PERIOPERATIVE HEMODYNAMIC PREDICTORS OF CARDIAC EVENTS

INTRAOPERATIVE HEMODYNAMIC PREDICTORS OF EARLY POSTOPERATIVE TROPONIN ELEVATION AND MORTALITY

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ABSTRACT

Background: Myocardial injury after noncardiac surgery (MINS) increases the risk of 30-day mortality. Intraoperative hemodynamic events (i.e., tachycardia, bradycardia, hypotension, and hypertension) may contribute to developing MINS.

Objectives: To determine if the addition of the duration spent within predefined intraoperative systolic blood pressure (BP; mmHg) (i.e., <100-90 and <90; >160-199 and ≥200) and heart rate (HR; bpm) (i.e., <55-45 and <45; >100-140 and >140) hemodynamic bands improved the prediction of Day 1 MINS (i.e., postoperative troponin T elevation ≥0.03 ng/ml within the first day after surgery) beyond preoperative risk model prediction.

Methods: Prospective observational data was used to developed a baseline risk model to predict Day 1 MINS. Preoperative HR, systolic BP, and hemoglobin as well as intraoperative duration spent within each predefined hemodynamic band were explored to identify optimal thresholds for the prediction of Day-1 MINS. Preoperative variables were added to the baseline risk model to create a preoperative model. Intraoperative variables were then added to the preoperative risk model to create the final model. Models were compared using discrimination (c-statistic) and net reclassification index (NRI).

Results: Adding preoperative hemoglobin ≤105 g/dL, systolic BP <100, and HR >110 improved baseline model discrimination (0.783 to 0.792, p<0.01)and NRI (54.7%; p<0.01). Adding intraoperative HR <55 bpm for >5min; HR >100 for >147min; systolic BP <90 for >59min and systolic BP >160 for >42min further improved discrimination (0.8; p<0.01); NRI (12.7%,p=0.01).

Conclusion: Adding intraoperative hemodynamic durations significantly improved Day-1 MINS model discrimination and risk stratification compared to the baseline risk model.

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LISTS OF ABBREVIATIONS AND SYMBOLS

aHR – adjusted hazard ratio

AKI – acute kidney injury

AUC – area under the curve

BP – blood pressure

Bpm – beats per minute

CI – confidence interval

DPTI – diastolic pressure time index

DO2 – oxygen tissue delivery

GAM – generalized additive model

g/L – grams per liter

Hb - hemoglobin

HR – hazard ratio

IQR – interquartile range

MAP – mean arterial pressure

MI – myocardial infarction

MINS – myocardial injury after noncardiac surgery

NRI – net reclassification index

OR – odds ratio

PACU – post anesthetic care unit

PaO2 – arterial oxygen tension

PAR – population attributable risk

Q – cardiac output

ROC – receiver operating characteristic curve

SaO2 – oxygen saturation

SD – standard deviation

TTI – tension time index

VISION - Vascular events In noncardiac Surgery cOhort evaluatioN

CHAPTER 1 – INTRODUCTION

1.1 The burden of adverse postoperative cardiovascular events

It is estimated that over 200 million major noncardiac surgeries are performed annually on adults worldwide. [1, 2] The majority of these cases are elective in nature, and are undertaken to improve patient quality of life, to extend its duration, or to prevent morbid events.

Recently a large 40,000 patient prospective cohort observational study identified risk factors independently associated with 30 day mortality.[3] Based on data from the first 15,133 patients the Vascular events In noncardiac Surgery cOhort evaluatioN (VISION) study identified age, recent high-risk coronary artery disease, history of peripheral vascular disease, stroke, chronic obstructive pulmonary disease, and active cancer as independent predictors of 30-day mortality. Urgent/ emergent surgery, major general, and major neurosurgery were surgery types that independently predicted the same outcome. In this cohort a postoperative 4th generation troponin T elevation ≥0.02 ng/ml was the greatest contributor to 30 day mortality with a population attributable risk [PAR] of 41.8 (95% confidence interval [CI] 34.5-49.0). Further analysis defined MINS as a peak troponin T ≥0.03 ng/mL judged due to myocardial ischemia and such elevations independently predicted 30-day mortality (adjusted hazard ratio [HR] 3.87, 95% CI 2.96-5.08; PAR 34%, 95% CI 26.6-41.5).[4]

This paper provided important information on which preoperative and postoperative factors contribute to 30-day mortality. However, it is unclear if intraoperative hemodynamics, such as tachycardia, bradycardia, hypotension, and hypertension, contribute to MINS and 30-day postoperative mortality. Identifying intraoperative hemodynamic predictors associated with MINS and 30-day all-cause mortality may allow physicians to prevent or modify the impact of these events.

1.2 The pathophysiology of myocardial injury after noncardiac surgery

MINS has been defined as "myocardial injury (that may or may not result in necrosis) caused by ischemia, has prognostic relevance (i.e., independent predictor of 30-day mortality), and occurs during or within 30 days after noncardiac surgery."[4] The exact pathophysiology of MINS is not clearly understood, but the definition assumes myocardial ischemia as the final common pathway. Short transient ischemic episodes cause reversible cellular membrane disruption or blebbing,[5, 6] while longer episodes lead to myocyte necrosis. [7] This entire spectrum of injury is reflected in troponin elevations that occur within hours of the insult, and peak 4 – 6 hours later.[8]

The two underlying primary mechanisms which drive myocardial ischemia are: 1) a reduction in oxygen supply to the myocardium; and 2) an increase in oxygen demand as a result of an increased myocardial work.[9, 10] Reductions in oxygen supply can be a

result of reduced coronary blood flow, caused by intracoronary plaque rupture, thrombus formation, coronary vasospasm, reduced diastolic filling time, or hypotension. Myocardial oxygen supply can also be reduced when hemoglobin is reduced or when arterial oxygen saturation falls. Stroke work is the force required to eject blood into the aorta and is the product of stroke volume and mean arterial pressure. Stroke work multiplied by heart rate produces an estimate of cardiac work and it therefore follows that increases in heart rate or blood pressure increase cardiac work. These mechanisms of supply and demand are not mutually exclusive, and it is likely that ischemic events are caused by a multitude of different factors involving both mechanisms.

This thesis will focus on how intraoperioperative hemodynamics (i.e., heart rate and blood pressure) contribute to early MINS and 30-day mortality.

1.3 The physiology of myocardial oxygen supply and demand

Overwhelmingly coronary perfusion, and therefore myocardial oxygen supply, occurs during diastole and can be expressed as the diastolic pressure time index (DPTI). The DPTI is the product of the coronary perfusion pressure (i.e., aortic mean blood pressure in diastole - left ventricular mean diastolic pressure) and diastolic time, and is expressed as follows:

DPTI = (aortic mean blood pressure in diastole - left ventricular mean diastolic pressure) x diastolic time.

A reduction in coronary perfusion pressure results in reduced myocardial oxygen supply. Similarly, a heart rate increase will reduce the time spent in diastole and so reduce myocardial oxygen supply. Conversely, increasing coronary perfusion pressure, or slowing the heart rate, will improve myocardial oxygen supply.

Myocardial oxygen consumption is related to the tension time index (TTI). The TTI is the product of the mean arterial pressure and systolic time and reflects the work done by the myocardium during systole. As the TTI, or myocardial work, increases so myocardial oxygen consumption increases. Similarly, as the TTI decreases so myocardial oxygen consumption decreases. The TTI is expressed as follows:

TTI = mean left ventricular systolic pressure x systolic time.

A reduction in mean arterial pressure will reduce the TTI, reduce myocardial work and thereby reduce myocardial oxygen consumption. Similarly, a heart rate reduction will reduce the time spent in systole and so reduce myocardial oxygen consumption. Conversely, increasing mean arterial pressure, or increasing heart rate, will increase myocardial oxygen consumption.

This provides a theoretical basis for hypothesizing that heart rate and blood pressure increases in vulnerable patients will increase myocardial oxygen demand, reduce supply, and predispose to the development of myocardial ischemia. Conversely, it suggests that heart rate reductions and lower mean systolic blood pressures will reduce demand, improve supply, and minimize myocardial ischemia.

When considering these mathematical descriptions of myocardial oxygen supply and demand it must be kept in mind that heart rate and blood pressure are closely interlinked. As heart rate reduces so myocardial oxygen demand reduces, however as heart rate reduces a point is reached at which cardiac output falls, blood pressure is reduced and myocardial oxygen supply is impaired. Similarly, while a lower blood pressure will reduce myocardial work and oxygen demand; excessive reduction will affect coronary perfusion pressure and impair myocardial oxygen delivery.

1.4 Intraoperative hemodynamic predictors

1.4.1 Low blood pressure

Low blood pressures are common during anesthesia. There is nonetheless no single value that defines intraoperative hypotension. For example, a recent systematic review identified more than 50 definitions for intraoperative hypotension, many of

which combined absolute blood pressure thresholds with relative thresholds.[11] The most commonly used thresholds were a decrease in systolic blood pressure >20% from baseline (18 studies); a systolic blood pressure <100 mmHg or >30% decrease from baseline (11 studies); and a systolic blood pressure <80 mmHg (10 studies).[11]

When applying these 50 thresholds to a retrospective data base the authors found an incidence of intraoperative hypotension ranging from 5% to 99%. None of these studies attempted to define clinically important blood pressure thresholds by examining the impact of low blood pressure on patient outcomes. This variation in the definition of intraoperative hypotension makes comparison across studies exceptionally challenging.

A systematic review conducted in March 2012 attempted to identify independent intra-operative predictors of adverse cardiac events in patients undergoing noncardiac surgery.[12] Adverse cardiac events that were considered included cardiac death, cardiac arrest, myocardial infarction, and myocardial ischemia. The review identified only one study reporting an independent association with low blood pressure and adverse cardiac outcomes.[13] In this study Charlson et. al. (n = 254) found a >20 mmHg decrease in mean arterial pressure (MAP) for >60 minutes was associated with an increase in the composite outcome of postoperative cardiac death, ischemia, or infarction (OR 3.0, 95% CI 1.8-4.9).

Unpublished data from a recent study by Walsh et al. has attempted to create an empiric definition of intraoperative hypotension.[14] Using retrospective data from 27,381 patients they found that the risk of postoperative acute kidney injury (AKI) and MINS (in this study defined as an elevation in troponin T 4th generation ≥0.04 μg/L within 7 days of surgery) increased significantly with any duration spent with a MAP<55 mmHg.

It is important to appreciate that there are many different processes that may cause intraoperative hypotension. Low cardiac output states such as seen with severe sepsis result in profound reductions in tissue oxygen delivery, while hypotension caused by general anesthesia or neuraxial techniques is often compensated by increases in cardiac output. It follows that outcomes between these two populations would differ despite both experiencing hypotension.

1.4.2 High blood pressure

Drugs commonly used during anesthesia induction and maintenance are characterized by their ability to induce hypotension. As a result prolonged periods of intraoperative hypertension, particularly while under general anesthesia, are rare. Intraoperative hypertensive emergencies (blood pressure >180 / 110 mmHg) potentially leading to acute organ dysfunction (i.e. cardiac failure, myocardial infarction, intra-cerebral hemorrhage) are generally only seen in patients having endocrine or neurosurgery. Short episodes of hypertension are common during intubation and with

surgical stimulation. Hypertension is far more common during recovery in the PACU than during surgery, with the PACU incidence reaching 20% in certain surgical populations.[15, 16]

Intraoperative and/or postoperative hypertension, defined as a systolic blood pressure >160 mmHg or diastolic blood pressure >90 mmHg, is associated with intracranial hemorrhage after craniotomy.[17] However, despite many observational studies attempting to show an independent relationship between intraoperative hypertension and adverse cardiac events in patients undergoing noncardiac surgery, this has relationship has rarely been demonstrated. In fact, a meta-analysis identified only a single relevant study of 211 high-risk patients who had emergent or urgent non-cardiac surgery. In that study, patient with >30% increase in baseline systolic blood pressure had an increased risk of troponin I >0.06 μg/L within 2 days after surgery (OR 8.0, 95% CI 1.3-50).[18]

1.4.3 Perioperative heart rate

A great deal of attention has been given to the impact of heart rate on perioperative cardiac outcomes and in recent years heart rate control has arguably been the primary focus in attempts to reduced perioperative cardiac mortality.[19-22] As is the case with intraoperative hypotension no commonly accepted definition for

intraoperative tachycardia or bradycardia exists. Most studies identify a heart rate threshold that that best discriminates between patients with and without complications. This rate is then reported as the threshold for an elevated heart rate which has lead to the publication of multiple thresholds, each specific to their own study population.

The impact of heart rate on patients having major noncardiac surgery was reviewed by Biccard.[23] The principle findings from this article suggest that sustained heart rates above 100 beats per minute (bpm) are detrimental in patients ≥60 years old (Table 1). An elevated heart rate in the post PACU >30 beats per min from a preoperative baseline for >5 minutes, has also been identified as an independent predictor of adverse cardiac events (OR 7, 95% 1.9-26).[18]

The association between intraoperative heart rate and ischemia has been extensively studied, and reviews by Landesberg [24] and Biccard[23] provide thoughtful insight into these. Both reviews suggest that an absolute intraoperative threshold is not able to reliably discriminate patients who will suffer myocardial ischemia and that an absolute change in heart rate or heart rate liability may be more reliable. In patients undergoing vascular surgery the absolute increase in intraoperative heart rate was independently associated with both troponin release (OR 1.57 95% CI 1.21 - 2.03, p <0.001) and mortality (OR 1.37 95% CI 1.09-1.70, p=0.005).[25] In a second vascular study myocardial ischemia was found to occur significantly more often in patients with heart

rate liability (i.e., a heart rate change of >20 bpm in a 5 minute period; 90% vs. 58%; p=0.03).[26]

Consistent with the hypothesis that elevated heart rates are associated with increased risk of adverse cardiovascular events, studies have reported an association with low intraoperative heart rates and improved outcomes. A large retrospective database review found that a heart rate <55 bpm was independently associated with the lowest incidence of perioperative death or major surgical complications.[27] Any heart rate increase above this threshold (i.e. ≥55 bpm) was associated with an increase in mortality and major surgical complications (OR 1.06, 95% CI 1.03-1.08, p <0.001).

This signal can also be seen in analysis of data from the POISE (PeriOperative ISchemic Evaluation) trial, an 8351 patient randomized control trial. In this trial the authors evaluated preoperative baseline heart rate and, after adjusting for baseline characteristics, found that for each 10 bpm/min increase in preoperative baseline heart rate there was a significant increase in the risk of perioperative MI (adjusted OR 1.31 [CI, 1.12 to 1.52]).

1.5 Conclusion

Current evidence indicates that intraoperative tachycardia, bradycardia, hypotension, and hypertension are all associated with adverse postoperative events. There is, however, substantial uncertainty regarding how to define these variables. This provides a basis for attempting to identifying intraoperative hemodynamic variables in the VISION data that are associated with MINS and 30-day all-cause mortality. Identification of such intraoperative hemodynamic predictors, together with thresholds at which they cause patient harm, would provide physicians with evidence based targets that could reduce the incidence of postoperative cardiovascular complications.

1.6 Scope of thesis

In this thesis I will use preoperative risk factors, previously identified as predictive of MINS, to develop a baseline risk model for the prediction of Day 1 MINS. I will then create a preoperative risk model by adding 3 preoperative variables (heart rate, blood pressure, and hemoglobin), all playing a key role in myocardial oxygen delivery, to the baseline risk model, and will determine if this model improves the prediction of Day 1 MINS. I will then create a final risk model by adding intraoperative heart rate and blood pressure variables to the preoperative risk model, and will determine if this model improves Day 1 MINS prediction.

CHAPTER 2 – OBJECTIVES

The primary objective of this analysis of VISION study participants was to determine if: 1) intraoperative heart rate and blood pressure duration variables (i.e. the duration spent within predefined hemodynamic thresholds) independently predicted MINS (i.e., postoperative troponin T elevation ≥ 0.03 ng/ml) within the first day after surgery (Day 1 MINS), and 2) the addition of intraoperative heart rate and blood pressure duration variables to a preoperative risk model significantly improved the prediction of Day 1 MINS.

The secondary objective of this study was to determine whether intraoperative heart rate and blood pressure duration variables were independent predictors of: 1) patients who suffered MINS within the first three days after surgery (Day 3 MINS), and 2) all-cause mortality up to 30 days after surgery.

CHAPTER 3 – METHODS

3.1 Design of the VISION study

The VISION study is an observational study of 40,000 patients ≥45 years of age undergoing noncardiac surgery. It aims to determine: 1) the incidence of major perioperative vascular events after noncardiac surgery, 2) the optimal predictive model for these events, and 3) the association between postoperative troponin T elevations and adverse vascular events. VISION is being conducted in 14 countries in Africa, Asia, Australia, Europe, and North and South America, and aims to obtain a representative sample of all patients ≥45 years of age undergoing noncardiac surgery.[3] At all participating sites systems have been implemented to ensure representative sampling by recruiting both elective and emergency patients and ensuring that recruitment occurs during the week, and on weekends.

The observed event rate in the first 15,133 patients of the study cohort was 3 times higher than originally expected. Given the higher than expected event rate a decision was made to subsequently switch from using the 4th generation Troponin T to the 5th generation high-sensitive Troponin T and to report the results on the patients who had a 4th generation Troponin T measurement. Further details with regard to the general study design are reported in the first VISION publication.[3]

3.2 Study endpoints

In all 15,133 patients troponin T sampling was performed using the fourth-generation troponin T assay. Troponin T was drawn at 6-12 hours after surgery, and on day 1, day 2, and day 3 after surgery. Research personnel followed patients throughout their hospitalization and contact patients by phone at 30 days after surgery to determine if they had experienced any outcome. The outcome of interest for the primary analyses were a peak troponin T elevation ≥0.03 ng/ml judged as due to an ischemic etiology (i.e., MINS) measured 6-12 hours or on 1 day after surgery. For the secondary analyses the outcomes were: 1) MINS within the first 3 days after surgery, and 2) 30-day all-cause mortality.

3.3 Collection of hemodynamic and hemoglobin data

The preoperative blood pressure, heart rate, and hemoglobin closest and prior to anesthesia induction were recorded. The intraoperative period was defined as being the point at which surgery started until the time that the surgeon closed the wound.

For the intraoperative duration we recorded the cumulative duration spent within the following hemodynamic bands: 1) systolic blood pressure <100 mmHg to 90

mmHg and <90 mmHg; 2) systolic blood pressure >160 mmHg to 199 mm Hg and ≥200 mmHg; 3) heart rate <55 bpm to 45 bpm and <45 bpm; 4) and heart rate >100 bpm to 140 bpm and >140 bpm. This provided the cumulative duration spent within each hemodynamic band during the intraoperative period, but did not provide information as to when these hemodynamic episodes occurred in relation to one another.

3.4 Inclusion and exclusion criteria

All patients enrolled in the VISION study were considered eligible for this analysis. From these patients we excluded patients who: 1) had no troponin assay measured after surgery, 2) had their peak troponin reported as <0.04, <0.03, or <0.02 ng/ml instead of the absolute value, 3) had missing preoperative data, including preoperative systolic blood pressure, heart rate or hemoglobin, or 4) had missing intraoperative hemodynamic data.

3.5 Statistical methods

3.5.1 Data description

Baseline study characteristics are summarized as percentages for categorical variables, mean and standard deviation for normally distributed continuous variables

and median and inter-quartile range for not normally distributed continuous data. Categorical variables were compared using chi-squared statistics; Students t-test was used to compare normally distributed continuous variables; and Wilcoxon rank sum test for not normally distributed continuous variables. Statistical analyses were conducted using R software (http://www.R-project.org).[28]

3.5.2 Variable selection

We examined three sets of variables: 1) preoperative baseline predictors; 2) preoperative hemodynamic and hemoglobin predictor variables; and 3) intraoperative hemodynamic duration variables.

Preoperative baseline variables and preoperative risk model

The selection of preoperative baseline variables was based on variables identified as preoperative predictors of MINS from a previous VISION paper that established the diagnostic criteria for MINS. In this paper MINS the authors established the diagnostic criterion for MINS within the first 30 days after surgery as a peak fourth generation troponin T ≥0.03 ng/mL judged to be as a result of an ischemic etiology. The independent predictive variables for MINS included age ≥75 years; female sex; current atrial fibrillation; a history of: diabetes, hypertension, congestive heart failure, coronary artery disease, high-risk coronary heart disease, peripheral vascular disease, or stroke;

preoperative eGFR (<30, 30-44, and 45-59ml/minute/1.73m^2); low risk surgery; and urgent/emergent surgery.

These variables predict MINS occurring anytime with the first 30 days after surgery, whereas the primary outcome for this substudy is MINS occurring within the first day after surgery. To address this we conducted regression analysis to identify only those preoperative variables that predicted Day 1 MINS. These variables formed the basis for the baseline risk model.

Preoperative hemodynamic and hemoglobin variables and preoperative risk model

Preoperative heart rate, systolic blood pressure, and preoperative baseline hemoglobin, all key factors in myocardial oxygen delivery, were selected as additional preoperative variables of interest. A priori, we chose to omit analysis of the diastolic and mean blood pressure because of their high correlation with systolic blood pressure and the practicality of focusing on systolic blood pressure in clinical practice. These variables were then added to the variables from the baseline model and this formed the basis of the preoperative risk model.

Intraoperative hemodynamic variables and final risk model

We added intraoperative hemodynamics to the preoperative risk model to explore their relationship to MINS diagnosed before the end of the first day after surgery and this was our final risk model for Day 1 MINS. Intraoperative hemodynamic

data, collected as described in Section 3.3, was transformed to provide the intraoperative duration spent with: 1) systolic blood pressure < 100 mmHg and < 90 mmHg; 2) systolic blood pressure > 160 mmHg and ≥ 200 mmHg; 3) heart rate < 55 beats per minute and < 45 beats per minute; 4) and heart rate > 100 beats per minute and > 140 beats per minute.

3.5.3 Identification of hemodynamic duration thresholds

In this study preoperative heart rate, systolic blood pressure, and hemoglobin and the intraoperative hemodynamic durations were all continuous variables. We used histograms to display the distribution of preoperative heart rate, systolic blood pressure, and hemoglobin in patients with Day 1 MINS and patients without Day 1 MINS. We used a generalized additive model (GAM), adjusted for model covariates, to assess the linearity of the relationship between the continuous preoperative and intraoperative variables and the outcome of Day 1 MINS.

We used the approach described by Mazumdar et al. to determine the preoperative heart rate, systolic blood pressure, and hemoglobin thresholds; and the intraoperative hemodynamic duration thresholds most strongly associated with Day 1 MINS.[30]

Where both risk categories for a hemodynamic pair (e.g., duration spent with a heart rate >100 and >140 bpm; or duration spent with a systolic blood pressure <90 and <100 mmHg) were independent predictors of day 1 MINS we included the less restrictive category (i.e, systolic blood pressure <100 mmHg; a systolic blood pressure >160 mmHg; heart rate >100 bpm; heart rate <55 bpm) as the duration spent in this less restrictive category would capture the signal seen with the duration spent in the more restrictive category.

3.5.4 Model development and validation

We used ROC curves to estimate how the inclusion of the intraoperative hemodynamic variables impacted the ability to predict the study endpoints. Model discrimination was assessed using the c-statistic which describes model discrimination based on the sample population used to build the model. When compared to the discrimination that can be expected in an external population this c-statistic is an over optimistic or biased estimation of model performance.

We therefore used k-fold cross validation to internally validate the model and to determine model optimism. [31] This approach randomly splits the study sample into *k* equal sized sub-samples. Of the *k* sub-samples, one sub-sample is retained as a validation set for testing the model, and the remaining (*k*–1) sub-samples are used as a

derivation set. The process is then repeated *k* times, with each of the *k* subsamples used exactly once as the validation set. The *k* results are then averaged to produce a single estimation of the difference between derivation and validation sets. This difference in model discrimination between the derivation and validation sets is called optimism. The advantage of this method over repeated random sub-sampling is that all observations are used for both training and validation, and each observation is used for validation exactly once. The number of sub-samples required (*k*) varies, however, 10-fold cross-validation, the method chosen for this analysis, has been shown in simulation studies to provide robust validation without causing artificial variance inflation seen with higher *k* values.[32] The corrected c-statistic is therefore the original c-statistic minus model optimism.

We drew calibration plots to assess the agreement between observed and predicted outcomes.[33] Observed outcomes were plotted on the y axis and initial model predictions were plotted on the x axis, therefore perfect predictions would fall on the 45^{o} line. In addition we used bootstrapping to obtain bias-corrected (i.e. corrected for over optimistic model prediction) outcome predictions which were plotted on the x axis. Using the calibrate function in the R (rms) package we created three apparent (smoothed) curves from the observed, predicted, and bias-corrected predictions.

Co-linearity was assessed using the variance inflation and variables with a variance inflation factor >10 considered to be collinear. If two variables were found to be collinear one of the variables were excluded from the analysis.

We compared the baseline risk model with the preoperative risk model; and the preoperative risk model with final risk model. All risk model comparisons were compared: 1) non-parametrically by comparing the area under the ROC curves; 2) with the Net Reclassification Index (NRI) using risk categorizes of <1%, 1 – 5%, >5 – 10%, and >10%, and 3) as continuous change in reclassification (i.e., category free reclassification).[34] This final model was then applied to the outcomes of MINS Day 3 and 30 day mortality.

3.5.5 Sensitivity analysis

We conducted sensitivity analysis by categorizing the intraoperative hemodynamic variables using prespecified thresholds, and then evaluating model prediction for Day 1 MINS. These thresholds are derived from work by Sessler et al. who, in an analysis of 22,000 patients, found a substantial increase in mortality when patients were exposed to 15 minutes or more of cumulative hypotension.[35] We defined patients who spent 0 to 14 minutes in a hemodynamic band as the reference strata and

categorized patients as having spent 15 – 29, 30 – 59, or ≥ 60 minutes in a hemodynamic stratum.

CHAPTER 4 – RESULTS

4.1 Data description

Figure 1 reports the patient flow for this study. From the 16,087 patients recruited we excluded the following: 774 patients who had no troponins measured after surgery, 140 patients who had their peak troponin reported as <0.04, <0.03, or <0.02 instead of the absolute value; 29 patients with missing preoperative data, and 1298 patients with missing intraoperative data. A total of 13,846 patients were therefore included in this analysis.

Table 2 reports the preoperative patient characteristics of the type of surgery for the included patients. There were an almost equal number of males (49.3%) and females (50.7%) in the cohort and just over a quarter of patients (25.5%) were ≥ 75 years of age. The most common types of surgeries were major general surgery (17.4%) and major orthopedic surgery (15.1%). Day 1 MINS occurred in 4.8% (666/13,846) of patients; Day 3 MINS in 8.5% (1172/13,846) of patients, and 30 day mortality in 1.5% of patients (210/13,636).

4.2 Variable selection

The independent preoperative variables used in the VISION model to predict MINS after noncardiac surgery were: age ≥75 years; female sex; a history of: diabetes, hypertension, congestive heart failure, coronary artery disease, high-risk coronary heart disease, peripheral vascular disease, or stroke; preoperative eGFR (<30, 30-44, 45-59, >60 ml/minute/1.73m2); low risk surgery; and urgent/emergent surgery. Regression identified all but age (OR 0.85 95% CI 0.7-1.03; p = 0.106) as predictive for Day 1 MINS (Table 3). Considering that age was included as a risk factor in the paper that defined the MINS criteria[36] we conducted a post-hoc analysis to further explore its relationship with Day 1 MINS.

The Day 1 MINS model had a c-statistic of 0.783; an optimism of 0.003, resulting in a corrected c-statistic of 0.780 (Figure 2). The Day 1 MINS model, with a mean absolute error of 0.002, showed good calibration until a predicted probability of around 0.25, at which the model began to under-predict risk.

The variables included in the baseline risk model were: female sex; current atrial fibrillation; a history of: diabetes, hypertension, congestive heart failure, coronary artery disease, high-risk coronary heart disease, peripheral vascular disease, or stroke; preoperative eGFR (<30, 30-44, and 45-59ml/minute/1.73m^2); low risk surgery; and urgent/emergent surgery.

For the preoperative risk model we added preoperative heart rate, systolic blood pressure, and preoperative baseline hemoglobin to the baseline risk model. For the final risk model we added the intraoperative duration spent with: 1) systolic blood pressure <100 mmHg to 90 mmHg and <90 mmHg; 2) systolic blood pressure >160 mmHg to 199 mm Hg and ≥200 mmHg; 3) heart rate <55 bpm to 45 bpm and <45 bpm; 4) and heart rate >100 bpm to 140 bpm and >140 bpm.

4.3 Exploration of hemodynamic thresholds

4.3.1 GAM exploration of continuous preoperative variables

Figure 3 shows the preoperative heart rate, preoperative systolic BP, and preoperative hemoglobin distributions for patients with Day 1 MINS, superimposed on the distribution of patients without Day 1 MINS. In patients without Day 1 MINS both the mean preoperative heart rate and preoperative hemoglobin differed substantially from those patients with Day 1 MINS (HR 76.4 vs. 81.3 bpm, p<0.001; hemoglobin 131.85 vs. 116.9 g/L, p<0.001) while these was no significant difference between preoperative systolic blood pressure means (140.2 vs. 142.7 mmHg, p=0.017)

Figure 4 provides the results of the GAM exploring the adjusted relationship between Day 1 MINS and preoperative heart rate, systolic BP, and hemoglobin respectively. This adjusted relationship could reasonably be assumed to be linear.

4.3.2 Threshold determination of preoperative variables

A preoperative heart rate >110 bpm, preoperative systolic blood pressure <100 mmHG, and preoperative hemoglobin of ≤ 105 g/dL had the smallest p values for the association with Day 1 MINS; their distributions are shown in Figure 5. Preoperative heart rate >110 bpm (OR 2.59; p <0.001); preoperative systolic blood pressure <100mmHg (OR 1.91; p = 0.004) and preoperative hemoglobin <105 g/dL (OR 2.26; p <0.001) were independent predictors of Day 1 MINS. Figure 6 shows the discrimination of the model using the continuous preoperative hemodynamic variables and compares it to the model using the dichotomized preoperative hemodynamic variables.

When including these variables into the model predicting Day 1 MINS the c-statistic improved from 0.783 (corrected = 0.780) to 0.800 with an optimism of 0.008 (corrected c-statistic 0.792); p <0.001 (Figure 6). The mean absolute error in the model calibration did not change but calibration remained good until a predicted probability of an event of 0.35 or greater, at which point the model under-predicted risk (Figure 7).

The categorical NRI, shown in Table 4, was 10% (95% CI 6.6 – 13.5%; p <0.001), the continuous NRI was 54.7% (95% CI 47 – 62.4%; p <0.001).

4.3.3 GAM exploration of intraoperative hemodynamic duration variables

Figure 8 shows the distribution for the less restrictive intraoperative hemodynamic categories (i.e., systolic blood pressure <100 mmHg; systolic blood pressure >160 mmHg; heart rate >100 bpm; heart rate <55 bpm). The adjusted GAM exploration of these thresholds is shown in Figure 9.

4.3.4 Duration thresholds for intraoperative variables

The duration thresholds, as determined by Mazumdar's approach, for intraoperative systolic blood pressure (mmHg) are shown in Table 5. A systolic blood pressure <90 mmHg for >59 minutes; systolic blood pressure >160 mmHg for >42 minutes; heart rate >100 bpm for >147 minutes; heart rate >140 bpm for >2 minutes; heart rate <55 bpm for >5 minutes, and heart rate <45 bpm for >8 minutes were each individually significant predictors of Day 1 MINS after adjusting for preoperative variables.

Based on the a priori selection rule, where, if both risk categories for a hemodynamic pair (e.g., duration spent with a heart rate >100 and >140 bpm; or duration spent with a systolic blood pressure <90 and <100 mmHg) were independent predictors of day 1 MINS we would include the less restrictive category (i.e, systolic blood pressure <100 mmHg; a systolic blood pressure >160 mmHg; heart rate >100 bpm; heart rate <55 bpm); the following duration thresholds were included into the final model: systolic blood pressure <90 mmHg for >59 minutes; systolic blood pressure >160 mmHg for >42 minutes; a heart rate >100 bpm for >147 minutes; and a heart rate <55 bpm for >5 minutes.

4.4 Day 1 MINS: Model development and validation

All significant baseline risk variables, additional preoperative variables (i.e., preoperative heart rate >110 bpm; preoperative systolic blood pressure <100mmHg, and preoperative hemoglobin <105 g/dL), and intraoperative hemodynamic duration variables (i.e., systolic blood pressure <90 mmHg for >59 minutes; systolic blood pressure >160 mmHg for >42 minutes; a heart rate >100 bpm for >147 minutes; and a heart rate <55 bpm for >5 minutes) were entered into a logistic regression for the outcome of Day 1 MINS.

All variables entered into the final model were significantly associated with the outcome of Day 1 MINS (Table 5). Of the three additional preoperative variables preoperative hemoglobin ≤ 105 g/dL was most strongly associated with Day 1 MINS (OR 2.2, 95% CI 1.81-2.7), and for the intraoperative variables a heart rate >100 bpm for >147 minutes was most strongly associated (OR 1.7, 95% CI 1.23-2.3). An intraoperative operative heart rate <55 bpm for >5 minutes (OR 0.58, 95% CI 0.45-0.73) was protective.

The c-statistic for the model was 0.808 (optimism corrected 0.8) which was greater than the preoperative hemodynamic model (c-statistic 0.808 vs. 0800; p<0.001) but calibration was similar between the models (Figures 10 and 11). Discrimination was greater than the baseline model (c-statistic 0.780; p<0.001) and calibration was improved (Figures 12 and 13). The categorical NRI from the preoperative model to the final model, shown in Table 7, was 2% (95% CI -0.8 – 4.7%; p = 0.17), and the continuous NRI was 12.7% (95% CI 4.6-20.2%; p = 0.002).

4.5 Secondary outcomes

For the outcome of Day 3 MINS the intraoperative variables of systolic BP <90 for >59 min (OR 1.28, 95% CI 0.93-1.75, p = 0.122) and systolic BP >160 for >42 min (OR 1.0, 95% CI 0.81-2.23, p = 0.992) were not predictive (Table 8). All other model variables

were predictive. Model discrimination was 0.786 (optimism corrected 0.781) and model calibration is shown in Figure 14.

For the outcome of mortality at 30 days preoperative heart rate >110 (OR 3.63, 95% CI 2.22-5.8), preoperative hemoglobin ≤ 105 g/dL (OR 2.43, 95% CI 1.76-3.34), and intraoperative heart rate >100 for >147 min (OR 1.78, 95% CI 1.12-2.76) and intraoperative systolic BP <90 for >59 min (OR 2.55, 95% CI 1.5-4.11) were all significant (Table 13). Model discrimination was 0.803 (optimism corrected 0.77) and model calibration is shown in Figure 15.

4.5 Sensitivity analysis

When the intraoperative hemodynamic duration variables were categorized as 0 -14, 15 – 29, 30 – 59, and ≥ 60 minutes the following variables were predictive: heart rate <55 bpms for 30 – 59 minutes (OR 0.42, 95% CI 0.25-0.67), and for ≥ 60 minutes (OR .059, 95% CI 0.39-0.85); heart rate >100 bpm for ≥ 60 minutes (OR 2.19, 95% CI 1.46-3.23); and systolic blood pressure <90 mmHg for ≥ 60 minutes (OR 2.19, 95% CI 1.46-3.23). Table 10 reports the ORs for the categorical intraoperative variables in this model.

With these variables model discrimination was 0.807 (optimism corrected 0.791) and was not statistically different from the final Day 1 MINS model (p=0.45, Figure 16). Model calibration is shown in Figure 17. The categorical NRI, shown in Table 11, was 1.4% (95% CI -1.2 – 4%; p =0.296), and the continuous NRI was 3.3% (95% CI -4.5% to 11.1%; p <0.001).

CHAPTER 5 – DISCUSSION

5.1 Summary of findings

5.1.1 Primary outcome

The baseline risk model developed to predict Day 1 MINS, which excluded age, performed better than the original model used to predict MINS at Day 30 (c-statistic 0.783 vs. 0.777; p<0.001). From a statistical perspective a preoperative heart rate >110 bpm, systolic blood pressure <100 mmHg, and hemoglobin <105 g/dL were the most significant thresholds for these variables to predict Day 1 MINS. Their inclusion into the baseline risk model improved: discrimination (from 0.783 to 0.800, p<0.001), calibration, and both categorical (10%, p<0.001) and continuous NRI (55%; p<0.001). Similarly, systolic blood pressure <90 mmHg for >59 minutes; systolic blood pressure >160 mmHg for >42 minutes; heart rate >100 bpm for >147 minutes; and heart rate <55 bpm for >5 minutes were intraoperative hemodynamic duration thresholds most significant for the prediction of Day 1 MINS.

All preoperative and intraoperative variables included in the final model were significantly associated with the outcome of Day 1 MINS. From the additional preoperative variables evaluated a preoperative hemoglobin ≤ 105 g/dL was associated with the greatest increase in risk (OR 2.2, 95% CI 1.81-2.7), and for the intraoperative variables it was a heart rate >100 bpm for >147 minutes (OR 1.7, 95% CI 1.23-2.3).

Intraoperative heart rate <55 for >5 minutes (OR 0.58, 95% CI 0.45-0.73) was protective. The c-statistic for the final risk model was greater than the preoperative hemodynamic model (c-statistic 0.808 vs. 0.800; <0.001), calibration was similar, categorical reclassification was not significant (NRI 2%, p = 0.17), but the continuous NRI was significant (NRI 12.7%, p = 0.002).

5.1.2 Secondary outcomes

For the outcome of Day 3 MINS only the intraoperative variable of systolic BP <90 for >59 min (OR 1.28, 95% CI 0.93-1.75, p = 0.122) and a systolic BP >160 for >42 min (OR 1.0, 95% CI 0.81-2.23, p = 0.992) were not predictive; model discrimination was 0.786. For the outcome of mortality at 30 days preoperative heart rate >110 (OR 3.63, 95% CI 2.22-5.8), preoperative hemoglobin ≤ 105 g/dL (OR 2.43, 95% CI 1.76-3.34), heart rate >100 for >147 min (OR 1.78, 95% CI 1.12-2.76) and systolic BP <90 for >59 min (OR 2.55, 95% CI 1.5-4.11) were all significant; model discrimination was 0.803 (optimism corrected 0.77)

5.1.3 Sensitivity analysis

When intraoperative variables were categorized as 0 -14, 15 – 29, 30 – 59, and ≥60 minutes the following variables were predictive: heart rate <55 bpm for 30 – 59 minutes (OR 0.42, 95% CI 0.25-0.67), and for ≥ 60 minutes (OR .059, 95% CI 0.39-0.85); heart rate >100 bpm for ≥ 60 minutes (OR 2.19, 95% CI 1.46-3.23); and systolic blood pressure <90 mmHg for ≥ 60 minutes (OR 2.19, 95% CI 1.46-3.23). With these variables model discrimination was 0.807 was not statistically different from the final Day 1 MINS model (p=0.45), calibration was similar, categorical reclassification was not significant (NRI 1.4%, p=0.296), but continuous reclassification was significant (NRI 3.3%, p<0.001).

5.2 Interpretation

5.2.1 Preoperative hemodynamic variables and risk reclassification

The inclusion of the three additional preoperative hemodynamic variables (i.e., systolic blood pressure, heart rate, and hemoglobin) into the baseline risk model improved model discrimination and improved stratification in a clinically significant manner. Of the three preoperative hemoglobin was associated with the greatest OR for Day 1 MINS (2.2; p <0.001) and as a continuous variable it showed the strongest association with Day 1 MINS after covariate adjustment. This finding is clinically plausible considering the central role hemoglobin plays in tissue oxygen delivery and the result of previous studies showing that low preoperative hemoglobin is associated with

postoperative mortality, cardiac arrest, and Q-wave myocardial infarction. [37, 38] Further, there is a credible physiological basis demonstrating that higher heart rates and blood pressures increase myocardial oxygen demand and that this may lead to MINS. However, anemia occurs commonly in patients with chronic disease and it is possible that patients with low preoperative hemoglobin represent a vulnerable sub-set of perioperative patients.

5.2.2 Intraoperative hemodynamic variables and risk reclassification

An intraoperative systolic blood pressure threshold of <90 mmHg has been used as the definition of intraoperative hypotension in many studies,[11] but none have been able to define a duration spent below this threshold that would increase cardiac injury risk. This analysis, supported by both the primary and sensitivity analyses, demonstrates that, for the outcome of Day 1 MINS, injury occurs after ≥ 60 minutes. Systolic blood pressure >160 mmHg for 45 minutes or more was protective in the primary analysis. However, in the sensitivity analysis, none of the duration thresholds (i.e., 15-29; 30-59; and ≥60 min) were significant predictors and this suggests that care should be taken when interpreting this result. It may be possible that in older or baseline hypertensive patients a sustained elevated intraoperative blood pressure is cardio-protective and that this analysis has adjusted incompletely for this association.

Heart rate is one of the primary factors in determining cardiac oxygen delivery. Tachycardia reduces the time the heart spends in diastole and so reduces myocardial oxygen delivery. In both the primary analysis and sensitivity analysis a heart rate of >100 bpm had to be sustained for an hour or more before it had any significant impact on Day 1 MINS. For heart rate <55 bpm a protective effect was seen in a substantially shorter time frame, >5 minutes in the primary analysis, and >30 minutes in the sensitivity analysis. The risk associated with these thresholds strongly suggests that intraoperative heart rate plays a key role in the development of Day 1 MINS. This finding is highly congruous with the finding of the POISE trial that found preoperative beta-blockade reduced postoperative MI,[19] and with meta-analyses showing that intraoperative esmolol administration reduced postoperative myocardial ischemia.[22, 39]

Pencina et al. discussed the limitations of using a categorical NRI highlighting the problems of defining meaningful risk categories that influence care decisions in emerging fields.[34] In addition, they have demonstrated how the results of a categorical NRI are affected by the number of categories defined. For these reasons they argue that the continuous NRI is the "most objective and versatile measure of improvement in risk prediction". This can be seen in these results where the addition of intraoperative hemodynamic variables improved statistical model discrimination for Day 1 MINS but did not improve risk stratification when using the prespecified risk categories. This was true when using the single duration thresholds identified by Mazumdar's approach (NRI

2%, p = 0.17), as well as when using the prespecified categorical thresholds (NRI 1.4%, p = 0.296). However, when the NRI was determine as a continuous statistic the number of patients reclassified became significant for both Mazumdar's approach (NRI 12.7%, p = 0.002) and the prespecified categorical thresholds (NRI 3.3%, p <0.001).

These results therefore demonstrate that for the outcome of Day 1 MINS adding the intraoperative duration spent with a heart rate <55 for >5 min, heart rate >100 for >147 min, systolic BP <90 for >59 min and systolic BP >160 for >42 min significantly improves the model discrimination and risk stratification.

5.2.3 Secondary outcomes

For the outcome of Day 3 MINS all the variables in the original model remained significant, with the exception of the intraoperative systolic blood pressure duration variables. As was the case for the outcome of Day 1 MINS, intraoperative heart rate duration variables remained predictive. This provides further support for targeting intraoperative heart rate as a perioperative therapeutic target provided adequate intraoperative blood pressures can be maintained.

When applying the Day 1 MINS model to 30 day mortality prolonged intraoperative periods spent with an elevated heart rate (>100 beats per min for >147

minutes), or with a low blood pressure (<90 mmHg for >59 minutes) were predictive of 30-day mortality. Once again preoperative hemoglobin remained a predictive variable likely emphasizing its importance as a predictor of Day 1 MINS.

5.2.4. Modeling limitations

Predictive modeling describes the application of a statistical model to data with the aim of providing valid outcome predictions for new patients. In such prediction models predictors are only *associated* with the primary endpoint.[40] No definitive statement can be made about the causal relationship between the predictor and the endpoint of interest. Predictors, no matter how strong, are not necessarily the cause of the endpoint. It follows therefore that reducing the frequency of a predictor does not necessarily result in a reduction in the frequency of the endpoint. This limitation should always be held in mind when interpreting findings from predictive models.

In addition the independence of the predictors used in a prediction model is assumed and not shown by the model. Statistical testing for interactions provides some degree of confidence that their magnitude will not impact significantly on model results, however true independence cannot be proven.

Assessing whether a causal relationship is plausible can only occur when a model includes the true predictor. If the "true" cause of the endpoint is left out of the model the causal effect will be falsely attributed to other confounding factors in the model. For example, if the variable "smoker" is replaced with "match box carrier" in a model predicting lung cancer, attempts to reduce lung cancer by eliminating match boxes is doomed to failure.

This becomes of particular importance in perioperative medicine where the timing of observations impacts substantially on the strength of the assumptions that can be made with regard to causal relationships. In this data set the preoperative variables remain static from the time of first observation and are assumed to be largely independent. In contrast the intraoperative variables assessed are much less robust as they are recorded at different times during the course of the surgery, interact with other unmeasured factors (e.g., surgical expertise, intraoperative blood loss), and are dependent on thresholds prespecified in the study design.

This analysis showed that heart rate <55 bpm minutes for >5 minutes was protective (OR 0.58). This suggests that prolonging the duration spent with a heart rate <55 bpm would also certainly reduce the risk of Day 1 MINS. However, this does not mean that if anesthetists should achieve this intraoperative threshold the incidence of Day 1 MINS will be reduced to the magnitude suggested in these analyses. It is likely

that some of the protective signal seen with a low heart rate is a surrogate for variables not included in the model. For example, patients who do not suffer a major intraoperative bleed will have a lower heart rates than those suffering a major bleed. Adding major bleeding into this model would dampen the protective effect of a low heart rate. Therefore clinicians should attempt to prolong the duration patients spend with their heart rates <55 bpm while at the same time being aware of, and attempting to correct, the root factors causing intraoperative heart rate elevations.

Similarly, it must be kept in mind that there are other mechanisms of myocardial injury and myocardial infarction that are not captured by the model presented here. Intraoperative plaque fissure or rupture, with subsequent intracoronary thrombosis, plays an important role in perioperative myocardial injury. The intraoperative hemodynamic factors introduced into this model are unlikely to predict MINS due to this mechanism.

5.2.5 Effect of variable categorization

Statistically, dichotomization of continuous variables is not recommended as it substantially reduces predictive power and may introduce residual confounding.[41] Where computer modeling is used to provide risk prediction continuous variables should be used as such. Such models provide important clinical messages that inform clinicians

as to the relationship between predictors and outcomes. However, when evaluating courses of treatment clinicians largely make use of decision thresholds and using continuous variables is not clinically feasible. Dichotomization or categorization of continuous variables is therefore a practical necessity. Thresholds may be may be derived from the data itself - as done in the primary analysis; or may be predefined by using previously know clinically significant values – as done in the sensitivity analysis. The results of this sensitivity analysis suggest that the duration thresholds identified by Mazundar's approach are robust and clinically applicable.

5.3 Strengths and weaknesses

This study has a number of strengths. This is one of the largest prospective perioperative observational studies ever conducted and provides a representative sample of global perioperative medicine. This analysis include over 13,000 patients with 666 events which means that we surpassed 10 events per variable in all our regression models, thus ensuring stable measures of association.[42] There was little preoperative or intraoperative data missing and complete follow-up was achieved on 99.7% of patients. Finally, all troponin elevations were assessed using the same troponin T 4th generation assay which provided consistency in the outcome assessment.

The primary weakness of this analysis is related to the manner in which the intraoperative heart rate and blood pressure data were collected. The VISION study is being run in many countries with differing levels of socio-economic development and as a result data collection had to be practical and achievable in all sites. As it was not feasible to collect real-time hemodynamic data the decision was made to define clinically important thresholds and to record the duration spent below them. The choice of heart rate thresholds (i.e., >100, >140, <55, <45 bpm and blood pressure thresholds (i.e., <100, <90, >160, and ≥200 mmHg) was informed by literature review and extensive discussions with anesthesiologists and other perioperative physicians. While it is likely that duration spent above or below other heart rate and blood pressure thresholds is associated with Day 1 MINS the threshold chosen for this analysis are both practical and clinically relevant.

An additional concern with this method of intraoperative hemodynamic data collection is that it does not allow reliable analysis of how the duration spent below the intraoperative heart rate and blood pressure thresholds interact with each other. The duration spent in each threshold was summated for the entire intraoperative period and there is no way to determine if for example the 30 minutes of low blood pressure occurred at the same time as the 5 minutes of high heart rate. Therefore exploring interactions between these duration variables would not have clinical significance.

A competing outcomes interest occurs when one outcome (e.g. death) reduces the incidence of a second outcome (e.g. stroke). For example; a drug that is thought to reduce stroke at 30 days is tested in a randomized controlled trial. Patients who receive this drug die within the first week of receiving it. When compared to the placebo it would seem that the drug reduces stroke at 30 days, but this would be due to the outcome of death competing for the outcome of stroke. It is unlikely that these results are affected by competing outcomes interests. For inclusion into this model patients had to have a Day 1 troponin sample drawn and therefore any patients who died intraoperatively would not have been included in the analysis.

5.4 Conclusion and future directions

The addition of preoperative hemodynamic variables, in particular preoperative hemoglobin, to the baseline risk model significantly improved the prediction of Day 1 MINS. The addition of the intraoperative duration spent with a heart rate <55 for >5 min, heart rate >100 for >147 min, systolic BP <90 for >59 min and systolic BP >160 for >42 min significantly improved both the model discrimination and risk stratification.

The strongly protective association seen with low intraoperative heart rate is encouraging and suggests that this could be a potential target for future interventions. Preoperative beta-blockers have been shown to reduce postoperative MI but increase

all cause mortality. Alternative methods such as intraoperative infusions of esmolol or ivabradine present themselves as interesting therapeutic options.[43]

While there is some value in targeting specific blood pressure and heart rate thresholds it should always be kept in mind that these act as surrogate markers for cardiac output and ultimately tissue oxygen delivery. It is vital to more clearly understand how hemoglobin, cardiac output, tissue oxygen delivery and perioperative bleeding contribute to Day 1 MINS. This is particularly important when considering strong association seen with preoperative hemoglobin and MINS in this study.

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CHAPTER 8 – TABLES

Table 1. Impact of intraoperative heart rate on perioperative outcomes

Author, date	Types of surgery	Age	Threshold (beats per min)	Outcome	Risk
Reich, 2002[44]	Major vascular, orthopedic, urological, gynecological, general (>220 minutes)	Median 60 years (IQR 43-73)	>110 for ≥5 minutes	Prolonged hospital stay or in-hospital death	OR 2.7, p=0.001
Leung, 2001[45]	General, orthopedic, neurological, urological, head and neck, gynecological, vascular, and thoracic	>70 years	>110 for >10 minutes	Any postoperative in-hospital adverse event	OR 3.8 (95% CI 1.9-7.6; p<0.001)
Rinfret, 2004[46]	Major noncardiac (vascular, thoracic, orthopedic, abdominal)	≥50 years	>120 at any point (no time duration)	In hospital MI	Not predictive
Feringa, 2006[25]	Vascular	Mean 67 years (SD ± 10)	10 bpm increase (from baseline)	Mortality and non fatal myocardial infarction at 2.6 years after surgery	HR 2.10 (95% CI 1.52-2.91; p<0.001)

Table 2. Baseline characteristics of patients who did and did not suffer Day 1 MINS

	No Day 1 MINS (N=13,180)	**Day 1 MINS** (N=666)	**p-value**
Age ≥ 75 years	3239 (24.6)	286 (42.9)	<0.001*
Females	6815 (51.7%)	307 (46.1%)	0.05
Current atrial fibrillation	410 (3.1%)	70 (10.5%)	<0.001*
History of			
Diabetes	2536 (19.2%)	227 (34.1%)	<0.001*
Hypertension	6664 (50.6%)	476 (71.9%)	<0.001*
Congestive heart failure	555 (4.2%)	116 (17.4%)	<0.001*
Coronary artery disease	1508 (11.4%)	202 (30.3%)	<0.001*
High-risk coronary artery disease	113 (0.9%)	44 (6.6%)	<0.001*
Peripheral vascular disease	619 (4.7%)	123 (18.5%)	<0.001*
Stroke	904 (6.9%)	122 (18.3%)	<0.001*
Preoperative eGFR*			<0.001*
<30 ml/minute/1.73m^2	454 (3.4%)	183 (27.5%)	
30-44 ml/minute/1.73m^2	1018 (7.7%)	101 (15.2%)	
45-59 ml/minute/1.73m^2	1938 (14.7%)	118 (17.7%)	
>60 ml/minute/1.73m^2	9970 (74.1%)	264 (39.6%)	
Type of Surgery			
Major vascular	677 (5.1%)	74 (11.1%)	<0.001*
Major general	2296 (17.4%)	111 (16.7%)	0.635
Major orthopedics	1980 (15%)	109 (16.4)	0.346
Major neurosurgery	735 (5.6%)	32 (4.8%)	0.432
Low risk surgery	5248 (39.8%)	208 (31.2%)	<0.001*
Urgent/emergent surgery	1585 (12%)	174 (26.1%)	<0.001*

* = p<0.05

Table 3. Odds ratios associated with the independent baseline variables predicting Day 1 MINS and Day 3 MINS

Preoperative variables	Day 1 MINS		Day 3 MINS	
	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age ≥75 years old	0.85 (0.7-1.03)	0.106*	1.27 (1.09-1.47)	0.002
Females	1.33 (1.12-1.57)	<0.001	1.39 (1.22-1.59)	<0.001
Current atrial fibrillation	1.49 (1.09-2.00)	0.011	1.74 (1.35-2.23)	<0.001
History of:				
Diabetes	1.37 (1.24-1.65)	<0.001	1.29 (1.11-1.5)	<0.001
Hypertension	1.33 (1.1-1.61)	0.004	1.46 (1.26-1.69)	<0.001
Congestive heart failure	1.98 (1.52-2.54)	<0.001	1.77 (1.42-2.19)	<0.001
Coronary artery disease	1.50 (1.21-1.86)	<0.001	1.61 (1.36-1.9)	<0.001
High-risk coronary artery disease	3.14 (2.04-4.78)	<0.001	2.16 (1.45-3.17)	<0.001
Peripheral vascular disease	2.27 (1.78-2.87)	<0.001	2.07 (1.69-2.52)	<0.001
Stroke	1.37 (1.09-1.72)	0.007	1.37 (1.13-1.65)	0.001
Preoperative eGFR:				
<30 ml/minute/1.73m^2	8.99 (7.16-11.27)	<0.001	7.16 (5.83-8.77)	<0.001
30-44 ml/minute/1.73m^2	2.38 (1.84-3.04)	<0.001	2.25 (1.83-2.75)	<0.001
45-59 ml/minute/1.73m^2	1.73 (1.37-2.17)	<0.001	1.59 (1.33-1.90)	<0.001
>60 ml/minute/1.73m^2	-		-	
Low risk surgery	0.81 (0.68-0.97)	0.022	0.63 (0.55-0.73)	<0.001
Urgent/emergent surgery	2.15 (1.77-2.61)	<0.001	1.85 (1.58-2.17)	<0.001

* not significant in the Day 1 MINS prediction model

Table 4. Change in risk classification for the probability of Day 1 MINS using a model including preoperative hemodynamic variables, as compared to a model using baseline variables only

Risk classification with baseline variables	**Risk classification with preoperative hemodynamics**				**Reclassified* as:**		**Net correctly reclassified[§] %**	**Net reclassification improvement[£] %**
	<1%	1 - 5%	5 - 10%	>10%	Higher risk	Lower risk		
Patients **with** Day 1 MINS (n=666)								
<1%	0	0	0	0	74	58	2.4%	10%
1 – 5%	12	189	35	4				
5 – 10%	0	28	57	35				
>10%	0	0	18	288				
Patients **without** Day 1 MINS (n=13,180)								
<1%	0	0	0	0	661	1669	7.6%	
1 – 5%	940	9293	402	29				
5 – 10%	0	532	753	230				
>10%	0	0	197	804				

Key

	Improved classification
	No classification change
	Worse classification

*The addition of preoperative hemodynamics to the baseline risk model reclassified: 74 patients with the primary outcome and 661 patients without the primary outcome to a higher risk category; and 58 patients with the primary outcome and 1669 patients without the primary outcome to a lower risk category. [§]In patients with the primary outcome 2.4% were correctly reclassified ([74 - 58] / 666). In patients without the primary outcome 7.6% were correctly reclassified ([1669-661] / 13,180).

[£]The net reclassification improvement is the sum of the correctly reclassified patients who did and did not survive (i.e., 2.4% + 7.6% = 10%)

Table 5. The optimal duration thresholds for each intraoperative hemodynamic variable for the outcome of Day 1 MINS

Intraoperative variable		Duration	Number of patients in each category	Events	OR	P value
Systolic blood pressure	<90 mmHg	59 min.	512 (3.5%)	31	1.68	0.013*
	<100 mmHg	147 min.	456 (3.3%)	24	1.57	0.051
	>160 mmHg	42 min.	491 (3.5%)	27	0.58	0.013*
	≥200 mmHg	10 min.	642 (4.6%)	35	0.7	0.069
Heart rate	>100	32 min	525 (3.8%)	77	2.0	<0.001*
	>140	2 min	421 (3.1%)	16	2.48	0.004*
	<45 bpm	8 min	535 (3.9%)	10	0.44	0.014*
	<55 bpm	5 min	3313 (24%)	91	0.56	<0.001*

Table 6. Results of the final risk model predicting Day 1 MINS

Final risk model variables	Day 1 MINS	
	Adjusted OR (95% CI)	**p-value**
Preoperative variables:		
Females	1.35 (1.14-1.61)	<0.001*
Current atrial fibrillation	1.33 (0.96-1.82)	0.075
History of:		
Diabetes	1.26 (1.04-1.52)	0.019*
Hypertension	1.45 (1.19-1.77)	<0.001*
Congestive heart failure	1.82 (1.39-2.6)	<0.001*
Coronary artery disease	1.64 (1.32-2.05)	<0.001*
High-risk coronary artery disease	2.7 (1.73-4.15)	<0.001*
Peripheral vascular disease	2.2 (1.71-2.8)	<0.001*
Stroke	1.39 (1.09-1.76)	0.007*
Preoperative eGFR:		
<30 ml/minute/1.73m^2	6.93 (5.43-8.83)	<0.001*
30-44 ml/minute/1.73m^2	2.19 (1.68-2.83)	<0.001*
45-59 ml/minute/1.73m^2	1.7 (1.34-2.14)	<0.001*
>60 ml/minute/1.73m^2	-	-
Low risk surgery	0.81 (0.68-0.98)	0.027*
Urgent/emergent surgery	1.84 (1.26-2.66)	0.001*
Preoperative hemodynamic variables:		
Preop heart rate >110	1.84 (1.26-2.66)	0.001*
Preop systolic BP <100	1.89 (1.18-2.93)	0.006*
Preop hemoglobin ≤ 105 g/dL	2.22 (1.81-2.7)	<0.001*
Intraoperative variables:		
Heart rate <55 for >5 min	0.58 (0.45-0.73)	<0.001*
Heart rate >100 for >147 min	1.7 (1.23-2.3)	<0.001*
Systolic BP <90 for >59 min	1.53 (1.02-2.22)	0.03*
Systolic BP >160 for >42 min	0.73 (0.54-0.97)	0.03*

* P <0.05

Table 7. Change in risk classification for the probability of Day 1 MINS using the final model including intraoperative hemodynamic variables, as compared to a model using preoperative hemodynamic variables only

Risk classification with preoperative hemodynamics	**Risk classification with pre- and intraoperative hemodynamics**				**Reclassified* as:**		**Net correctly reclassified[§] %**	**Net reclassification improvement[£] %**
	<1%	1 - 5%	5 - 10%	>10%	Higher risk	Lower risk		
Patients **with** Day 1 MINS (n=666)								
<1%	1	11	0	0	54	29	3.8%	2%
1 – 5%	4	187	25	1				
5 – 10%	0	9	84	17				
>10%	0	0	16	311				
Patients **without** Day 1 MINS (n=13,180)								
<1%	241	699	0	0	1209	972	-1.8%	
1 – 5%	567	8861	394	3				
5 – 10%	0	284	955	113				
>10%	0	3	118	942				

Key

	Improved classification
	No classification change
	Worse classification

*The addition of intraoperative hemodynamics to the risk model containing preoperative hemodynamic variables reclassified: 64 patients with the primary outcome and 1209 patients without the primary outcome to a higher risk category; and 349 patients with the primary outcome and 972 patients without the primary outcome to a lower risk category. [§]In patients with the primary outcome 5.3% were correctly reclassified ([54 – 29] / 666). In patients without the primary outcome -1.8% were

correctly reclassified ([972-1209] / 13,180). [£]The net reclassification improvement is the sum of the correctly reclassified patients who did and did not survive (i.e., 3.8% - 1.8% = 2%)

Table 8. Results for the prediction of Day 3 MINS

Final risk model variables	Day 3 MINS	
	Adjusted OR* (95% CI)	**p-value**
Preoperative variables:		
Females	1.4 (1.23-1.61)	<0.001*
Current atrial fibrillation	1.71 (1.33-2.21)	<0.001*
History of:		
Diabetes	1.17 (1.33-2.21)	<0.001*
Hypertension	1.58 (1.36-1.84)	<0.001*
Congestive heart failure	1.67 (1.33-2.08)	<0.001*
Coronary artery disease	1.74 (1.47-2.07)	<0.001*
High-risk coronary artery disease	1.8 (1.2-2.67)	<0.001*
Peripheral vascular disease	2.0 (1.63-2.45)	<0.001*
Stroke	1.41 (1.16-1.7)	<0.001*
Preoperative eGFR:		
<30 ml/minute/1.73m^2	6.09 (4.95-7.49)	<0.001*
30-44 ml/minute/1.73m^2	2.36 (1.94-2.87)	<0.001*
45-59 ml/minute/1.73m^2	1.65 (1.39-1.97)	<0.001*
>60 ml/minute/1.73m^2	-	-
Low risk surgery	0.62 (0.54-0.72)	<0.001*
Urgent/emergent surgery	1.68 (1.42-1.98)	<0.001*
Preoperative hemodynamic variables:		
Preop heart rate >110	1.76 (1.27-2.42)	<0.001*
Preop systolic BP <100	1.63 (1.08-2.38)	0.015*
Preop hemoglobin ≤ 105 g/dL	2.07 (1.75-2.43)	<0.001*
Intraoperative variables:		
Heart rate <55 for >5 min	0.74 (0.63-0.88)	<0.001*
Heart rate >100 for >147 min	1.39 (1.07-1.81)	0.012*
Systolic BP <90 for >59 min	1.28 (0.93-1.75)	0.122
Systolic BP >160 for >42 min	1.0 (0.81-2.23)	0.992

* p <0.05

Table 9. Results of the prediction of 30 day mortality

Final risk model variables	30 day mortality	
	Adjusted OR (95% CI)	**p-value**
Preoperative variables:		
Females	1.52 (1.14-2.03)	0.004*
Current atrial fibrillation	1.48 (0.87-2.4)	0.128
History of:		
Diabetes	0.88 (0.62-1.1.24)	0.474
Hypertension	1.2 (0.87-1.66)	0.264
Congestive heart failure	1.58 (0.9902.49)	0.05*
Coronary artery disease	0.86 (0.55-1.3)	0.492
High-risk coronary artery disease	2.41 (1.05-5.13)	0.028*
Peripheral vascular disease	1.28 (0.79-1.98)	0.305
Stroke	1.57 (1.05-2.3)	0.022*
Preoperative eGFR:		
<30 ml/minute/1.73m^2	4.24 (2.77-6.42)	<0.001*
30-44 ml/minute/1.73m^2	2.39 (1.54-3.63)	<0.001*
45-59 ml/minute/1.73m^2	2.01 (1.36-2.94)	<0.001*
>60 ml/minute/1.73m^2	-	-
Low risk surgery	0.68 (0.4900.93)	0.018*
Urgent/emergent surgery	2.08 (1.5-2.85)	0.001*
Preoperative hemodynamic variables:		
Preop heart rate >110	3.63 (2.22-5.8)	0.001*
Preop systolic BP <100	1.35 (0.6-2.7)	0.434
Preop hemoglobin ≤ 105 g/dL	2.43 (1.76-3.34)	<0.001*
Intraoperative variables:		
Heart rate <55 for >5 min	0.8 (0.53-1.17)	0.259
Heart rate >100 for >147 min	1.78 (1.12-2.76)	0.013*
Systolic BP <90 for >59 min	2.55 (1.5-4.11)	<0.001*
Systolic BP >160 for >42 min	1.05 (0.65-1.62)	0.828

*=p<0.05

Table 10. Sensitivity analysis using prespecified categorical intraoperative variables for the prediction of Day 1 MINS

Intraoperative variables:	Day 1 MINS	
	Adjusted OR (95% CI)	**p-value**
Heart rate <55 beats per min		
0 – 14 min	-	-
15 – 29 min	0.83 (0.55-1.22)	0.373
30 – 59 min	0.42 (0.25-0.67)	<0.001*
≥ 60 min	0.59 (0.39-0.85)	0.007*
Heart rate >100 beats per min		
0 – 14 min	-	-
15 – 29 min	1.15 (0.75-1.7)	0.512
30 – 59 min	1.32 (0.83-2.02)	0.224
≥ 60 min	2.19 (1.46-3.23)	<0.001*
Systolic BP <90 mmHg		
0 – 14 min	-	-
15 – 29 min	1.06 (0.79-1.39)	0.701
30 – 59 min	1.04 (0.72-1.47)	0.817
≥ 60 min	1.66 (1.08-2.48)	0.016*
Systolic BP >160 mmHg		
0 – 14 min	-	-
15 – 29 min	0.87 (0.65-1.15)	0.326
30 – 59 min	0.87 (0.58-1.25)	0.466
≥ 60 min	0.64 (0.37-1.06)	0.099

* = p <0.05

Table 11. Change in risk classification for the probability of Day 1 MINS using the final model with prespecified intraoperative hemodynamic thresholds, as compared to a model using preoperative hemodynamic variables only

Risk classification with preoperative hemodynamics	**Risk classification with prespecified thresholds for intraoperative hemodynamics**				**Reclassified* as:**		**Net correctly reclassified[§] %**	**Net reclassification improvement[£] %**
	<1%	1 - 5%	5 - 10%	>10%	Higher risk	Lower risk		
Patients **with** Day 1 MINS (n=666)								
<1%	2	10	0	0	44	28	2.4%	1.4%
1 – 5%	4	194	16	3				
5 – 10%	0	11	84	15				
>10%	0	0	13	314				
Patients **without** Day 1 MINS (n=13,180)								
<1%	244	696	0	0	1087	952	-1%	
1 – 5%	572	8971	278	4				
5 – 10%	0	277	966	109				
>10%	0	6	97	960				

Key

	Improved classification
	No classification change
	Worse classification

*The addition of intraoperative hemodynamics using prespecified thresholds to the risk model containing preoperative hemodynamic variables reclassified: 44 patients with the primary outcome and 1087 patients without the primary outcome to a higher risk category; and 28 patients with the primary outcome and 952 patients without the primary outcome to a lower risk category. [§]In patients with the primary outcome2.4% were correctly reclassified ([44 – 28]] / 666). In patients

without the primary outcome -1.0% were correctly reclassified ([952 - 1087] / 13,180). [£]The net reclassification improvement is the sum of the correctly reclassified patients who did and did not survive (i.e., 2.4% - 1% = 1.4%

CHAPTER 9 – FIGURES

Figure 1 Flow chart of study population

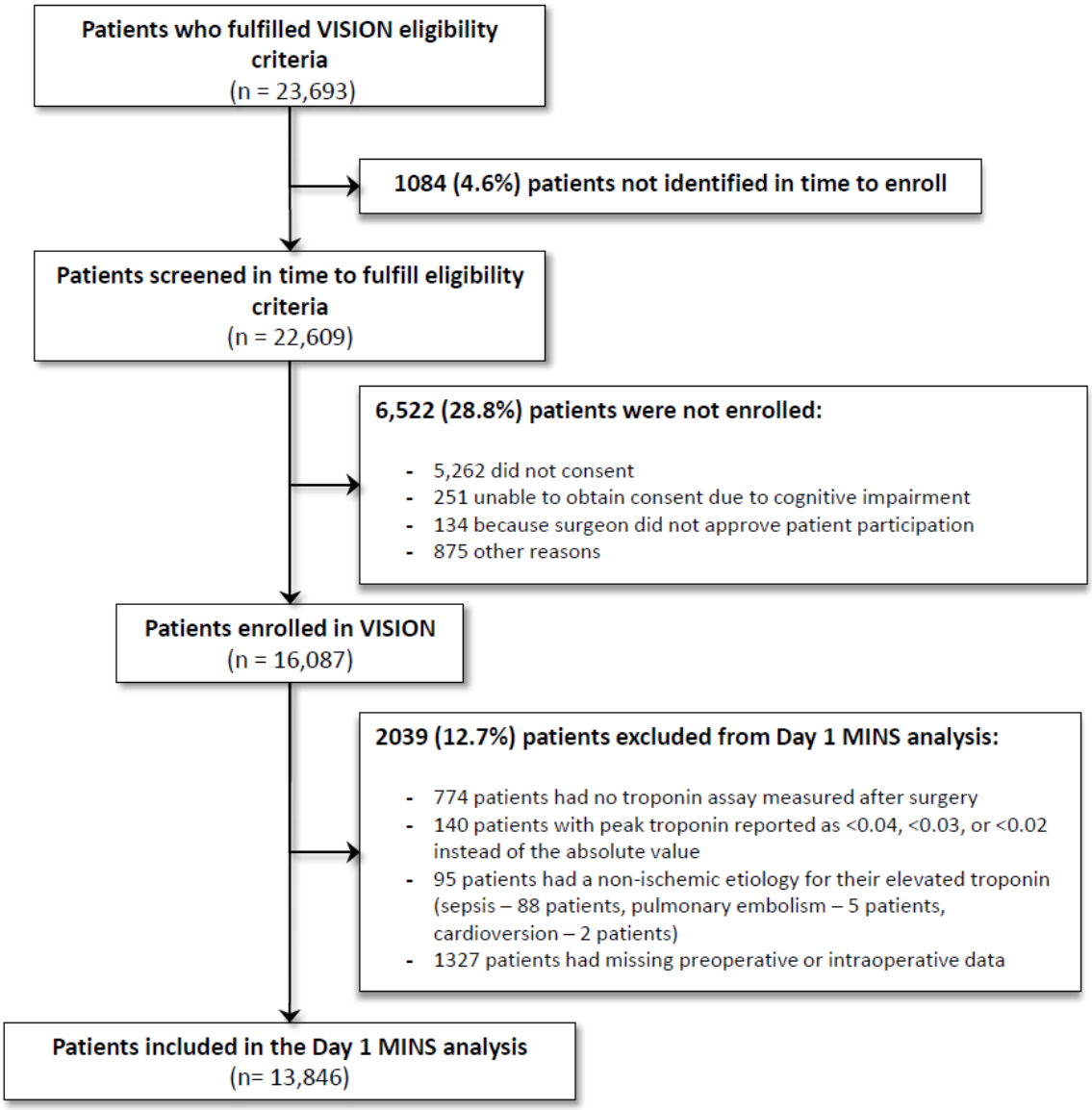
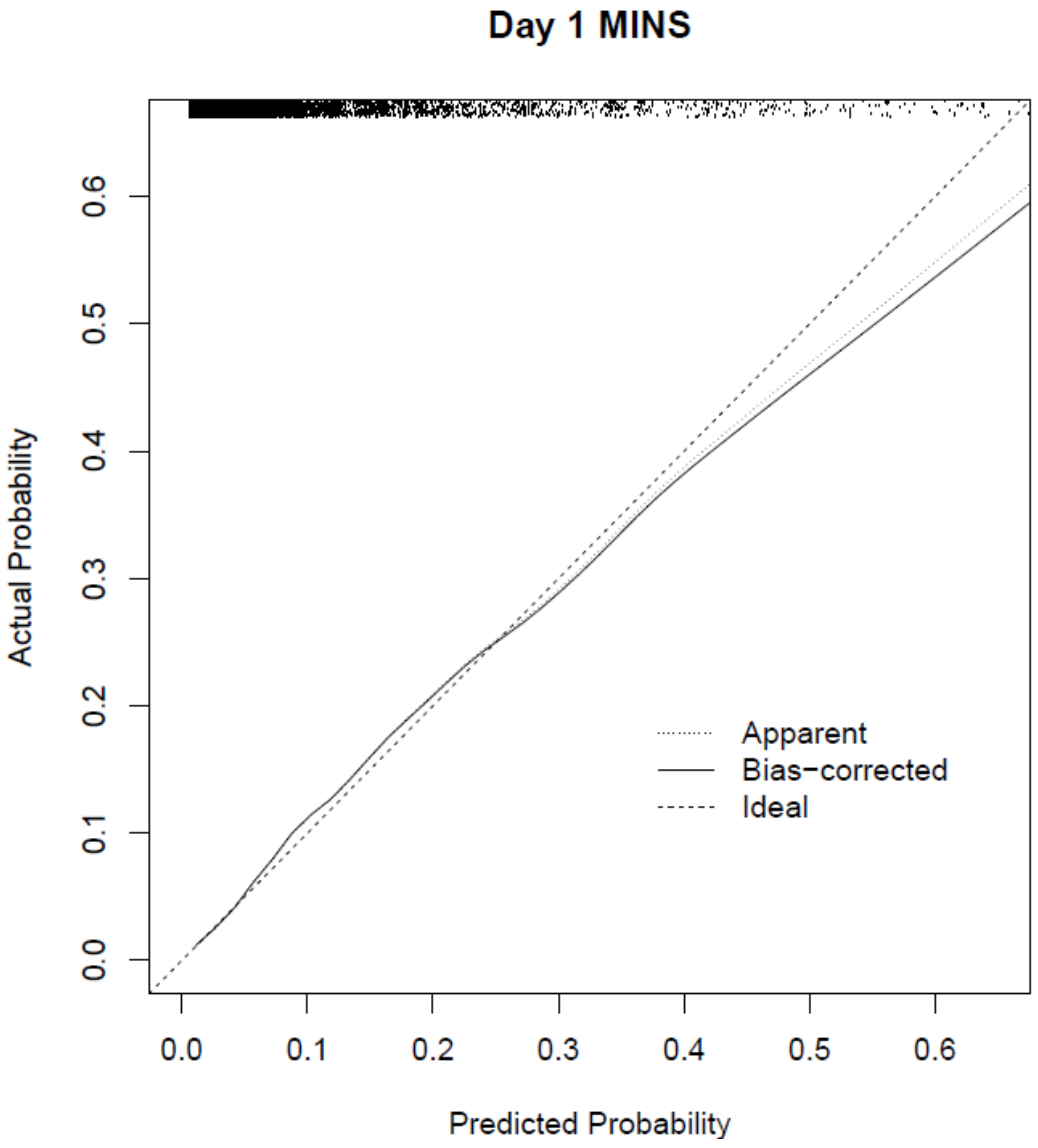


Figure 2. Calibration of Day 1 MINS model

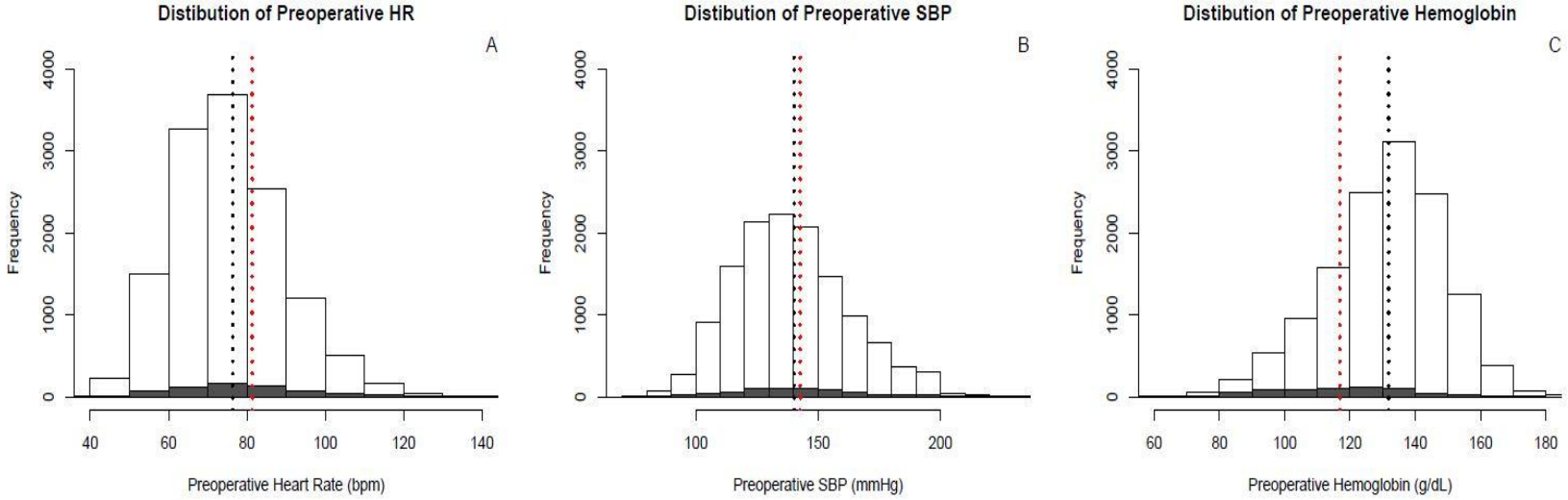


The Apparent line (light line) represents the predicted probability of the outcome as shown by the risk model.

The Bias-correct line (dark line) represents the bias corrected probability of the outcome as determined by bootstrapping with 400 repetitions.

The Ideal line (dotted light line) represents the ideal model as based on the actual probability of the outcome

Figure 3. Distribution of preoperative heart rate (A), preoperative systolic blood pressure (B), and preoperative hemoglobin (C) in patients with (dark bars) and without (light bars) Day 1 MINS.



The black dotted line represents the mean for patients without Day 1 MINS and the red dotted line represents the mean for patients with Day 1 MINS. For patients without Day 1 MINS as compared to those with Day 1 MINS the mean preoperative HR 76.4 vs. 81.3 bpm, p<0.001; mean preoperative systolic blood pressure 140.2 vs. 142.7 mmHg, p=0.017; mean preoperative hemoglobin 131.85 vs. 116.9 g/L, p<0.001 .

Figure 4. The adjusted relationship (beta) between Day 1 MINS and preoperative heart rate (G), preoperative systolic blood pressure (H), and preoperative hemoglobin (I) analysed using a GAM

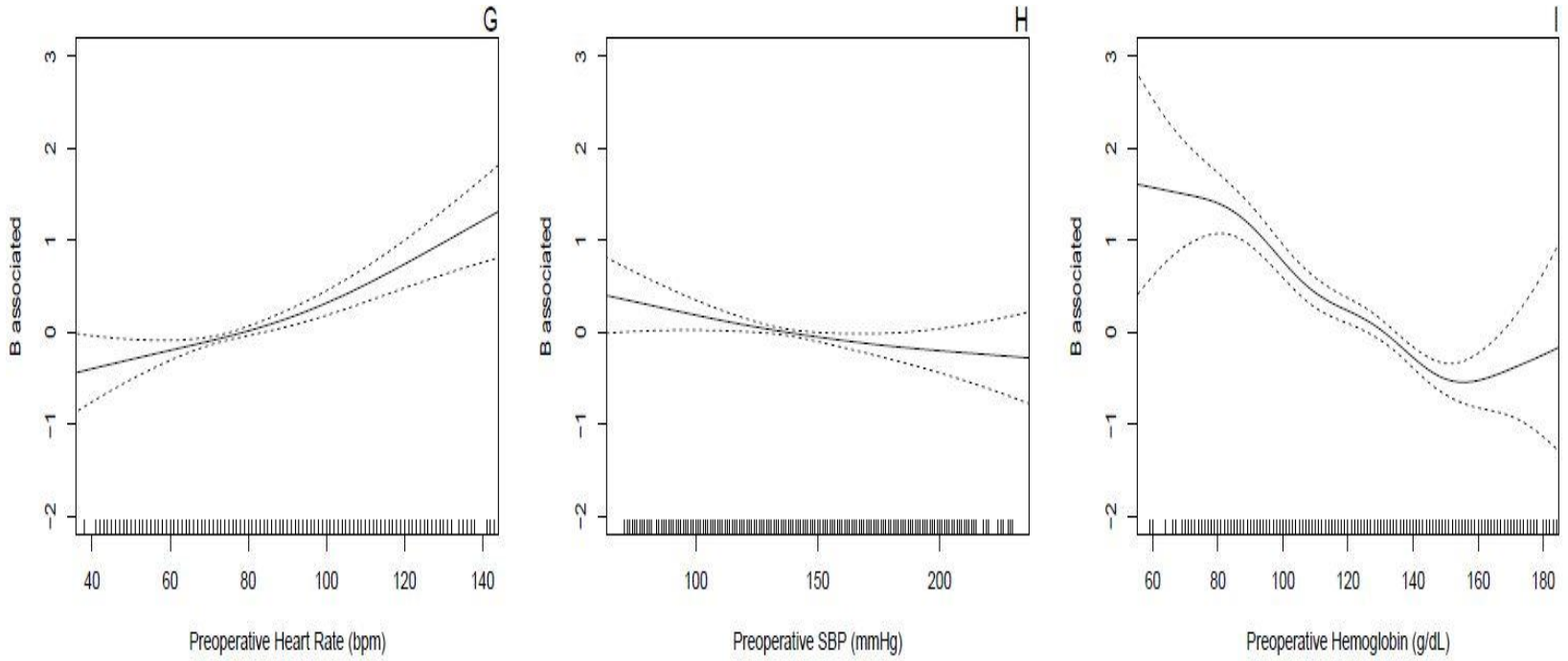
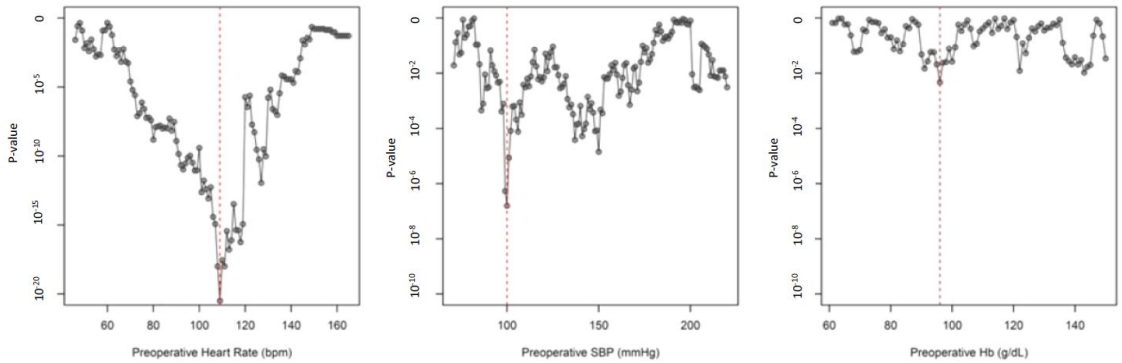
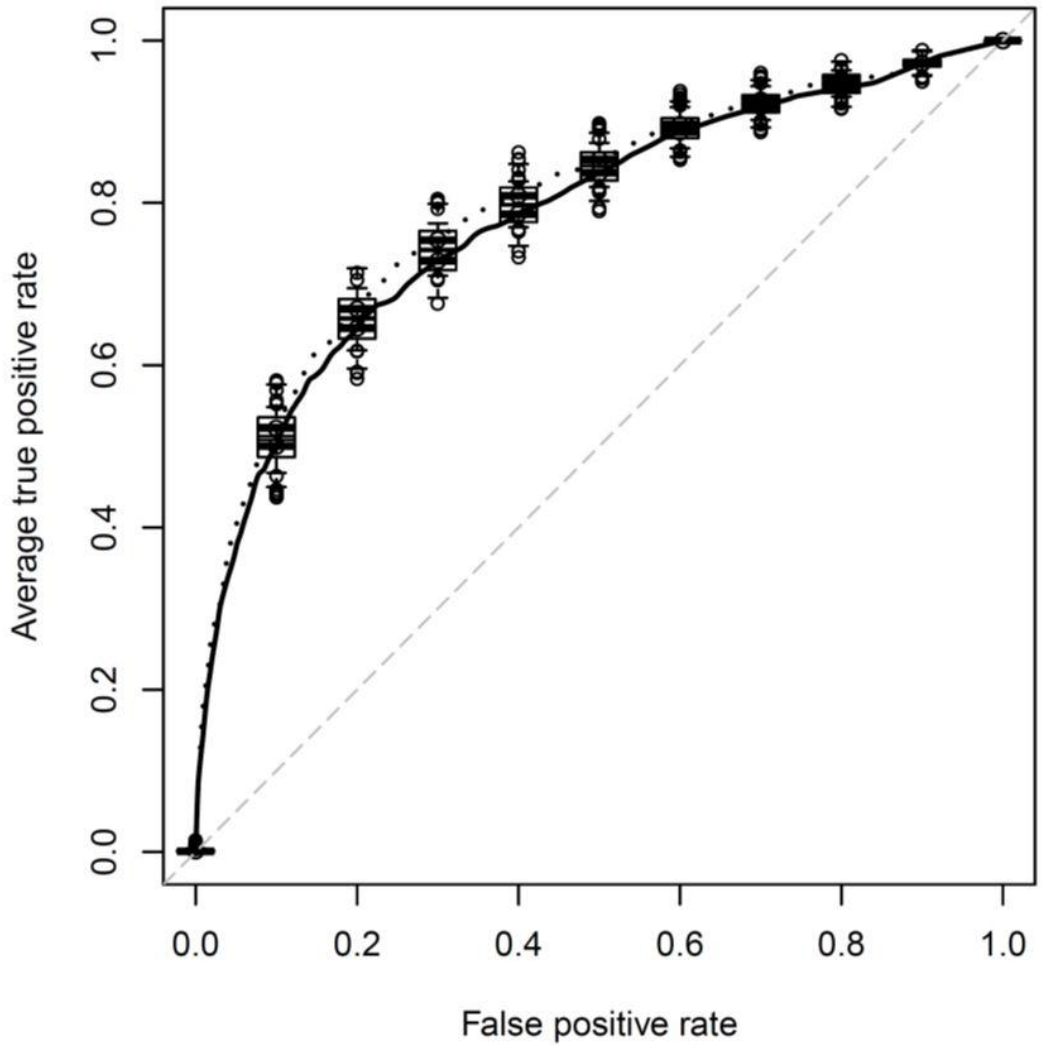


Figure 5 Results of the optimal threshold analysis for preoperative heart rate (left panel), preoperative systolic blood pressure (centre panel) and preoperative hemoglobin (right panel).



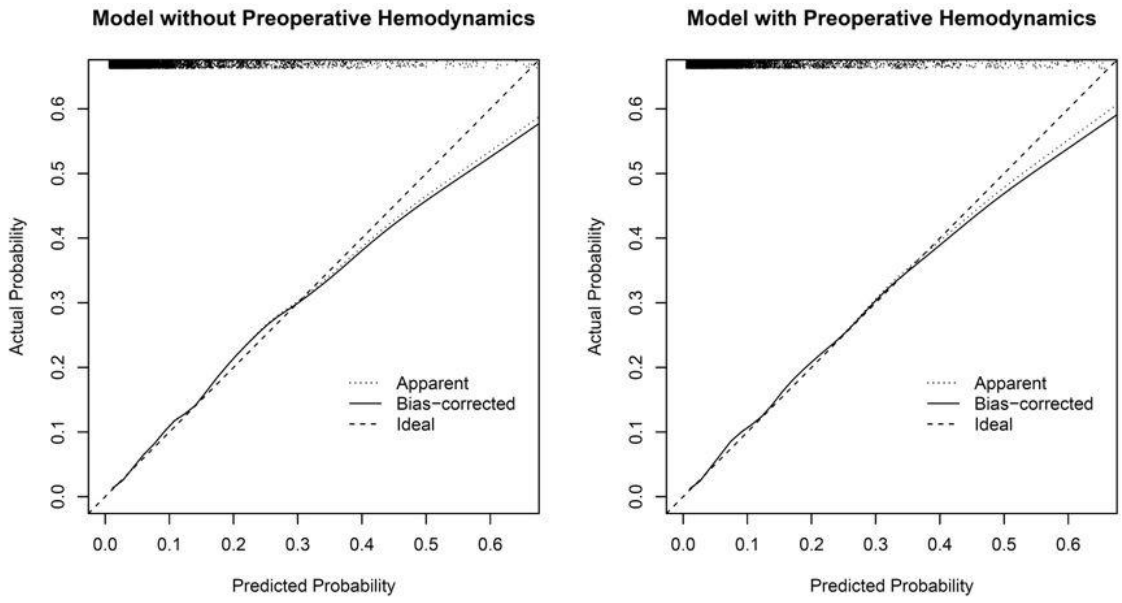
The dotted red line represents the absolute lowest p value for each variable.

Figure 6. The discrimination of Day 1 MINS model using categorical preoperative hemodynamic variables (dotted line) and compared to Day 1 MINS model using baseline variables alone (solid line).



Box plots determined by bootstrapping with 1000 samples

Figure 7. Calibration of Day 1 MINS model without preoperative hemodynamic variables (left panel) and Day 1 MINS model with preoperative hemodynamic variables (right panel).

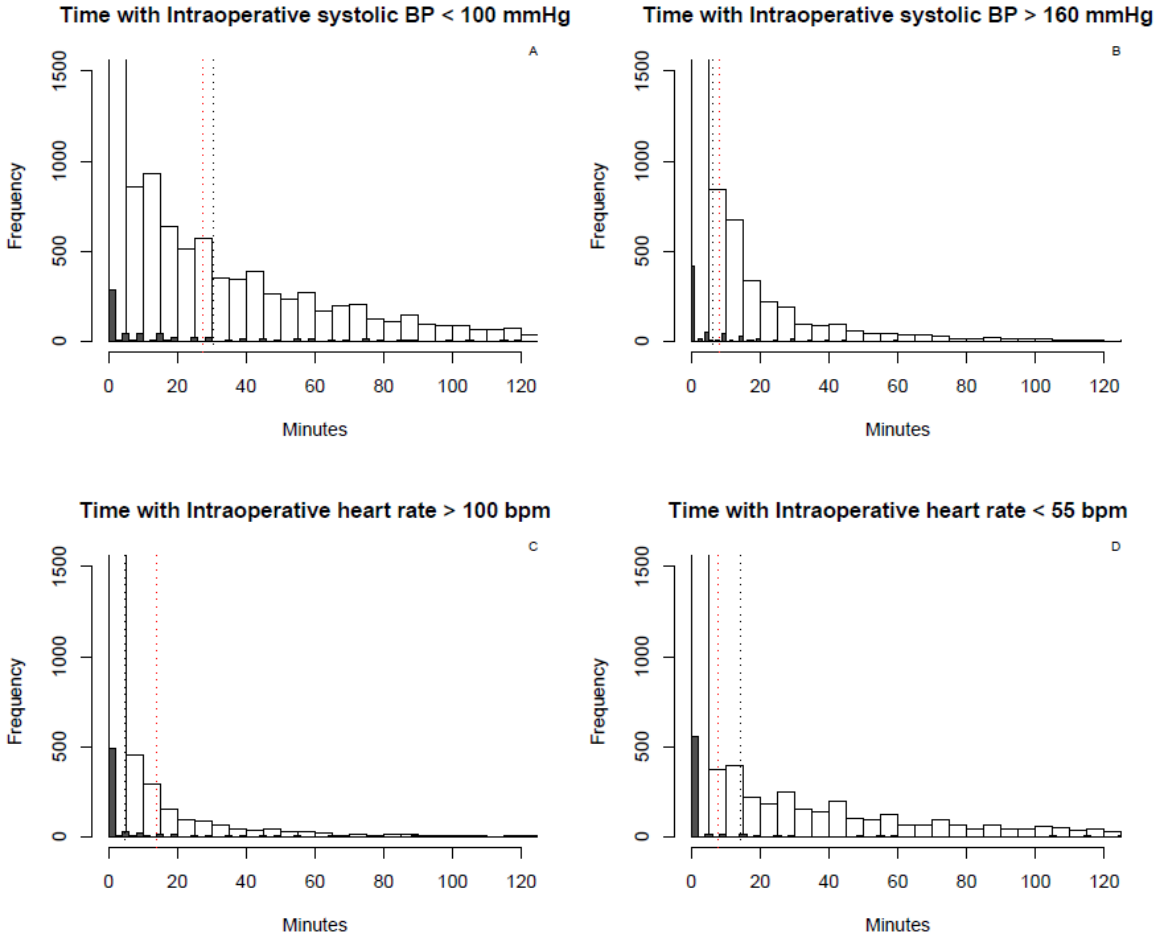


The Apparent line (light line) represents the predicted probability of the outcome as shown by the risk model.

The Bias-correct line (dark line) represents the bias corrected probability of the outcome as determined by bootstrapping with 400 repetitions.

The Ideal line (dotted light line) represents the ideal model as based on the actual probability of the outcome

Figure 8. Distribution of duration spent with intraoperative systolic blood pressure <100 mmHg (A), systolic blood pressure >160 mmHg (B), heart rate >100 bpm (C) and heart rate <55 bpm (D) in patients with (dark bars) and without (light bars) Day 1 MINS.



The black dotted line represents the mean duration in each hemodynamic category for patients without Day 1 MINS and the red dotted line represents the mean for patients with Day 1 MINS.

Figure 9. The adjusted relationship (beta) between Day 1 MINS and the duration spent with intraoperative systolic blood pressure <100 mmHg (A), systolic blood pressure >160 mmHg (B), heart rate >100 bpm (C) and heart rate <55 bpm (D) analysed using a GAM.

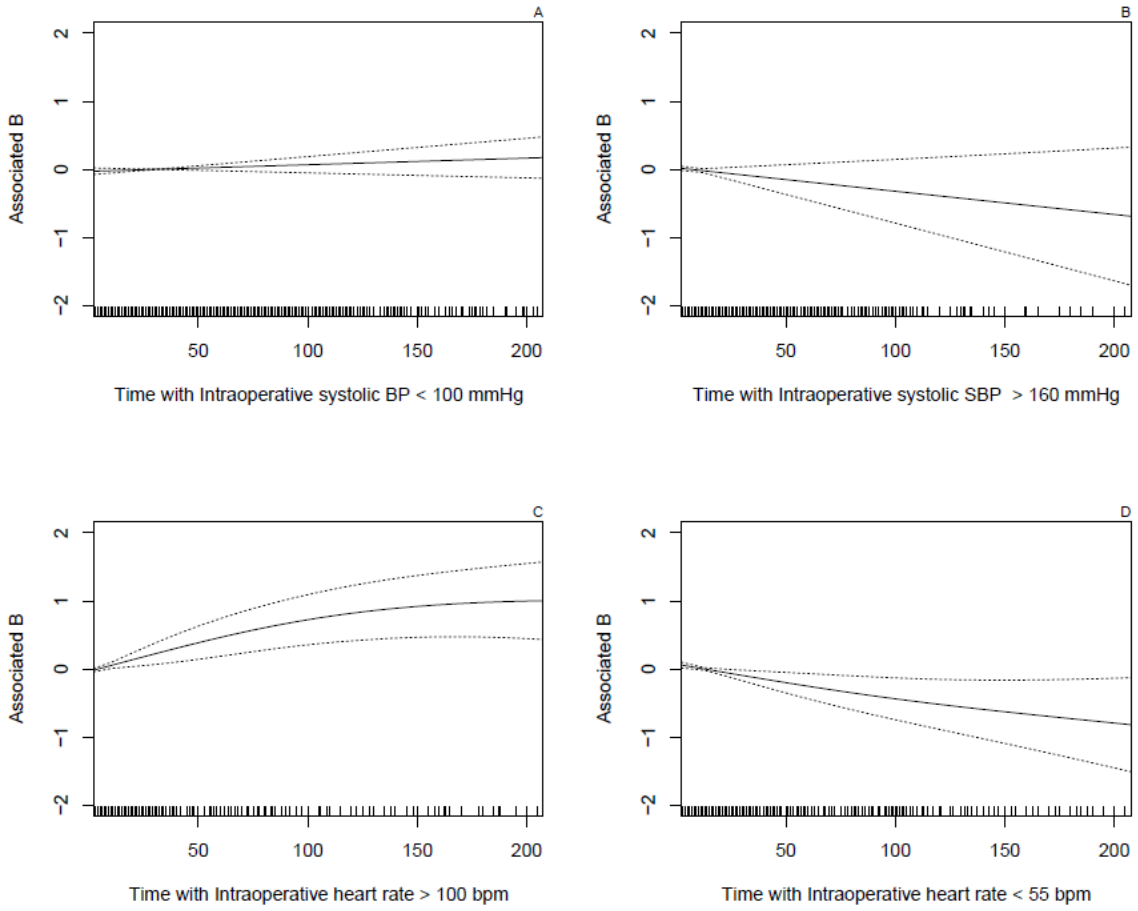
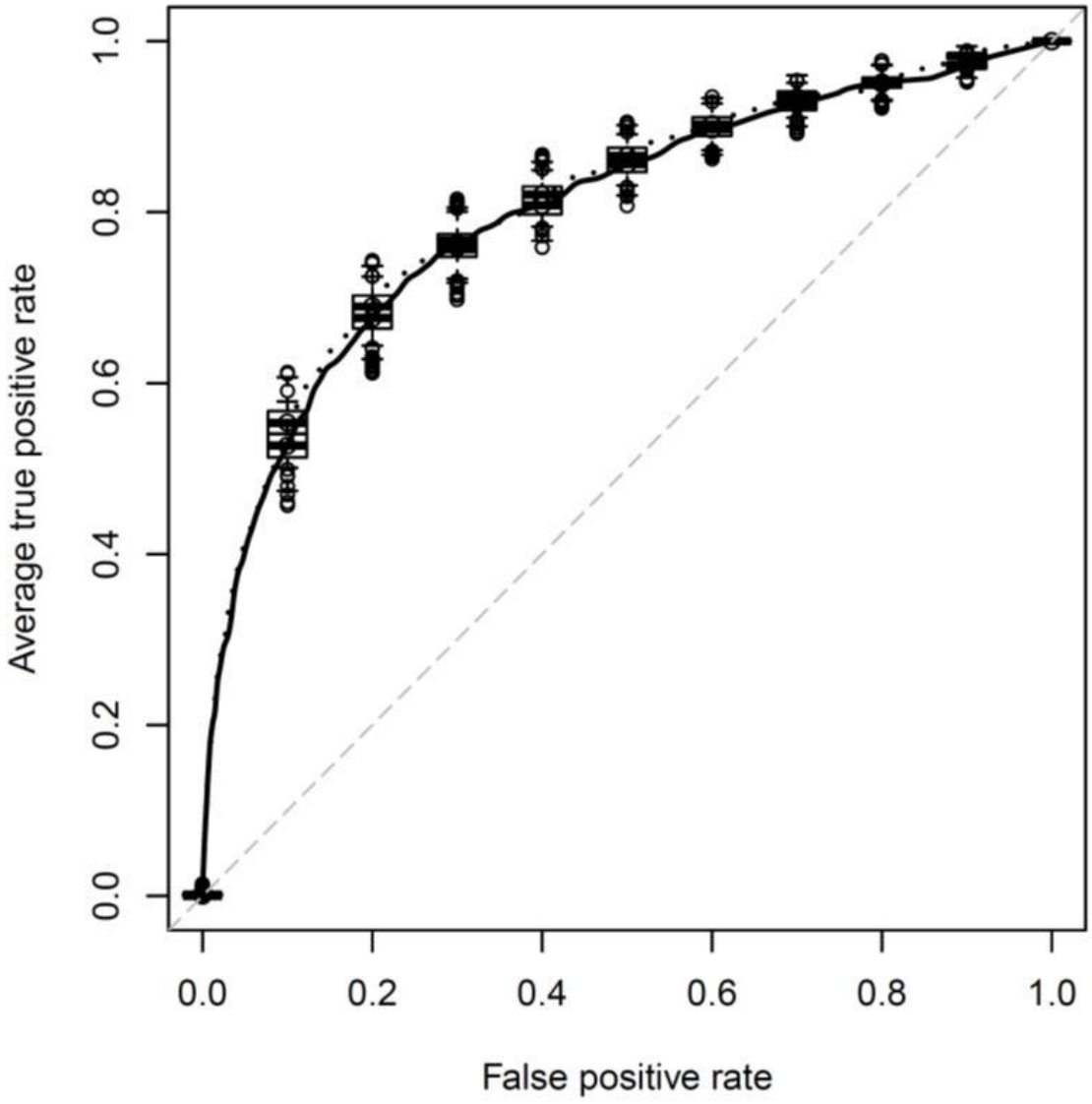


Figure 10. Discrimination of the final Day 1 MINS model (dotted line) compared to the preoperative hemodynamic Day 1 MINS model (solid line).



Box plots determined by bootstrapping with 1000 samples

Figure 11. Calibration of the preoperative hemodynamic model predicting Day 1 MINS (left panel) as compared to the final model predicting Day 1 MINS (right panel).

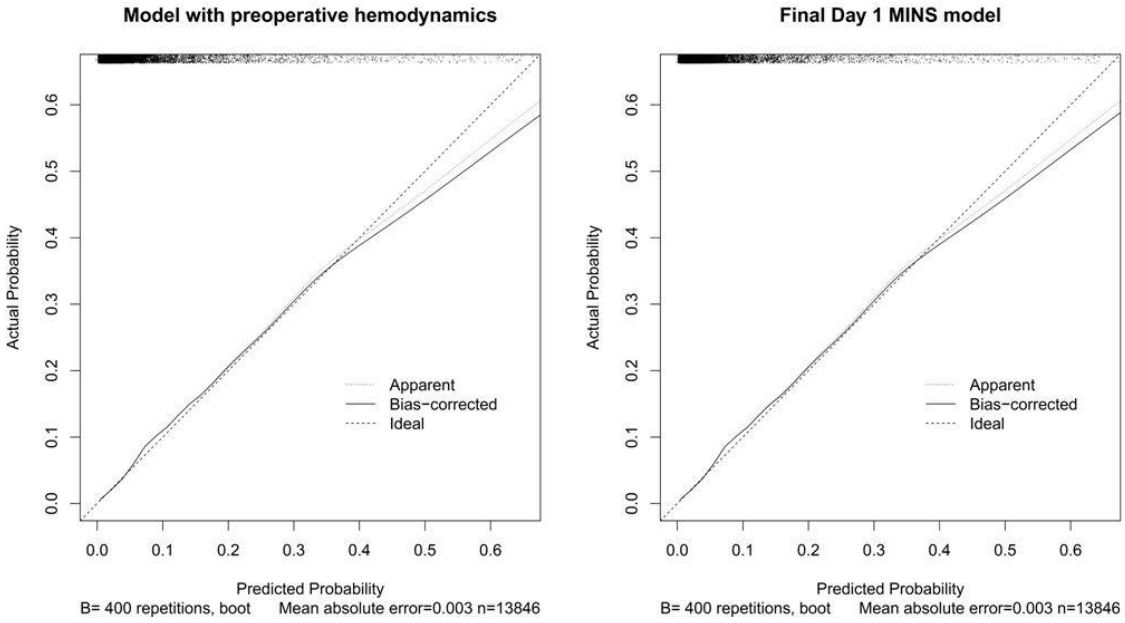
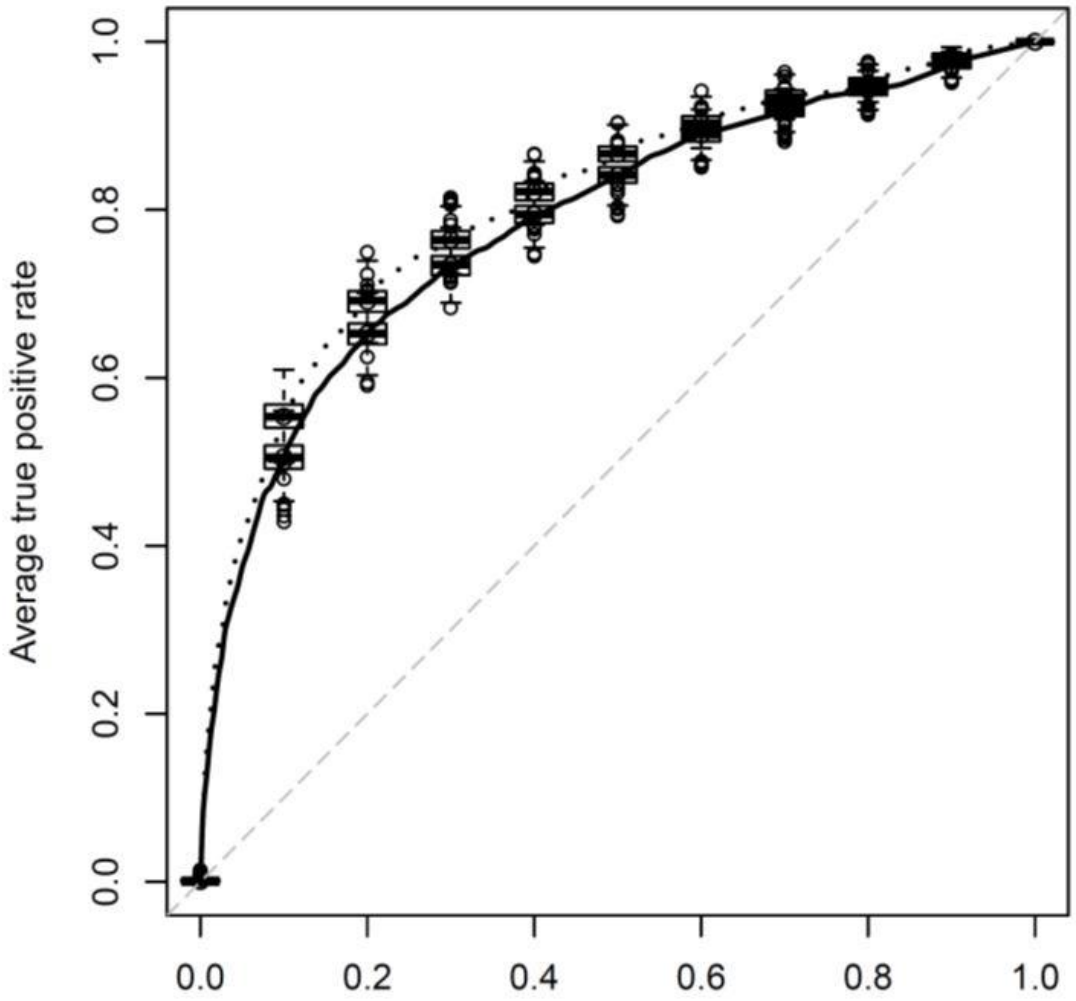


Figure 12. Discrimination of the final Day 1 MINS model (dotted line) compared to baseline Day 1 MINS model (solid line)



Box plots determined by bootstrapping with 1000 samples

Figure 13. Calibration of the baseline model predicting Day 1 MINS (left panel) as compared to the final model predicting Day 1 MINS (right panel).

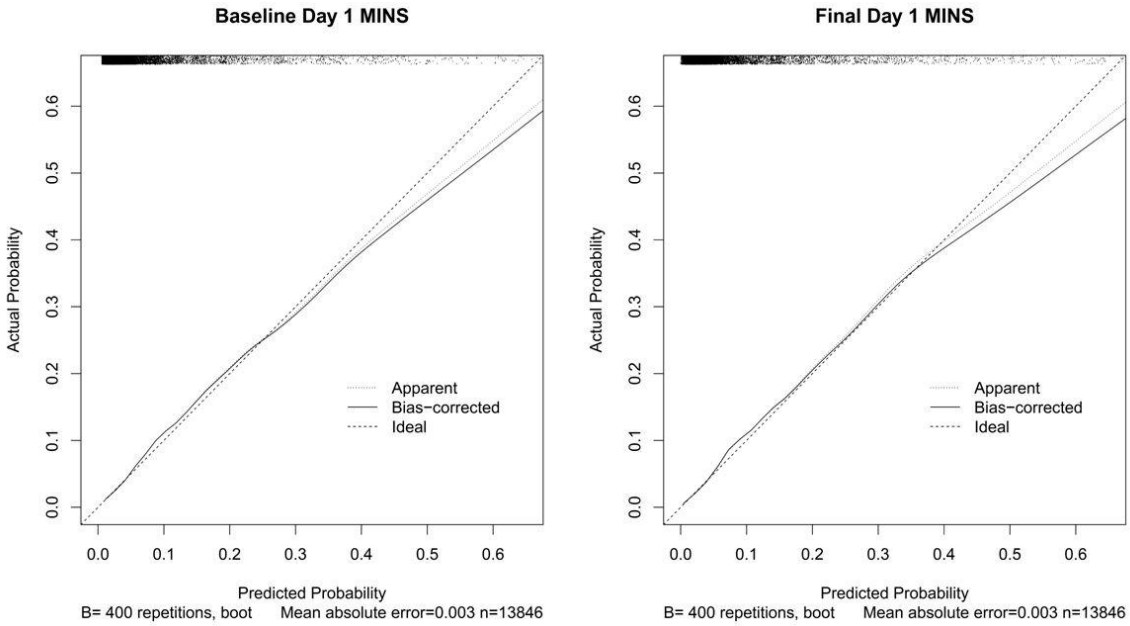


Figure 14. Calibration of final model when predicting Day 1 MINS (left panel) as compared to predicting Day 3 MINS (right panel).

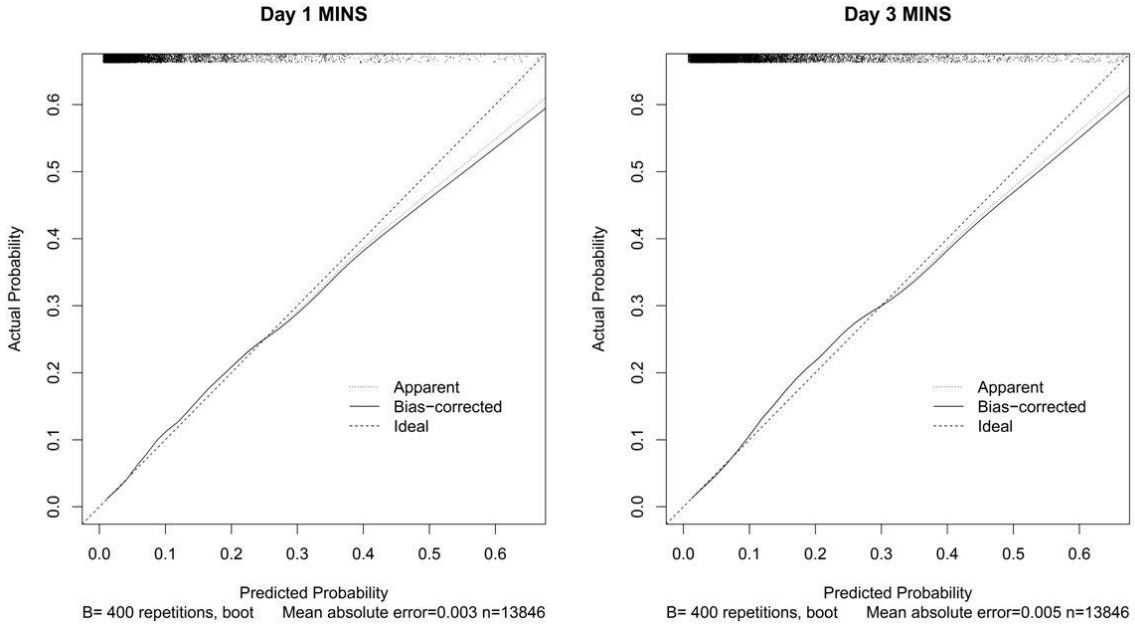


Figure 15. Calibration of final model when predicting Day 1 MINS (left panel) as compared to predicting 30 day mortality (right panel).

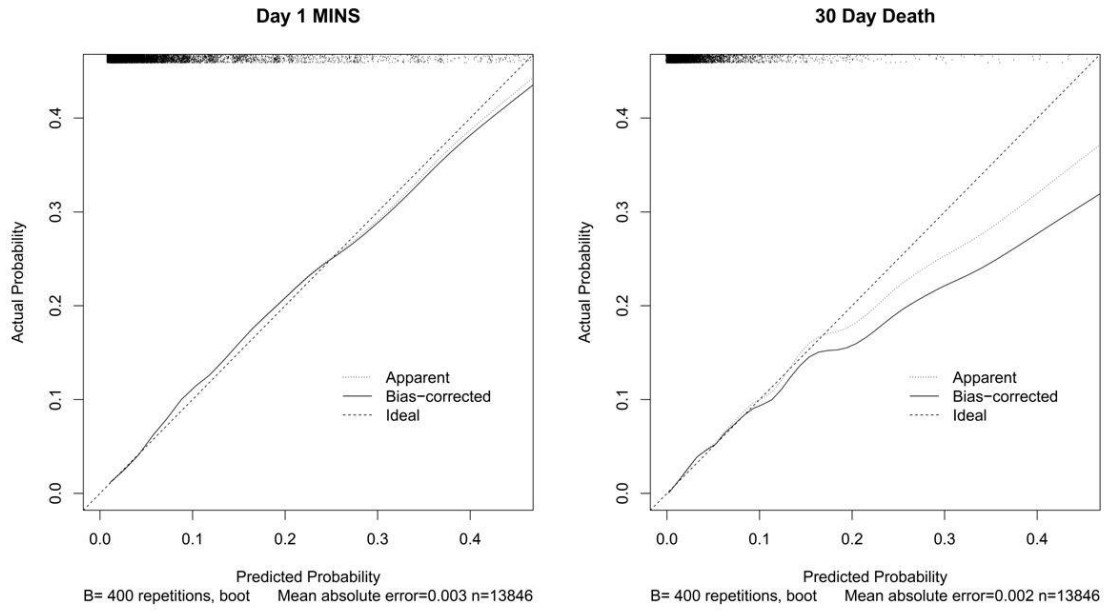
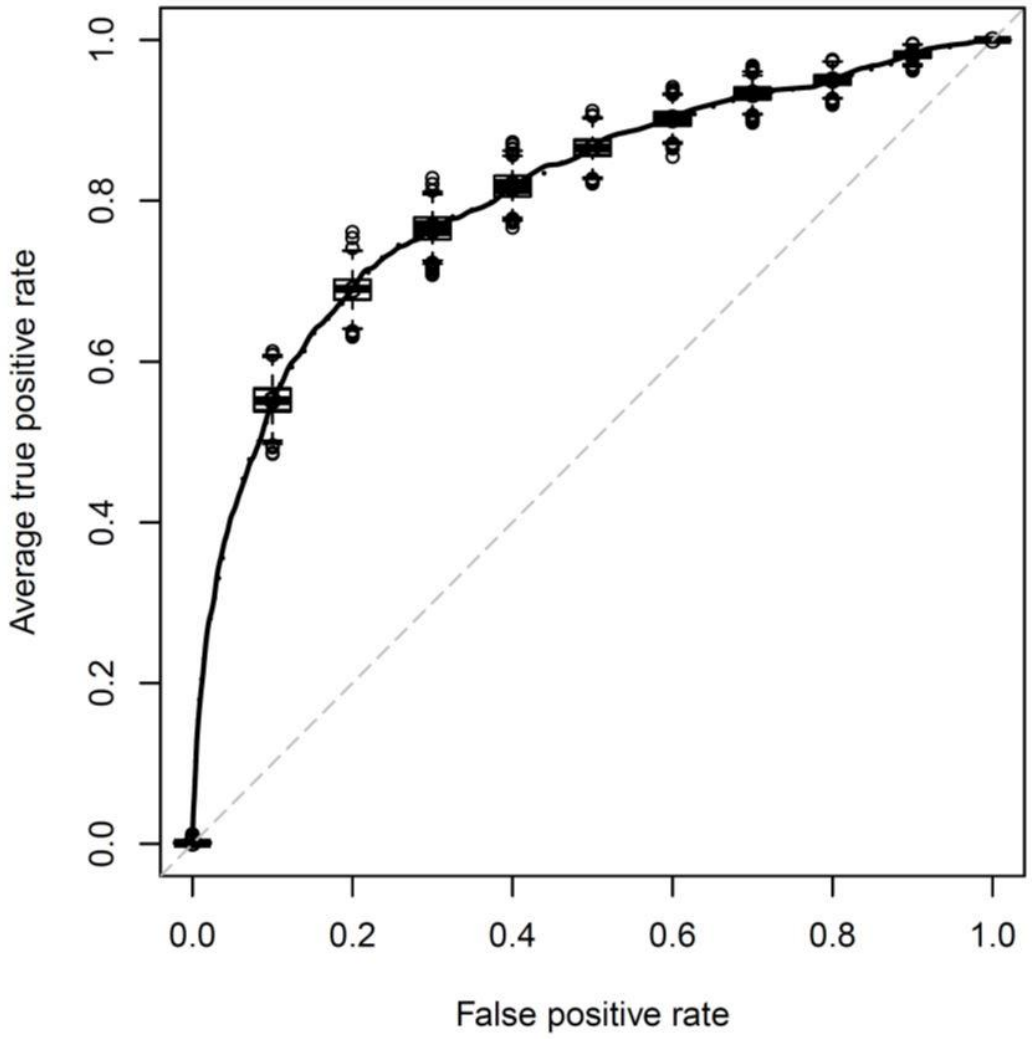
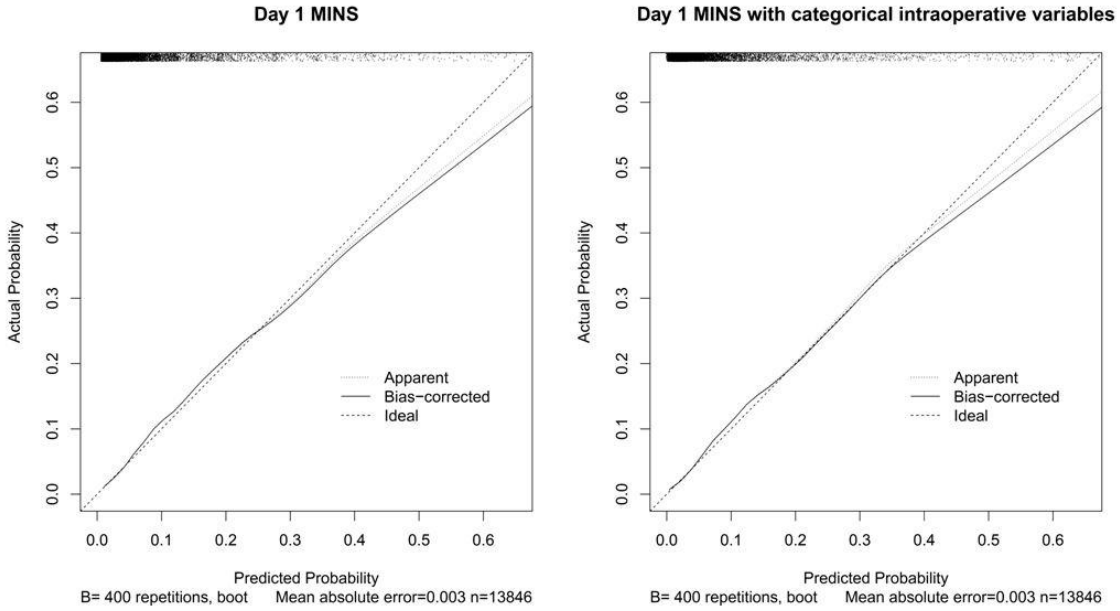


Figure 16. Discrimination of the final Day 1 MINS model compared to the same model using prespecified intraoperative hemodynamic thresholds.



Box plots determined by bootstrapping with 1000 samples

Figure 17. Calibration of final Day 1 MINS predicting 30 day mortality (left panel) compared to Day 1 MINS with prespecified categorical intraoperative hemodynamic variables (right panel) model

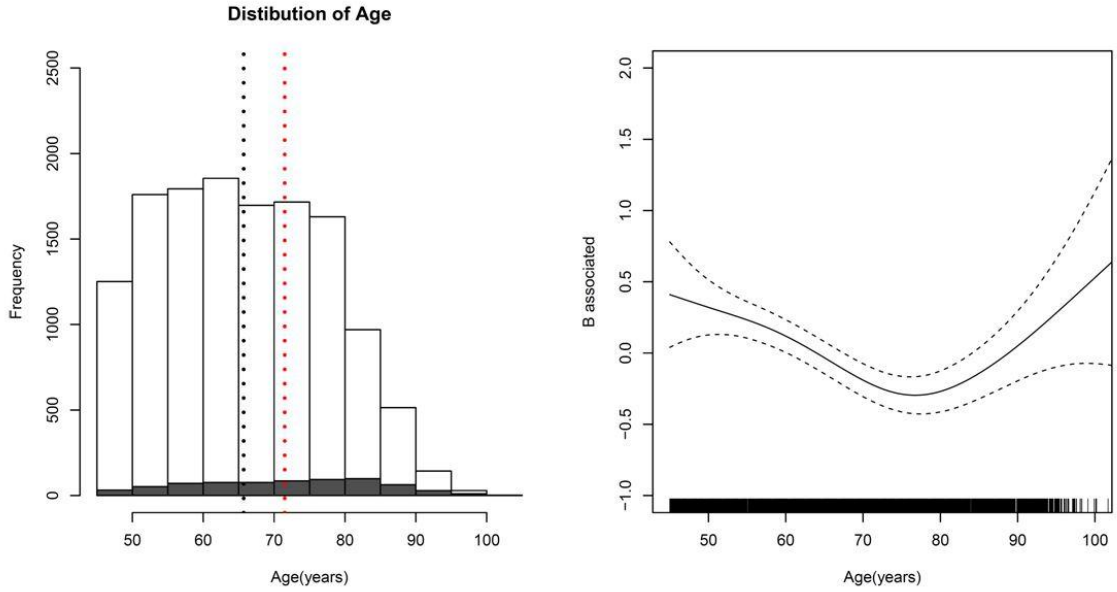


CHAPTER 10 – APPENDICES

Appendix 1. Sub-exploration of age in relation to Day 1 MINS

The exclusion of age from the model predicting Day 1 MINS was unexpected. We conducted a post-hoc exploration of the adjusted association between age and Day 1 MINS using a GAM. The results of this analysis clearly demonstrate a U-shaped relationship between age and Day 1 MINS. This explains why, when dichotomized, age was not predictive. Based on our a priori analysis plan we excluded age from the model, however, age could be added to the model as a fractional polynomial.[47] This may increase both discrimination and calibration. However, the creation of a model containing a continuous term would substantially increase model complexity and possibly increase the risk of overfitting.

Appendix 1. Figure 1. The left hand panel shows the distribution of age in patients with (dark bars) and without (light bars) Day 1 MINS. The right hand panel shows the adjusted relationship (beta) between Day 1 MINS and age analyzed using a GAM. The dark bars at the base of the graph represent the number of patients in each age category



The red dotted line represents the mean age in those with Day 1 MINS and the dark dotted line the mean in those without Day 1 MINS