# Precursor Events in Cardiac Surgery:
# Are they Associated with Post-operative Outcomes?

by

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Signature of Author

This thesis is dedicated to Bill, my parents and my sisters for their unwavering support in whatever I do.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

**Background:** The purpose of this study is to determine whether precursor events are associated with a post-operative composite outcome in a low-medium risk cardiac surgical population. These precursor events may be promising targets for strategies aimed at quality improvement.

**Methods:** This study was a case control design where the outcome of major adverse events (MACE) was assessed in patients exposed to four intra-operative precursor events. Cases and controls were matched 1:1 using propensity score matching, Univariate comparison of ≥1 precursor event in the matched groups was performed.

**Results:** The primary outcome of ≥1 precursor event occurred significantly more frequently in the MACE patient group vs the non-MACE patients group (33% vs. 24%; p=0.015). The individual events of bleeding and difficulty weaning from CPB were significantly higher in the MACE group whereas incomplete revascularization/repair and repair/regrafting were not.

**Conclusion:** Quality improvement techniques aimed at mitigating the consequences of precursor events may improve surgical outcomes for these patients.

LIST OF ABBREVIATIONS USED

| | |
|---|---|
| AFIB | Atrial Fibrillation |
| ASA | Acetylsalicylic Acid |
| AVR | Aortic Valve Replacement |
| BMI | Body Mass Index |
| CABG | Coronary Artery Bypass Grafts |
| CPB | Cardio-Pulmonary Bypass |
| COPD | Chronic Obstructive Pulmonary Disease |
| CQI | Continuous Quality Improvement |
| CVD | Cerebro-Vascular Disease |
| DNM | Death or Near Miss |
| EF | Ejection Fraction |
| HGB | Haemoglobin |
| HTN | Hypertension |
| IABP | Intra-aortic Balloon Pump |
| ICU | Intensive Care Unit |
| IMA | Internal mammary Artery |
| IQR | Inter Quartile Range |
| LOESS | Locally Weighted Scatter Plot Smoothing |
| MACE | Major Adverse Cardiac Events |
| MVR | Mitral Valve Replacement |
| NYHA | New York Heart Association |
| O/E | Observed to Expected |
| OR | Operating Room |
| PVD | Peripheral Vascular Disease |
| QEII HSC | Queen Elizabeth II Health Science Center |
| QI | Quality Improvement |
| ROC | Receiver Operating Characteristic |
| TEE | Trans-Esophageal Echocardiogram |
| VIF | Variance Inflation Factor |
| WHO | World Health Organization |

ACKNOWLEDGEMENTS

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# CHAPTER 1 INTRODUCTION

An important component of continued quality improvement (CQI) in cardiac surgery is evaluation of the events leading to death and major morbidity in patients undergoing cardiac surgery. These events can serve as quality indicators for outcomes, process, and structure of care (1, 2). Preventable death and morbidity are targets for quality improvement strategies. Recently the details of processes of care and errors have been the focus of study in QI in cardiac surgery (3,4). Errors or precursor events, events that precede adverse outcomes, have been of interest in hopes of reducing their occurrence (5). Precursor events are unintended occurrences that may lead to the development of a subsequent adverse event such as, death, in surgical patients. Preliminary work at our hospital, the Queen Elizabeth II Health Science Center, identified precursor events as being associated with mortality in a low-risk coronary artery bypass population (6). That population however is only a portion of a contemporary clinical cardiac surgical practice. The purpose of this study is to determine whether precursor events are associated with a post-operative composite outcome (death, acute renal failure, stroke, infection) in low-medium risk CABG, valve, and valve + CABG populations.

The body of this thesis is written as four chapters. The second chapter, the literature review outlines the progress of QI in cardiac surgery, the more recent focus on precursor events, and the need to examine the association between precursor events and important outcomes in a contemporary cardiac surgical clinical practice. The third chapter outlines the development of a logistic regression model that describes a composite outcome of important surgical outcomes in a mixed cardiac population. This model is required to complete the retrospective cohort study designed to examine the association between precursor events and major adverse cardiac events, which is outlined in the fourth chapter. As the third and fourth chapters are written in manuscript format, some of the content in these chapters are repeated in the introduction and conclusion.

# CHAPTER 2 LITERATURE REVIEW

Central to quality improvement strategies in cardiac surgery is ongoing prospective data collection of patient outcomes, continued feedback on surgeon, hospital, and region specific outcomes, training in theory and techniques of CQI, site visits to observe process of care and group meetings (1-4). Many groups have illustrated that the application of efforts in quality improvement and outcomes reporting can improve understanding of cardiac surgery process of care and patients outcomes. Prospective database collection has led to a description of modes of death, identification of risk factors and development of risk predictive models of mortality in coronary artery bypass grafting (CABG) and valve surgery as well as prediction of post-operative heart failure (5-15). Similar initiatives in surgery field have also led to the investigation of variables affecting outcomes in the post-operative intensive care unit (ICU) period (16-18). CQI exercises have also lead to the identification of heart failure as the most common mode of death post CABG, accounting for 64.8% of deaths, reported by the Northern New England Research Group (5). The Alabama CABG Project specifically targeted internal mammary artery (IMA) use, duration of intubation, post-operative acetylsalicylic (ASA) utilization, and mortality as quality improvement goals (3). Performance rates of the quality indicators where measured before and after initiation of a quality improvement initiative. During the study period median duration of intubation for CABG patients decreased from 12 to 7 hours ($p<.001$) and the percentage of patients intubated <6 hours increased from 9% to 41% ($p<.001$), IMA use, which has a survival benefit in CABG patients, increased to 84% from 73% ($p<.001$), ASA use increased from 88% to 92% ($p<.001$) and mortality decreased from 4.9% to 2.9% ($p<0.001$). Although similar mortality rates were observe in another neighbouring state that had not initiated a quality improvement initiative, the improvement in the other quality indicators was not observed. The North West Quality Improvement Programme in Cardiac Interventions observed a decrease in mortality from 2.4% to 1.8% ($p=0.014$) in patients undergoing isolated CABG surgery when a quality improvement initiative was instituted in this state (19). The Veterans Affairs Continuous Improvement in Cardiac Surgery Study Group also observed a decrease in mortality over a seven-year period and identified a significant survival benefit with the use of IMA (4). The Northern New England Cardiovascular Disease Study Group observed a significant relative reduction in mortality of 24% in all patients, a 25% relative reduction in mortality for urgent/emergent patients and similar significant reduction in mortality for men and women (5) during a three year quality improvement initiative. The New York Registry also noted a decrease mortality rate for isolated CABG from 3.5% to 2.7% over a four year period after outcomes reporting was initiated (20), despite an increase in predicted mortality. The risk-adjusted mortality rate decreased from 4.1% to 2.4%. Guru et al. (30) reported a risk-adjusted 29% decrease in mortality rate after the initiation of reporting in Ontario. The rate of decrease was significantly faster than in other regions of Canada. Importantly, they observed that after a six-year period there were no further decreases in mortality.

The impact of outcomes reporting and quality improvement initiatives on patient's outcomes is not entirely straightforward. In Massachusetts, which did not have formalized outcomes reporting, co-morbidities and mortality across three years, 1990, 1992, and 1994 were examined (21). Thirty-day mortality rates in 1992 and 1994 were compared to 1990, which was used as the baseline. They found that unadjusted mortality decreased from 4.7% (1990) to 3.5% (1992) and 3.3% (1994). This improvement was despite an increase in predicted mortality creating a relative risk reduction of 35% and 42% in 1992 and 1994, respectively. When mortality rates were risk adjusted, the result was almost identical to the unadjusted rates with mortality decreasing from 5.3% (1990) to 3.0% (1994). Conclusions from this study were that outcomes reporting might not have been the only factor influencing mortality rates as decrease in these rates were occurring in states without outcomes reporting. Other changes in process such as, improved bypass, cardio-plegia techniques and peri-operative care, may have been responsible for universal decline in that mortality rates (20). However with the introduction of outcomes reporting came an increase in reporting of co-morbidities, which elevates the perceived risk of these patients. The New York Registry authors noted that coding of preoperative renal failure, COPD, unstable angina, congestive heart failure, low ejection fraction all increased during the period. The phenomenon of surgeons deliberately upcoding co-morbid conditions to improve adjusted mortality rates is called 'gaming' and has been widely reported in the literature (22-26). Some observers suggested that decreases in mortality might be influenced by avoidance of high-risk patients in an effort to improve surgeon performance assessments (27-28). Omoigui et al (29) reported that 483 high-risk patients, that had been refused surgery in New York, underwent surgery at the Cleveland Clinic during the period that the New York Registry reported mortality decreases. Although the relevance of the findings of the latter study are discussed in the literature, a survey of New York cardiac surgeons found that 62% of them refused at least one high-risk patients in the preceding year due to performance report cards (22), confirming at least some high-risk patient avoidance.

Although it appears that outcomes reporting influences outcomes and in the very least creates surgeon awareness of individual and group outcomes, the effectiveness of that initiatives are limited by a variety of factors. Established CQI initiatives likely reach a threshold of diminishing returns, as seen in the Guru *et al* study. Plateau of CABG mortality has also been seen in Nova Scotia despite ongoing CQI initiatives (Figure 1). Subsequently more novel techniques must be employed to achieve further reductions in mortality and morbidity. To date CQI efforts have relied largely on pre-operative patient specific variables that are largely non-modifiable at the time of surgery. Pre-operative risk assessment can only go so far in helping to gain insight into the details of care that can affect patient outcomes, and thus be potentially changed. Recently the details of processes of care and errors have been the focus of some preliminary research in cardiac surgery (31, 32). In particular errors or adverse/precursor events have been studied in order to reduce their occurrence (33). Precursor events are unintended occurrences that may lead to the development of a subsequent adverse event such as, death, in surgical patients. These events may provide a new target for CQI initiatives and morbidity/mortality reduction.

In cardiac surgery, it has been reported that a mean of 3.5 precursor events occurs per cardiac case with at least one reported in 73.3% of all cases (31). One third of these events were considered major events and were more likely to occur during the cardiopulmonary bypass and post-cardiopulmonary bypass period. Approximately 90% of all events were reported as being adequately addressed. Precursor events occurred more frequently in patients having death or near miss (DNM), which was defined as a serious complication or morbidity, or markers of significant but non-fatal cardio-respiratory, hemodynamic, or other compromise. The number of major precursor events per procedure and the number of precursor events per surgeon were independent predictors of DNM. At the QEII HSC, precursor event were the focus of study when an unexplained increase in mortality in low-risk patients was noted during routine QI initiatives. Among patients with low predicted risk of mortality, those who died post-operatively had a significantly higher rate of intra-operative precursor events (56% vs. 28%, $p<0.001$) (34). Both groups of patients had similar pre-operative predicted mortality, 2.0% (IQR 1.3-3.0) in the survival group and 2.0% (IQR 1.3-3.6) in the mortality group ($p=0.9$). Furthermore, three of the four pre-defined precursor events (bleeding, difficulty to wean from cardiopulmonary bypass (CPB), and graft revision) were significantly associated with in-hospital mortality (all $p<0.04$). In addition, intra-operative difficulties were associated with return to the operating room for bleeding, blood transfusion, peri-operative MI, and prolonged ventilation (all $p<0.001$).

In order to target precursor events at the QEII HSC and have the greatest impact, QI initiatives must apply to the largest proportion of clinical practice possible. Three issues must be considered in order for this to be successful. First, with declining rates of CABG surgery, focusing solely on this procedure will eliminate a larger percent of current clinical practice. Therefore, these QI initiatives must focus on a mixed population including, CABG, valve and CABG + valve. Second, high-risk patients have high rates of disease burden and acuity. Consequently, they are managed intra and post-operatively differently than low and medium risk patients. As such, QI initiatives directed at mitigating the consequences of precursor events may not be appropriate for high-risk patients. Lastly, although death is an important surgical outcome, other adverse events are also important and may occur in greater frequency. In summary, QI initiatives should target major adverse cardiac events (MACE) in a mixed population of low and medium risk patients. Currently no studies exist that examine the association of precursor events and MACE in this patient population.

Hence, a determination of the pre-operative risk of MACE was performed so as to eliminate the high risk patients. Most published predictive models focus either on isolated procedures groups or isolated outcomes (35-49). Largely, mixed procedural models have focused on aortic/mitral or valve +/- CABG, with few CABG, valve and valve + CABG models present in the literature. The Euroscore model, one of the mostly widely used cardiac surgical prognostic models, has successfully achieved both statistical and clinical relevance as it applies to a mixed surgical practice including CABG, valve, and valve + CABG (50). However its development and validation cohort were derived from a population sample that is over fifteen years old (51) limiting its applicability to a contemporary surgical practice as patient risk profiles and surgical technique and indications have changed over time. In addition, Euroscore is only a mortality model omitting other important outcomes experienced by patients.

Many models describe mortality as a lone end point, such as the Euroscore, despite the fact that cardiac patients experience a variety of important outcomes such as, infection, renal failure and stroke. These surgical outcomes are also important quality indicators for cardiac surgical care (52) and targets for QI initiatives. Subsequently, modeling composite end points such as, MACE, that included both important morbidity and mortality may provide more insight to the surgical outcomes experienced by patients as well as increase statistical power for low frequency end points. To our knowledge no study model exists that describes MACE in a mixed cardiac surgery population.

**FIGURE #1—Coronary Artery Bypass Grafting Mortality Rates in Nova Scotia**

2009 represent data collection for only 6 months

# CHAPTER 3 MODEL DEVELOPMENT

## 3.1 Introduction

For the last two decades, coronary artery bypass grafting (CABG) has dominated clinical practice in cardiac surgery, and therefore the majority of quality improvement initiatives have focused on surgical outcomes following isolated CABG surgery (1-9). More recently, however, there has been an increase in valve and valve + CABG cases in cardiac surgery (10) and existing predictive models for isolated CABG may not accurately reflect current practice profiles. These models may be statistically sound but they lack clinical validity as the models are applicable to a decreasing percentage of the clinical practice. In order to achieve continued success in quality improvement, it is important to delineate risk profiles for a group of mixed procedures, including CABG, valve, and valve + CABG, that characterize current clinical practice.

To accommodate the shift in the profile of cardiac surgical practice isolated valve and valve + CABG models have been developed (10-18). Some debate exists regarding the validity of developing models that include heterogeneous procedures (CABG, valve, valve + CABG) with some advocating for single procedure models (14, 16, 18). Homogeneity within the procedure allows for simplicity of model development with improved reliability but limits sample size available for development and validation (10). Although models with heterogeneous procedures may be confounded or biased by different pathophysiological and risk profiles, they improve sample size (10) and increase their relevance to current surgical practice.

Largely, mixed procedural models have focused on aortic/mitral or valve +/- CABG, with few CABG, valve and CABG +valve models present in the literature. The Euroscore model, one of the mostly widely used cardiac surgical prognostic models, has successfully achieved both statistical and clinical relevance as it applies to a mixed surgical practice including CABG, valve, and valve + CABG (19). However its development and validation cohort were derived from a population sample that is over fifteen years old limiting its applicability to a contemporary surgical practice as current patients risk profiles, surgical techniques and surgical guidelines have evolved over time. In addition, Euroscore is only a mortality model. Cardiac surgery patients experience a variety of important post-operative outcomes in addition to mortality that are not accounted for in the Euroscore.

Many models describe death as a lone end point, despite the fact that cardiac patients experience a variety of relevant morbidity. These alternate surgical outcomes are also important quality indicators for cardiac surgical care (20) and targets for QI initiatives. Subsequently, modeling composite end points such as, major adverse cardiac events (MACE), that include both important morbidity and mortality may provide more insight to the surgical outcomes experienced by patients as well as increase statistical power.

Comprehensive models that include most major cardiac surgical procedures may allow for better understanding of patient risk profiles and facilitate quality improvement initiatives directed towards the majority of patients seen in current practice. The objective of this study is to develop a CABG, valve, CABG + valve morbidity and mortality (MACE) model that can be applied to the majority of patients undergoing cardiac surgery.

## 3.2 Methods

Data Source and Study Population

This study employed a retrospective cohort design. The Maritime Heart Center Cardiac Surgery Registry is a detailed clinical database housed at the Queen Elizabeth II Health Science Center (QEII HSC) Halifax, Nova Scotia, an academic tertiary care centre performing 1200 cardiac cases per year. It includes pre-, intra-, and post-operative data prospectively collected on all cardiac surgical cases performed at the QEII HSC from 1995 to present. Trained abstractors collect data, and a database administrator maintains the registry. The database is regularly audited.

The cohort included all patients undergoing isolated CABG, isolated aortic valve replacement, isolated mitral valve repair or replacement with or without concomitant CABG performed at the QEII HSC between 2004 to 2009. The development cohort was restricted to these years in order to maintain a modern population relevant to current clinical practice and to provide an adequate sample size. The frequency of MACE was consistent throughout this period (Figure #1).

The primary outcome was a composite end point defined as MACE that included in-hospital death, stroke (persisting at discharge or transient), acute renal failure (new post-operative renal failure or acute on chronic (>50% increase from baseline creatinine)), or infection (sepsis, pneumonia, or deep sternal wound infection).

## Statistical Methods

### *Variable Selection*

Candidate variables for model development included the following preoperative characteristics: age, sex, diabetes, frailty, chronic obstructive pulmonary disease, redo sternotomy, atrial fibrillation, hemoglobin, peripheral vascular disease, cerebro-vascular disease, creatinine, ejection fraction < 40%, New York Heart Association classification (NYHA I-IV) and body mass index (BMI). Surgery-related data such as urgency of surgery, surgeon and procedure type were also included. These candidate variables were chosen a priori and selected through rigorous review of the literature (1-3, 5-7, 9-17, 21-23) (see Appendix for full description of variables).

Multi-colinearity of candidate variables was assessed (see Appendix). The linear relationships of the natural variables and their transformations were assessed through locally weighted scatterplot smoothing (LOESS) regression (24) (see Appendix). The WHO classification of BMI was used. The interaction of hemoglobin and status and the interaction of hemoglobin and sex were examined separately within the model. Interactions between hemoglobin/status and hemoglobin/sex were examined separately within the model. Any interaction that contributed to model discrimination remained in the model as assessed by the -2 log likelihood and the c-statistic.

*Model Evaluation*

A non-parsimonious multivariate logistic regression analysis was used to describe MACE.

Age, sex, procedure type and surgical priority were chosen a priori and included in the model. Stepwise selection was implemented for the remainder of the candidate variables. The concordance statistic and -2 log likelihood were evaluated to assess the contribution of each variable to the model. If a variable did not contribute to an increase in the C or -2 log likelihood statistic it was not retained in the model.

Model discrimination was determined using the concordance statistic (25). Model calibration was assessed by the Hosmer-Lemeshow goodness-of-fit statistic (17, 26, 27) as well as calibration plots (28). Deciles of observed and predicted probabilities of MACE were plotted for the calibration plots (10). Bootstrap procedure was used to internally validate the model.

All statistical analysis was performed using SAS software version 9.2 (SAS, Cary, NC).

Approval for conducting this study was obtained from the Institutional Review Board of the Capital District Health Authority. The requirement to obtain informed consent was waived under Section 2.1c of the Tri-Council Policy Statement. All personal identifiers were stripped prior to data analysis to ensure patient anonymity and confidentiality. The authors had full access to the data and take full responsibility for their integrity.

## 3.3 Results

Population

A total of 4,270 patients underwent CABG, valve, and valve + CABG at the QEII HSC from Jan 2004 to Dec 2009. The distributions of risk factors in the development cohort are displayed in Table 1. The prevalence of MACE in this cohort was 15.7% (n=669). The prevalence of MACE was higher in the valve + CABG group (32%, n=155) than in the isolated procedures (CABG 13%, n=416; Valve 14%, n=98). The frequencies of MACE for each procedure as well as the components of MACE are summarized in Table 2.

Model Development

Assessment of the variance inflation for each variable revealed that no variable exceeded 1.5 allowing all variables to remain in the final model.

By LOESS regression, the squared transformation of the continuous variable age had the most linear relationship with the logodds of the outcome of MACE (see Appendix). Hemoglobin and creatinine had non-linear relationships with the outcome despite transformations. The inflection points of the natural variable were taken to create categorical variables. Hemoglobin inflection points were 115 and 135 and creatinine was 115, 140, and 160.

A total of nineteen variables remained in the logistic regression model (Table 3). Significant predictors of MACE included frailty, BMI >35, all levels of creatinine, DM, emergent and urgent status and valve + CABG procedure type. A nested interaction between hemoglobin and status remained in the model.

Model Performance

The concordance statistic for the logistic regression was 0.764, which is equivalent to an ROC of 76% (95% CI; 75-79). The Hosmer-Lemeshow goodness of fit statistic was not significant (p=0.3133).

The deciles of observed over predicted probabilities of MACE are plotted (Figure 2). Each data points falls on or very near the ideal line indicating excellent calibration.

## 3.4 Discussion

This study outlines the development of a non-parsimonious logistic regression model predictive of MACE. Our model is unique for three reasons: 1) it performs well with heterogeneous procedures including CABG, valve, and valve + CABG patients, 2) it predicts a composite outcome of quality indicators including death and major morbidities and, 3) it was developed for a contemporary cohort that represents a contemporary cardiac surgery practice. Also, we could not identify in the literature any models that include a CABG, valve and valve + CABG population with a composite end point.

Although many models exist that describe isolated CABG or isolated valve (2-19, 22), their use is limited to only a percentage of the cardiac surgical population. Euroscore, perhaps the most widely recognized cardiac surgical predictive model, is a mixed population model that has had great success in research and as a quality improvement tool (19, 23). However, its derivation cohort is over 15 years old restricting its applicability to a contemporary practice. Furthermore, Euroscore only predicts mortality, and not other important quality indicators. Our model is derived from a 2004-2009 cohort allowing for more current application. Clearly, a model that describes a heterogeneous cardiac surgical population is required so that research efforts represent a contemporary clinical practice.

Many models describe death as a lone end point, despite that fact that cardiac patients experience a variety of relevant morbidities. These alternate surgical outcomes are also important quality indicators for cardiac surgical care (24) and targets for QI initiatives. Subsequently, modeling composite end points such as, major adverse cardiac events (MACE), that include both important morbidity and mortality may provide more insight to the surgical outcomes experienced by patients as well as increase statistical power in low frequency end points. To our knowledge no model exists that describes MACE in a mixed population.

Provided the model performs well, the advantage of a heterogeneous population model over a single-procedure models is its ability to describe to majority of surgical patients and help facilitate quality improvement efforts. However, certain predictive variables, such as descriptions of coronary artery disease or valve disease severity, cannot be included in the model, as they do not apply to the entire model derivation cohort. This might be problematic, as some variables like left main disease have previously been identified in the literature as important variables to include in CABG mortality models (25). Although our model cannot contain this variable (as it would be entirely co-linear with CABG patients), it does contain other clinically relevant variables previously used in other published models (2-19). Our cohort was truncated at 2004 to provide a sample that had a stable MACE rate and afforded us a large sample size. Clinical patient characteristics have changed over time these are accounted for in the model. No large changes in the conduct of the procedures or care that have had an impact on patients' outcomes have occurred at the QEI II HSC since 2004. However, there may be shifts in surgical practice or process of care over time that impact patient outcome but go unnoticed by the surgical team. Including time as an independent variable would assure that patients would be match from the appropriate time interval. A limitation to our study is that we did not include this variable however; because of the stability of surgical technique in cardiac practice many published models also do not include this variable (9, 12-14).

Modeling composite outcomes allows for a broader prediction of important post-operative events rather than being limited to a single outcome. Also, the components of our composite are each identified as quality indicators in cardiac surgery (26) allowing for improved clinical validity. The benefit of a correctly chosen composite outcome allows for more detailed description and prediction of the clinical population increasing the clinical relevance of the model.

Although we assessed and included a variety of important predictor variables there is always a possibility that and important independent variables was not included in the model.

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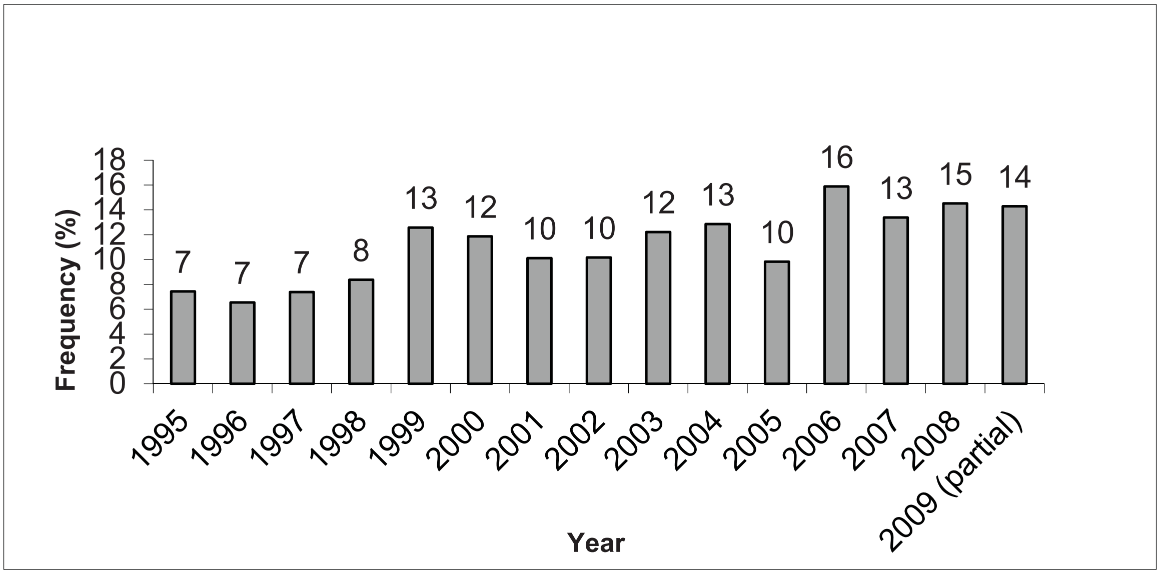
The model discrimination is high with a ROC 77% (95% CI; 76-80) that exceeds published recommendations (32) and is similar to other published cardiac surgical models (1-3, 5-7, 9-17, 21-23). This indicates that the model has good predictive ability. The bootstrap procedure, a form of internal validation (33, 34), allows for estimation of the 95% confidence interval. The tight 95% confidence interval provides a further estimation of reliability of the model. The calibration plot allows for a visual representation of the model's performance (Figure #3). The observed to expected (O/E) data points fall on or very near the ideal line indicating excellent calibration of the model.

As the profile of the cardiac surgery patients changes, so must the predictive models used to describe this group. This is of utmost importance in the field of quality assessment and improvement. Models such as the one reported in this manuscript, assists many QI techniques. They can be used to perform pre-operative predictive risk matching to allow for comparison of matched groups and can risk adjust surgeon specific surgical outcomes for report carding (28, 35, 36). The benefit of the mixed population and composite end points facilitates describing a contemporary clinical practice so that QI efforts are more generalizable. As QI efforts become a staple in cardiac surgery practice, models such as these are essential in propelling advancement in this field and improving outcomes for our patients.

## 3.5 Acknowledgments

This study was funded through a Heart and Stroke Foundation of Canada grant-in-aid and a Nova Scotia Health Research Foundation grant.

**Figure #2—Frequency of Major Adverse Cardiac Events by Year**



| Variable | | No MACE n=286 (%) | MACE n=286 (%) | p value |
|---|---|---|---|---|
| Predicted Probability | | 11.9 (0.084-17.90)* | 11.9 (0.08-17.98)* | |
| Age | | 67 (60-74)* | 68 (60-75)* | |
| Female | | 23.78 | 24.48 | 0.845 |
| BMI | <25 | 16.78 | 24.13 | 0.0982 |
| | 25-30 | 39.51 | 37.06 | |
| | 30-35 | 30.07 | 23.78 | |
| | >35 | 13.64 | 15.03 | |
| Diabetes | | 38.11 | 38.81 | 0.8635 |
| Hypertension | | 74.13 | 77.62 | 0.3284 |
| Afib | | 10.49 | 11.54 | 0.6887 |
| COPD | | 17.83 | 17.83 | 0.9999 |
| CVD | | 13.99 | 13.29 | 0.8075 |
| PVD | | 15.03 | 15.73 | 0.8167 |
| Frailty | | 2.8 | 2.8 | 0.9999 |
| EF<40 | | 13.99 | 12.24 | 0.5357 |
| NYHA | I | 26.92 | 30.07 | 0.6038 |
| | II | 24.13 | 25.52 | |
| | III | 35.66 | 30.42 | |
| | IV | 13.29 | 13.99 | |
| HGB | <115 | 51.05 | 51.75 | 0.9225 |
| | 115-135 | 40.21 | 38.81 | |
| | >135 | 8.74 | 9.44 | |
| Creatinine | <115 | 75.17 | 76.22 | 0.9332 |
| | 115-140 | 15.73 | 14.69 | |
| | 140-160 | 3.85 | 4.55 | |
| | >160 | 5.24 | 4.55 | |
| Redo surgery | | 9.09 | 6.29 | 0.2094 |
| Status | Elective | 49.3 | 51.05 | 0.5915 |
| | In-House | 43.36 | 41.96 | |
| | Urgent | 6.64 | 5.24 | |
| | Emergent | 0.7 | 1.75 | |

| Variable | | No MACE n=286 (%) | MACE n=286 (%) | p value |
|---|---|---|---|---|
| Procedure Type | CABG | 57.34 | 55.94 | 0.9403 |
| | Valve | 13.64 | 14.34 | |
| | Valve/CABG | 29.02 | 29.72 | |
| Surgeon | A | 10.49 | 14.34 | 0.6071 |
| | B | 11.19 | 11.54 | |
| | C | 9.79 | 11.89 | |
| | D | 2.45 | 2.45 | |
| | E | 9.79 | 8.04 | |
| | F | 9.79 | 9.79 | |
| | G | 3.15 | 3.85 | |
| | H | 19.93 | 16.08 | |
| | I | 9.09 | 11.89 | |
| | J | 14.34 | 10.14 | |

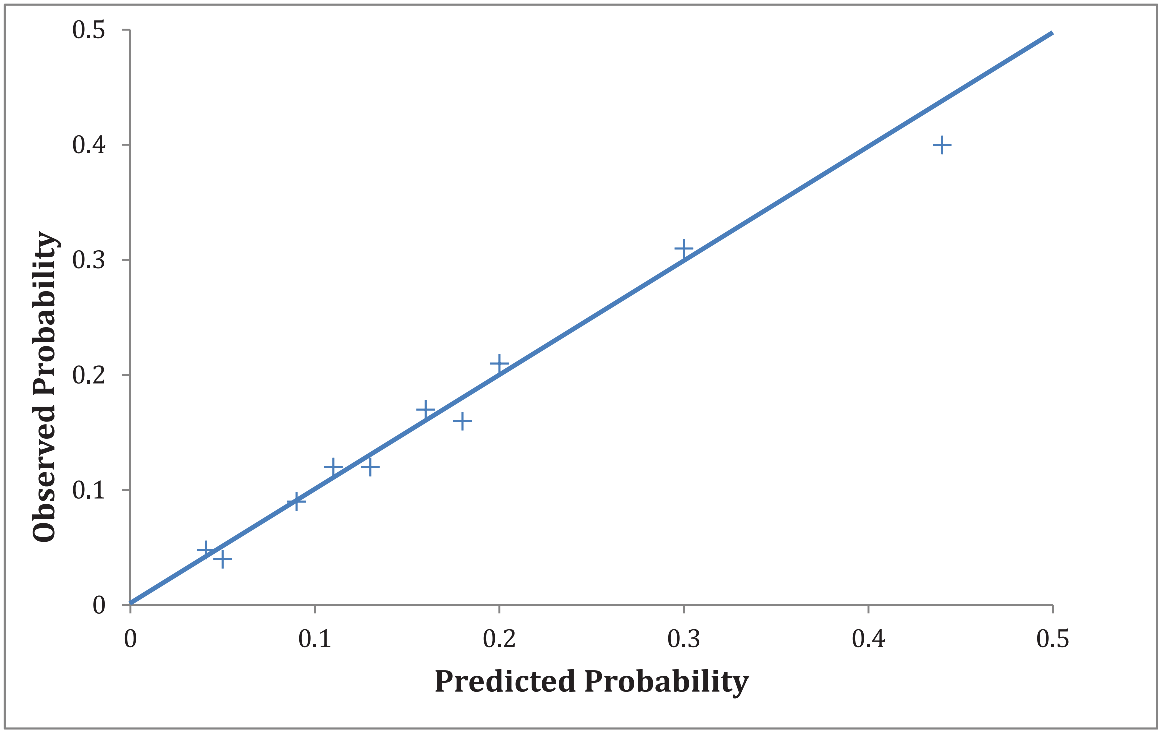
*Inter-quartile Range

**Table #1—Distribution of Risk Factors in the Model Development Cohort**

| Variable | | All Procedures n=669 (%) | CABG n=416 (%) | AVR/MVR/MVrpr n=98 (%) | CABG + Valve n=155 (%) |
|---|---|---|---|---|---|
| MACE | | 15.7 | 13 | 14 | 32 |
| Mortality | | 4.19 | 3.26 | 3.3 | 11.48 |
| Acute Renal Failure | | 6.46 | 5.53 | 5.46 | 13.99 |
| Any Stroke | | 2.88 | 2.29 | 2.44 | 7.31 |
| | Transient | 1.71 | 0.87 | 1.15 | 3.13 |
| | Permanent | 1.71 | 1.42 | 1.29 | 4.18 |
| Infection | | 7.99 | 7.11 | 6.32 | 16.08 |
| | Deep Sternal Wound Infection | 1.05 | 0.97 | 0.14 | 2.92 |
| | Sepsis | 2.83 | 2.36 | 1.87 | 7.31 |
| | Pneumonia | 6.51 | 5.69 | 5.32 | 13.57 |

**Table #2—Frequency of MACE and MACE Components in the Model Development Cohort**

**Figure #3—Calibration Plot of Observed Risk versus Predicted Risk**



| Variable | | Odds Ratio | 95% Confidence Limit |
|---|---|---|---|
| Age Square | | 1.0 | 1.0-1.03 |
| Female | | 0.8 | 0.6-1.0 |
| PVD | | 1.6 | 1.2-1.9 |
| Frailty | | 1.7 | 1.2-2.5 |
| BMI | 25-30 | 1.0 | - |
| | <25 | 1.2 | 0.9-1.5 |
| | 30-35 | 1.2 | 0.9-1.5 |
| | >35 | 1.5 | 1.1-2.1 |
| NYHA I | | 1.0 | - |
| NYHA II | | 1.3 | 1.0-1.6 |
| NYHA III | | 1.2 | 0.9-1.5 |
| NYHA IV | | 1.3 | 1.0-1.8 |
| HGB <115 | (Elective) | 1.2 | 0.7-2.2 |
| HGB 115-135 | (Elective) | 1.1 | 0.9-1.6 |
| HGB >135 | (Elective) | 1.0 | - |
| HGB <115 | (In-house) | 1.8 | 1.3-2.6 |
| HGB 115-135 | (In-house) | 1.4 | 0.9-1.9 |
| HGB >135 | (In-house) | 1.0 | - |
| HGB <115 | (Urgent) | 2.9 | 1.5-2.5 |
| HGB 115-135 | (Urgent) | 1.4 | 0.7-2.7 |
| HGB >135 | (Urgent) | 1.0 | - |
| HGB <115 | (Emergent) | 1.6 | 0.6-4.0 |
| HGB 115-135 | (Emergent) | 1.3 | 0.5-3.2 |
| HGB >135 | (Emergent) | 1.0 | - |
| Creatinine | <115 | 1.0 | - |
| | 115-140 | 1.3 | 1.1-1.7 |
| | 140-160 | 1.6 | 1.1-2.2 |
| | >160 | 1.6 | 1.2-2.2 |
| Preop Afib | | 1.4 | 1.1-1.8 |
| Diabetes | | 1.5 | 1.1-1.8 |
| EF < 40 | | 1.3 | 1.0-1.7 |
| COPD | | 1.2 | 0.9-1.5 |
| CVD | | 1.2 | 1.0-1.6 |
| HTN | | 1.1 | 0.9-1.5 |
| Preop RF | | 1.3 | 0.9-1.9 |
| Procedure | CABG | 1.0 | - |
| | Valve | 1.2 | 0.9-1.5 |
| | CABG + Valve | 2.3 | 1.8-3.0 |

| Variable | | Odds Ratio | 95% Confidence Limit |
|---|---|---|---|
| Status | In-House | 1.1 | 0.9-1.5 |
| | Urgent | 1.8 | 1.8-3.6 |
| | Emergent | 4.3 | 2.9-7.4 |
| Redo | | 1.4 | 0.9-1.9 |
| Surgeon A | | 1.0 | - |
| Surgeon B | | 1.1 | 0.7-1.6 |
| Surgeon C | | 1.1 | 0.7-1.6 |
| Surgeon D | | 1.1 | 0.6-2.2 |
| Surgeon E | | 1.2 | 0.8-1.7 |
| Surgeon F | | 0.7 | 0.5-1.1 |
| Surgeon G | | 1.1 | 0.6-1.9 |
| Surgeon H | | 1.1 | 0.8-1.5 |
| Surgeon I | | 0.8 | 0.5-1.1 |
| Surgeon J | | 1.1 | 0.8-1.6 |

**Table #3-Non-parsimonious Logistic Regression for MACE in a CABG/Valve Population**

### 3.6 Appendix

Statistical Methods

*Colinearity*

Multi-colinearity of the variables included in the model was assessed via the variance inflation factor (VIF). A VIF of greater than 4.0 indicates excessive multi-colinearity (36) and any variables exceeding this threshold would be reconsidered for analysis or collapsed.

*Linearity and Transformations*

As logistic regression assumes that every predictor variable X has a linear relationship with the logodds of the dependent variable Y (28, 37), scatterplots of the continuous variables, creatinine, age, and pre-operative hemoglobin, were examine to assess the relationship of the candidate variables with MACE. Locally weighted least squares regression (LOESS), which estimates regression surfaces by implementing nonparametric methods (24), was applied to each variable and transformation scatterplot to visually represent the linear relationship. A smoothing bandwidth of 0.1-0.5 was applied to each LOESS regression and the variable or transformation with the most linear relationship was presented to the model (38). Transformations including squared, square root, and spline were also plotted. If the variable still violated the linear assumption after transformations, the inflection points from the loess regression were used to create categorical variables. Inflection points indicate a change in the slope of the relationship between the variables and the outcome. Subsequently, by using the inflection points as cutoff values, each category has a homogeneous relationship with MACE.

The relationship of BMI with the dependent variable is traditionally parabolic. The World Health Organization (WHO) definition of BMI was used to create a categorical variable.

*Model Validation*

As the bootstrap procedure provides nearly unbiased estimates of the models accuracy (28), it was used as a validation tool. The model was run on two hundred sub-samples of 63.2% of the model cohort with replacements. Confidence limits (95%) for the ROC were taken from the 2.5$^{th}$ and 97.5$^{th}$ percentiles of the bootstrap procedure (18).

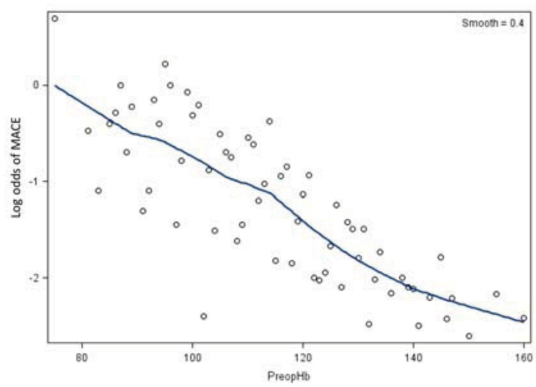
| Variable | Definition |
|---|---|
| Age | Patient age at the time of surgery |
| Gender | Male or Female |
| Body Mass Index | Calculated in kilograms and centimeters. |
| Diabetes | Any history of Diabetes Mellitus, regardless of duration |
| Pre-op Afib | Any previously documented history of Atrial Fibrillation |
| COPD | Any previous documented history of Chronic Obstructive Pulmonary Disease |
| CVD | Any Transient Ischemic Attack, Cerebrovascular Accident/Stroke, history of cerebrovascular surgery, or any carotid disease. |
| PVD | Whether the patient has Peripheral Vascular Disease, as indicated by claudication; amputation for arterial insufficiency; aorto-iliac occlusive disease reconstruction; peripheral vascular bypass surgery, angioplasty, or stent; documented AAA. |
| Frailty | Any deficiency in the Katz index of Activities of Daily Living (independence in feeding, bathing, dressing, transferring, toileting, and urinary continence), as well as independence in ambulation (no walking aid or assist required) or any clear evidence of a previous diagnosis of dementia by a physician. |
| EF<40 | Ejection fraction measured less than 40% by any modality. |
| NYHA (I-IV) | New York Heart Association Class. I = Patients with cardiac disease but without limitation of physical activity. II = Patients with cardiac disease resulting in slight limitation of physical activity (fatigue, palpitations, dyspnea, or anginal pain). III = Patients with cardiac disease resulting in marked limitation of physical activity. IV = Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. |
| Hemoglobin | Most recent hemoglobin level prior to day of surgery. |
| Pre-op Creatinine | Highest preop serum creatinine for this admission. |
| Redo Sternotomy | Any history of previous surgery that traversed the anterior mediastinum. |
| Surgical Priority | Elective [stable at home], in-house [requiring hospitalization until the time of surgery], urgent [requiring surgery within 24 hours to minimize further clinical deterioration], or emergent [no delay in surgery]. |
| Procedure | Any Coronary artery bypass grafting, aortic valve replacement or repair with/without CABG, or Mitral valve replacement or repair with/without CABG. |

**TABLE #4-Model Variable Definitions**

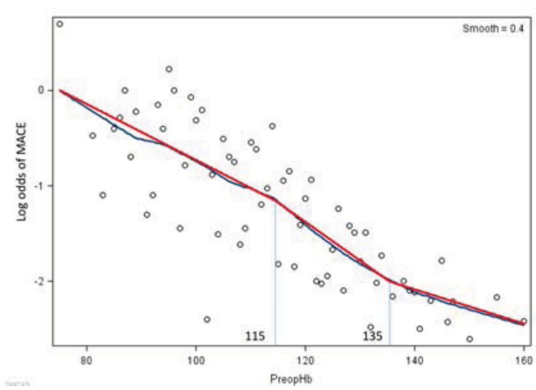
**Figure #4—Loess Regression for the Continuous Variable Pre-operative Hemoglobin**

(A) Loess regression was applied to the variable hemoglobin. (B) As no transformations yielded a suitable linear relationship, categories were created based on inflection points in the slope of the regression line. The red line highlights the inflection points. A smoothing bandwidth of 0.4 was applied to the regressions.

A




B



# CHAPTER 4 PRECURSOR EVENTS

## 4.1 Introduction

An important component of quality improvement (QI) in cardiac surgery is an impartial evaluation of the cause of death and major morbidity in patients undergoing cardiac surgery. These metrics serve as quality indicators for outcomes, process, and structure of care (1, 2). In particular, preventable death and morbidity are targets for quality improvement strategies. Non-preventable or unavoidable injury, on the other hand, is thought to occur unexpectedly with the temporal sequence of the inciting event to the injury being very short. The literature suggests that between 56 and 87% of deaths in cardiac patients are non-preventable (3, 4) potentially impacting the success of QI efforts.

It is possible that the causal pathway of these ‘unavoidable’ injuries begins long before any overt warning signs. Upstream events, such as precursor events, have received recent attention as a focus for alterability. Precursor events are events that precede an adverse event such as death or major morbidity (5). They are defined as undesirable incidents that are proximal in the causal pathway of an adverse event. They are required for the adverse event to occur but do not always result in said event. As such, precursor events occur with more frequency than adverse events (5). Most precursor events are easily compensated for by the care team and are seldom recognized as a critical event in the causal pathway of the adverse event. Intra-operative precursor events have been reported as occurring in 73.3% of cardiac cases with a mean of 3.5 precursor events per case (6). Also, precursor events occurred more frequently in patients having death or near miss

(DNM). Intra-operative near misses and major complications have also been associated with increased post-operative death (7, 8) especially if the event went uncompensated. Appropriate responses to critical intra-operative events are important to prevent a potential adverse event from developing downstream (9). If addressed appropriately, a surgical team may feel that a precursor event no longer posses a risk for if compensated for. It may rather be that these 'forgotten' events, whether compensated for or not, are the nidus in which begins the propagation of the precursor event towards an adverse event. Usually, such propagation is prevented through system safeguards (10) however, failure to recognize the importance of the precursor event may act as a hole in this layer of defence. As such, even seemingly inconsequential events may pose a potential risk to patient and may contribute to death or major injury regardless of perceived 'preventability'.

The goal of this study was to determine whether intra-operative precursor events, regardless of compensation or seriousness, contribute to post-operative death or major morbidity. We examined coronary artery bypass graft (CABG), valve, and CABG + valve patient population since this patient group encompasses the majority of current cardiac surgery clinical practice. We limited the risk profile to low-medium preoperative predicted risk as high risk patients represent a small proportion of clinical practice and their acuity may overwhelm the ability to detect any effect precursor events have downstream.

## 4.2 Materials and Methods

*Data Source*

This study is a retrospective cohort design. The Maritime Heart Center Cardiac Surgery Registry is a detailed clinical database housed at the Queen Elizabeth II Health Science Center (QEII HSC) Halifax, Nova Scotia. It includes pre-, intra-, and post-operative data prospectively collected on all cardiac surgical cases performed at the QEII HSC from 1995 to present. Data is collected through trained abstractors and a database administrator maintains the Registry. The registry is regularly audited.

*Study Population*

A cohort was assembled that included all consecutive CABG, aortic valve replacement, mitral valve repair mitral valve replacement with or without CABG from 2004-2009. This cohort was used to develop a non-parsimonious logistic regression model that described the composite outcome of Major Adverse Cardiac Events (MACE). MACE was defined as in-hospital death, stroke (permanent or transient), acute renal failure (>176 mmol or 50% increase from baseline if chronic renal failure), or infection (sepsis, pneumonia, or deep sternal wound infection). Predictor variables included in the model were important pre-operative variables that might influence the probability of having post-operative MACE. A detailed description of model development is found in the appendix.

Predicted probability of MACE was calculated for each individual in the model cohort. To define a study cohort of patients with low-medium risk of MACE, the model cohort was truncated at the 75th percentile. Using predicted probability of MACE, each individual with post-operative MACE was matched 1:1 with an individual who did not have a post-operative MACE. A greedy-match that proceeds from a 5-digit to a 1-digit match on risk was used.

*Precursor Events*

Four intra-operative precursor events of interest were identified through previous quality assessment exercises at our institution; 1) bleeding, 2) failure to wean from cardiopulmonary bypass (CPB), 3) regrafting or repair of conduit or valve, 4) incomplete revascularization or repair.

Bleeding is defined as any instance of surgical bleeding (other than related to grafts) or coagulopathy requiring intervention such as repair, return to CPB for repair, administration of blood products, or delay in termination of surgery. Failure to wean from CPB is any instance where the patient did not wean or struggled to wean requiring return to CPB, insertion of intra-aortic balloon pump (IABP), additional inotropic support, insertion of ventricular assist device, pacing or pre-wean pacing required to wean in the specific instance of valve surgery. Regrafting or repair of conduit or valve is any instance where regrafting or repair was undertaken because of issues with conduit length, lie, poor flow reading, wall motion abnormality on trans-esophageal echo (TEE), bleeding, peri-valvular leak, persistent stenosis or regurgitation despite repair or replacement. Incomplete revascularization or repair occurred when not all critically diseased territories were grafted, or persistent stenosis, regurgitation or peri-valvular leak considered significant by best standard of care practices, was not corrected. This may be due to inadequate size of target vessel, paucity of conduit, or other patient or technical factors.

The primary outcome was having ≥1 intra-operative precursor event.

Operative notes were used to identify precursor events based on the surgeons description of the events of the OR. These operative notes were dictated immediately after the OR before a MACE occurred, allowing for an unbiased measure of the prevalence of precursor events. Patient and surgeon identifiers were removed from the operative notes for all cases and controls, and the anonymous operative notes were distributed to five surgeons for review and identification of precursor events. No surgeon received his or her own operative note. Any operative note that reported a death in the operating room or that was reported as a late dictation was removed from the review, as was the matched partner note. Inter-rater reliability was assessed.

A secondary analysis was planned to examine whether precursor events are associated with other secondary outcomes including, cardio-pulmonary bypass time, cross-clamp time, intra-operative inotropic use, post-operative blood products, low cardiac output syndrome, and ventilator and ICU length of stay. This was achieved by excluding MACE events from the matched groups and then comparing all patients who had a precursor event to those who did not. This is a hypothesis generating analysis only.

*Statistical Analysis*

Previous research from our institution examining precursor events and death in a low risk CABG population revealed that patients who died post-operatively had 30% more precursor events that those who did not die. For the study to achieve 80% power with alpha of 0.05, the required sample size per group for a 50%, 40%, and 30% relative risk difference was 48, 112, and 243, respectively. As the current study has a mixed population with unknown risk difference, the largest sample size was used.

Continuous variables, such as age, hemoglobin, and creatinine, were compared using a two-tailed t-test or Wilcoxon rank sum test, and categorical variables were analyzed by chi-square or Fisher's exact test, as appropriate. Prevalence of precursor events was compared between the matched groups (individuals with MACE vs. individuals without MACE). Outcomes were analyzed by $\chi^2$ or Fisher's exact test, as appropriate. Because of debate in the literature on appropriate statistical handling of paired observations using propensity score matching, the outcome was also analyzed using McNemars test. All statistical analysis was performed using SAS software version 9.2 (SAS, Cary, NC). Approval for conducting this study was obtained from the Institutional Review Board of the Capital District Health Authority. The requirement to obtain informed consent was waived under Section 2.1c of the Tri-Council Policy Statement. All personal identifiers were stripped prior to data analysis to ensure patient anonymity and confidentiality.

## 4.3 Results

*Study population*

The model derivation cohort included consecutive 4270 patients and included 17 variables (see Appendix). The predicted probability of MACE was calculated using the model, and assigned to each patient. In order to create a low-medium risk group, the cohort was truncated at the 75$^{th}$ percentile of predicted risk (n=3192). The mean predicted percent probability for the entire cohort and the low-medium risk was 10.5 (IQR 6.1-20.2) and 8 (IQR 5.4-12), respectively. The low-medium risk group experienced 316 MACE events (9.9%).

A total of 311 (98.4%) patients with MACE events were matched 1:1 (Figure #1). Twenty-five of these 311 cases (8%) and their matched case were eliminated from the analysis because the patient died in the OR, the dictation was reported as late, or the OR dictation was not found. The preoperative clinical characteristics were similar between the matched MACE (n=286) and non-MACE (n-286) cases available for analysis (Table 1). The predicted probability of MACE was almost identical in the no-MACE {11.9 (IQR 0.084-17.90)} and MACE {11.9 (IQR 0.08-17.98)} groups.

Five surgeons reviewed and identified precursor events in all cases. A total of 11.5% of the entire sample was re-scored by a different surgeon with 86.2% in accordance with the original score.

*Exposure*

The primary outcome of ≥1 precursor event occurred significantly more frequently in the MACE group (33% vs. 24%; p=0.015) (Figure 2). Using paired observation analysis the odds ratio was 1.6 (95% CI; 1.1-2.2: p=0.01).

**McNemars contingency table**

| | Controls + | Control - |
|---|---|---|
| Cases + | 22 | 72 |
| Cases - | 46 | 146 |

Each individual precursor event, bleeding, difficulty weaning, repair/regrafting, and incomplete revascularization/repair, was identified in the MACE and no-MACE groups (Figure 2). The precursor events of bleeding and difficulty weaning contribute to the outcome the most while repair/regrafting and incomplete revascularization occur in similar frequencies in both the MACE and non-MACE groups.

When MACE is excluded and patients with precursor events are compared to patients without precursor events, pump and clamp time appear similar whereas intra-operative inotropic use, post-operative blood product utilization and low cardiac output syndrome appear to have a higher prevalence. Patients with no precursor events have similar prevalence of secondary outcomes to the total low-medium risk population (MACE excluded).

## 4.4 Discussion

The objective of this study was to describe the association of intra-operative precursor events and post-operative MACE. We found that cardiac surgery patients who are exposed to at least one or more intra-operative precursor event are more likely to have a post-operative MACE (33% vs. 24%; p=0.015). Individually, the bleeding and difficulty weaning from cardio-pulmonary bypass precursor events appear to contribute the most to the primary outcome.

Although hypothesis generating only, the secondary analysis suggests that other important outcomes (other than MACE) may be higher in patients who are exposed to a precursor event.   Also, patients without precursor events have similar prevalence of these events compared to the entire low-medium risk population (excluding MACE patients) indicating that they are representative of the entire low-medium risk population. Therefore, precursor events alone may be driving the higher prevalence of secondary outcomes in this group.

The process by which precursor events lead to downstream adverse events is well described in the literature (11-13).  In short, precursor events regardless of their seriousness or compensation penetrate the system safeguards designed to prevent error. They then snowball leading to an adverse event downstream.  Because the precursor event may have occurred early on in the causal pathway and may even have gone unnoticed, it may not even by recognized as the inciting event.  Consequently, major morbidity and mortality may be attributed to false causal events making QI initiatives that focus on improving these outcomes less successful.

In cardiac surgery, it has been reported that a mean of 3.5 precursor events occurs per cardiac case with at least one reported in 73.3% of all cases (6).  One third of these events were considered major events and were more likely to occur during the bypass and post-bypass period.  Approximately 90% of all events were reported as being adequately compensated.  Precursor events occurred more frequently in patients having death or near miss (DNM), which was defined as a serious complication or morbidity, or markers of significant but non-fatal cardio-respiratory, hemodynamic, or other compromise. The number of major precursor events per procedure and the number of precursor events per surgeon were independent predictors of DNM.

With the great frequency of precursor events the surgical teams ability to compensate for these events is important. Intra-operative near misses and major complications have also been associated with increased post-operative death if the event went uncompensated in a cardiac population (7, 8). Although compensation deals with the immediate consequences of a precursor event is does not necessarily influence any downstream affect. In fact, approximately 90% of all precursor events are reported as being adequately compensated (6) however they are still associated increased death or near miss (DNM). This may indicate that compensation alone may not be adequate to prevent downstream adverse events. The precursor event sets in motion a chain reaction that may accumulate over time eventually causing an adverse event downstream. As such, patients who are exposed to intra-operative precursor events may require more intensive care in the post-operative period in order to mitigate the potential of an adverse event from occurring.

The study has several limitations. Identification of the exposure relied on operative report, which are a description of the procedure, conduct, findings, and results of the surgical procedure. The principal surgeon of the operation dictates this report. There are variations in dictation style between surgeons as some may include more detail then others and consequently may not include details of precursor events. As surgeon was controlled for in the model, this measurement bias was evenly distributed between the cases and controls. The ability to recall events in the operating room will certainly influence whether precursor events appear in the report or not. This is especially true if the surgeon dictates the operation late. Operative reports dictated later then 24 hours were excluded from the analysis and the time to dictation is most likely a random event and consequently evenly distributed amongst cases and controls. As a result of these biases, precursor events are most likely under-reported by this technique of exposure capture.

The sample population does not represent an actual random sample of the cardiac surgical population. This is demonstrated in Figure #4 where the lower risk patients are proportionally underrepresented compared to the medium risk patients (high-risk was excluded). The sample is skewed towards the medium risk patients. As such, a determination of an actual rate of precursor events in the cardiac surgical population cannot be made. Also, although recall bias led to under-reporting of the exposure this selection bias has led to an over-estimation of the rate of precursor events.

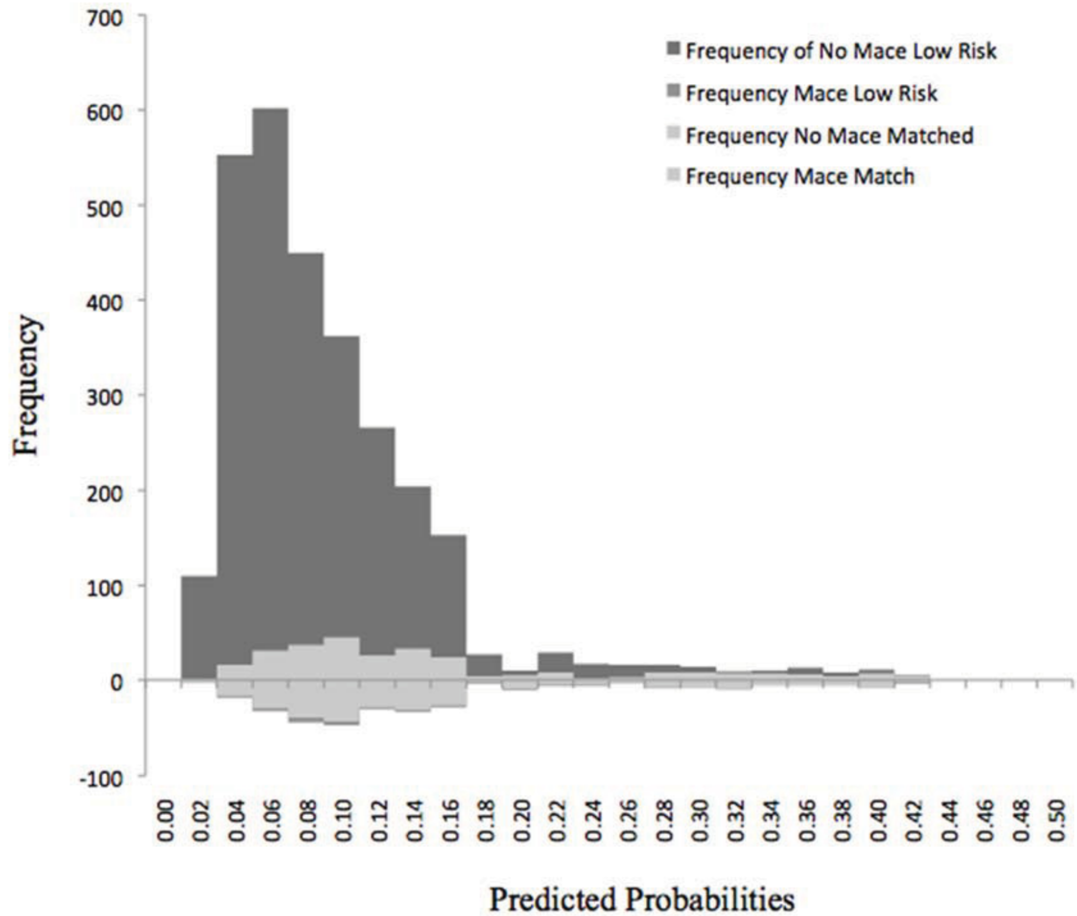
A time variable was not included in the model. Although practice has not changed much over the study period, including a time variable would have assured any practice change would not have acted as a confounder. Table 7 demonstrates that without the time variable the OR dates for the matched pairs of cases and controls vary nicely across the study period. The decreases the likelihood of time acting as a confounder.

It should be noted that the data was treated as both dependent and independent observations for comparison. Traditionally, propensity-matched paired observations are considered dependent observations using statistics such as McNemars for analysis (14). Recent literature has called into question the necessity for considering the matched nature of the data while estimating the effect of the exposure (15-17). As much as 65% of published literature what employ propensity score matching did not treat the data as dependent pairs (14). Propensity score matching does not require that the pairs be matched on the exact same covariate or values of covariates as such, two patient with identical propensity scores may have entirely different values of the covariates (eg older man matched with a younger woman). That being said, the cases and controls should have similar distributions of the covariates so that the case and control samples are well balanced. In both forms of analysis the effect of the exposure was statistically significant and had similar magnitudes.

Our study demonstrates that precursor events are common and that they impact post-operative adverse events. As the importance of even nominal precursor events becomes clear, efforts aimed at either preventing these events or mitigating their consequences are essential in decreasing post-operative adverse events. As quality improvement is a cornerstone of cardiac surgery, these types of initiatives are vital in closing the quality improvement loop and providing continued improved outcomes for our patients.

**Figure #5-Histogram of MACE Cases Matched Compared to Total Population**

The dark blue columns on the upper and lower axes indicate the total number of cases without MACE (upper axis) and with MACE (lower axis). The light blue columns indicate the proportion of match no-MACE cases (upper axis) to MACE cases (lower axis). The light blues columns represent all the matched cases.



| Variable | | No MACE n=286 (%) | MACE n=286 (%) | p value |
|---|---|---|---|---|
| Predicted Probability | | 11.9 (0.084-17.9)* | 11.9 (0.08-17.9)* | |
| Age | | 67 (60-74)* | 68 (60-75)* | |
| Female | | 23.78 | 24.48 | 0.845 |
| BMI | <25 | 16.78 | 24.13 | 0.0982 |
| | 25-30 | 39.51 | 37.06 | |
| | 30-35 | 30.07 | 23.78 | |
| | >35 | 13.64 | 15.03 | |
| Diabetes | | 38.11 | 38.81 | 0.8635 |
| Hypertension | | 74.13 | 77.62 | 0.3284 |
| Afib | | 10.49 | 11.54 | 0.6887 |
| COPD | | 17.83 | 17.83 | 0.9999 |
| CVD | | 13.99 | 13.29 | 0.8075 |
| PVD | | 15.03 | 15.73 | 0.8167 |
| Frailty | | 2.8 | 2.8 | 0.9999 |
| EF<40 | | 13.99 | 12.24 | 0.5357 |
| NYHA | I | 26.92 | 30.07 | 0.6038 |
| | II | 24.13 | 25.52 | |
| | III | 35.66 | 30.42 | |
| | IV | 13.29 | 13.99 | |
| HGB | <115 | 51.05 | 51.75 | 0.9225 |
| | 115-135 | 40.21 | 38.81 | |
| | >135 | 8.74 | 9.44 | |
| Creatinine | <115 | 75.17 | 76.22 | 0.9332 |
| | 115-140 | 15.73 | 14.69 | |
| | 140-160 | 3.85 | 4.55 | |
| | >160 | 5.24 | 4.55 | |
| Redo surgery | | 9.09 | 6.29 | 0.2094 |
| Status | Elective | 49.3 | 51.05 | 0.5915 |
| | In-House | 43.36 | 41.96 | |
| | Urgent | 6.64 | 5.24 | |
| | Emergent | 0.7 | 1.75 | |

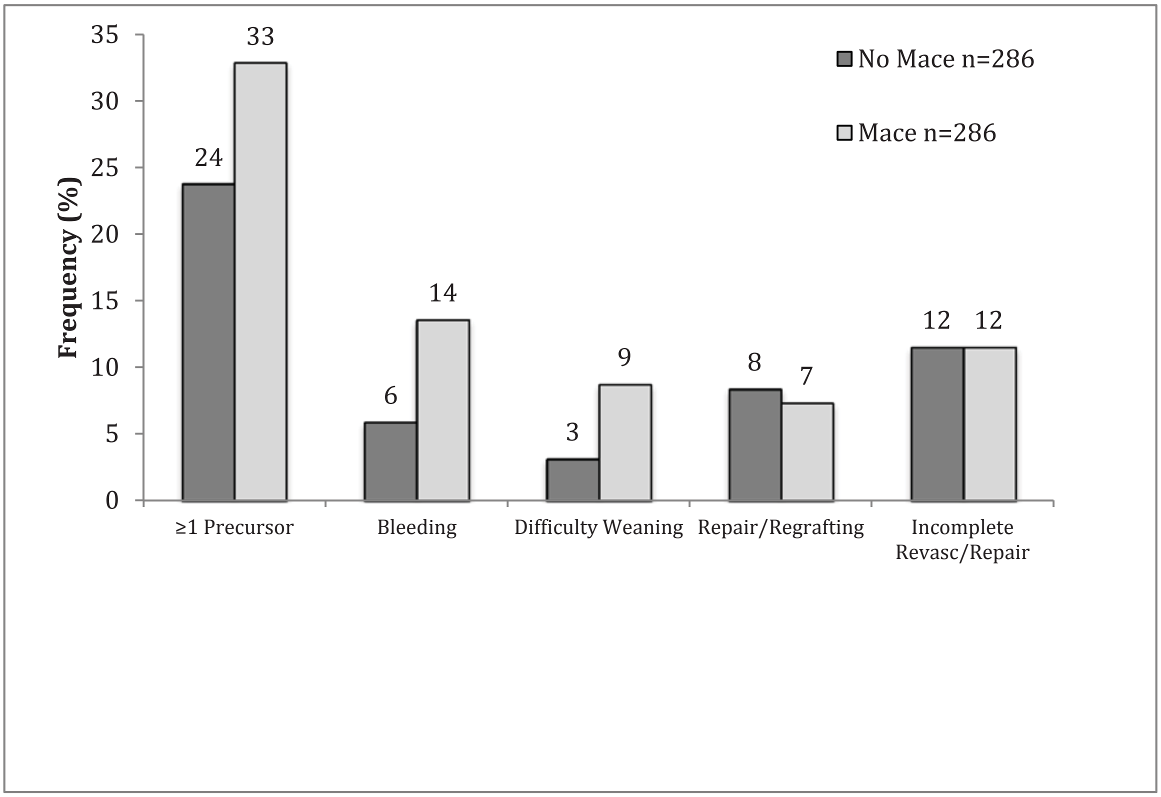
| | | | | |
|---|---|---|---|---|
| Procedure Type | CABG | 57.34 | 55.94 | 0.9403 |
| | Valve | 13.64 | 14.34 | |
| | CABG + Valve | 29.02 | 29.72 | |
| Surgeon | A | 10.49 | 14.34 | 0.6071 |
| | B | 11.19 | 11.54 | |
| | C | 9.79 | 11.89 | |
| | D | 2.45 | 2.45 | |
| | E | 9.79 | 8.04 | |
| | F | 9.79 | 9.79 | |
| | G | 3.15 | 3.85 | |
| | H | 19.93 | 16.08 | |
| | I | 9.09 | 11.89 | |
| | J | 14.34 | 10.14 | |

*Inter-quartile Range

**Table #5-Pre-operative Variables in the Matched Groups (No-MACE vs. MACE)**

**Figure #6-Frequency of Precursor Events for MACE and No-MACE Groups**

The dark bars represent patients who did not have a post-operative MACE whereas the light bars are those patients who did.



### 4.5 Appendix

**Model**

The concordance statistic for the logistic regression was 0.77, which is equivalent to an ROC of 77% (95% CI; 76-80) (area under the curve). The Hosmer-Lemeshow goodness of fit statistic was 0.1218.

| Variable | | Odds Ratio | 95% Confidence Limit |
|---|---|---|---|
| Age Square | | 1.0 | 1.0-1.03 |
| Female | | 0.8 | 0.6-1.0 |
| PVD | | 1.6 | 1.2-1.9 |
| Frailty | | 1.7 | 1.2-2.5 |
| BMI | 25-30 | 1.0 | - |
| | <25 | 1.2 | 0.9-1.5 |
| | 30-35 | 1.2 | 0.9-1.5 |
| | >35 | 1.5 | 1.1-2.1 |
| NYHA I | | 1.0 | - |
| NYHA II | | 1.3 | 1.0-1.6 |
| NYHA III | | 1.2 | 0.9-1.5 |
| NYHA IV | | 1.3 | 1.0-1.8 |
| HGB <115 | (Elective) | 1.2 | 0.7-2.2 |
| HGB 115-135 | (Elective) | 1.1 | 0.9-1.6 |
| HGB >135 | (Elective) | 1.0 | - |
| HGB <115 | (In-house) | 1.8 | 1.3-2.6 |
| HGB 115-135 | (In-house) | 1.4 | 0.9-1.9 |
| HGB >135 | (In-house) | 1.0 | - |
| HGB <115 | (Urgent) | 2.9 | 1.5-2.5 |
| HGB 115-135 | (Urgent) | 1.4 | 0.7-2.7 |
| HGB >135 | (Urgent) | 1.0 | - |
| HGB <115 | (Emergent) | 1.6 | 0.6-4.0 |
| HGB 115-135 | (Emergent) | 1.3 | 0.5-3.2 |
| HGB >135 | (Emergent) | 1.0 | - |

| Variable | | Odds Ratio | 95% Confidence Limit |
|---|---|---|---|
| Creatinine | <115 | 1.0 | - |
| | 115-140 | 1.3 | 1.1-1.7 |
| | 140-160 | 1.6 | 1.1-2.2 |
| | >160 | 1.6 | 1.2-2.2 |
| Preop Afib | | 1.4 | 1.1-1.8 |
| Diabetes | | 1.5 | 1.1-1.8 |
| EF < 40 | | 1.3 | 1.0-1.7 |
| COPD | | 1.2 | 0.9-1.5 |
| CVD | | 1.2 | 1.0-1.6 |
| HTN | | 1.1 | 0.9-1.5 |
| Preop RF | | 1.3 | 0.9-1.9 |
| Procedure | CABG | 1.0 | - |
| | Valve | 1.2 | 0.9-1.5 |
| | CABG + Valve | 2.3 | 1.8-3.0 |
| Status | In-House | 1.1 | 0.9-1.5 |
| | Urgent | 1.8 | 1.8-3.6 |
| | Emergent | 4.3 | 2.9-7.4 |
| Redo | | 1.4 | 0.9-1.9 |
| Surgeon A | | 1.0 | - |
| Surgeon B | | 1.1 | 0.7-1.6 |
| Surgeon C | | 1.1 | 0.7-1.6 |
| Surgeon D | | 1.1 | 0.6-2.2 |
| Surgeon E | | 1.2 | 0.8-1.7 |
| Surgeon F | | 0.7 | 0.5-1.1 |
| Surgeon G | | 1.1 | 0.6-1.9 |
| Surgeon H | | 1.1 | 0.8-1.5 |
| Surgeon I | | 0.8 | 0.5-1.1 |
| Surgeon J | | 1.1 | 0.8-1.6 |

**Table 6#-Non-parsimonious Logistic Regression for MACE in a CABG/Valve Population**

| Matched Pairs OR date | |
|---|---|
| Cases | Controls |
| Jun-04 | Jun-06 |
| Jun-04 | Nov-07 |
| Jun-04 | Apr-05 |
| Jun-04 | Jun-09 |
| Jun-04 | Sep-04 |
| Jun-04 | Oct-08 |
| Jun-04 | Oct-06 |
| Jul-04 | Apr-08 |
| Jul-04 | Mar-07 |
| Jul-04 | Oct-05 |
| Jul-04 | Mar-05 |
| Jul-04 | Dec-05 |
| Jul-04 | Dec-06 |
| Aug-04 | Aug-06 |
| Aug-04 | Dec-07 |
| Aug-04 | Jun-07 |
| Aug-04 | Jun-08 |
| Sep-04 | Jun-06 |
| Sep-04 | Jan-05 |
| Sep-04 | Jul-06 |
| Oct-04 | Jul-07 |
| Oct-04 | Feb-08 |
| Oct-04 | Jul-05 |
| Oct-04 | Sep-04 |
| Nov-04 | Jun-05 |
| Nov-04 | Dec-07 |
| Nov-04 | Jul-07 |
| Nov-04 | Jul-07 |
| Nov-04 | Jul-08 |
| Dec-04 | Nov-06 |
| Dec-04 | Dec-08 |
| Dec-04 | Sep-08 |

**Table #7—Matched Pairs OR Dates**

Only 10% of the study sample is represented in this table for size. There are no concordant pairs for OR date within the entire sample.

# CHAPTER 5 CONCLUSION

The purpose of this study was to examine whether precursor events were associated with post-operative outcomes in a mixed contemporary cardiac surgical population. This was accomplished in two parts: 1) development of and in-house model and 2) answering the study question. In order to accomplish this, development of an in-house model predictive of MACE in patients undergoing CABG, AVR and MVR with or without CABG was required as we could not identify in the literature any models that include this population with a composite end point. The model is unique for several reasons; 1) it performs well in a heterogeneous population including CABG, valve, and CABG + valve patients, 2) it predicts a composite outcome of quality indicators including death and major morbidities and, 3) it was developed for a contemporary cohort that represents a contemporary cardiac surgery practice. Furthermore, the model discrimination is high with a ROC 76.4% (75-79, 95% CI) that exceeds published recommendations (1) and is similar to other published cardiac surgical models (2-19). This indicates that the model has good predictive ability. The bootstrap procedure, a form of internal validation (20, 21), allows for estimation of the 95% confidence interval. The tight 95% confidence interval provides a further estimation of reliability of the model. The calibration plot allows for a visual representation of the model's performance (Figure #3). The observed to expected (O/E) data points fall on or very near the ideal line indicating excellent calibration of the model.

Although many models exist that describe isolated CABG or isolated valve (2-19, 22), their use is limited to only a percentage of the cardiac surgical population. Euroscore, perhaps the most widely recognized cardiac surgical predictive model, is a mixed population model that has had great success in research and as a quality improvement tool (19, 23). However, its derivation cohort is over 15 years old restricting its applicability to a contemporary practice. Furthermore, Euroscore only predicts mortality, and not other important quality indicators. Our model is derived from a 2004-2009 cohort allowing for more current application. Clearly, a model that describes a heterogeneous cardiac surgical population is required so that research efforts represent a contemporary clinical practice.

Many models describe death as a lone end point, despite that fact that cardiac patients experience a variety of relevant morbidities. These alternate surgical outcomes are also important quality indicators for cardiac surgical care (24) and targets for QI initiatives. Subsequently, modeling composite end points such as, major adverse cardiac events (MACE), that include both important morbidity and mortality may provide more insight to the surgical outcomes experienced by patients as well as increase statistical power in low frequency end points. To our knowledge no model exists that describes MACE in a mixed population.

Provided the model performs well, the advantage of a heterogeneous population model exceeds that of single-procedure models in its ability to describe to majority of surgical patients and can help facilitate the quality improvement efforts. However, certain predictive variables, such as descriptions of coronary artery disease or valve disease severity, cannot be included in the model, as they do not apply to the entire model derivation cohort. This might be problematic, as some variables like left main disease have previously been identified in the literature as highly important variables to include in CABG mortality models (25). Although our model cannot contain this variable (as it would be entirely co-linear with CABG patients), it does contain other clinically relevant variables previously used in other published models (2-19). Our cohort was truncated at 2004 to provide a sample that had a stable MACE rate and was afforded us a large sample size. Clinical patient characteristics have changed over time these are accounted fro in the model. No large changes in procedure that have had an impact on patients' outcomes have occurred at the QEI II HSC since 2004. However, there may be shifts in surgical practice or process of care over time that impact patient outcome but go unnoticed by the surgical team. Including time as an independent variable would assure that patients would be match from the appropriate time interval. A limitation to our study is that we did not include this variable however; because of the stability of surgical technique in cardiac practice many published models also do not include this variable (9, 12-14).

Modeling composite outcomes allows for a broader prediction of important post-operative events rather than being limited to a single outcome. Also, the components of our composite are each identified as quality indicators in cardiac surgery (26) allowing for improved clinical validity. The benefit of a correctly chosen composite outcome allows for more detailed description and prediction of the clinical population increasing the clinical relevance of the model.

Although we assessed and included a variety of important predictor variables there is always a possibility that and important independent variables was not included in the model.

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The clinically and statistically valid model provided the means by which we could evaluate the study question in a low to medium risk patient population. This population was determined by truncating the assigned pre-operative predicted risk of MACE provided by the model facilitating a comparison of precursor event frequency in patients with post-operative MACE and those without post-operative MACE. We found that cardiac surgery patients who are exposed to at least one or more intra-operative precursor event are more likely to have a post-operative MACE (33% vs. 24%; p=0.015). Individually, bleeding and difficulty weaning from cardio-pulmonary bypass were the precursor events that appear to contribute the most to the primary outcome of MACE.

The process by which precursor events lead to downstream adverse events is well described in the literature (27-29). In short, precursor events regardless of their seriousness or compensation penetrate the system safeguards designed to prevent error. They then snowball leading to an adverse event downstream. Because the precursor event may have occurred early on in the causal pathway and may even have gone unnoticed, it may not even by recognized as the inciting event. Consequently, major morbidity and mortality may be attributed to false causal events making QI initiatives that focus on improving these outcomes less successful.

In cardiac surgery, it has been reported that a mean of 3.5 precursor events occurs per cardiac case with at least one reported in 73.3% of all cases (30). One third of these events were considered major events and were more likely to occur during the bypass and post-bypass period. Approximately 90% of all events were reported as being adequately compensated. Precursor events occurred more frequently in patients having death or near miss (DNM), which was defined as a serious complication or morbidity, or markers of significant but non-fatal cardio-respiratory, hemodynamic, or other compromise. The number of major precursor events per procedure and the number of precursor events per surgeon were independent predictors of DNM.

With the great frequency of precursor events the surgical teams ability to compensate for these events is important. Intra-operative near misses and major complications have also been associated with increased post-operative death if the event went uncompensated in a cardiac population (31, 32). Although compensation deals with the immediate consequences of a precursor event it does not necessarily have any downstream affect. In fact, approximately 90% of all precursor events are reported as being adequately compensated (30) however they are still associated increased death or near miss (DNM). This may indicate that compensation alone may not be adequate to prevent downstream adverse events. The precursor event sets in motion a chain reaction that may accumulate over time eventually causing an adverse event downstream. As such, patients who are exposed to intra-operative precursor events may require more intensive care in the post-operative period in order to eliminate the potential of an adverse event from occurring.

The second portion of our study was limited by the measurement of the exposure. Identification of the exposure relied on operative report, which are a description of the procedure, conduct, findings, and results of the surgical procedure. The principal surgeon

of the operation dictates this report. There are variations in dictation style between surgeons as some may include more detail then others. As surgeon was controlled for in the model, this measurement bias was evenly distributed between the cases and controls. The ability to recall events in the operating room will certainly influence whether precursor events appear in the report or not. This is especially true if the surgeon dictates the operation late. Operative reports dictated later then 24 hours were excluded from the analysis and the time to dictation is most likely a random event and consequently evenly distributed amongst cases and controls. As a result of these biases, precursor events are most likely under-reported by this technique of exposure capture.
The sample population does not represent an actual random sample of the cardiac surgical population. This is demonstrated in Figure #4 where the lower risk patients are proportionally underrepresented compared to the medium risk patients (high-risk was excluded). The sample is skewed towards the medium risk patients. As such, a determination of an actual rate of precursor events in the cardiac surgical population cannot be made. Although recall bias led to under-reporting of the exposure this selection bias has led to an over-estimation of the rate of precursor events.

As the profile of the cardiac surgery patients changes, so must the predictive models used to describe this group. This is of utmost importance in the field of quality assessment and improvement. Models such as the one reported in this manuscript, assist many QI techniques. They can be used to perform pre-operative predictive risk matching to allow for comparison of matched groups and can risk adjust surgeon specific surgical outcomes for report carding (33-35). The benefit of the mixed population and composite end points facilitates describing a contemporary clinical practice so that QI efforts are more productive. Developers of such models must be dedicated to upholding high statistical standards, so that the QI efforts actually benefit the patients. As QI efforts become a staple in cardiac surgery practice, models such as these are essential in propelling advancement in this field and improving outcomes for our patients.

This study has some limitations. Firstly, the low-medium cohort was selected by truncating the population at the 75$^{th}$ percentile of predicted risk for post-operative MACE. It may be that as the risk of the patient goes up, the effect of a precursor event is less impactful due to the various other risk factor and consequently, the impact of precursor events on MACE is blunted. Secondly, the only measure of time delay of dictation (which would produce a less detailed and more biased operative note) was surgeon report in the dictation. No other attempt, for practical reason, was made to validate time to dictation. As such, late dictations, which are less likely to report a precursor event may be included in the analysis. Assuming that this is a random occurrence, both group should be biased in an equal fashion. Also, the selection of the four precursor events were chosen through quality assessment work done at our institution and represent events felt common and potentially important at our institution. It may be that we did not include other potentially important events. Some precursor events may behave differently for different procedures. For example, re-grafting/repair and incomplete revascularization/repair was not different between the two groups when compared in the mixed population. It may be that this event is more relevant for when compared in a single procedure group.

As the profile of the cardiac surgery patient's changes, CQI efforts must strive to target the bulk of clinical practice so that the greatest success is gained. Our model describes not only a mixed cardiac population but also a composite outcome making it ideal for CQI efforts. Once such target for quality improvement effort is precursor events and their association with post-operative adverse events is described in this thesis. Our study demonstrates that precursor events are common and that they impact post-operative adverse events, an important discovery in quality assessment. As the importance of even nominal precursor events becomes clear, efforts aimed at either preventing these events or mitigating their consequences are essential in decreasing post-operative adverse events. As quality improvement is a cornerstone of cardiac surgery, these types of initiatives are vital in closing the quality improvement loop and providing continued improved outcomes for our patients.

In order to lessen the burden of precursor events in the cardiac operating room, the event tolerance and recovery mechanisms needs to elaborated. If precursor events lead to mortality or other outcomes, then patients exposed to these events should be targeted for an intervention aimed specifically at mitigating their consequences. Safety checklist, standardised practice algorithms, improved and required communication between surgical team members, flagging exposed patients, and improved ICU hand-over may result in improved outcomes for cardiac surgical outcomes. Subsequently, understanding the relationship between intra-operative precursor events and post-operative outcomes may identify targets for CQI initiatives that could reduce morbidity and mortality in cardiac surgery patients.

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CHAPTER 4 PRECURSOR EVENTS

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