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Preoperative and Intraoperative Predictors of Cardiac Adverse Events after General, Vascular, and Urological Surgery

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Background: **The authors sought to determine the incidence and risk factors for perioperative cardiac adverse events (CAEs) after noncardiac surgery using detailed preoperative and intraoperative hemodynamic data.**

Methods: **The authors conducted a prospective observational study at a single university hospital from 2002 to 2006. All American College of Surgeons–National Surgical Quality Improvement Program patients undergoing general, vascular, and urological surgery were included. The CAE outcome definition included cardiac arrest, non-ST elevation myocardial infarction, Q-wave myocardial infarction, and new clinically significant cardiac dysrhythmia within the first 30 postoperative days.**

Results: **Four years of data demonstrated that of 7,740 noncardiac operations, 83 patients (1.1%) experienced a CAE within 30 days. Nine independent predictors were identified ($P \leq 0.05$): age ≥ 68, body mass index ≥ 30, emergent surgery, previous coronary intervention or cardiac surgery, active congestive heart failure, cerebrovascular disease, hypertension, operative duration ≥ 3.8 h, and the administration of 1 or more units of packed red blood cells intraoperatively. The c-statistic of this model was 0.81 ± 0.02. Univariate analysis demonstrated that high-risk patients experiencing a CAE were more likely to experience an episode of mean arterial pressure < 50 mmHg (6% *vs.* 24%, $P = 0.02$), experience an episode of 40% decrease in mean arterial pressure (26% *vs.* 53%, $P = 0.01$), and an episode of heart rate > 100 (22% *vs.* 34%, $P = 0.05$).**

Conclusions: **In comparison with current risk stratification indices, the inclusion of intraoperative elements improves the ability to predict a perioperative CAE after noncardiac surgery.**

PERIOPERATIVE cardiac events remain a lethal complication after noncardiac surgery.[1,2] Despite decades of research into event prediction and prevention, the incidence of the events has remained largely unchanged at approximately 1% for a general surgery population.[1,3–6] Even classically held preoperative optimization techniques such as preoperative coronary revascularization and β blockade have failed to demonstrate convincing benefits in all but the highest-risk patients.[2,7,8] Furthermore, it has been nearly a decade since the publication of the Lee Revised Cardiac Risk Index (RCRI), the most widely used cardiac event risk stratification system.[6] The medical management of chronic conditions such as diabetes mellitus and renal insufficiency has evolved since the advent of the Lee RCRI.[9–14] In addition, there is no current literature addressing the impact of intraoperative anesthetic hemodynamic management on perioperative cardiac events. Despite the widespread clinical assumption that intraoperative hypotension and tachycardia may cause perioperative cardiac events, there are no clear data establishing what specific level of intraoperative hypotension is associated with cardiac events, and no large dataset evaluating intraoperative tachycardia.

The American College of Surgeons–National Surgical Quality Improvement Program (ACS-NSQIP) initiative uses trained and tested clinical data collectors to extract perioperative information regarding a random sample of general surgery operative cases throughout the United States.[15] It includes a detailed 30-day follow-up with a structured interview and standardized definitions. When combined with a given institution's automated anesthesia intraoperative record, the ACS-NSQIP dataset offers a unique opportunity to assess the relationship between a patient's preoperative comorbidities, intraoperative hemodynamics, and 30-day cardiac adverse events (CAEs).[16] A comprehensive model incorporating these patient characteristics and hemodynamics could improve the care of patients by guiding intraoperative and postoperative management.

Materials and Methods

Institutional review board approval was obtained for this prospective observational study at a single, large, tertiary-care university hospital. Because no care interventions were mandated and no protected health information was collected, signed patient consent was waived.

The ACS-NSQIP methodology has been described in detail elsewhere and is summarized here.[15,17] A systematic sampling process is used to select cases for data collection and analysis. At our institution, general, vascular, and urologic surgery operations requiring general, epidural, or spinal anesthesia are prospectively divided into 8-day cycles. The first 40 operations within each 8-day cycle are included. High-volume, low-risk operations such as inguinal hernia repair or breast lumpectomies are limited to 5 operations in an 8-day cycle to provide a broad operative procedure sampling. Vascular

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operations involving the thoracic aorta were excluded. For each operation, a trained risk assessment nurse prospectively collects preoperative patient demographics, preoperative comorbidities, operative informative and selected intraoperative elements, and postoperative adverse occurrences up to 30 days after the operation. Detailed definitions of ACS-NSQIP preoperative patient demographics and comorbidities are available in the appendix. High-risk procedures were defined as intrathoracic, suprainguinal vascular, or intraperitoneal procedures, excluding hernia repairs.[6]

On the 30th postoperative day, the nurse obtains outcome information through chart review, reports from morbidity and mortality conferences, and communication with each patient by letter or by telephone. CAEs were defined to include any of four events: Q-wave acute myocardial infarction, non-ST elevation myocardial infarction, cardiac arrest requiring cardiopulmonary resuscitation, or new cardiac dysrhythmia. According to ACS-NSQIP definitions, acute myocardial infarction was defined as a new transmural acute myocardial infarction occurring during the operation or within 30 days after operation, as manifested by new Q-waves on an electrocardiogram. Non-Q-wave infarctions with abnormal serum troponin-I were included in the non-ST elevation myocardial infarction group. The 99th-percentile value for normal patients undergoing a troponin-I assay at our institution is 0.06 ng/dl, and the 10% coefficient of variation for the assay is 0.30 ng/dl. According to American Heart Association guidelines, patients exhibiting a peak serum troponin-I above this 10% coefficient of variation (0.30 ng/dl) were defined as experiencing a perioperative myocardial infarction, based on serum biomarkers.[18] Cardiac arrest was defined as the absence of cardiac rhythm or the presence of chaotic cardiac rhythm that results in loss of consciousness, requiring the initiation of any component of basic or advanced cardiac life support. Patients who have automatic implantable cardiac defibrillators that fire, but who have no loss of consciousness, are excluded from this definition. A new cardiac dysrhythmia event required electrocardiogram evidence of atrial flutter, atrial fibrillation, or new second- or third-degree atrioventricular conduction block.

A surgical clinical nurse reviewer is assigned at each medical center to collect the ACS-NSQIP data. The nurses complete in-depth training on all study definitions and data collection methods. Periodically, interrater reliability site visits are conducted, in which a national nurse clinical specialist visits the site, reviews the case selection, reabstracts a sample of charts, and compares the results with the locally obtained variable values.

Intraoperative hemodynamic monitoring data were acquired *via* an automated, validated electronic interface from the physiologic monitors (Solar 9500®; General Electric Healthcare, Waukesha, WI). The interface records one invasive arterial catheter blood pressure measurement each minute, and all noninvasive blood pressure measurements. Each intraoperative anesthesia record was analyzed as a series of 10-min periods. For each 10-min period, the median systolic blood pressure (SBP), median mean arterial pressure (MAP), and median heart rate (HR) were calculated. Clinically aberrant values defined as a SBP $>$ 280 mmHg, SBP $<$ 50 mmHg, MAP $>$ 200 mmHg, MAP $<$ 40 mmHg, or HR $<$ 30 beats/min were excluded from the median calculation. The use of a median value and exclusion of aberrant values has been demonstrated to decrease the impact of monitoring artifacts and clinically transient physiologic derangement.[19,20] These median values were compared to absolute and relative hypotension thresholds, SBP $<$ 80 mmHg, SBP $<$ 70 mmHg, MAP $<$ 60 mmHg, MAP $<$ 50 mmHg, 30% decrease in SBP from preoperative baseline, 40% decrease in SBP, 30% decrease in MAP, 40% decrease in MAP, and absolute tachycardia thresholds of HR $>$ 80 beats/min, HR $>$ 90 beats/min, or HR $>$ 100 beats/min. If a patient exceeded a given threshold, he or she was noted to have experienced that specific level of hypotension or tachycardia. Finally, case length in hours and the number of units of packed red blood cells (PRBC) administered intraoperatively were recorded for each operation.

Statistical Analysis

Statistical analysis was performed using SPSS® Version 15 software (SPSS Inc., Chicago, IL). Collinearity diagnostics were evaluated for all preoperative predictors.[21] To improve clinical usability, continuous variables were transformed into dichotomous variables by identifying the maximal sum of sensitivity and specificity. The preoperative variables (table 1) were entered into a logistic regression full model fit. A preoperative predicted probability for CAE based on this model was calculated for each patient and then used for patient risk stratification.[22,23] This predicted probability is based on the ß coefficient of each variable entered in the full model fit. A given patient's predicted probability represents the probability (ranging from 0 to 1) of a CAE outcome based on the preoperative characteristics. This predicted probability was then used for patient risk stratification by separating patients into four risk quartiles.[22,23]

All variables deemed to be significant in the full model fit ($P \leq 0.05$) were established as independent predictors. Each variable was also assessed for effect size using the adjusted odds ratio calculated by the logistic regression full model fit.[24] The resulting model's predictive value was evaluated using a receiver-operating characteristic curve area under the curve, also known as a c-statistic for dichotomous outcomes.[25] In addition, an unweighted risk scale assigning one point to each risk factor was created, using the independent risk factors. This unweighted risk scale was compared to the full model fit logistic regression predictive value using the c-statistic.[25]

Intraoperative hemodynamic management and interventions were assessed by two different methods. First, the preoperative and intraoperative variables were combined

Table 1. Preoperative Patient and Operative Characteristics

Risk Factor	Cardiovascular Adverse Event Yes (n = 83)	Cardiovascular Adverse Event No (n = 7,657)	*P* Value
Age ≥ 68	41 (49%)	1787 (23%)	< 0.001
Body mass index ≥ 30 kg/m^2	41 (51%)	2825 (37%)	0.01
Male sex	51 (61%)	3910 (51%)	0.06
Orally controlled diabetes mellitus	8 (9.6%)	546 (7.1%)	0.38
Insulin controlled diabetes mellitus	9 (11%)	441 (5.8%)	0.05
History of chronic obstructive pulmonary disease	5 (6.0%)	319 (4.2%)	0.40
Ascites	2 (2.4%)	63 (0.8%)	0.15
Active congestive heart failure	7 (8.4%)	84 (1.1%)	< 0.001
Acute renal failure	1 (1.2%)	55 (0.7%)	0.46
Preoperative dialysis dependence	5 (6.0%)	129 (1.7%)	0.01
Cerebrovascular disease	15 (18%)	368 (4.8%)	< 0.001
History of myocardial infarction within past 6 months	2 (2.4%)	39 (0.5%)	0.07
Previous cardiac intervention*	25 (30%)	720 (9.4%)	< 0.001
History of angina within 1 month before surgery	2 (2.4%)	47 (0.6%)	0.10
Hypertension requiring medications	57 (69%)	3093 (40%)	< 0.001
History of peripheral vascular occlusive disease	10 (12%)	323 (4.2%)	< 0.001
Emergency surgery	18 (22%)	879 (12%)	0.00
High-risk surgery	30 (36%)	1646 (22%)	0.00

Please see the appendix for detailed definitions of each clinical data element.

* Defined as either a percutaneous coronary artery intervention (stent, balloon angioplasty) or cardiac surgery other than implantation of defibrillator or pacemaker.

into one comprehensive logistic regression full model fit. This comprehensive model's c-statistic was compared to the preoperative model c-statistic to assess for incremental predictive value. Second, patients were stratified into four CAE risk quartiles to create groups of patients with similar preoperative risk (Quartile 1 = low risk, 2 = medium risk, 3 = medium-high risk, 4 = high risk).[26] The predicted probability describing the preoperative likelihood of experiencing a CAE was used to create the risk quartiles. This predicted probability was based on the preoperative predictor logistic regression, full model fit β coefficients. After collinearity diagnostics and correlation adjustment, intraoperative variables were entered into logistic regression full model fit performed within each quartile.

Results

A total of 8,290 ACS-NSQIP patients operated on between 2003 and 2007 were reviewed. A total of 550 patients were excluded: 264 because of the absence of intraoperative hemodynamic data, 252 because the 30-day follow up period had not elapsed, 25 because the operative procedure involved the thoracic aorta, and 9 because the patient's age was less than 18 yr. Three primary surgical services were represented in the resulting 7,740-patient data set: general surgery (n = 4,937), vascular surgery (n = 1,846), and urological surgery (n = 957). Eighty-three CAEs were observed among the 7,740 patients (1.1%), with cardiac arrest and cardiac dysrhythmia representing the most common event (table 2).

In general, patients experiencing a CAE demonstrated higher rates of most systemic comorbidities (table 1). Collinearity diagnostics did not reveal a condition index over 30, so a bivariate correlation matrix was not necessary, and all 18 preoperative variables listed in table 1 were entered into the full model fit. Age was converted into a categorical variable through the use of a receiver-operating-characteristic curve, and demonstrated the optimal balance of sensitivity and specificity at a cutoff of age ≥ 68 (data not shown). Body mass index (BMI) demonstrated an optimal balance at a cutoff of BMI ≥ 30 kg/m^2 (data not shown).

The logistic regression full model fit was performed on 7,672 patients, and revealed 7 independent preoperative predictors ($P < 0.05$): age ≥ 68, BMI ≥ 30, emergent surgery, previous coronary intervention or cardiac surgery, active congestive heart failure, cerebrovascular disease, and hypertension requiring medication (table 3). This model was evaluated using the omnibus tests of model coefficients, which demonstrated a chi-square value of 88 with 18 degrees of freedom, and a *P* value of < 0.001. The adjusted odds ratio for each risk factor and 95% confidence interval were reviewed and found to be significant. The c-statistic for this preoperative model was 0.77 ± 0.03 (fig. 1). The receiver operating characteristic curve for the unweighted model assigning one point for each risk factor dem-

Table 2. Cardiovascular Adverse Events

Event Type	Number of Patients
Cardiac arrest	36
Non-ST elevation myocardial infarction	13
Q-wave myocardial infarction	8
New cardiac dysrhythmia*	37

There are a total of 83 patients experiencing cardiovascular events. Some patients experienced more than one event.

* Atrial flutter, atrial fibrillation, or new second- or third-degree atrioventricular conduction block.

Table 3. Independent Predictors of a Perioperative Cardiovascular Adverse Event after General, Vascular, and Urologic Surgery

	Preoperative Variables Only			Preoperative and Intraoperative Variables		
Predictor	*P* Value	β Coefficient	Standard Error	*P* Value	β Coefficient	Standard Error
Age ≥ 68	0.001	0.867	0.250	0.002	0.806	0.259
Active congestive heart failure	0.024	1.128	0.498	0.003	1.409	0.469
Body mass index ≥ 30 kg/m^2	0.002	0.735	0.236	0.007	0.643	0.237
Emergency surgery	0.036	0.639	0.305	0.010	0.797	0.309
Previous cardiac intervention	0.019	0.656	0.281	0.014	0.686	0.278
Cerebrovascular disease	0.026	0.723	0.324	0.026	0.735	0.330
Hypertension	0.019	0.635	0.271	0.050	0.535	0.274
Operative duration	N/A	N/A	N/A	< 0.001	0.196	0.053
Number of packed red blood cells units	N/A	N/A	N/A	0.004	0.081	0.028

Independent predictors of cardiovascular adverse events among patients were derived using a logistic regression full model fit, including preoperative and intraoperative variables. Two different models were derived, one using preoperative variables only, and a comprehensive model evaluating preoperative and intraoperative variables.

N/A = not applicable.

onstrated a c-statistic of 0.76 ± 0.03, very similar to the 0.77 ± 0.03 for the full model fit. Patients were assigned to a Class I, II, III, or IV preoperative risk class if they possessed exactly 0, exactly 1, exactly 2, or 3 or more risk factors, respectively. The incidence of CAE increased as the risk class increased, as did the hazard ratio for experiencing a CAE (table 4).

The intraoperative variables listed in table 5 and the independent preoperative predictor variables were combined into a single comprehensive logistic regression full model fit to evaluate intraoperative variables. This model included 7,668 patients with complete data. The model confirmed the predictive validity of the previously mentioned seven preoperative risk factors. In addition, this model also demonstrated significance ($P < 0.05$) for 2 intraoperative variables: the number of units of PRBCs administered (0.2 among patients without CAEs and 2.0 among patients with CAEs, $P = 0.014$), and the operative duration (2.9 h among patients without CAEs and 4.2 h among patients with CAEs, $P < 0.001$) (table 3). The model was evaluated using the omnibus tests of model coefficients, which demonstrated a chi-square value of 122 with 21 degrees of freedom and a *P* value of < 0.001. This model had a c-statistic of 0.81 ± 0.02. When compared to the c-statistic of 0.77 ± 0.03 for the preoperative variables only, the inclusion of the intraoperative variables did improve the predictive value of the model. The adjusted odds ratio for each predictor was statistically significant (fig. 2). Receiver operating characteristic curve analysis demonstrated an optimal sum of sensitivity and specificity at a threshold of 1 unit of PRBCs and an operative duration of 3.8 h (data not shown).

A second intraoperative predictor analysis was performed after patients were divided into four CAE preoperative risk quartiles (table 5). These quartiles were based on

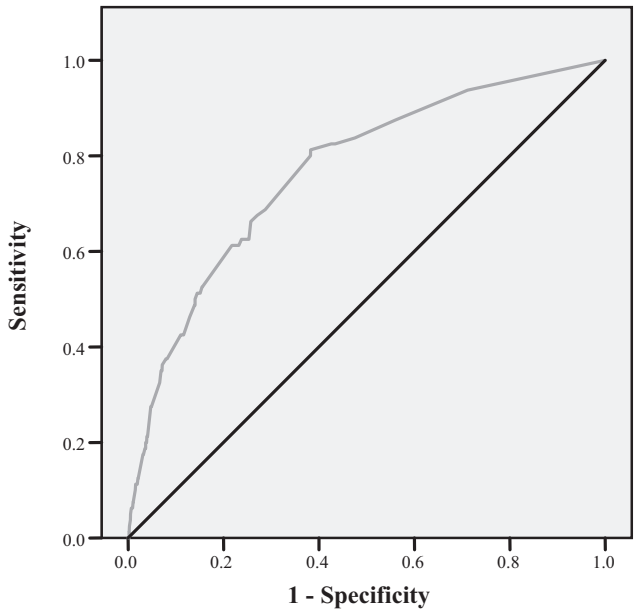

Fig. 1. Perioperative cardiovascular adverse event preoperative predictor receiver operating characteristic curve. A receiver operating characteristic curve evaluating the sensitivity and specificity of preoperative independent risk factors for perioperative cardiovascular adverse events is demonstrated. Seven independent preoperative predictors were identified ($P < 0.05$): age ≥ 68, body mass index ≥ 30 kg/m^2, emergent surgery, previous coronary intervention or cardiac surgery, active congestive heart failure, cerebrovascular disease, and hypertension. The weighted receiver operative characteristic curve is based on the predicted probability calculated for each patient using the logistic regression full model fit. The curve assists practitioners in evaluating the value of a test. The c-statistic for the weighted preoperative predictor curve was 0.77 ± 0.03.

Table 4. Frequency and Hazard Ratio of a Cardiovascular Adverse Event Based on Number of Preoperative Risk Factors

Preoperative Risk Class	Cardiovascular Adverse Event	Hazard Ratio (95% CI)
Class I (0 risk factors) (n = 2,222)	5 (0.2%)	
Class II (1 risk factor) (n = 2,531)	13 (0.5%)	2.3 (0.8–6.4)
Class III (2 risk factors) (n = 1,885)	25 (1.3%)	6.0 (2.3–15.6)
Class IV (3+ risk factors) (n = 1,102)	40 (3.6%)	16.7 (6.6–42.4)

Seven independent preoperative predictors were identified ($P < 0.05$): age ≥ 68, body mass index ≥ 30 kg/m^2, emergent surgery, previous coronary intervention or cardiac surgery, active congestive heart failure, cerebrovascular disease, and hypertension.

CI = confidence interval.

Table 5. Univariate Analysis of Intraoperative Patient Characteristics

	Quartile 1* (Low Preoperative Risk) (n = 2,195)			Quartile 2* (Medium Preoperative Risk) (n = 1,803)			Quartile 3* (Medium-high Preoperative Risk) (n = 1,702)			Quartile 4* (High Preoperative Risk) (n = 1,972)		
	No CAE	CAE	*P* Value*	No CAE	CAE	*P* Value*	No CAE	CAE	*P* Value*	No CAE	CAE	*P* Value*
	(n = 2,190)	(n = 5)		(n = 1,795)	(n = 8)		(n = 1,685)	(n = 17)		(n = 1,922)	(n = 50)	
General anesthesia	1941 (89%)	5 (100%)	1.00	1619 (90%)	7 (88%)	0.56	1541 (92%)	17 (100%)	0.39	1653 (86%)	42 (84%)	0.69
Case length in h (mean)	2.7	3.7	0.23	2.9†	3.9†	0.14†	2.8†	4.9†	< 0.001†	3.1	4.0	0.02
PRBC units (mean)	0.1†	7.8†	0.35†	0.12	0.00	0.71	0.2	1.4	0.12	0.4†	1.9†	0.08†
Episode of SBP < 80‡	477 (22%)	1 (20%)	1.00	359 (20%)	1 (13%)	1.00	389 (23%)	5 (29%)	0.56	383 (20%)	8 (16%)	0.49
Episode of SBP < 70	73 (3.3%)	0 (0%)	1.00	81 (4.5%)	1 (13%)	0.31	88 (5.2%)	3 (18%)	0.06	91 (4.7%)	3 (6.0%)	0.73
Episode of MAP < 60	777 (36%)	0 (0%)	0.17	609 (34%)	1 (13%)	0.28	658 (39%)	8 (47%)	0.50	777 (40%)	24 (48%)	0.28
Episode of MAP < 50	88 (4.0%)	0 (0%)	1.00	89 (5.0%)	0 (0%)	1.00	99 (5.9%)	4 (24%)	0.02	154 (8.0%)	5 (10%)	0.60
Episode of 30% ↓ in SBP	979 (45%)	3 (60%)	0.66	999 (56%)	5 (63%)	1.00	963 (57%)	11 (65%)	0.53	1151 (60%)	25 (50%)	0.16
Episode of 40% ↓ in SBP	369 (17%)	2 (40%)	0.20	515 (29%)	2 (25%)	1.00	500 (30%)	8 (47%)	0.12	638 (33%)	14 (28%)	0.44
Episode of 30% ↓ in MAP	1008 (46%)	1 (20%)	0.38	998 (56%)	3 (38%)	0.48	929 (55%)	12 (71%)	0.23	1113 (58%)	29 (58%)	0.99
Episode of 40% ↓ in MAP	377 (17%)	1 (20%)	1.00	456 (25%)	2 (25%)	1.00	439 (26%)	9 (53%)	0.01	548 (29%)	15 (30%)	0.82
Episode of HR > 80	1586 (72%)	5 (100%)	0.33	1400 (78%)	7 (88%)	1.00	1301 (77%)	14 (82%)	0.78	1206 (63%)	32 (64%)	0.86
Episode of HR > 90	1116 (51%)	4 (80%)	0.38	1009 (56%)	4 (50%)	0.74	927 (55%)	11 (65%)	0.42	756 (39%)	24 (48%)	0.22
Episode of HR > 100	667 (31%)	2 (40%)	0.64	579 (32%)	3 (38%)	0.72	545 (32%)	9 (53%)	0.07	425 (22%)	17 (34%)	0.05

* Patients were risk-stratified based on preoperative predicted probability quartiles. Univariate analysis using chi-square, Fisher's exact, or Student *t* test was performed within each quartile. The univariate analysis *P* value is shown for each variable. † Elements identified as independent predictors in a logistic regression full model fit. ‡ Each intraoperative anesthesia record was analyzed as a series of 10-min periods. For each 10-min period, the median SBP, median MAP, and median HR were calculated. These median values were compared to absolute and relative hypotension thresholds, SBP < 80 mmHg, SBP < 70 mmHg, MAP < 60 mmHg, MAP < 50 mmHg, 30% SBP decrease from preoperative baseline, 40% SBP decrease, 30% MAP decrease, 40% MAP decrease, and absolute tachycardia thresholds of HR > 80 beats/min, HR > 90 beats/min, or HR > 100 beats/min. If a patient exceeded a given threshold, he or she was noted to have experienced that specific level of hypotension or tachycardia.

CAE = cardiovascular adverse event; HR = heart rate; MAP = mean arterial pressure; PRBC = packed red blood cells; SBP = systolic blood pressure.

the preoperative full model fit predicted probability of a CAE. The univariate analysis within each quartile comparing intraoperative variables among patients with and without a CAE demonstrated several statistically significant differences (table 5). Among Quartile 3 (medium-high risk) patients, patients experiencing a CAE were more likely to experience an episode of MAP < 50 mmHg (6% *vs.* 24%, $P = 0.02$), experience an episode of 40% decrease in MAP (26% *vs.* 53%, $P = 0.01$), and a longer operative duration (2.8 h *vs.* 4.9 h, $P < 0.001$). Among Quartile 4 (high risk) patients, patients experiencing a CAE were more likely to experience an episode of HR > 100 (22% *vs.*. 34%, $P = 0.05$) and a longer operative duration (3.1 h *vs.* 4.0 h, $P = 0.02$). Next, a logistic regression full model fit was performed within each quartile to identify independent predictors. For Quartile 1 (low risk) patients, the number of units of PRBCs administered was a significant independent predictor of a CAE (0.1 units *vs.* 7.8 units, $P = 0.02$). For Quartile 2 (medium risk) patients, operative duration was a significant independent predictor (2.9 h *vs.* 3.9 h, $P = 0.04$). Among Quartile 3 (medium-high risk) patients, operative duration was also a significant independent predictor (2.8 h *vs.* 4.9 h, $P < 0.001$). Finally, for Quartile 4 (high risk) patients, the number of units of PRBCs administered was a significant independent predictor of a CAE (0.4 units *vs.* 1.9 units, $P = 0.008$).

Discussion

Our data are consistent with recent studies demonstrating that the incidence of perioperative CAEs is approximately 1 to 2% in a noncardiac surgery population.[1,6] This consistency is observed despite variations in patient population, CAE definitions, and surveillance techniques. Lee's RCRI excluded patients younger than

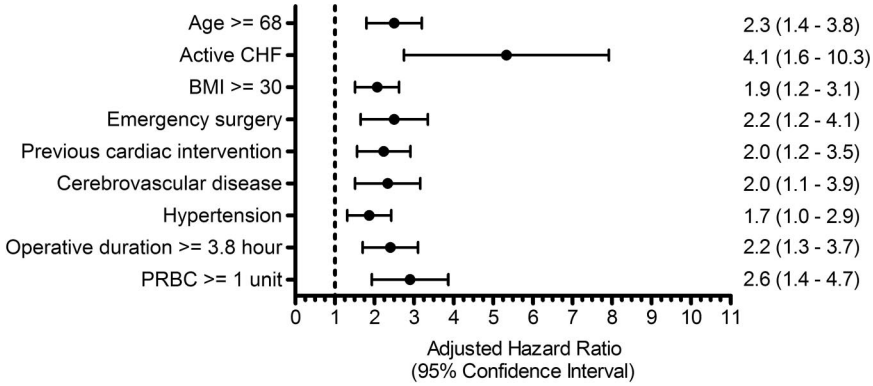

Fig. 2. Perioperative cardiovascular adverse event risk factors and adjusted hazard ratios. Seven preoperative and two intraoperative independent predictors of perioperative cardiovascular adverse events were identified using a logistic regression full model fit. An adjusted hazard ratio (± 95% confidence interval) for each risk factor reflects the full model fit adjusted odds ratio. BMI = body mass index; CHF = congestive heart failure; PRBC = packed red blood cells.

50 yr and emergency surgeries.[6] As a result, our analysis, which includes these patient populations, may be a more accurate reflection of routine clinical experience. In addition, our CAE definition did not include isolated pulmonary edema as an outcome measure. This arguably subjective diagnosis of a primary cardiac event accounted for 42 of the 92 events observed in Lee's study protocol.[6] Finally, unlike the majority of Lee's patient population, our study protocol did not include surveillance biomarker and electrocardiogram monitoring.

We are able to confirm several preoperative predictors of a perioperative CAE previously reported by Lee and Goldman.[5,6] Advanced age, congestive heart failure, and emergency surgery were first identified by Goldman *et al.* in their review of 1,001 patients undergoing noncardiac surgery.[5] We are also able to confirm Lee's finding that cerebrovascular disease, a history of ischemic heart disease, and congestive heart failure predict a perioperative CAE.[6] Unique to this study, we found that hypertension requiring medication and obesity (BMI $\geq$ 30 kg/m^2) were significant independent predictors for CAE that are not found in Lee or Goldman's risk indices.

We are unable to confirm three RCRI predictors: insulin-dependent diabetes mellitus, serum creatinine $>$ 2.0, and high-risk surgery. The medical management of both insulin-dependent diabetes mellitus and chronic renal insufficiency has made marked advances since 1994, when the enrollment period for Lee *et al.*'s study closed.[6] Aggressive outpatient and inpatient regimens demand tight glycemic control *via* oral hypoglycemics and insulin.[10,11] The absence of insulin-dependent diabetes mellitus in our predictive model may reveal the value of the 10 yr of improved glycemic management standards. Neither Goldman nor Lee evaluated obesity as a predictor, so it is possible that we have identified an underlying comorbidity associated with insulin-dependent diabetes mellitus. Entirely new medication classes modulating the angiotensin system have become the standard of care in managing renal insufficiency, congestive heart failure, and essential hypertension.[9,13] Previous data demonstrate that the use of angiotensin-converting enzyme inhibitors improves cardiac outcomes in the nonoperative setting.[12,14] Unfortunately, this dataset does not offer objective elements that may help us assess the quality of the comorbidity management, such as hemoglobin A1c or serum creatinine trends, or severity of disease.

We are also unable to confirm high-risk surgery as a predictor, despite multiple previous studies suggesting its role.[1,5,6,27] This may be because of variations in definitions of high-risk surgery. For example, although an umbilical hernia repair would be considered intraperitoneal, and thus high-risk by Lee's methodology, we did not code all hernia repairs as high-risk. In addition, our patient population did not include "low-risk" procedures such as orthopedics, which accounted for 35% of Lee's study group. Finally, Lee's exclusion of emergency surgeries may have resulted in a greater predictive role for high-risk procedures. Despite these variations from previous studies, our preoperative model did have an excellent predictive capability, demonstrating a c-statistic of 0.77, as compared with 0.76 for Lee's RCRI.

The model also compares well to other prominent perioperative risk indices offered by Detsky and Boersma.[27,28] In one study, Boersma *et al.* modified the Lee RCRI and evaluated its ability to predict perioperative death using a large administrative database.[27] By adding patient age, emergency status, a modified high-risk surgery definition, and laparoscopic technique into the Lee model, they were able to demonstrate a c-statistic of 0.85 for predicting 30-day cardiovascular death. We are able to confirm the importance of age and emergency surgery and suggest that clinical risk stratification must incorporate these elements. However, our data did not demonstrate a role for laparoscopic surgery in predicting CAEs. Although the Boersma model did demonstrate an impressive predictive power, the outcome studied was restricted to cardiovascular death only; these data fail to incorporate clinically significant myocardial ischemia or dysrhythmias. Detsky *et al.* modified the Goldman risk model, and their model is consistent with our incorporation of age and emergency operation as predictors.[28] Unfortunately, the Detsky model requires clinicians to ascertain their institution-specific CAE risk and tabulate a patient risk score, with different risk factors contributing 5, 10, or 20 points. These data are then combined using a nomogram that yields a patient-specific post-test probability. These data were based upon a unique and small dataset of 455 patients referred to a preoperative medicine clinic. The risk index demonstrated a c-statistic of 0.75, similar to our preoperative model's 0.77.

Our addition to the CAE risk stratification literature provides an essential update. Although the perioperative CAE literature has evolved from prediction to optimization, the recent controversies regarding classically held therapies such as coronary revascularization and beta blockade call into question the maturity of our risk stratification literature.[2,7,8] Perhaps the failure of our therapeutic options is based on inaccurate prediction of which patients are at high risk for a perioperative CAE. Our data demonstrate that the role of comorbidities such as diabetes and renal insufficiency may require reevaluation. More importantly, our data offer further evidence that obesity itself may be an independent predictor of perioperative CAE. Although neither Lee nor Goldman evaluated patient BMI, recent national data also identifies elevated BMI as an independent predictor of perioperative CAE.[1] Recent guidelines regarding perioperative CAE risk stratification only mention obesity as a risk factor for coronary artery disease, not as a predictor of a CAE itself.[3]

Our comprehensive preoperative and intraoperative predictor model demonstrated that operative duration and increased PRBC administration are associated with perioperative CAE, independent of preoperative patient risk factors. Operative duration has previously been

noted to be associated with postoperative CAE, using the ACS-NSQIP dataset.[1] We cannot assess whether operative duration is simply a proxy for case complexity, or whether prolonged physiologic perturbations associated with surgery and anesthesia itself are playing a primary role. PRBC administration poses a similar quandary in that this predictor could reflect the deleterious effects of transfusion, or be a proxy for complex surgery or blood loss. Estimated blood loss has been identified as a predictor of postoperative morbidity and mortality,[16] although it has not been specifically associated with perioperative CAEs. In summary, the inclusion of operative duration and PRBC administration in our final predictor model improves the c-statistic from 0.77 for the preoperative model to 0.81 for the comprehensive preoperative and intraoperative model. These data demonstrate that the inclusion of intraoperative variables improves the identification of patients at risk for a CAE. Although the preoperative predictor model may be used to make a decision to proceed with surgery or defer awaiting optimization, the comprehensive model incorporating both preoperative and intraoperative predictors may prove invaluable when deciding on postoperative management of the patient. Patients found to be at high risk because of a combination of preoperative and intraoperative risk factors could be guided to aggressive postoperative surveillance, monitoring, and management.

The intraoperative predictor analysis within preoperative risk quartiles detailed in table 5 hoped to evaluate whether patients with variant *a priori* risk demonstrated differential response to intraoperative physiologic insults. Univariate analysis did demonstrate that Quartile 3 (medium-high risk) patients demonstrating a CAE were more likely to have experienced a 10-min period of MAP $<$ 50 mmHg (P = 0.02) or a 40% reduction in MAP (P = 0.01), as compared with preoperative baseline MAP (table 5). In addition, tachycardia $>$ 100 beats/min (P = 0.05) was associated with a perioperative CAE for Quartile 4 (high risk) patients (table 5). Our data are consistent with existing vascular surgery literature, which suggests that tachycardia is associated with postoperative myocardial ischemia.[29,30] Of note, our observed tachycardia threshold of $>$ 100 beats/min is more extreme than previously reported.[29] Because there are very limited data evaluating intraoperative hypotension and postoperative CAE in noncardiac surgery, we struggle to compare our findings with the existing literature.[3,31] The term "intraoperative hypotension" itself is ill-defined.[31] Outcome-based definitions of the concept require large datasets and the ability to risk-stratify patients based on preoperative comorbidities that may be associated with hypotension. As a result, our data should be viewed as a first step toward an important endpoint. Future studies should combine similar datasets and definitions to attempt to define "intraoperative hypotension" by objective outcomes. Despite a large overall study size, the quartile-based analysis struggles with accurate prediction of CAEs because of the smaller divided dataset. As a result, although we observed univariate relationships between hemodynamic derangements and perioperative CAEs, no specific level of hypotension or tachycardia demonstrated an independent association with the CAE outcome after adjusting for operative length and blood product administration.

There are several limitations to our analysis. First, it is restricted to patients undergoing general, vascular, and urologic surgery. Although this dataset comprises a broad group of patients and operative risk categories, it does not include common orthopedic, gynecologic, neurosurgical, and otorhinolaryngology procedures. Although the CAE risk factors are likely similar, our conclusions are based on a different procedural population. Second, these data are collected from a single tertiary-care hospital. Most of the current literature and existing models such as the Lee RCRI suffer from a similar limitation. Nevertheless, our study's conclusions must be validated at additional centers and with a nonuniversity hospital patient population. Next, the event detection process did not include a surveillance protocol with scheduled laboratory testing or patient evaluation. Routine clinical care was administered and postoperative CAE were recorded based on a review of clinical documentation, laboratory values, morbidity conferences, and personal interviews with patients. However, clinically silent ischemic events which are known to confer increased long-term mortality risk would not have been detected unless the primary service ordered a diagnostic test that identified an abnormality. Finally, much like the Lee RCRI derivation, our analysis offers a relatively low number of events available for statistical analysis when compared with the number of clinical variables to be evaluated. As a result, we are at risk for possibly "overfitting" the regression model, and the independent predictors we have identified should be validated in a distinct data set.[32] Nevertheless, the predictors' significant adjusted odds ratios and tight confidence intervals suggest that the model offers a valid starting point. Finally, we cannot comment on the role of perioperative medical management in modifying the risk of a CAE, a topic of much controversy in the perioperative literature.[33] We did not include medication regimens in the analysis for several reasons. First, the addition of more variables would only exacerbate any "overfitting" of the model, a limitation already discussed. Second, it difficult to define and verify "compliance" with preoperative medication regimens, an essential criterion when trying to address the value of a given medication. Most importantly, a robust commentary on medication effects would require detailed propensity score matching regarding the likelihood to receive the medication. It is unlikely that a dataset containing only 83 events would be large enough to result in a robust propensity score match and commentary. Finally, the current perioperative CAE literature has typically separated the risk stratification and optimization analytics.[1,3,6,7,28,34,35]

In summary, our data offers a much-needed update to the perioperative CAE prediction literature. The management of the chronic medical conditions previously reported to be associated with CAEs has advanced markedly, and may reflect why our prediction model does not include previously reported risk factors. Our data also suggest a role for obesity as an independent predictor of a perioperative CAE. Our comprehensive preoperative and intraoperative model demonstrates a predictive value superior to current risk prediction tools, and should be incorporated into clinical decision-making throughout the perioperative continuum—preoperative, intraoperative, and postoperative. Our data also offers a starting point for larger studies seeking to identify specific hypotension thresholds independently associated with perioperative CAE.

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Appendix 1. American College of Surgeons–National Surgery Quality Improvement Program Data Element Definitions

Data Element	Definition
Orally controlled diabetes mellitus	Report the treatment regimen of the patient's chronic, long-term management. Do not include a patient if diabetes is controlled by diet alone. A diagnosis of diabetes requiring therapy with an oral hypoglycemic agent.
Insulin controlled diabetes mellitus	Report the treatment regimen of the patient's chronic, long-term management. Do not include a patient if diabetes is controlled by diet alone. A diagnosis of diabetes requiring daily insulin therapy.
Alcohol use	The patient admits to drinking greater than 2 ounces of hard liquor or greater than two 12-ounce cans of beer or greater than two 6-ounce glasses of wine per day in the two weeks prior to admission. If the patient is a binge drinker, divide out the numbers of drinks during the binge by seven days, then apply the definition.
History of chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease (such as emphysema and/or chronic bronchitis) resulting in any one or more of the following: 1) functional disability from chronic obstructive pulmonary disease (*e.g.*, dyspnea, inability to perform activities of daily living), 2) hospitalization in the past for treatment of chronic obstructive pulmonary disease, 3) requires chronic bronchodilator therapy with oral or inhaled agents, and 4) a Forced Expiratory Volume in 1 s of less than 75% of predicted on pulmonary function testing. Do not include patients whose only pulmonary disease is asthma, an acute and chronic inflammatory disease of the airways resulting in bronchospasm. Do not include patients with diffuse interstitial fibrosis or sarcoidosis.
Ascites	The presence of fluid accumulation in the peritoneal cavity noted on physical examination, abdominal ultrasound, or abdominal computed tomography or magnetic resonance imaging within 30 days prior to the operation.
Active congestive heart failure	Congestive heart failure is the inability of the heart to pump a sufficient quantity of blood to meet the metabolic needs of the body or can do so only at increased ventricular filling pressure. Only newly diagnosed congestive heart failure within the previous 30 days or a diagnosis of chronic congestive heart failure with new signs or symptoms in the 30 days prior to surgery fulfills this definition. Common manifestations are abnormal limitation in exercise tolerance due to dyspnea or fatigue, orthopnea (dyspnea on lying supine), paroxysmal nocturnal dyspnea (awakening from sleep with dyspnea), increased jugular venous pressure, pulmonary rales on physical examination, cardiomegaly, and pulmonary vascular engorgement. Should be noted in the medical record as congestive heart failure or pulmonary edema.
Acute renal failure	The clinical condition associated with rapid, steadily increasing azotemia (increase in blood urea nitrogen) and a rising creatinine of above 3 mg/dl. Acute renal failure should be noted within 24 h prior to surgery.
Preoperative dialysis dependence	Acute or chronic renal failure requiring treatment with peritoneal dialysis, hemodialysis, hemofiltration, hemodiafiltration, or ultrafiltration within 2 weeks prior to surgery.
Cerebrovascular disease	History of transient ischemic attacks: Transient ischemic attacks are focal neurologic deficits (*e.g.*, numbness of an arm or amaurosis fugax) of sudden onset and brief duration (usually < 30 min) that usually reflects dysfunction in a cerebral vascular distribution. These attacks may be recurrent and, at times, may precede a stroke. OR Cerebrovascular accident/stroke with or without neurological deficit: History of a cerebrovascular accident (embolic, thrombotic, or hemorrhagic) lasting at least 30 min with or without persistent residual motor, sensory, or cognitive dysfunction.
History of myocardial infarction within past six months	The history of a non-Q wave or a Q-wave infarct in the 6 months prior to surgery as diagnosed in the patient's medical record.
Previous cardiac intervention	The patient has undergone percutaneous coronary intervention at any time (including any attempted intervention). This includes either balloon dilatation or stent placement. This does not include valvuloplasty procedures. OR Any major cardiac surgical procedure (performed either as an "off-pump" repair or utilizing cardiopulmonary bypass). This includes coronary artery bypass graft surgery, valve replacement or repair, repair of atrial or ventricular septal defects, great thoracic vessel repair, cardiac transplant, left ventricular aneurysmectomy, insertion of left ventricular assist devices, etc. Do not include pacemaker insertions or automatic implantable cardioverter defibrillator insertions.
History of angina within one month prior to surgery	Pain or discomfort between the diaphragm and the mandible resulting from myocardial ischemia. Typically angina is a dull, diffuse (fist-sized or larger) substernal chest discomfort precipitated by exertion or emotion and relieved by rest or nitroglycerine. Radiation to the arms and shoulders often occurs, and occasionally to the neck, jaw (mandible, not maxilla), or interscapular region. Documentation in the chart by the physician should state "angina" or "anginal equivalent." For patients on antianginal medications, enter "yes" *only* if the patient has had angina at any time within 1 month prior to surgery.
Hypertension requiring medications	The patient has a persistent elevation of systolic blood pressure greater than 140 mmHg or a diastolic blood pressure greater than 90 mmHg or requires an antihypertensive treatment (*e.g.*, diuretics, beta blockers, angiotensin-converting-enzyme inhibitors, calcium channel blockers) at the time the patient is being considered as a candidate for surgery (which should be no longer than 30 days prior to surgery). Hypertension must be documented in the patient's chart.
History of peripheral vascular occlusive disease	Any type of angioplasty (including stent placement) or revascularization procedure for atherosclerotic peripheral vascular disease (*e.g.*, aorta-femoral, femoral-femoral, femoral-popliteal) or a patient who has had any type of amputation procedure for peripheral vascular disease (*e.g.*, toe amputations, transmetatarsal amputations, below the knee or above the knee amputations). Patients who have had amputation for trauma or a resection of abdominal aortic aneurysms should not be included.
Serum creatinine ≥ 2	The most recent serum creatinine drawn prior to the patient's arrival to the operating room.
Emergency surgery	An emergency case is usually performed as soon as possible and no later than 12 h after the patient has been admitted to the hospital or after the onset of related preoperative symptomatology. Answer "yes" if the surgeon and anesthesiologist report the case as emergent.