 day delay period may be the best time to proceed with noncardiac surgery after an MI; however, this was based on 1 retrospective cohort study. Overall, we believe that there is still a high degree of uncertainty in applying this to the contemporary setting.

Reasons that suggest the risk of recurrent events may be higher than prior studies estimate:

1. Older patients are increasingly being sent for non-cardiac surgery and many of these patients have prior high-risk CAD and will likely have more events. Older patients fare worse after a recurrent event than younger patients.
2. More patients are surviving MIs and other high-risk CAD events than before and subsequently are undergoing more non-cardiac surgery. This increases the risk of recurrent events.
3. After the recognition of the prevalence of perioperative myocardial events, more troponin screening is being done routinely. Troponin monitoring will increase the detection rate of perioperative MINS including MIs. We may

detect that events are still occurring frequently despite the 4-6 week delay period recommended in guidelines.

Reasons that suggest that the risk of recurrent events may be lower than prior studies estimate:

1. Surgical techniques have changed and are generally less invasive and likely safer
2. Better perioperative monitoring of hemodynamics is occurring and this may reduce the recurrent MI and mortality rate
3. There is better medical therapies for CAD particularly wider use of statin medication which may translate into better perioperative outcomes especially as it relates to prevent plaque fissuring and thrombotic events

Based on these uncertainties, the optimal timing of non-cardiac surgery after a prior high-risk CAD event is unknown. It is also unknown whether a safer period even exists. This will be one of the main objectives of this current project.

Compared to the ACC/AHA guidelines that recommend waiting at least 1 month after a BMS and 12 months after a DES before proceeding with NCS, more recent studies suggest a more liberal approach. A study based on the Canadian cardiac care network suggest that the optimal time period may be 46 to 180 days after bare-metal-stent implantation, and >180 days after drug-eluting-stent implantation. The US VA trial

suggested the risk of recurrent events after a stent stabilized at 6 months for both DES and BMS. Stent type ranked last among predictors for MACE. Once again, we see shortcoming in the current methods of assessing risk amongst patients who have had prior high-risk CAD and this further justifies the rationale for the objectives of this study.

Table 1: Mayo Clinic study evaluating effect of delay time after MI on postoperative reinfarction rate and mortality.²⁵

Timing of Surgery After MI (mos)	Patients (n)	Postoperative Reinfarctions (n,%)	Deaths(n,%)
0-3	15	4 (27)	4 (100)
4-6	18	2 (11)	1 (50)
7-12	31	2 (6)	2 (100)
13-18	30	1 (3)	0(0)
19-24	17	1 (6)	1(100)
>25	383	15 (4)	8(53)

Table 2: 30-day postoperative MI rate by time elapsed from recent MI for all non-cardiac surgeries (California Patient Discharge Database).²⁸

Time Elapsed from Preoperative MI (days)	30-day postoperative MI rate
0-30 days	32.8%
31-60 days	18.7%
61-90 days	8.4%
91-180 days	5.9%
181-365 days	6.0%
No MI	1.4%

Table 3: 30-day mortality rate by time elapsed from recent MI for all non-cardiac surgeries (California Patient Discharge Database).²⁸

Time Elapsed from Preoperative MI (days)	30-day mortality rate
0-30 days	14.3%
31-60 days	11.5%
61-90 days	10.5%
91-180 days	8.3%
181-365 days	7.8%
No MI	3.9%

Table 4: 1-year mortality rate by time elapsed from recent MI for all non-cardiac surgeries (California Patient Discharge Database).²⁸

Time Elapsed from Preoperative MI (days)	1-year postoperative MI rate
0-30 days	41.2%
31-60 days	39.4%
61-90 days	34.5%
91-180 days	32.2%
181-365 days	29.9%
No MI	13.3%

Table 5: Adjusted association of stent type and time interval from stent insertion to surgery within 30 days after elective non-cardiac surgery. ³⁴

Stent Type	Time Elapsed from Stent Placement to Surgery	Adjusted OR and 95%CI for MACE
BMS	1-45 days	2.35 (0.98-5.64)
BMS	46-180 days	1.06 (0.58-1.92)
BMS	181-365 days	1.89 (1.08-3.32)
BMS	366-730 days	1.13 (0.67-1.92)
DES	1-45 days	11.58 (4.08-32.80)
DES	46-180 days	1.71 (0.73-4.01)
DES	181-365 days	0.64 (0.20-2.04)
DES	366-730 days	1.14 (0.59-2.22)
Any Stent	2-10 years	1.0 (Reference)

Table 6: Reinfarction rates associated with non-cardiac surgery following myocardial infarction in observational studies.

Time from MI to non-cardiac surgery	Tarhan et al. 1977 ²⁴	Steen et al. 1978 ²⁵	Rao et al. 1983 ²⁶	Shah et al. 1990 ²⁷	Livhits et al. 2011 ²⁸
	(n= 422)	(n=587)	(n=364 retrospective, n=733 prospective)	(n=275)	(n=16242)
Design	Retrospective	Retrospective	Retrospective/ Prospective	Retrospective	Retrospective
Cardiac Enzymes Routinely Monitored	No	No	No	No	No
0-3mos	37%	27%	5.8%	4.3%	6.4%
4-6mos	16%	11%	2.3%	0%	5.3%
>6mos	5.6%	4.1%	1.5%	5.7%	NA

Table 7: Modified Multifactorial Index by Detsky et al.⁸

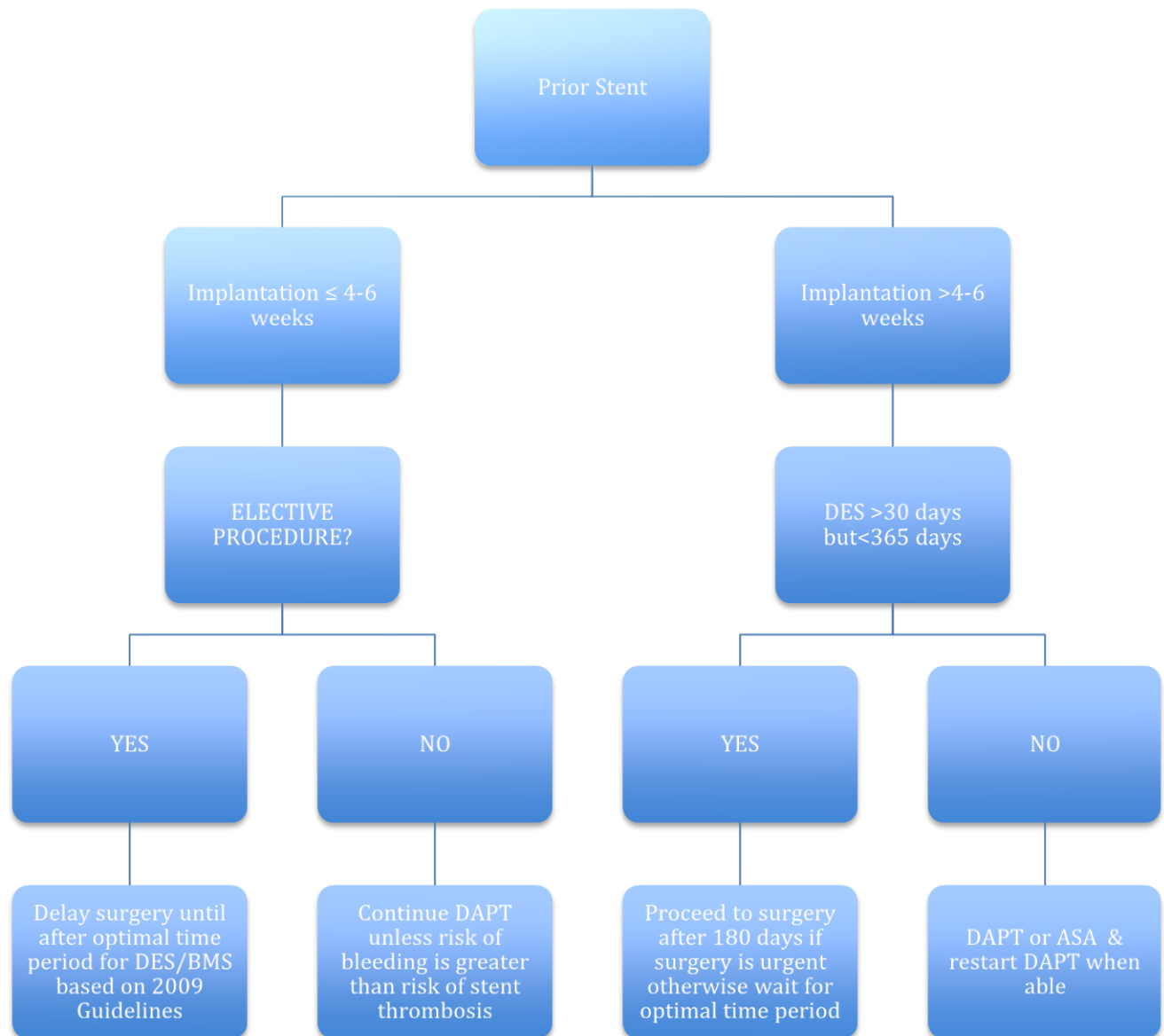
Variable	Points
MI within 6 months	10
MI more than 6 months	5
CCS class III	10
CCS class IV	20
Unstable angina within 3 months	10
Pulmonary edema within 1 week	10
Pulmonary edema ever	5
Critical Aortic Stenosis	20
Sinus with premature beats or any rhythm other than sinus rhythm	5
>5 VPCs any time prior to surgery	5
Poor medical status*	5
Age > 70 years	5
Emergent Procedure	10

0-5 points= 6% postoperative complication rate
6-12 points = 7% postoperative complication rate
13-25 points = 20% postoperative complication rate
26-100 points = 100% postoperative complication rate

Table 8: ACC/AHA guideline approach to the management of patients with previous percutaneous coronary intervention (PCI) who require non-cardiac surgery, based on expert opinion.⁴⁰

Balloon Angioplasty	Bare Metal Stent	Drug-Eluting Stent
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> <14 days--Delay surgery for elective or non-urgent surgery	<input type="checkbox"/> >30 -45 days--Proceed to NCS with ASA	<input type="checkbox"/> >365 days--Proceed to NCS with ASA
<input type="checkbox"/> ≥14 days--Proceed to NCS with ASA	<input type="checkbox"/> ≤ 30-45 days--Delay surgery for elective or non-urgent surgery	<input type="checkbox"/> ≤ 365 days--Delay surgery for elective or non-urgent surgery

Figure 1: ACC/AHA guideline approach in 2014 to the management of patients with previous percutaneous coronary intervention (PCI) who require non-cardiac surgery.¹¹



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3.0 HIGH RISK CAD STUDY (4th Generation Troponin):

3.1 Abstract:

Background:

Recent high-risk coronary artery disease (CAD) (i.e., acute coronary syndrome [ACS] or class III/IV angina) within 6 months of non-cardiac surgery is independently associated with increased perioperative mortality and myocardial injury after non-cardiac surgery (MINS). Whether individual components of high risk CAD (ACS or class III/IV angina), use of stents or elapsed time from high-risk CAD to non-cardiac surgery contribute to risk is unclear.

Hypotheses:

We hypothesize that: 1. all components of high-risk CAD will be independently associated with an increased risk of a major perioperative cardiovascular complications; 2. prior stents will be associated with an increased risk of a major perioperative cardiovascular complication; and 3. delaying non-cardiac surgery ≥ 60 days after high-risk CAD will be associated with a reduction in the risk of 30-day mortality and MINS.

Methods:

We assessed whether ACS or class III/IV angina, presence or absence of stents and delay times prior to NCS (<60 day versus ≥ 60 -day surgical delay-times) independently impacted the risk of 30-day mortality and MINS by performing multivariable regression analyses on patients, ≥ 45 years of age who underwent in-hospital non-cardiac surgery and were enrolled in the VISION study, an international prospective cohort study of a representative sample of 16,064 patients who underwent non-cardiac surgery.

Results:

Among 16 064 patients, 190 patients had recent high-risk CAD (134 had an ACS and 56 had class III/IV angina) in the 6 months prior to non-cardiac surgery. Among 15 874 patients without recent high-risk CAD, the 30-day mortality rate was 1.9% and the 30-day MINS rate was 7.9%, whereas patients with a recent high-risk CAD event had a significantly higher 30-day mortality rate of 10% (adjusted hazard ratio [aHR] 3.12; 95% CI, 1.94-5.0; $p < 0.001$) and a significantly higher 30-day MINS rate of 31.8% (aHR 1.64; 95% CI, 1.22-2.20; $p = 0.001$). There were 134 patients with ACS (unstable angina (UA)/myocardial infarction (MI)) who had a 30-day mortality rate of 11.2% (aHR 3.32; 95% CI, 1.96-5.62; $p < 0.001$) and a 30-day MINS rate of 37% (aHR 1.60; 95% CI, 1.16-2.22; $p = 0.005$). There were 56 patients with class III/IV angina who had a 30-day mortality rate of 7.1% (aHR 2.55; 95% CI, 0.94-6.90; $p = 0.065$) and a 30-day MINS rate of 19.6% (aHR 1.80; 95% CI, 0.95-3.38; $p = 0.070$). A total of 28 patients had recent high-risk CAD with a stent and had a 30-day mortality rate of 3.6% (aHR 0.9; 95%CI 0.13-6.48; $p = 0.919$) and a 30-day MINS rate of 19.2% (aHR 0.93; 95%CI, 0.38-2.27; $p = 0.879$). A total of 162 patients had recent high-risk CAD without a stent and had a 30-day mortality rate of 11.1% (aHR 3.59; 95%CI 2.22-5.82; $p < 0.001$) and a 30-day MINS rate of 34% (aHR 1.78; 95%CI, 1.30-2.42; $p < 0.001$). Compared to patients without recent high-risk CAD, patients having non-cardiac surgery < 60 days of a high-risk CAD event had a mortality rate of 11.4% (aHR 3.58; 95%CI, 2.08-6.17; $p < 0.001$) and patients who had non-cardiac surgery ≥ 60 days after a high-risk CAD event had a mortality rate of 7.5% (aHR 2.29; 95%CI, 0.94-5.57; $p = 0.068$). Surgery < 60 days from high-risk CAD was associated with a 30-day MINS rate of 36.4% (aHR 1.82; 95%CI, 1.30-2.55;

$p < 0.001$) and surgery ≥ 60 days was associated with a 30-day MINS rate of 23.3% (aHR 1.27; 95% CI, 0.74-2.18; $p = 0.390$) compared to patients without recent high-risk CAD.

Conclusions: High-risk cardiac events in the 6-month period prior to non-cardiac surgery were associated with an increased 30-day risk of postoperative mortality and MINS. Among the different components of high-risk CAD, the 30-day risk of mortality and MINS is associated with ACS (UA/MI) only and not class III/IV angina; however, there were substantially fewer patients who had class III/IV angina and the results demonstrated a trend towards increased risk. The risk of mortality and MINS was present in those without prior stents. Finally, delaying surgery for ≥ 60 days after a high-risk CAD event was associated with a reduced risk of 30-day mortality and MINS.

3.2 Introduction:

More than 200 million major non-cardiac surgeries occur each year.¹ Despite the obvious benefits provided by surgery, contemporary studies indicate that >2 million people will die within 30 days with nearly 50 percent of deaths attributed to a cardiovascular cause.^{2,3} Furthermore, an estimated 6-10 million patients will suffer a myocardial injury after non-cardiac surgery (MINS) during the perioperative period which further contributes to perioperative mortality and morbidity.³ These statistics firmly establish perioperative cardiac events as an important public health issue and so identifying these events and the antecedent risk factors is paramount to addressing this issue.

Recent high-risk coronary artery disease (CAD) prior to non-cardiac surgery, defined as Canadian Cardiovascular Society (CCS) class III or IV angina or acute coronary syndromes (ACS), which includes MI or unstable angina, are independently associated with an increased risk of mortality and morbidity following surgery.⁴ This has long been recognized as an important risk factor for perioperative complications in several well-known risk stratification tools.^{5,6} Given our aging population, the number of patients with a history of high-risk CAD undergoing non-cardiac surgery will likely increase and so there is a need to better understand the risks faced by patients with recent high-risk CAD who undergo non-cardiac surgery.⁷⁻⁹

The most recent iteration of the perioperative guidelines address many of the issues surrounding recent high-risk CAD.¹⁰ While the American College of Cardiology/American Heart Association (ACC/AHA) guidelines do not address each component of high-risk CAD, they do mention that non-cardiac surgery should be

delayed until ACS (including recent MI or unstable angina) and stable angina are treated according to their respective guidelines. The perioperative guidelines have recently updated their recommendations with regard to timing of non-cardiac surgery after a recent MI primarily based on a study of a California patient discharge database by Livhits et al.¹¹ The 2014 guidelines now recommend waiting at least 60 days after a recent MI.¹² They continue to recommend waiting 30 days after a BMS is implanted—however if the BMS was implanted primarily for an MI, then the 60 day window would still apply. The new guidelines continue to recommend waiting ≥ 365 days if a DES is implanted.¹⁰ While delaying non-cardiac surgery for truly elective procedure may be prudent, some surgical procedures need to occur expeditiously due to time-sensitive serious conditions (e.g., cancer).

Despite numerous studies and guideline directives^{9,12,13} on managing high-risk CAD patients prior to non-cardiac surgery, it remains unclear what the exact risk and the best perioperative management is for these patients in the modern era since most of the studies used to inform this issue had small sample sizes or evaluated data more than 30-years old when medical and revascularization therapy were different or non-existent compared to contemporary approaches. Furthermore, many of these studies, with the exception of Livhits et al.¹¹, were done in an era when older patients were less likely to be operated on and less invasive surgical options were not available. Given this, there is uncertainty regarding how each component of high-risk CAD contributes to risk, what effect prior stenting has on risk and the appropriate time necessary to delay surgery to reduce risk or whether delaying surgery reduces risk at all in contemporary practice.^{11,12,14} The three major themes from prior studies thus far are that (1) all

components of high-risk CAD contribute to risk, (notably unstable angina, MI and CCS class III/IV angina), (2) revascularization and stenting in particular does not necessarily mitigate this risk and may be harmful due to thrombosis risk from premature discontinuation of dual antiplatelet therapy and (3) delaying non-cardiac surgery after a high-risk CAD event reduces perioperative mortality and MI.

The Vascular Events In Non-Cardiac Surgery Patients Cohort Evaluation (VISION) Study (clinicaltrials.gov identifier NCT 00512109) is an international, contemporary, multi-centre prospective cohort study that has evaluated major complications among a planned 40 000 patient cohort undergoing non-cardiac surgery—interim results for the have already been published.¹⁵ The major finding of this study was that troponin-T elevations were an independent predictor of 30-day mortality. Further, analyses also found that even patients with troponin elevations that did not meet the universal definition of MI yet were nonetheless a consequence of cardiac ischemia, were also an independent predictor for 30-day mortality ushering in the concept of “myocardial injury in the setting of non-cardiac surgery” (MINS).¹⁶ In both these studies, prior high-risk CAD in particular was found to be an independent predictor for both 30-day mortality (aHR of 8.7; 95%CI, 5.3-13.8; $p<0.001$) and 30-day MINS (aHR 1.63; 95%CI, 1.21-2.19; $p=0.001$).^{15 16}

Given the uncertainty that remains on managing perioperative patients with prior high-risk CAD, the purpose of this study will be to clarify how each component of high-risk CAD contributes to risk, how stents modify this risk and what the optimal timing is after a high-risk CAD event to proceed with non-cardiac surgery.

3.3 Study Population:

The design and results of the VISION study have been reported previously.¹⁵ To summarize, the VISION study was an international, multicentre, prospective cohort study of 40,000 representative patients undertaken to evaluate major complications including 30-day mortality and troponin-T (TnT) elevation after non-cardiac surgery. After the first 15,000 patients were analyzed, event rates were noted to be 3 fold higher than expected thereby providing sufficient events to address an original study objective related to the 4th generation TnT measurements and the risk of 30-day mortality. Based on this, the steering committee decided to use the 5th generation assay for the remaining portion of the study. This analysis therefore is based solely on 16,064 patients with 4th generation TnT assay results.

Noteworthy aspects of the VISION study design included (1) simple entry criteria and collection of essential baseline and outcome data (2) wide sampling strategy throughout 8 countries across 5 continents with both university and non-university hospitals and (3) a large sample size to ensure a large number of events.

3.3.1 Inclusion Criteria:

Patients were included if they were at least 45 years of age undergoing elective, urgent or emergent non-cardiac surgery that required general or regional anesthesia.

3.3.2 Exclusion Criteria:

Patients were excluded if they did not require an overnight hospital admission postoperatively, were previously enrolled in the VISION study, did not have an absolute 4th generation TnT measurement after surgery or failed to provide informed consent. Additional exclusion criteria pertinent for this subgroup analysis included patients without a high-risk cardiac event who received a stent within 6 months prior to their non-cardiac surgery.

Patients were identified by screening daily patient lists in preoperative assessment clinics, on surgical wards and in intensive care units; daily and previous day surgical lists and patients in the preoperative holding area. Research staff obtained consent prior to surgery. Research personnel obtained consent within the first 24 hours after surgery for those who could not provide consent prior to surgery (e.g. emergency cases). Eight centres used a deferred consent process for patients unable to provide consent (e.g. patients on ventilators and no next-of-kin available).¹⁵

Procedures:

Patients had blood collected to measure a 4th generation troponin-T (Roche Elecsys™) 6-12 hours postoperatively and on the first, second and third days after surgery. Patients enrolled between 12-24 hours after surgery had a TnT drawn immediately and testing continued as described above. During their hospitalization, research personnel examined patients and reviewed medical records and noted outcome events. Patients or their next of kin were also contacted by telephone at 30

days after surgery. If an outcome was reported, their physicians were contacted to obtain further documentation.

3.4 Outcomes:

The primary outcome was all-cause mortality at 30 days after surgery. The secondary outcome was MINS (myocardial injury in non-cardiac surgery) defined as a troponin-T elevation $\geq 0.03\text{ng/mL}$ judged to be ischemic in etiology. Detailed definitions of endpoints are listed in appendix 2. The diagnostic characteristics and predictors for MINS have been accepted and published in the anesthesiology literature which highlights the fact that MINS carries a poor prognosis.¹⁶ Troponin elevations that were adjudicated as not resulting from an ischemic cause (e.g. sepsis or pulmonary embolism) were not included as an outcome for this study.

3.4.1 Data Quality:

Research personnel at each centre submitted case report forms and documentation directly to the data management system (iDataFax, coordinating center, McMaster University, Canada). Data monitoring in VISION consisted of central data consistency checks, statistical monitoring and on-site monitoring for all centres.

3.4.2 Statistical Analysis:

A statistical analysis plan outlining the analyses in this paper was written a priori. Patients were divided based on the presence or absence of a recent high-risk cardiac event in the 6 months before their non-cardiac surgery. Baseline characteristics between these groups were compared with a one-way ANOVA test, Fisher's exact test

or chi-square tests as appropriate. Exact definitions of baseline characteristics are included in appendix 1. All objectives were exploratory for this analysis with the intention of determining the feasibility of this study. Hence no formal sample size calculation was attempted. Formal sample size calculations will be done for the entire 40 0000 patient sample.

The first objective was to determine whether the individual components of high-risk CAD was associated with 30-day postoperative mortality or MINS. The individual components of high-risk CAD included (1) ACS which comprised unstable angina or MI and (2) CCS class III or IV angina. We undertook a Cox proportional hazards model where the dependent variable was 30-day mortality and 30-day MINS.

For 30-day mortality, the independent variables were those that were found to be predictive of mortality from the original VISION paper. These included: (a) age (3 separate categories), (b) presence or absence of stroke, (c) presence or absence of peripheral vascular disease (PVD), (d) presence or absence of urgent/emergent surgery (e) presence or absence of cancer (f) presence or absence of general surgery (g) presence or absence of neurosurgery, (h) the various components of high-risk CAD.

For 30-day MINS, the independent variables were those found to be predictive of MINS from the original MINS paper. These included: (a) age (3 separate categories), (b) male gender, (c) presence or absence of current atrial fibrillation (d) presence or absence of diabetes mellitus (e) presence or absence of hypertension (f) presence or absence of congestive heart failure (CHF) (g) presence or absence of a prior history of CAD (h) presence or absence of stroke (i) presence or absence of peripheral vascular

disease (j) preoperative GFR (as a continuous variable) (k) presence or absence of urgent/emergent surgery (l) presence or absence of low risk surgery. The model was run including ACS and class III/IV angina as independent variables.

The second objective was to determine whether the presence or absence of stents among recent high-risk CAD patients was associated with 30-day mortality or MINS use. Here we also undertook a Cox proportional hazards model where the dependent variables were 30-day mortality and MINS rate. We included the same independent variables listed previously in the mortality analysis and MINS analysis along with high-risk CAD in patients with and separately without a prior stent.

The third objective was to determine the effect of delaying <60 day versus ≥60 day after a high-risk cardiac event and mortality and the development of MINS. Here we also undertook a Cox proportional hazards model where the dependent variables were 30-day mortality and MINS rate. We included the same independent variables listed above in the mortality analysis and MINS analysis along with high-risk CAD within 60 days of surgery and separately ≥60 day after a high-risk cardiac event.

3.4.3 Ethical Considerations and Funding Sources:

All centre principal investigators obtained Ethics Review Board approval. Research personnel approached all potentially eligible patients who fulfilled eligibility criteria for consent. All patients signed a consent form to participate in VISION Study. Confidentiality of patient data was maintained at local hospitals and the project office. Research personnel stored paper copies of case report forms (CRFs) in locked cabinets at their hospitals. The project office stored the electronic files of CRFs on a high-security

computer system that has password protection. All study personnel ensured no patient identifiers were present on any files transmitted to any committee or clinical centre. We also ensured de-identification of all data in final reports. Funding for this study came from over 60 grants for VISION and its substudies.

3.5 Results:

Figure 1 reports the patient flow throughout the study. There were a total of 23 693 patients who met the VISION eligibility criteria outlines. 1084 (4.6 percent) were not identified in time to enroll in the study. 22 609 patients were screened in time to fulfill eligibility criteria. From this group, 6522 patients (28.8 percent) were not enrolled for the following: they did not consent (5262 patients), were unable to consent due to cognitive impairment (251 patients), their surgeon did not approve of their participation (134 patients) or for other reasons (875 patients). This left 16,064 patients from which this analysis derives. 13,978 patients were left after excluding patients with troponin elevations due to non-ischemic etiologies or no troponin values recorded.

The baseline characteristics of patients varied between those with and without a recent high risk CAD event in the preceding 6 months prior to non-cardiac surgery as shown in Table 1. Overall, patients with recent high-risk CAD were older, had worse renal function, more likely to have peripheral vascular disease, diabetes, atrial fibrillation, stroke / transient ischemic attacks (TIA), chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF). Prior CAD was predictably higher among those with recent high-risk CAD. Cases of cancer were similar between groups. The numbers of urgent or emergent surgeries were similar. Patients in the recent high-risk CAD group did have more vascular surgery procedures. No thoracic surgery procedures were undertaken in patients with a recent high-risk CAD event but 398 patients (2.5 percent) without recent high-risk CAD had thoracic surgical procedures.

All-cause mortality rates were described previously in the original VISION study. The overall 30-day mortality rate for the entire cohort of 16064 patients was 2.0% (315 deaths; 95% CI, 1.8-2.2). The 30-day mortality rate for the 190 patients with recent high risk CAD was 10.0% (19 deaths; 95% CI, 6.5-15.1). The 30-day mortality rate for patients without recent high risk CAD was 1.9% (296 deaths, 95% CI, 1.7-2.1).

Myocardial injury (MINS) rates were then examined. After excluding patients without usable troponin values or troponin elevations deemed non-ischemic, there were a total of 13,978 patients included in the MINS analysis. The overall MINS rate for the entire cohort was 8.2% (n=1146; 95% CI, 7.7-8.7). The MINS rate for patients with recent high-risk CAD was 31.8% (aHR 1.64; 95% CI, 1.22-2.20). The MINS rate for patients without recent high-risk CAD was 7.9% (n=1090, 95% CI, 7.5-8.4).

For objective 1, table 2 outlines the model looking at 30-day mortality for each component of high-risk CAD. Compared to patients without high risk CAD, patients having ACS (UA/MI) had an adjusted hazard ratio of 3.32 (95% CI, 1.96-5.62) $p < 0.001$ compared with patients without high risk CAD. Class III/IV angina had a trend toward increased mortality with an adjusted hazard ratio of 2.55 (95% CI, 0.94-6.9) $p = 0.065$.

Table 3 outlines the model looking at 30-day MINS for each component of high-risk CAD. Compared with patients without high-risk CAD, patients having ACS (UA/MI) had an adjusted hazard ratio of 1.6 (95% CI, 1.16-2.22) $p = 0.005$ for MINS compared with patients without high risk CAD. Class III/IV angina also had a trend toward increased MINS rate with an adjusted hazard ratio of 1.80 (95% CI, 0.95-3.38) $p = 0.070$.

For objective 2, table 4 outlines the model looking at 30-day mortality depending on whether patients with high-risk CAD had a prior stent. Compared with patients without high-risk CAD, high-risk CAD patients with a stent had an adjusted hazard ratio of 0.90 (95% CI, 0.13-6.48) $p=0.919$. High-risk CAD patients without a stent had an adjusted hazard ratio of 3.59 (95% CI, 2.22-5.82) $p<0.001$.

Table 5 outlines the model looking at 30-day MINS depending on whether a patient had a prior stent or not. Compared to patients without recent high risk CAD, patients with recent high-risk CAD and a stent had an adjusted hazard ratio of 0.93 (95% CI, 0.38-2.27) $p=0.879$ for MINS compared with patients without high risk CAD. High-risk CAD patients without a stent had an adjusted hazard ratio of 1.78 (95% CI, 1.30-2.42) $p<0.001$.

For objective 3, table 6 outlines the model looking at 30-day mortality depending on the timing of non-cardiac surgery after the high-risk CAD event. Compared with patients without high-risk CAD, high-risk CAD patients who had their non-cardiac surgery <60 days from their high-risk CAD event had an adjusted hazard ratio of 3.58 (95% CI, 2.08-6.17) $p<0.001$. High-risk CAD who had their NCS at ≥ 60 days from their high-risk event had an adjusted hazard ratio of 2.29 (95% CI, 0.94-5.57) $p=0.068$.

Table 7 outlines the model looking at 30-day MINS depending on timing of non-cardiac surgery. Compared to patients without high risk CAD, patients who had their NCS < 60 days of their high-risk event had an adjusted hazard ratio of 1.82 (95% CI, 1.30-2.55; $p<0.001$) for MINS. High-risk CAD patients who had their surgery ≥ 60 days

from their high-risk CAD event had an adjusted hazard ratio of 1.27 (95% CI, 0.74-2.18);
p=0.390.

3.6 Discussion:

This study provides important data on perioperative outcomes among patients with recent high-risk CAD events. The original paper did confirm that having a recent high risk CAD event in the 6 months prior to non-cardiac surgery was associated with higher risk of 30-day mortality and MINS compared to patients without prior high-risk CAD events.¹⁶ In this analysis, we further explored perioperative risk among patients who have had prior high-risk CAD.

With respect to components of high-risk CAD, this analysis found a significant increase in mortality among patients with ACS but not CCS class III/IV angina in the 6 months prior to high-risk CAD. For 30-day MINS rates, again we see an increase in risk with ACS but not CCS class III/IV angina. There was, however, a trend toward increased 30-day mortality and 30-day MINS among class III/IV angina patients but this was not statistically significant potentially due to the relatively smaller number of patients with class III/IV angina (type II error). This suggests that CCS class III/IV angina may infer the same risk as ACS.

With respect to stenting, among high-risk CAD patients, those who did not have a stent in the 6 months prior had an associated increased risk-adjusted mortality rate. Among high-risk CAD patients who did have a stent in the 6 months prior to non-cardiac surgery, there was no longer an associated increased risk of mortality. Among patients with a prior high-risk CAD event, not having a prior stent was associated with an increased 30-day MINS rate. Patients who had a prior stent no longer had a statistically significant 30-day MINS rates. These data suggest the possibility that recent stents are

associated with reduced risk at the time of non-cardiac surgery; however, the number of patients with a stent was too small to make definitive associations.

Finally, when we look at the delay time prior to non-cardiac surgery after a high-risk CAD event, having non-cardiac surgery <60 days was associated with both increased 30-day mortality and 30-day MINS compared to those without prior high-risk CAD. Waiting ≥60 days after a high risk CAD event resulted in 30-day mortality rates and 30-day MINS that were not increased compared to those without prior high-risk CAD. This suggests that delaying surgery after a high-risk CAD event seemed to be protective against both 30-day mortality and 30-day MINS. The ACC/AHA joint taskforce recommendations most recently in 2014 recommend waiting ≥60 days after an MI and up to 1 year after a DES.¹⁰ This recommendation is primarily based on a study using discharge summaries that demonstrated that the postoperative MI rate decreased substantially as the length of time from MI to operation increased (0 to 30 days =32.8%; 31 to 60 days =18.7%; 61 to 90 days =8.4%; and 91 to 180 days =5.9%), as did 30-day mortality rates (0 to 30 days =14.2%; 31 to 60 days =11.5%; 61 to 90 days =10.5%; and 91 to 180 days =9.9%)¹¹. Taken together, the data suggest that ≥60 days should elapse after a MI before non-cardiac surgery in the absence of a recent stent. It is reassuring that our study also confirms this finding. However we cannot exclude other important time intervals, as our study was underpowered to evaluate further time points.

3.6.1 Limitations of this Study:

This study should be interpreted in the context of several limitations. First of, being an observational cohort study, we need to consider whether patients had similar prognostic factors known to be associated with the outcome of interest.

Measured baseline characteristics confirmed that high-risk CAD patients were older, had worse renal function, more likely to have peripheral vascular disease, diabetes, atrial fibrillation, stroke / transient ischemic attacks (TIA), chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF). All of these risk factors would likely increase the risk of mortality and MINS with the exception of COPD which would probably only increase the risk of mortality and not MINS necessarily. While our models tried to adjust for this, it is still possible that these are contributing factors as well.

Baseline medication use was also not accounted for in this study. High-risk CAD patients would likely be on more antiplatelet therapy and statin medications for instance. Antiplatelet therapy especially in the form of DAPT could increase the risk of perioperative bleeding thus leading to more perioperative complications and potentially increasing mortality. DAPT could reduce stent thrombosis and therefore reduce MINS events however with bleeding, the type II MI rate could increase and therefore increase overall MINS rates. POISE-2 found that perioperative ASA use was not associated with lower rates of postoperative MI or death but it did not address the role of DAPT—in fact, patients with stents who had not completed their recommended duration of antiplatelet therapy were excluded.¹⁸ Statin use would also likely reduce risk as there have been

multiple observational studies showing that their use was associated with reduced morbidity and mortality.¹⁹⁻²¹

It is unclear whether high-risk CAD patients were similar to other patients with respect to other important prognostic factors that could contribute to the outcomes of mortality or MINS. We can assume that given current guideline recommendations, most clinicians would try to avoid sending recent high-risk CAD patients for non-cardiac surgery unless there was a compelling indication to proceed such as an urgent/emergent surgery. While there were no significant differences in the number of patients undergoing urgent/emergent surgery, there are several types of procedures that are life-threatening and time-sensitive yet still do not meet standard definitions including the VISION definition of “urgent/emergent.” This would mean that patients with high-risk CAD patients could be sicker in that they were undergoing non-cardiac surgery because there was no alternative. This would be a type of survival/residual bias. For example a septic patient with an abscess would have to be operated on for source control even if they had a recent high-risk CAD event whereas procedures such as joint replacement would be delayed in patients with recent high-risk CAD events.

It is also possible that recent high-risk CAD patients would be treated with less invasive procedures initially that could be suboptimal with respect to treatment. For example a patient with subacute cholecystitis without high-risk CAD may be sent for surgery (cholecystectomy) sooner whereas in high-risk CAD patients this may be delayed and treated non-surgically with stents/percutaneous biliary drains. These treatments do not necessarily require a 24-hour inpatient stay and thus would not be captured in the VISION analysis. In the end, this could be a suboptimal treatment for

cholecystitis rendering these patients more susceptible to infection for instance. They may then need the surgery later, which could make the recent high-risk CAD patients more likely to suffer an event. This illustrates how clinicians may have delayed surgery for a longer period of time in patients with high-risk CAD when they were enrolled into VISION. These patients would then be sicker and perhaps need to go to surgery on a more urgent basis. This could result in a prognostic imbalance not fully controlled for in our model.

The particular definitions for high-risk CAD while explicit in the VISION protocol, can be interpreted differently by clinicians. For instance, class IV angina and unstable angina could be considered similar entities by some clinicians. It is also not clear how patients who fit multiple categories of high-risk CAD in the 6 months preceding their non-cardiac surgery would be categorized. A patient with a prior MI who then develops class III/IV angina may eventually have unstable angina prior to surgery. This patient could conceivably fit several definitions of high-risk CAD and it is unclear how investigators classified such patients. If only the most recent classification of high-risk CAD was used, this could affect the estimates of risk.

Our multivariable model also did not control for renal function for the mortality outcome while it was controlled for with the MINS outcome. This is because renal function was found to contribute to poor outcomes in the MINS study but not to peak troponin elevations in VISION.^{15,16} In the original VISION study, a post-hoc sensitivity analysis did not however reveal a significant interaction with renal function and troponin-T thresholds among the 14 008 (92.6%) patients in whom preoperative creatinine levels were measured. Reduced GFR however is an independent risk factor for mortality

among high-risk CAD patients however; it is unknown whether renal function specifically affects those with prior high-risk CAD in the VISION study.¹⁷

Observational cohort studies also do not control for unknown prognostic factors that randomization would control for better. For instance we do not know whether dyslipidemia, smoking status or socioeconomic status for example may contribute to risk. We also do not know whether there were significant differences in baseline medication use that could contribute uniquely to prognosis in the perioperative setting. For instance premature cessation of dual antiplatelet therapy could predispose patients to stent thrombosis. Also, operating urgently on high-risk CAD patients could lead to more bleeding since they are more likely to be on antiplatelet and antithrombotic agents whose effects may not have fully worn off at the time of surgery.

This study also relied solely on 4th generation troponins. Much of the world has now moved toward the high sensitivity 5th generation troponin assays that can detect troponin much more readily. It is possible that the number of MINS events would have been even higher had the more sensitive assay been utilized.

With regard to stents, this study did not have enough patients to determine outcomes separate for DES or BMS. This is important, since there is a known increased thrombosis risk with DES given delay in stent endothelialization. Also, patients with DES are more likely to be on dual antiplatelet therapy at the time of their surgery which could increase bleeding events and contribute to MINS events as well.

This study did not assess other forms a cardiac revascularization notably bypass surgery. When we compared recent high-risk CAD with stents versus those without

stents, it is possible that bypass patients could be included among those without stents. Patients who underwent bypass surgery usually have more severe CAD including three-vessel disease or left main coronary involvement. They also tend to have lower ejection fractions and this was not captured in the baseline characteristics. This could positively affect the prognostic balance in favour of stenting. Therefore the “protective” effect of stenting that was seen may be due to patients who had to undergo bypass. Also, some patients may not be eligible for any form of surgical or percutaneous revascularization due to diffuse CAD disease as is often seen in diabetic patients. If this were the case, they would be included among high-risk CAD patients without stent and analysis would reveal better outcomes among those stented.

Another important weakness of this study is that we only tested the 60 day threshold after a high-risk CAD event prior to non-cardiac surgery. It is possible that other inflection points in time exist where the risk changes appreciably however due to the small number of patients, we cannot exclude these.

This study also was affected by several of the limitations of the main VISION analysis. Notably, we are not certain whether patients were recruited prior to non-cardiac surgery or soon after. It is possible that high-risk CAD patients may have been more likely to be recruited prior to non-cardiac surgery and this could represent patients who are motivated in their own care and this could affect outcomes. Also, we do not have information on how clinicians treated patients after a MINS event. It is very likely that patients with known prior high-risk CAD received more intense treatment and this could certainly affect their 30-day outcomes. Patients with isolated troponin elevations may not have been as aggressively treated.

3.6.2: Strengths of this Study:

The main strengths of this study lie in the design of the original VISION study. Its main strengths include the large sample size—largest prospective perioperative cohort study to date. It also sampled patients from 8 countries spanning 5 continents who were undergoing several different surgery types. Sensitivity studies in VISION demonstrate that results were consistent across all sites for the different troponin thresholds. This makes this study easier to translate into daily practice because of its large sample size and broad inclusion criteria. This study was also unique in that it had a routine troponin monitoring protocol. Without routine monitoring, as was seen in several of the prior studies in the literature review, it is likely that many MINS events could be missed. This is especially true in an era where (1) we have good anesthesia and analgesia techniques where patients may not necessarily complain of chest pain and (2) routine perioperative ECGs or troponins are still not routinely checked. This study also used absolute values of troponins and not just predetermined cut-offs. Thus, all relevant troponin values that determine prognosis were included and helped to ensure a broader and more clinically useful definition for MINS that was ascertained in this paper.

Finally, the follow up of patients in this cohort study was extremely good. 99.7% of patients were able to complete the 30-day follow up and data was available on all the preoperative variables evaluated.

Table 1: Baseline Characteristics of Patients with and without a Recent High-Risk CAD

Event

	All Patients (N=16066)	No Recent High Risk CAD (N=15876)	Recent High Risk CAD (N=190)	p-value for difference
Age, n (%)				<0.001
45-64 years old	8202 (51.1)	8156 (51.4)	46 (24.2)	
65-74 years old	3988 (24.8)	3926 (24.7)	62 (32.6)	
≥75 years old	3876 (24.1)	3794 (23.9)	82 (43.2)	
BMI, mean (SD)*	27.1 (6.1)	27.1 (6.1)	26.5 (6.2)	0.192
Preoperative eGFR, n (%)**				<0.001
<30 or on dialysis	562 (3.8)	541 (3.7)	21 (11.3)	
30-44	828 (5.6)	801 (5.4)	27 (14.5)	
45-59	1578 (10.6)	1548 (10.5)	30 (16.1)	
≥60	11933 (80.1)	11825 (80.4)	108 (58.1)	
Non-European, n (%)†	6001 (37.4)	5929 (37.4)	72 (38.1)	0.880
History of PVD, n (%)	856 (5.3)	817 (5.1)	39 (20.5)	<0.001
History of diabetes, n (%)	3139 (19.5)	3059 (19.3)	80 (42.1)	<0.001
Current atrial fibrillation, n (%)	544 (3.4)	517 (3.3)	27 (14.2)	<0.001
Obstructive sleep apnea, n (%)	823 (5.1)	811 (5.1)	12 (6.3)	0.408
History of stroke or TIA, n (%)	1166 (7.3)	1120 (7.1)	46 (24.2)	<0.001
History of COPD, n (%)	1334 (8.3)	1295 (8.2)	39 (20.5)	<0.001
History of CHF, n (%)	758 (4.7)	699 (4.4)	59 (31.1)	<0.001
History of CAD, n (%)	1938 (12.1)	1748 (11.0)	190 (100.0)	<0.001
Cancer, n (%)	4219 (26.3)	4171 (26.3)	48 (25.3)	0.804
Urgent/Emergent surgery, n (%)	2310 (14.4)	2278 (14.3)	32 (16.8)	0.348

Major general surgery, n (%)	3207 (20.0)	3169 (20.0)	38 (20.0)	1.000
Major vascular surgery, n (%)	520 (3.2)	506 (3.2)	14 (7.4)	0.006
Major neurosurgery, n (%)	930 (5.8)	916 (5.8)	14 (7.4)	0.346
Major orthopaedic surgery, n (%)	3265 (20.3)	3217 (20.3)	48 (25.3)	0.102
Major thoracic surgery, n (%)	398 (2.5)	398 (2.5)	0 (0.0)	0.016

* N=15543 (15363 and 180)

** N=14901 (14715 and 186)

† N=16028 (15839 and 189)

Table 2: 30-day mortality rates and hazard ratios for the components of high-risk CAD.

Cohort	Number of Patients (%)	30-day Mortality Rate (n, %)	Adjusted Hazard Ratio	95% CI	p-value
Reference Group No high risk CAD	 15874 (98.8)	 296 (1.9)	 1.00		
ACS (UA/MI)	134 (0.8)	15 (11.2)	3.32	1.96-5.62	<0.001
Class III/IV angina	56 (0.3)	4 (7.1)	2.55	0.94-6.90	0.065

Model was adjusted for (a) age (3 separate categories), (b) presence or absence of stroke, (c) presence or absence of peripheral vascular disease (PVD), (d) presence or absence of urgent/emergent surgery (e) presence or absence of cancer (f) presence or absence of general surgery (g) presence or absence of neurosurgery.

Table 3: 30-day MINS rates and hazard ratios for the components of high-risk CAD.

Cohort	Number of Patients (%)	30-day MINS Rate (n, %)	Adjusted Hazard Ratio	95% CI	p-value
Reference Group No high risk CAD	 13808 (98.8)	 1092 (7.9)	 1.00		
ACS (UA/MI)	119 (0.9)	44 (37.0)	1.60	1.16-2.22	0.005
Class III/IV angina	51 (0.4)	10 (19.6)	1.80	0.95-3.38	0.070

Model was adjusted for (a) age (3 separate categories), (b) male gender, (c) presence or absence of current atrial fibrillation (d) presence or absence of diabetes mellitus (e) presence or absence of hypertension (f) presence or absence of congestive heart failure (CHF) (g) presence or absence of a prior history of CAD (h) presence or absence of stroke (i) presence or absence of peripheral vascular disease (j) preoperative GFR (as a continuous variable) (k) presence or absence of urgent/emergent surgery and (l) presence or absence of low risk surgery.

Table 4: 30-day mortality rates and hazard ratios for high-risk CAD patients with and without prior stents.

Cohort	Number of Patients (%)	30-day Mortality Rate (n, %)	Adjusted Hazard Ratio	95% CI	p-value
Reference Group No high risk CAD	 15874 (98.8)	 296 (1.9)	 1.00		
High risk CAD with stent	28 (0.2)	1(3.6)	0.90	0.13-6.48	0.919
High risk CAD without stent	162 (1.0)	18 (11.1)	3.59	2.22-5.82	<0.001

Model was adjusted for (a) age (3 separate categories), (b) presence or absence of stroke, (c) presence or absence of peripheral vascular disease (PVD), (d) presence or absence of urgent/emergent surgery (e) presence or absence of cancer (f) presence or absence of general surgery (g) presence or absence of neurosurgery.

Table 5: 30-day MINS rates and hazard ratios for high-risk CAD patients with and without a prior stent.

Cohort	Number of Patients (%)	30-day MINS Rate (n, %)	Adjusted Hazard Ratio	95% CI	p-value
Reference Group					
No high risk CAD	13808 (98.8)	1092 (7.9)	1.00		
High risk CAD with stent	26 (0.2)	5 (19.2)	0.93	0.38-2.27	0.879
High risk CAD without stent	144 (1.0)	49 (34.0)	1.78	1.30-2.42	<0.001

Model was adjusted for (a) age (3 separate categories), (b) male gender, (c) presence or absence of current atrial fibrillation (d) presence or absence of diabetes mellitus (e) presence or absence of hypertension (f) presence or absence of congestive heart failure (CHF) (g) presence or absence of a prior history of CAD (h) presence or absence of stroke (i) presence or absence of peripheral vascular disease (j) preoperative GFR (as a continuous variable) (k) presence or absence of urgent/emergent surgery (l) presence or absence of low risk surgery.

Table 6: 30-day mortality rates and hazard ratios for high-risk CAD patients who had surgery performed <60 days versus ≥60 days of their non-cardiac surgery.

Cohort	Number of Patients (%)	30-day mortality rate (n, %)	Adjusted Hazard Ratio	95% CI	p-value
Reference Group No high risk CAD	 15874 (98.8)	 296 (1.9)	 1.00		
High Risk CAD <60 days of NCS	123 (0.8)	14 (11.4)	3.58	2.08-6.17	<0.001
High Risk CAD ≥60 days of NCS	67 (0.4)	5 (7.5)	2.29	0.94-5.57	0.068

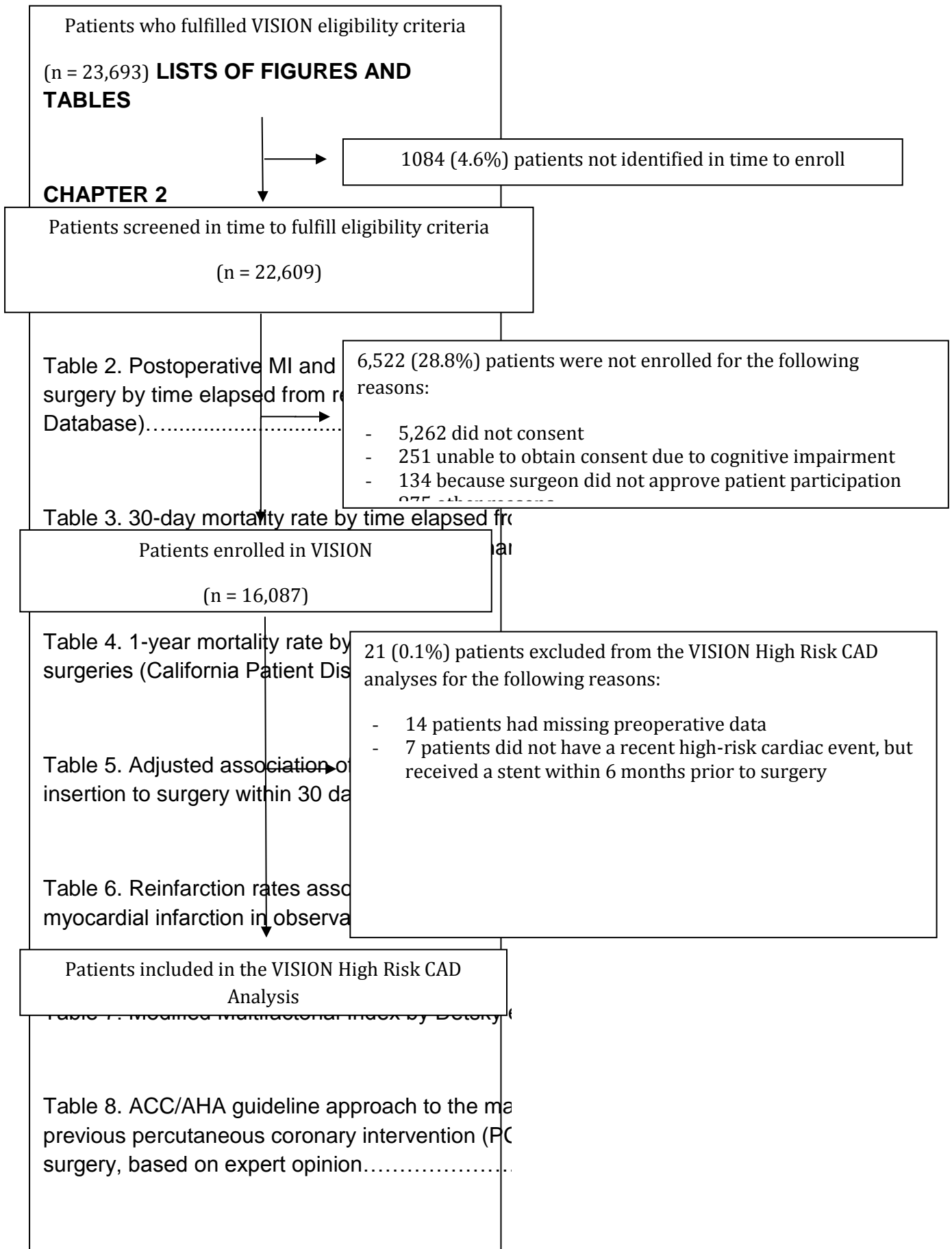
Model was adjusted for (a) age (3 separate categories), (b) presence or absence of stroke, (c) presence or absence of peripheral vascular disease (PVD), (d) presence or absence of urgent/emergent surgery (e) presence or absence of cancer (f) presence or absence of general surgery (g) presence or absence of neurosurgery.

Table 7: 30-day MINS rates and hazard ratios for high-risk CAD patients who had surgery performed at 1 month versus 2-6 months of their NCS

Cohort	Number of Patients (%)	30-day MINS Rate (n, %)	Adjusted Hazard Ratio	95% CI	p-value
Reference Group No high risk CAD	13808 (98.8)	1092 (7.9)	1.00		
High Risk CAD <60 days of NCS	110(0.8)	40 (36.4)	1.82	1.30-2.55	<0.001
High Risk CAD ≥60 days of NCS	60(0.4)	14 (23.3)	1.27	0.74-2.18	0.390

Model was adjusted for (a) age (3 separate categories), (b) male gender, (c) presence or absence of current atrial fibrillation (d) presence or absence of diabetes mellitus (e) presence or absence of hypertension (f) presence or absence of congestive heart failure (CHF) (g) presence or absence of a prior history of CAD (h) presence or absence of stroke (i) presence or absence of peripheral vascular disease (j) preoperative GFR (as a continuous variable) (k) presence or absence of urgent/emergent surgery (l) presence or absence of low risk surgery.

Figure 1: Patient flow chart



3.7 Appendix 1: Baseline Definitions:

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

2. Sex – Male or female.

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

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

- 5. History of cardiac arrest** – A patient with a prior history of a cardiac arrest.
- 6. History of congestive heart failure** – A physician diagnosis of a current or prior episode of congestive heart failure or prior radiographic evidence of vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema.
- 7. History of peripheral vascular disease** – A physician diagnosis of a current or prior history of: intermittent claudication, vascular surgery for atherosclerotic disease, an ankle/arm systolic blood pressure ratio <0.90 in either leg at rest, or angiographic or doppler study demonstrating $>70\%$ stenosis in a noncardiac artery.
- 8. History of stroke** – A physician diagnosis of a current or prior stroke, or CT or magnetic resonance (MR) evidence of a stroke.
- 9. History of deep venous thrombosis (DVT) or pulmonary embolus (PE)** – A patient with a current or prior history of a DVT or PE.
- 10. Diabetes** – Patient stated that they have a diagnosis of diabetes or a physician has previously recorded that the patient has diabetes. This included gestational diabetes at the time of noncardiac surgery, but not past gestational diabetes that had resolved.
- 11. Hypertension** – A physician diagnosis of hypertension.

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

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

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

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

16. Chronic obstructive pulmonary disease (COPD) – A physician current or prior diagnosis of chronic bronchitis, emphysema, or COPD, or a patient provided a history of daily production of sputum for at least 3 months in 2 consecutive years.

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

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

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

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

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

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

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

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

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

3.8 Appendix 2. Study outcome definitions

1. Sub Classification of Death

Judicial outcome assessors will classify all deaths as either vascular or non-vascular.

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

2. Myocardial Infarction

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

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

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

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

C. ECG changes indicative of ischemia (i.e., ST segment elevation [> 2 mm in leads V1, V2, or V3 OR > 1 mm in the other leads], ST segment depression [> 1 mm], or symmetric inversion of T waves > 1 mm) in at least two contiguous leads

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

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

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

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

3. Nonfatal Cardiac Arrest

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

4. Stroke

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

5. Leg or arm DVT/PE

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

1. A persistent intraluminal filling defect on contrast venography

2. Noncompressibility of one or more venous segments on B mode compression ultrasonography

3. A clearly defined intraluminal filling defect on contrast enhanced computed

tomography

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

1. A high probability ventilation/perfusion lung scan
2. An intraluminal filling defect of segmental or larger artery on a helical CT scan
3. An intraluminal filling defect on pulmonary angiography
4. A positive diagnostic test for DVT (e.g., positive compression ultrasound) and one of the following:
 - A. non-diagnostic (i.e., low or intermediate probability) ventilation/perfusion lung scan.
 - B. non-diagnostic (subsegmental defects or technically inadequate study) helical CT scan.

6. Bleeding:

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

7. New Acute Renal Failure Requiring Dialysis

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

8. Sepsis/Infection.

Infection is defined as a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic organisms. Sepsis

is a clinical syndrome defined by the presence of both infection and a systemic inflammatory response. Systemic inflammatory response requires 2 or more of the following factors: core temperature $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$; heart rate > 90 bpm; respiratory rate > 20 breaths/min; white blood cell count $> 12 \times 10^9/\text{L}$ or $< 4 \times 10^9/\text{L}$.

9. Pneumonia

The diagnosis of postoperative pneumonia requires any one of the following:⁵⁶

1. Rales or dullness to percussion on physical examinations of chest AND any of the following:

- A. New onset of purulent sputum or change in character of sputum
- B. Isolation of organism from blood culture
- C. Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy

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

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

10. New Clinically Important Atrial Fibrillation

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

11. Congestive Heart Failure

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

12. Cardiac Revascularization Procedures

Cardiac revascularization procedures include PCI and CABG surgery.

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4.0 SUMMARY AND FUTURE DIRECTIONS:

This study has highlighted an ongoing area of uncertainty in the perioperative literature regarding the impact of high-risk CAD on major vascular complications after non-cardiac surgery. The prior literature in this area has generally concluded that:

1. Patients with prior high-risk CAD events have worse perioperative outcomes and this extends to all components of high-risk CAD including ACS and CCS class III/IV angina.
2. Revascularization prior to non-cardiac surgery is of little benefit in patients with stable ischemic heart disease regardless whether stenting or bypass is used. It is unclear what benefit is extended to those with recent high-risk CAD with respect to stents or bypass.
3. Delaying non-cardiac surgery among those with high-risk CAD will result in less postoperative events such as mortality or MI and the best evidence thus far suggested a 60 day cut point after an MI to proceed with non-cardiac surgery.

The prior literature however may underestimate risk for several important reasons. Patients are now older and more patients are surviving MI's and other high-risk CAD events which may increase perioperative events. Furthermore, no prior study was done where troponins or other biomarkers of myocardial injury were systematically monitored. This leaves us with significant uncertainty regarding the true perioperative

event rate in these high-risk patients. The prior literature may also overestimate risk since surgical techniques today are less invasive and potentially safer, better perioperative monitoring is done and better medical therapy for CAD exists.

Overall, there remains significant gaps in the literature on the impact of high-risk CAD on MINS and mortality and this served as the main impetus for our study—which was an analysis of the VISION study. The main conclusions of our study were that:

1. Among the components of high-risk CAD, ACS, which further comprises MI and unstable angina, is associated with increased mortality and MINS. CCS class III/IV angina had a trend toward increased mortality and MINS; however, the number of patients with CCS class III/IV angina in the 6 months prior to surgery was small and thus an important effect cannot be excluded.
2. Among patients with recent high-risk CAD with prior stents, there was no associated increased risk of mortality and MINS compared to patients who did not have high-risk CAD. Not having a stent was associated with increased mortality and MINS.
3. Waiting ≥ 60 days seems to be associated with reduced mortality and MINS. This confirms what the prior literature and perioperative guidelines directives have said. We cannot yet determine if there are other important cutpoints in time where the risk appreciably changes.

Assessing perioperative risk among high-risk CAD patients will certainly continue to be an area of active research. This is because an increasing number of

patients with prior high-risk events will need to undergo non-cardiac surgery, treatments for CAD are frequently evolving and surgical techniques are also changing. This year alone for instance, a new study recommended a longer duration of dual anti-platelet therapy for those with DES and this may change perioperative guidelines as well.¹⁴ Clinicians are also constantly faced with doubt regarding the optimal time to proceed with surgery. We propose the following future areas for improving this research:

1. This analysis will need to be redone once the full 40 000 patient cohort study for VISION is completed. There will be more MINS and mortality events which will give us a better estimate of risk. The MINS events will in particular be higher because the remaining patients in VISION will be systematically screened with the 5th generation troponin. It will also allow us to look at differences between DES and BMS and how stents differentially affect ACS and CCS class III/IV angina. It will also allow us to look for different cutpoints in time after a high-risk CAD event prior to non-cardiac surgery.
2. Large prospective cohort studies will need to be completed in real time once the concept of routine troponin monitoring is accepted by the medical community in the post VISION era. A study similar to Livhits et al¹⁸ where routine 5th generation troponin screening is done could likely give us better estimates on the impact of various delay times prior to non-cardiac surgery. In order for this to happen, major societies would have to routinely endorse the use of troponin screening in the perioperative setting as a class I indication. Combining this with a propensity analysis where patients would be assigned scores to determine their “risk” of undergoing the non-cardiac surgery given their pre-existing

comorbidities and then comparing patients with similar propensity scores would be a more reliable way at estimating risk and would improve the contextual issues faced by this study.

3. Selective use of randomized controlled trials (RCT) may ultimately need to be done to better inform this issue. We would recommend considering the following randomized trials as a starting point:
 - a. A cluster RCT comparing 2 different perioperative strategies among high-risk CAD patients. Some centres would send all its high-risk CAD patients without delay to surgery when necessary after a high-risk event. While other centres would delay non-cardiac surgery. A cluster design would be important to avoid differential treatment of patients once clinicians realize which arm a patient was randomized to as it would be difficult to blind this information among clinicians at a single centre. Also, without a cluster design, clinicians may be less likely to randomize patients who are scheduled to undergo intermediate to higher risk procedures.
 - b. An RCT comparing routine stenting plus optimal medical therapy versus optimal medical therapy alone for patients with stable class III/IV angina scheduled for an elective non-cardiac surgical procedure. We could not do this study for patients with ACS as revascularization is usually indicated in these cases.

In conclusion, this project has tried to address an important and rapidly evolving area of perioperative medicine—the optimal management of patients

who have sustained a high-risk CAD event. Given our aging population combined with the fact that an increasing number of patients are surviving high-risk CAD events, how best to manage these patients in a perioperative setting will continue to challenge clinicians. We look forward to seeing how this particular area of perioperative medicine will evolve especially as it relates to improving overall mortality and morbidity.