

## **Supplemental Appendix**

### **Improving identification of patients at low risk for major cardiac events after noncardiac surgery using intraoperative data**

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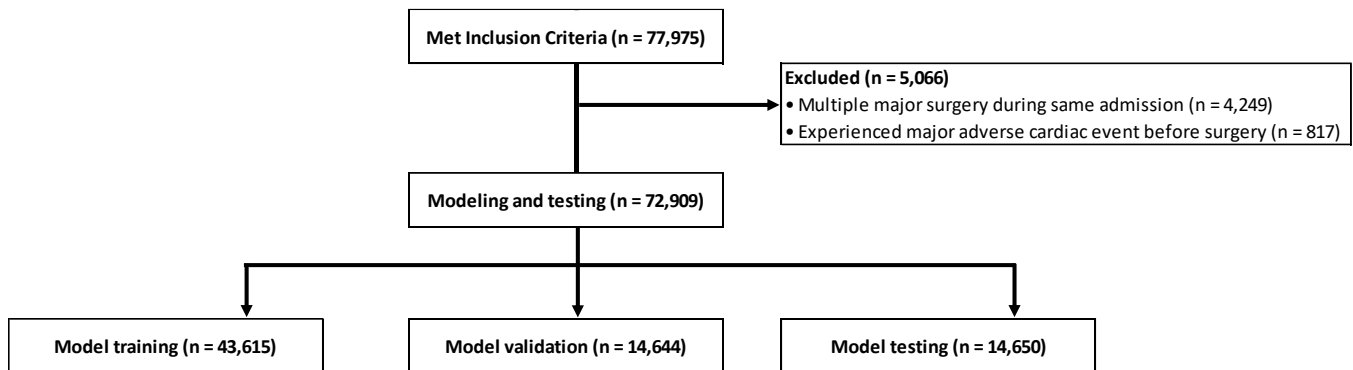
## **Supplemental Methods**

### **Study Sample**

*Inclusion Criteria:* Individuals age 18 or greater; recorded inpatient hospital admission; undergoing a major noncardiac surgery.

Noncardiac surgery was identified using primary Current Procedural Terminology (CPT®) code specification ranges for noncardiac surgeries 10021-32999 and 34001-69990. The Agency for Healthcare Research Quality Healthcare Cost Utilization Project (AHRQ HCUP) Surgery Flag Software was then used to restrict the sample to surgeries classified as major therapeutic procedures.

*Exclusion Criteria:* Patients who underwent multiple major surgeries during the same visit were excluded (N=4,249 or 5.5% of surgical cases) to avoid overlap between preoperative and postoperative time periods. Additionally, we excluded patients who experienced MACE prior to surgery in the same hospitalization (N = 817 or 1.1%).



### **Variables**

A total of 351 baseline, preoperative, and intraoperative variables were constructed. Final models in main and sensitivity analyses were derived using a set of components of these variables. All categorical variables were one-hot encoded to unique binary variables.

Because some variables contain data artifacts and extreme values, we set variables with values below the 1st percentile to the 1<sup>st</sup> percentile value and values greater than the 99th percentile to the 99<sup>th</sup> percentile value. After data cleaning, many variables contained missing values, missingness ranged from 0.1% for intraoperative mean arterial pressure and 99.1% for preoperative B-type natriuretic peptide (NT-proBNP) (Supplemental Table 1). We used multiple imputation to address missingness, but also examined an alternative method for handling missing data in a sensitivity analysis.

#### **Baseline Variables (36)**

Age, sex, marital status, race, insurance, Elixhauser comorbidities (31)<sup>1</sup>

#### **Preoperative Variables (279)**

Last known laboratory measurement value up to 30 days (26; NT-proBNP, creatine kinase, GFR-non African American, glucose POC, glucose level, sodium level, potassium level, chloride level, creatinine level, blood urea nitrogen, bicarbonate venous, whole blood glucose, hemoglobin, hematocrit, white blood cell, red blood cell, platelet count, alanine aminotransferase, bilirubin total, aspartate aminotransferase, alkaline phosphatase, bilirubin direct, bilirubin indirect, international normalization ratio, prothrombin time, partial thromboplastin time)

Laboratory measurement ordered (2; troponin-I point of care, troponin-T)

ASA physical status, Revised Cardiac Risk Index (6), Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project's Clinical Classification Software for Procedures (244)<sup>2</sup>

### *Intraoperative Variables (36)*

Time to surgery (min), surgery duration (min), urine output (ml), total of crystalloid administration (ml), estimated blood loss (ml), arterial line placement, Minutes under mean arterial pressure of 50, Minutes under mean arterial pressure of 60. Intraoperative fluid administration (5; platelets, fresh frozen plasma, packed red blood cells, salvaged red blood cells, whole blood autologous). Total dose medication (5; epinephrine, phenylephrine, norepinephrine, ephedrine, vasopressin). Intraoperative medication administration (3; sodium bicarbonate, atropine, calcium chloride). Lowest recorded vital sign value (4; heart rate, mean arterial pressure, systolic blood pressure, diastolic blood pressure). Highest recorded vital sign value (4; heart rate, mean arterial pressure, systolic blood pressure, diastolic blood pressure). Mean (calculated) vital sign value (4; heart rate, mean arterial pressure, systolic blood pressure, diastolic blood pressure). Delta (Highest – Lowest) vital sign value (3; heart rate, systolic blood pressure, diastolic blood pressure)

### *Dataset Sensitivity Analyses*

Due to the high missingness of variables in the dataset, we ran multiple sensitivity analyses to test multiple approaches to addressing it.

#### *1) Multiple Imputation (Main Analysis)*

We used multiple imputation to address missingness in the main analysis. This approach involved several steps. First, because multiple imputation would not be possible on 351 candidate variables, we used the missing-indicator approach in which we used dichotomous dummy variables that were created for each covariate that indicated whether an observation had a missing value. When the observation had a missing value, this approach sets the missing covariate value to a fixed value (e.g., the study population mean for that covariate). Second, we ran the elastic net selection algorithm on this dataset. Third, we ran a traditional multiple imputation using 5 imputations for missing values for the selected variables (we removed the imputed fixed values and replaced with results of multiple imputation). Lastly, we ran the logistic regression model on each imputed data set and combined estimates using the rule of Rubin.<sup>3</sup>

#### *2) Missing-Indicator Approach*

We used dichotomous dummy variables that were created for each covariate that indicated whether an observation had a missing value. When the observation had a missing value, this approach sets the missing covariate value to a fixed value (e.g., the study population mean for that covariate). This allowed us to preserve information on those who had missing values versus not, which is more flexible and less stringent than the common “missing at random” assumption required in multiple imputation.<sup>4</sup>

#### *3) Complete Case Analysis*

We performed an analysis on individuals with complete data only. This is a simple method to examine if results are robust to missing covariate data by omitting observations that contain missing data from the analysis.

#### *4) Random Forest*

The random forest is an “ensemble learning” technique consisting of the aggregation of a large number of decision trees, resulting in a reduction of variance compared to the single decision trees. It is able to use data with missingness without having to impute values and thus provides an additional approach to evaluating robustness of results to missingness.<sup>5</sup>

### Revised Cardiac Risk Index Scoring Algorithm<sup>1</sup>

The Revised Cardiac Risk Index (RCRI) estimates preoperative risk for cardiac complications after noncardiac surgery on a 6-point scale.<sup>6</sup> RCRI variables were identified using administrative diagnosis codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) for congestive heart failure, ischemic heart disease, and cerebrovascular disease; ICD-9-CM /Current Procedural Terminology (CPT) codes associated with high-risk surgery using Schwarze et al method of identifying high risk surgery<sup>7</sup> and laboratory data identifying 1 or more serum creatinine values greater than 2 mg/dL in the year prior to surgery.

For this study, we implemented the RCRI algorithm in our data in two ways. First, we replicated the original logistic regression model that was used to derive the RCRI and calculated the Area Under Receiver Operating Characteristics (AUC) scores. This was similar to the original “weighted” version of the RCRI score and enabled comparison of predictive performance via AUCs. Second, we calculated the RCRI point scores for our sample based on input variables and used standard cutoffs to define high and low risk (i.e., RCRI score  $\geq 1$  (out of six points) was considered high We also compared the weighted RCRI model to the RCRI score.

<b>Risk factor</b>	<b>Description</b>	<b>Points</b>
High-risk surgery	CPT and ICD-9-CM codes based on Schwarze method <sup>7</sup>	1
History of ischemic heart disease	ICD-9-CM codes of 410.xx, 411.xx, 412.xx, 413.xx, 414.xx, 429.2x, V4581, or 492.2x	1
History of congestive heart failure	ICD-9-CM codes of 428.xx	1
History of cerebrovascular disease	ICD-9-CM codes of 362.34, 430.xx, 431.xx, 432.xx, 433.xx, 434.xx, 435.xx, 436.xx, 437.xx, or 438.xx	1
Pre-operative treatment with insulin	Any medication administration record of insulin given to patient before surgery	1
Pre-operative creatinine >2 mg/dL / 176.8 $\mu$ mol/L	Any creatinine > 2mg/dL measured after start of encounter and before surgery	1

**2017 Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery: Which Patients Should Undergo Cardiac Risk Assessment Before Noncardiac Surgery?**

**Postoperative monitoring with daily troponin measurements for 48-72 hours was recommended for patients that met one of the following<sup>8</sup>:**

Emergency/Urgent/Semiurgent Surgery

- Patients age  $\geq 65$  years, Patients age 18-64 with significant cardiovascular disease\*

Elective Surgery

- Patients age  $\geq 65$  years, Patients with RCRI score  $\geq 1$ , Patients age 45-64 with significant cardiovascular disease\* with one of the following:
  - No preoperative NT-proBNP or BNP measurement OR
  - positive preoperative NT-proBNP ( $\geq 300$  mg/L) OR
  - positive preoperative BNP ( $\geq 92$  mg/L)

**2017 Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery: Figure 1<sup>8</sup>**

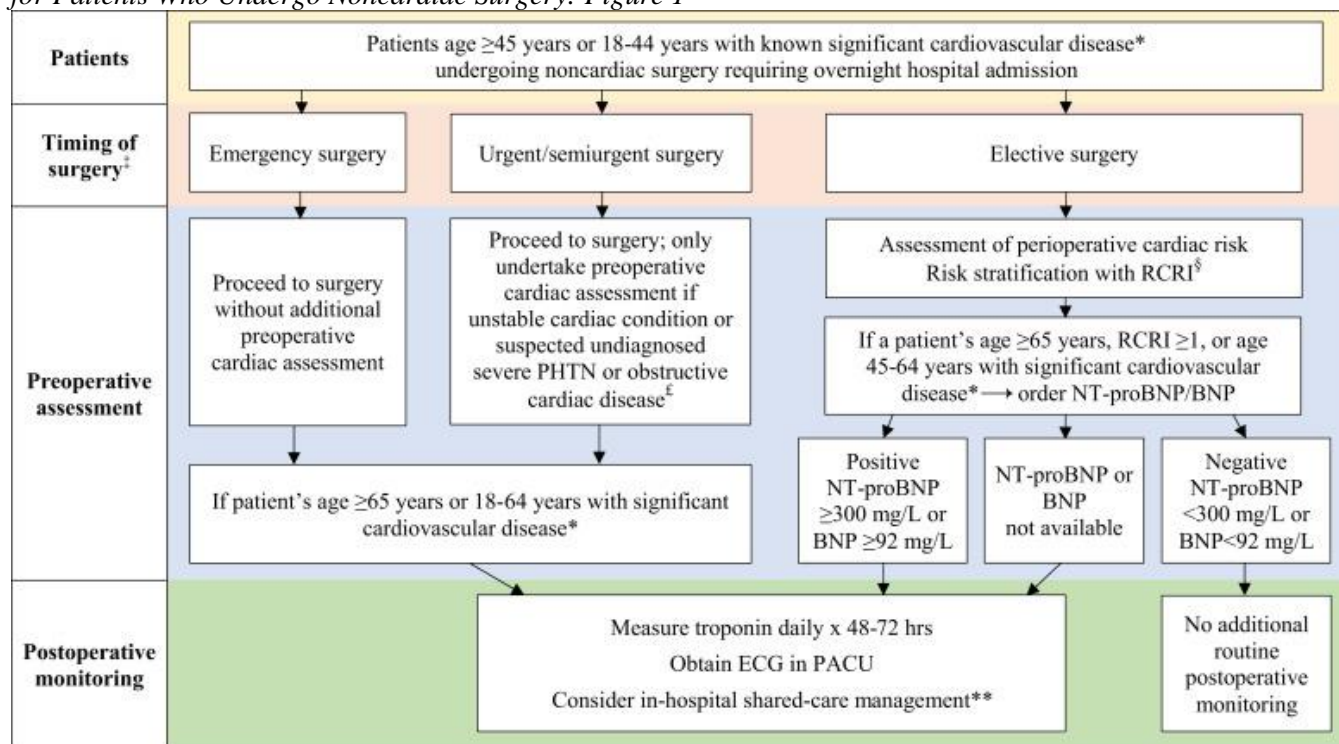


Figure 1. Preoperative risk assessment and postoperative monitoring flow diagram. BNP, brain natriuretic peptide; ECG, electrocardiogram; NT-proBNP, N-terminal pro-brain natriuretic peptide; PACU, postanesthesia care unit; PHTN, pulmonary hypertension; RCRI, Revised Cardiac Risk Index. \* Significant cardiovascular disease includes known history of coronary artery disease, cerebral vascular disease, peripheral artery disease, congestive heart failure, severe PHTN or a severe obstructive intracardiac abnormality (eg, severe aortic stenosis, severe mitral stenosis, or severe hypertrophic obstructive cardiomyopathy). † Timing of surgery refers to emergency surgery (eg, severe trauma, ruptured aortic aneurysm), urgent surgery (eg, hip fracture, bowel obstruction), semiurgent surgery (eg, cancer with potential to metastasize), or elective surgery (eg, knee arthroplasty). £ If physical examination suggests there is an unknown severe obstructive intracardiac abnormality (eg, severe aortic stenosis, severe mitral stenosis, or severe hypertrophic obstructive cardiomyopathy) or severe PHTN, then obtain an echocardiogram before surgery to inform the anesthesiologist, surgeon, and medical team of the type and degree of disease. If the history suggests the patient has an unstable cardiac condition (eg, unstable angina) then discussion with the patient and surgical/medical team is required to decide whether to delay, cancel, or proceed with surgery. § RCRI score (each worth 1 point): history of coronary artery disease, cerebrovascular disease, congestive heart failure, preoperative insulin use, preoperative creatinine  $> 177$   $\mu\text{mol/L}$ , and high-risk surgery (ie, intraperitoneal, intrathoracic, or suprainguinal vascular surgery). \*\* Shared-care management refers to a multidisciplinary approach to inpatient postoperative care; this includes the surgeon and a medical specialist (eg, internist, cardiologist, gerontologist), who will help with perioperative monitoring and management of cardiovascular complications.

### **Supplemental Table 1. Rates of Missing Data in Variables**

The number of observations with missing data for variables were calculated in the study sample (n = 72,909). The table below shows the number of observations with missing data only for the variables that contain missing data.

<b>Source</b>	<b>Variable</b>	<b>Type</b>	<b>Number of Observations with Missing Values</b>	<b>% Observations with Missing Values</b>
Elixhauser Comorbidity	AIDS_HIV	binary	727	1.0
Elixhauser Comorbidity	Alcohol abuse	binary	727	1.0
Elixhauser Comorbidity	Blood loss anemia	binary	727	1.0
Elixhauser Comorbidity	Cardiac_arrhythmias	binary	727	1.0
Elixhauser Comorbidity	Chronic_pulmonary_disorders	binary	727	1.0
Elixhauser Comorbidity	Coagulopathy	binary	727	1.0
Elixhauser Comorbidity	Congestive_heart_failure	binary	727	1.0
Elixhauser Comorbidity	Deficiency_anemia	binary	727	1.0
Elixhauser Comorbidity	Depression	binary	727	1.0
Elixhauser Comorbidity	Diabetes_complicated	binary	727	1.0
Elixhauser Comorbidity	Diabetes_uncomplicated	binary	727	1.0
Elixhauser Comorbidity	Drug_abuse	binary	727	1.0
Elixhauser Comorbidity	Fluid_and_electrolyte_disorders	binary	727	1.0
Elixhauser Comorbidity	Hypertension__complicated	binary	727	1.0
Elixhauser Comorbidity	Hypertension__uncomplicated	binary	727	1.0
Elixhauser Comorbidity	Hypothyroidism	binary	727	1.0
Elixhauser Comorbidity	Liver_disease	binary	727	1.0
Elixhauser Comorbidity	Lymphoma	binary	727	1.0
Elixhauser Comorbidity	Metastatic_cancer	binary	727	1.0
Elixhauser Comorbidity	Obesity	binary	727	1.0
Elixhauser Comorbidity	Other_neurological_disorders	binary	727	1.0
Elixhauser Comorbidity	Paralysis	binary	727	1.0
Elixhauser Comorbidity	Peptic_ulcer_disease	binary	727	1.0
Elixhauser Comorbidity	Peripheral_vascular_disorders	binary	727	1.0
Elixhauser Comorbidity	Psychoses	binary	727	1.0
Elixhauser Comorbidity	Pulmonary_circulation	binary	727	1.0
Elixhauser Comorbidity	Renal_failure	binary	727	1.0
Elixhauser Comorbidity	Rheumatoid_arthritis_collagen_vascular_disease	binary	727	1.0
Elixhauser Comorbidity	Solid_tumor_without_metastasis	binary	727	1.0
Elixhauser Comorbidity	Valvular_disease	binary	727	1.0
Elixhauser Comorbidity	Weight_loss	binary	727	1.0
Revised Cardiac Risk Index	Cardiovascular disease	binary	727	1.0
Revised Cardiac Risk Index	Congestive heart failure	binary	727	1.0
Revised Cardiac Risk Index	Ischemic heart disease	binary	727	1.0
Revised Cardiac Risk Index	Abnormal preoperative serum creatinine	binary	54,352	74.5
Preoperative	NT_proBNP	continuous	72,221	99.1
Preoperative	Creatine_Kinase	continuous	72,041	98.8
Preoperative	GFR_Non_African_American	continuous	36,741	50.4

Preoperative	Glucose_POC	continuous	70,851	97.2
Preoperative	Glucose_Level	continuous	23,912	32.8
Preoperative	Sodium_Level	continuous	26,563	36.4
Preoperative	Potassium_Level	continuous	26,758	36.7
Preoperative	Chloride_Level	continuous	26,834	36.8
Preoperative	Creatinine_Level	continuous	26,619	36.5
Preoperative	Blood_Urea_Nitrogen	continuous	26,657	36.6
Preoperative	Bicarbonate__Venous	continuous	69,233	95.0
Preoperative	Whole_Blood_Glucose	continuous	69,736	95.6
Preoperative	Hemoglobin	continuous	23,402	32.1
Preoperative	Hematocrit	continuous	23,399	32.1
Preoperative	White_Blood_Cell	continuous	23,947	32.8
Preoperative	Red_Blood_Cell	continuous	23,940	32.8
Preoperative	Platelet_Count	continuous	23,618	32.4
Preoperative	Alanine_Aminotransferase	continuous	44,737	61.4
Preoperative	Bilirubin_Total	continuous	44,655	61.2
Preoperative	Aspartate_Aminotransferase	continuous	44,747	61.4
Preoperative	Alkaline_Phosphatase	continuous	44,697	61.3
Preoperative	Bilirubin_Direct	continuous	64,133	88.0
Preoperative	Bilirubin_Indirect	continuous	64,175	88.0
Preoperative	International_Normalization_Ratio	continuous	31,294	42.9
Preoperative	Prothrombin_Time	continuous	31,294	42.9
Preoperative	Partial_Thromboplastin_Time	continuous	31,943	43.8
Intraoperative	Max estimated blood loss	continuous	16,974	23.3
Intraoperative	Max urine output	continuous	30,194	41.4
Intraoperative	Min heart rate	continuous	45	0.1
Intraoperative	Max heart rate	continuous	45	0.1
Intraoperative	Mean heart rate	continuous	45	0.1
Intraoperative	Delta heart rate	continuous	45	0.1
Intraoperative	Min systolic blood pressure	continuous	415	0.6
Intraoperative	Max systolic blood pressure	continuous	415	0.6
Intraoperative	Mean systolic blood pressure	continuous	415	0.6
Intraoperative	Delta systolic blood pressure	continuous	415	0.6
Intraoperative	Min diastolic blood pressure	continuous	422	0.6
Intraoperative	Max diastolic blood pressure	continuous	422	0.6
Intraoperative	Mean diastolic blood pressure	continuous	422	0.6
Intraoperative	Delta diastolic blood pressure	continuous	422	0.6
Intraoperative	Min mean arterial pressure	continuous	43	0.1
Intraoperative	Max mean arterial pressure	continuous	43	0.1
Intraoperative	Mean mean arterial pressure	continuous	43	0.1
Intraoperative	Minute under mean arterial pressure of 50mmHg	continuous	43	0.1
Intraoperative	Minute under mean arterial pressure of 60mmHg	continuous	43	0.1

**Supplemental Table 2. Elastic Net Selection Variables Used in Final Perioperative Model**

Variable Number	Source	Variable Name	Type	Reference Level	Estimate	P-value
1	Intraoperative	Time to surgery (min)	continuous		0.000	0.0021
2	Preoperative	Troponin-I point of care measured	binary	No	0.017	<.0001
3	Preoperative	Troponin-T measured	binary	No	0.027	<.0001
4	Preoperative	Glucose level	continuous		0.000	<.0001
5	Preoperative	Blood urea nitrogen	continuous		0.000	<.0001
6	Preoperative	Red blood cell count	continuous		-0.002	0.0252
7	Preoperative	Bilirubin direct	continuous		0.011	<.0001
8	Preoperative	Partial thromboplastin time	continuous		0.001	<.0001
9	Intraoperative	Fresh frozen plasma administration	binary	No	0.003	0.4257
10	Intraoperative	Sodium Bicarbonate administration	binary	No	0.116	<.0001
11	Intraoperative	Platelets administration	binary	No	0.030	<.0001
12	Intraoperative	Packed red blood cells administration	binary	No	0.006	0.079
13	Intraoperative	CaCl Administration	binary	No	0.008	0.0101
14	Intraoperative	Total dose epinephrine	continuous		0.000	<.0001
15	Intraoperative	Total dose phenylephrine	continuous		0.000	<.0001
16	Intraoperative	Total dose vasopressin	continuous		0.004	<.0001
17	Intraoperative	Total dose norepinephrine	continuous		0.000	<.0001
18	Intraoperative	Mean heart rate	continuous		0.000	<.0001
19	RCRI	Ischemic heart disease	binary	No	0.007	<.0001
20	RCRI	Insulin dependent diabetes	binary	No	0.005	0.0196
21	RCRI	High Risk Surgery	binary	No	0.003	0.0061
22	Preoperative	ASA physical status, Revised Cardiac Risk Index	continuous		0.005	<.0001
23	Intraoperative	Arterial line placement	binary	No	0.004	0.0001
24	Preoperative	AHRQCCS_Tracheostomy	binary	No	0.061	<.0001
25	Preoperative	AHRQCCS_Exploratory laparotomy	binary	No	0.020	<.0001
26	Preoperative	AHRQCCS_Other organ transplantation	binary	No	-0.096	<.0001
	Missing indicator**	Creatine kinase	binary	No	-0.013	0.0017
	Missing indicator**	Bicarbonate Venous	binary	No	-0.002	0.5484
	Missing indicator**	whole blood glucose	binary	No	-0.006	0.1115
	Missing indicator**	min systolic blood pressure	binary	No	0.098	<.0001
	Missing indicator**	min diastolic blood pressure	binary	No	0.005	0.8331

Abbreviation: AHRQ\_CCS, Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project's Clinical Classification Software for Procedures<sup>2</sup>; RCRI, Revised Cardiac Risk Index

\*High risk surgery was defined using a specific list of ICD-9-CM/CPT codes<sup>7</sup>

\*\*Additional variables selected for missing indicator sensitivity analysis



**Supplemental Table 3. Distribution of Outcomes for Perioperative Model Predicted Risk in Test Set (n = 14,650)**

Distribution of outcome by decile cutoffs and percentage cutoffs in perioperative model.

Ascending Risk Decile	Predicted MACE Risk Minimum (%)	Predicted MACE Risk Maximum (%)	Number of Surgeries	MACE, % (n = 92)	STEMI/NSTEMI, % (n = 19)	Cardiac Arrest, % (n = 18)	In-Hospital Death, % (n = 70)
1	0.003%	0.048%	1,465	0 (0)	0 (0)	0 (0)	0 (0)
2	0.048%	0.062%	1,465	0 (0)	0 (0)	0 (0)	0 (0)
3	0.062%	0.081%	1,465	1 (0.1)	0 (0)	1 (0.1)	1 (0.1)
4	0.081%	0.116%	1,465	1 (0.1)	0 (0)	0 (0)	1 (0.1)
5	0.116%	0.180%	1,465	2 (0.1)	1 (0.1)	0 (0)	1 (0.1)
6	0.180%	0.249%	1,465	5 (0.3)	3 (0.2)	1 (0.1)	1 (0.1)
7	0.249%	0.358%	1,465	5 (0.3)	2 (0.1)	1 (0.1)	3 (0.2)
8	0.358%	0.569%	1,465	7 (0.5)	2 (0.1)	1 (0.1)	5 (0.3)
9	0.569%	1.160%	1,465	13 (0.9)	2 (0.1)	7 (0.5)	8 (0.5)
10	1.161%	96.352%	1,465	58 (4)	9 (0.6)	7 (0.5)	50 (3.4)

Abbreviations: MACE, major adverse cardiovascular event; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction

Predicted MACE Risk % Cutoff	Number of Surgeries, % (n = 14,650)	MACE, %	STEMI/NSTEMI, %	Cardiac Arrest, %	In-Hospital Mortality, %
≤ 0.10	5,309 (36.05)	2 (0.04)	0 (0)	1 (0.02)	2 (0.04)
≤ 0.25	8,796 (59.73)	9 (0.1)	4 (0.05)	2 (0.02)	4 (0.05)
≤ 0.50	11,335 (76.97)	19 (0.17)	7 (0.06)	4 (0.04)	11 (0.1)
< 1.00	12,972 (88.08)	32 (0.25)	10 (0.08)	10 (0.08)	18 (0.14)

Abbreviations: MACE, major adverse cardiovascular event; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction

**Supplemental Table 4. Extended Comparison of Perioperative Model Risk in Deciles by Risk-Factor Based Recommendations\***

Ascending Risk Decile	Number of Surgeries (n = 14,650)	CCS Guidelines High Risk					
		CCS Guidelines Low Risk (n = 7,053)		All CCS Guidelines High Risk (n = 7,597)		CCS Guidelines High Risk and No Troponin† (n = 7,089)	
		Number of Surgeries	MACE, % (n = 9)	Number of Surgeries	MACE, % (n = 83)	Number of Surgeries	MACE, % (n = 55)
1	1,465	1,119	0 (0)	346	0 (0)	337	0 (0)
2	1,465	1,022	0 (0)	443	0 (0)	429	0 (0)
3	1,465	1,034	0 (0)	431	1 (0.2)	421	1 (0.2)
4	1,465	993	0 (0)	472	1 (0.2)	452	0 (0)
5	1,465	816	0 (0)	649	2 (0.3)	618	1 (0.2)
6	1,465	696	2 (0.3)	769	3 (0.4)	726	0 (0)
7	1,465	581	3 (0.5)	884	2 (0.2)	835	1 (0.1)
8	1,465	404	0 (0)	1,061	7 (0.7)	984	4 (0.4)
9	1,465	275	1 (0.4)	1,190	12 (1)	1,101	8 (0.7)
10	1,465	113	3 (2.7)	1,352	55 (4.1)	1,186	40 (3.4)

Abbreviations: CCS, Canadian Cardiovascular; MACE, major adverse cardiovascular event

\* Data in the test set are stratified by decile of model-predicted composite MACE risk and then grouped by CCS guidelines high-risk (those for whom the CCS guidelines algorithm would recommend postoperative troponin surveillance testing) and CCS guidelines low risk (those for whom the CCS guidelines algorithm would not recommend surveillance testing). Decile 1 denotes the lowest predicted risk decile; decile 10, the highest. Rates of outcomes are calculated within decile.

† No postoperative troponin was ordered within 72 hours after surgery.

**Supplemental Table 5. Model Results Extended with Sensitivity Analysis**

Method	Perioperative Model		Revised Cardiac Risk Index	
	Sample Size	MACE AUC (95% CI)	Sample Size	MACE AUC (95% CI)
<b>Multiple Imputation</b>				
Training Set	43,615	0.919 (0.905, 0.934)	43,615	0.802 (0.778, 0.825)
Validation Set	14,644	0.914 (0.884, 0.944)	14,644	0.799 (0.752, 0.845)
Test Set	14,650	0.880 (0.846, 0.915)	14,650	0.786 (0.735, 0.836)
<b>Missing Indicator<sup>a</sup></b>				
Training Set	43,615	0.919 (0.905, 0.934)	43,615	0.798 (0.774, 0.822)
Validation Set	14,644	0.913 (0.884, 0.942)	14,644	0.801 (0.757, 0.846)
Test Set	14,650	0.883 (0.849, 0.917)	14,650	0.778 (0.726, 0.829)
<b>Complete Case</b>				
Training Set	13,942	0.906 (0.882, 0.931)	11,053	0.734 (0.704, 0.764)
Validation Set	4,657	0.911 (0.873, 0.949)	3,639	0.756 (0.704, 0.808)
Test Set	4,652	0.861 (0.807, 0.916)	3,633	0.745 (0.685, 0.805)
<b>Random Forest</b>				
Training Set	43,615	1.000 (1.000, 1.000)	43,615	0.827 (0.805, 0.848)
Validation Set	14,644	0.907 (0.873, 0.939)	14,644	0.818 (0.777, 0.860)
Test Set	14,650	0.874 (0.827, 0.912)	14,650	0.808 (0.761, 0.855)

Abbreviations: MACE, major adverse cardiovascular event

Results from multiple sensitivity analyses to address missing data and model selection.

**Supplemental Table 6. Comparison of Model Results by Revised Cardiac Risk Index (Age  $\geq$  50)**

To account for the original study population of the Revised Cardiac Risk Index, we reran our analysis on patients  $>$  49.

Ascending Risk Decile	Number of Surgeries (n = 9,810)	Revised Cardiac Risk Index: Low Risk (n = 6,258)		Revised Cardiac Risk Index: High Risk (n = 3,552)	
		Number of Surgeries	MACE, % (n = 22)	Number of Surgeries	MACE, % (n = 64)
1	981	945	0 (0)	36	0 (0)
2	981	933	0 (0)	48	0 (0)
3	981	822	0 (0)	159	2 (1.3)
4	981	773	1 (0.1)	208	1 (0.5)
5	981	769	2 (0.3)	212	1 (0.5)
6	981	718	4 (0.6)	263	1 (0.4)
7	981	537	2 (0.4)	444	4 (0.9)
8	981	384	4 (1)	597	4 (0.7)
9	981	242	1 (0.4)	739	7 (1)
10	981	135	8 (5.9)	846	44 (5.2)

\* Patients who are age  $>$  49 in the test set are stratified by decile of perioperative model-predicted composite MACE risk and then grouped by Revised Cardiac Risk Index low risk (score = 0) and Revised Cardiac Risk Index high risk (score  $\geq$  1). Decile 1 denotes the lowest predicted risk decile; decile 10, the highest. Rates of outcomes are calculated within decile.

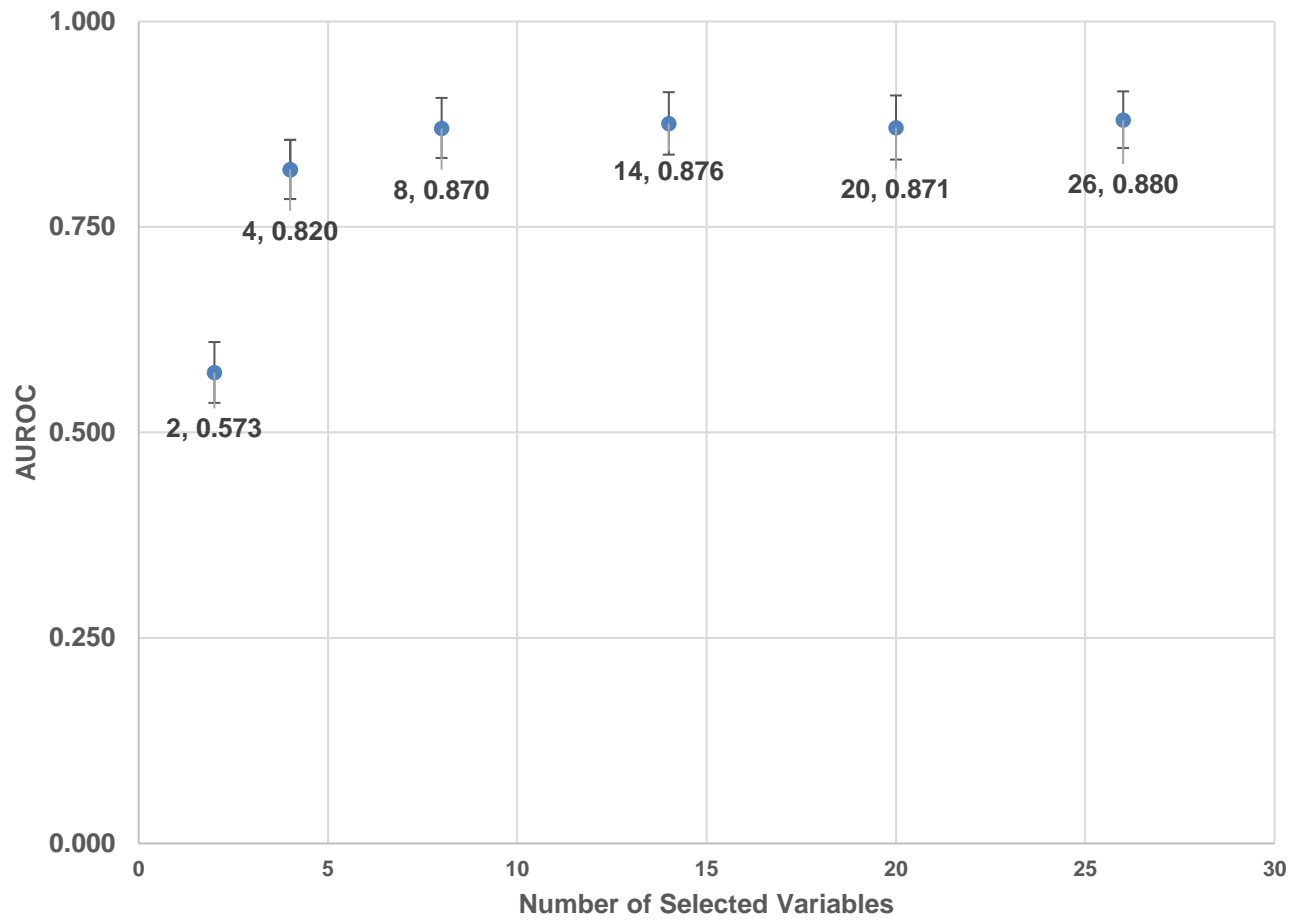
**Supplemental Table 7. Comparison of Model Results by Revised Cardiac Risk Index (Low Risk = 0 or 1)**

In some clinical institutions, the indication of low risk for cardiac risk is determined with a RCRI score of 0 or 1. Below we redo our main analysis using this instead using RCRI score of 0 as low risk.

Ascending Risk Decile	Number of Surgeries (n = 14,650)	Revised Cardiac Risk Index: Low Risk (n = 13,245)		Revised Cardiac Risk Index: High Risk (n = 1,405)	
		Number of Surgeries	MACE, % (n = 47)	Number of Surgeries	MACE, % (n = 45)
1	1,465	1,462	0 (0)	3	0 (0)
2	1,465	1,463	0 (0)	2	0 (0)
3	1,465	1,458	1 (0.1)	7	0 (0)
4	1,465	1,451	1 (0.1)	14	0 (0)
5	1,465	1444	1 (0.1)	21	1 (4.8)
6	1,465	1427	3 (0.2)	38	2 (5.3)
7	1,465	1404	5 (0.4)	61	0 (0)
8	1,465	1288	4 (0.3)	177	3 (1.7)
9	1,465	1091	8 (0.7)	374	5 (1.3)
10	1,465	757	24 (3.2)	708	34 (4.8)

\* Data in the test set are stratified by decile of perioperative model-predicted composite MACE risk and then grouped by **Revised Cardiac Risk Index low risk (score = 0 or 1)** and Revised Cardiac Risk Index high risk (score  $\geq 2$ ). Decile 1 denotes the lowest predicted risk decile; decile 10, the highest. Rates of outcomes are calculated within decile.

**Supplemental Figure 1. Model Performance When Further Selecting Variables for a Potential Risk Tool**  
*Performance of Perioperative Models across Different Number of Selected Variables*



Abbreviations: AUROC, Area under the receiver operating characteristics curve

**Supplemental Table 8. Variables for a Potential MACE Risk Tool**

Number of Variables Selected	AUROC (95% CI)	Variables Selected
26	0.880 (0.846, 0.915)	<p><b>Preoperative:</b> Troponin-I POC measured, Troponin_T measured, Glucose_Level, Sodium_Level, Blood_Urea_Nitrogen, Whole_Blood_Glucose, Red_Blood_Cell, Bilirubin_Direct, Partial_Thromboplastin_Time, History of CongestiveHeartFailure, History of Ischemic Heart Disease, History of Insulin-Dependent Diabetes, ASA Score</p> <p><b>Intraoperative:</b> Time to surgery (min), Use of Frozen Fresh Plasma, Use of Sodium Bicarbonate, Platelets administration, Packed RedBloodCells administration, CalciumChloride administration, Total_Dose_Epinephrine, Total_Dose_Phenylephrine, Total_Dose_Vasopressin, Total_Dose_Norepinephrine, mean HeartRate, mean DiastolicBloodPressure, Minutes of MeanArterialPressure &lt;60mmHg, Arterial Line placement</p> <p><b>Surgery Types (AHRQ CCS Category):</b> High Risk*, Incision and excision of CNS, Tracheostomy, Aortic resection, Exploratory laparotomy, Other organ transplantation</p>
20	0.871 (0.832, 0.910)	<p><b>Preoperative:</b> Troponin_T measured, Glucose_Level, Blood_Urea_Nitrogen, Red_Blood_Cell, Partial_Thromboplastin_Time, History of Insulin-Dependent Diabetes, ASA Score,</p> <p><b>Intraoperative:</b> Time to surgery (min), Use of Sodium Bicarbonate, Platelets administration, CalciumChloride administration, Total_Dose_Epinephrine, Total_Dose_Phenylephrine, Total_Dose_Vasopressin, Total_Dose_Norepinephrine, mean HeartRate, Arterial Line placement</p> <p><b>Surgery Types (AHRQ CCS Category):</b> Tracheostomy, Exploratory laparotomy, Other organ transplantation</p>
14	0.876 (0.838, 0.914)	<p><b>Preoperative:</b> Troponin_T measured, Blood_Urea_Nitrogen, Red_Blood_Cell, Partial_Thromboplastin_Time, History of Insulin-Dependent Diabetes, ASA Score,</p> <p><b>Intraoperative:</b> Time to surgery (min), Use of Sodium Bicarbonate, CalciumChloride administration, Total_Dose_Epinephrine, Total_Dose_Vasopressin, Total_Dose_Norepinephrine, Arterial Line placement</p> <p><b>Surgery Types (AHRQ CCS Category):</b> Tracheostomy</p>
9	0.865 (0.828, 0.903)	<p><b>Preoperative:</b> Troponin_T measured, Partial_Thromboplastin_Time, ASA Score</p> <p><b>Intraoperative:</b> Time to surgery (min), Use of Sodium Bicarbonate, Total_Dose_Epinephrine, Total_Dose_Vasopressin, Total_Dose_Norepinephrine</p> <p><b>Surgery Types (AHRQ CCS Category):</b> Tracheostomy</p>
8	0.870 (0.834, 0.907)	<p><b>Preoperative:</b> Troponin_T measured, ASA Score</p> <p><b>Intraoperative:</b> Time to surgery (min), Use of Sodium Bicarbonate, Total_Dose_Epinephrine, Total_Dose_Vasopressin, Total_Dose_Norepinephrine,</p> <p><b>Surgery Types (AHRQ CCS Category):</b> Tracheostomy</p>
4	0.820 (0.784, 0.856)	<p><b>Preoperative:</b> ASA Score</p> <p><b>Intraoperative:</b> Use of Sodium Bicarbonate, Total_Dose_Vasopressin, Total_Dose_Norepinephrine</p>
2	0.573 (0.536, 0.610)	<p><b>Intraoperative:</b> Use of Sodium Bicarbonate, Total_Dose_Norepinephrine</p>

Abbreviations: AUROC, Area under the receiver operating characteristics curve

\*High risk surgery was defined using a specific lift of ICD-9-CM/CPT codes<sup>7</sup>

**Supplemental Table 9. Factors Associated with MACE in Final Perioperative Model**

Source	Variable Name	Type	Reference	Sample Standard Deviation	Odds Ratio (95% CI)	P-value
Intraoperative	Sodium Bicarbonate administration	binary	No		3.53 (2.03, 6.13)	<.0001
Preoperative	ASA physical status, Revised Cardiac Risk Index	continuous			3.37 (2.76, 4.11)	<.0001
Preoperative	AHRQ CCS Tracheostomy	binary	No		2.99 (1.81, 4.93)	<.0001
Preoperative	Troponin-I point of care measured	binary	No		2.51 (1.60, 3.94)	<.0001
Preoperative	Troponin-T measured	binary	No		2.31 (1.62, 3.29)	<.0001
Intraoperative	Arterial line placement	binary	No		2.13 (1.59, 2.86)	<.0001
Preoperative	Ischemic heart disease	binary	No		1.90 (1.43, 2.52)	<.0001
Preoperative	High Risk Surgery*	binary	No		1.63 (1.25, 2.14)	0.0004
Intraoperative	Platelets administration	binary	No		1.49 (0.75, 2.96)	0.257
Preoperative	Insulin dependent diabetes	binary	No		1.39 (1.02, 1.88)	0.035
Intraoperative	CaCl Administration	binary	No		1.24 (0.77, 2.02)	0.3782
Intraoperative	Packed red blood cells administration	binary	No		1.22 (0.78, 1.92)	0.3844
Preoperative	AHRQ CCS Exploratory laparotomy	binary	No		1.22 (0.72, 2.06)	0.4614
Preoperative	Bilirubin direct	continuous		0.5 mg/dl	1.06 (0.99, 1.14)†	0.1239
Intraoperative	Mean heart rate	continuous		12 bpm	1.38 (1.23, 1.54)†	<.0001
Preoperative	Blood urea nitrogen	continuous		11 mg/dl	1.11 (1.03, 1.19)†	0.0042
Preoperative	Partial thromboplastin time	continuous		7.35	1.10 (1.04, 1.17)†	0.0027
Intraoperative	Total dose vasopressin	continuous		1 Unit	1.01 (0.97, 1.06)†	0.5234
Preoperative	Glucose level	continuous		36 mg/dl	1.13 (1.04, 1.22)†	0.0051
Intraoperative	Time to surgery (min)	continuous		4057 min	1.04 (0.99, 1.08)†	0.0931
Intraoperative	Total dose epinephrine	continuous		80 mcg	1.02 (0.98, 1.06)†	0.3676
Intraoperative	Total dose phenylephrine	continuous		4652 mcg	1.21 (1.12, 1.31)†	<.0001
Intraoperative	Total dose norepinephrine	continuous		135 mcg	1.03 (1.00, 1.07)†	0.0585
Intraoperative	Fresh frozen plasma administration	binary	No		0.74 (0.40, 1.36)	0.3331
Preoperative	Red blood cell count	continuous		0.66x10 <sup>6</sup> /mL	0.81 (0.72, 0.91)†	0.0004
Preoperative	AHRQ CCS Other organ transplantation	binary	No		0.07 (0.02, 0.22)	<.0001

Abbreviation: AHRQ\_CCS, Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project's Clinical Classification Software for Procedures<sup>2</sup>; RCRI, Revised Cardiac Risk Index

\*High risk surgery was defined using a specific list of ICD-9-CM/CPT codes<sup>7</sup>

†Odds ratio represents the change in the odds when the variable is increased by one sample standard deviation



### **Supplemental References**

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