Improving Prediction of Postoperative Myocardial Infarction With High-Sensitivity Cardiac Troponin T and NT-proBNP

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BACKGROUND: This study sought to determine whether preoperatively measured high-sensitivity cardiac troponin T (hs-cTnT) and *N*-terminal pro-brain natriuretic peptide (NT-proBNP) improve cardiac risk prediction in patients undergoing major noncardiac surgery compared with the standard risk indices.

METHODS: In this ancillary study to the Vitamins in Nitrous Oxide trial, patients were included who had preoperative hs-cTnT and NT-proBNP measured (n = 572). Study outcome was the incidence of postoperative myocardial infarction (MI) within the first 3 postoperative days. hs-cTnT was considered elevated if >14 ng/L and NT-proBNP if >300 ng/L. Additional cutoff values were investigated on the basis of receiver operating characteristic statistics. Biomarker risk prediction was compared with Lee's Revised Cardiac Risk Index (RCRI) with the use of standard methods and net reclassification index.

RESULTS: The addition of hs-cTnT (>14 ng/L) and NT-proBNP (>300 ng/L) to RCRI significantly improved the prediction of postoperative MI (event rate 30/572 [5.2%], Area under the receiver operating characteristic curve increased from 0.590 to 0.716 with a 0.66 net reclassification index [95% confidence interval 0.32–0.99], $P < .001$). The use of 108 ng/L as a cutoff for NT-proBNP improved sensitivity compared with 300 ng/L (0.87 vs 0.53). Sensitivity, specificity, positive, and negative predictive value for hs-cTnT were 0.70, 0.60, 0.09, and 0.97 and for NT-proBNP were 0.53, 0.68, 0.08, and 0.96.

CONCLUSIONS: The addition of cardiac biomarkers hs-cTnT and NT-proBNP to RCRI improves the prediction of adverse cardiac events in the immediate postoperative period after major noncardiac surgery. The high negative predictive value of preoperative hs-cTnT and NT-proBNP suggest usefulness as a "rule-out" test to confirm low risk of postoperative MI. (Anesth Analg 2016;XXX:00–00)

Adverse cardiac events, including acute myocardial infarction (MI), are serious and frequent complications after noncardiac surgery and portend an adverse prognosis.[1–3] The reliable identification of patients at risk for such events before surgery is an important goal of perioperative medicine, because it may allow targeted interventions; however, how to achieve accurate preoperative prediction of postoperative cardiac events is rudimentary at best.[4,5] Most practitioners rely on simple scores and risk indices such as Lee's Revised Cardiac Risk Index (RCRI)[6] or the American Society of Anesthesiologists (ASA) physical status (PS),[7] whose 6 and 5 levels, respectively, do not provide an adequate level of discrimination among patients.

Cardiac biomarkers, such as high-sensitivity cardiac troponin T (hs-cTnT) and *N*-terminal pro-B-type natriuretic peptide (NT-proBNP), are used in cardiology and general medical practice for risk prediction and case management.[8–13] We recently have reported that hs-cTnT improves preoperative risk prediction.[14] We now sought to investigate whether NT-proBNP[15–21] and hs-cTnT augment the accuracy of standard risk indices such as RCRI and ASA PS to predict postoperative MI. Accordingly, we conducted a nested cohort study within the completed vitamins in nitrous oxide (VINO) trial. The primary purpose of VINO was to investigate the effects of nitrous oxide plus B vitamins on perioperative cardiac events.[22]

METHODS

Study Design and Population

This was an ancillary nested cohort study of patients enrolled in the VINO trial (Clinicaltrials.gov number NCT00655980).

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Reprints will not be available from the authors.

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Hypotheses tested in this ancillary study were post hoc and not designed a priori. VINO was a double-blind, randomized, placebo-controlled, single-center trial; patients were enrolled between March 2008 and December 2011. A detailed description of the trial methods and main results have been published elsewhere.[22] VINO enrolled 625 adult patients with either known coronary artery disease or multiple risk factors for coronary artery disease who were scheduled for major noncardiac surgery under general anesthesia. Patients were assigned randomly to receive nitrous oxide and B vitamins (250 patients) or nitrous oxide and placebo (250 patients). A concurrent reference group who received neither nitrous oxide nor B vitamins also was enrolled (125 patients). The trial results were negative, that is, B vitamins had no effect on cardiac events.

Inclusion criteria for this ancillary study were the availability of a preoperative hs-cTnT and NT-proBNP value (572 patients fulfilled this criterion) plus at least 1 postoperative value for each biomarker. The study was approved by the Washington University in St. Louis institutional review board, and all patients provided written, informed consent.

Biomarker Assays

Blood and 12-lead electrocardiograms (ECGs) were obtained at 5 predefined time points: preoperative (baseline), which was within 2 hours before surgery; within 30 minutes after arrival in the postanesthesia care unit; and on the mornings of postoperative days 1, 2, and 3. Samples were collected in lithium heparin tubes and immediately put on ice and centrifuged within 30 minutes after collection. Plasma was then transferred into cryogenic tubes and stored at −70°C. Biomarker measurements were performed in batches (samples had no more than 2 freeze–thaw cycles) and were performed by study personnel unaware of clinical outcomes.

hs-cTnT and NT-proBNP concentrations were measured on a Roche Elecsys 2010 analyzer (Roche Diagnostics, Indianapolis, IN; for hs-cTnT: limit of detection: 5.0 ng/L; 99th percentile: 14 ng/L; a 10% CV at 13 ng/L; NT-proBNP: limit of detection: 1.0 ng/L; <5% CV at concentrations >70 ng/L).[23] Standard cTnI concentrations were measured with a contemporary assay on a Siemens Dimension RxL analyzer (Siemens Medical Solutions, Malvern, PA; 99th percentile URL is 0.07 µg/L). Please note that concentrations for the hs-cTn assays are designated in ng/L to distinguish from contemporary cTn assays.

Outcomes

The outcome of this study was postoperative MI within the first 3 days after surgery. MI was defined according to the universal definition (rising pattern of cTnI with at least 1 elevation > 99th percentile plus new ECG changes indicative of myocardial ischemia and/or clinical symptoms).[24] New Q-waves, ST-segment depression or T-wave inversion ≥ 0.1 mV, or ST-elevation ≥ 0.2 mV in at least 2 contiguous leads were considered indicative of myocardial ischemia. ECGs were read and analyzed by a physician blinded to biomarker results.

Statistical Analysis

All cTn and NT-proBNP values are reported as medians plus interquartile ranges because of skewness of the data. The estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration creatinine formula.[25] Preoperative hs-cTnT and NT-proBNP levels were assessed as both continuous as well as categorical variables. We used 14 ng/L (99th percentile URL) as the cutoff value for hs-cTnT. Because sex-specific cutoff values for hs-cTnT were not helpful in our previous analysis, they were not used in this analysis.[14]

For NT-proBNP, we initially used continuous data, probed 300 ng/L as the cutoff value as proposed in the literature, and determined the optimal cutoff value based on Youden's J statistic (J = sensitivity + specificity − 1) on the receiver operating characteristic curve value that maximizes J.[15,17,21]

Univariate and multiple logistic regression, unadjusted or adjusted for age, sex, eGFR, and a history of coronary artery disease, were used to assess the association of preoperative RCRI, ASA status, hs-cTnT, and NT-proBNP with postoperative MI (RCRI and ASA status were only adjusted for age and sex). Wald's test was used to determine the contribution of individual covariates. The ability of Lee's RCRI and each biomarker to predict postoperative cardiac events was determined by the area under the receiver operating characteristic (AUROC) curve.

The biomarker AUROC values were compared with Lee's index AUC via the methods of DeLong et al.[26] The ability of the biomarkers to improve on Lee's RCRI was evaluated by calculating the category-free net reclassification improvement (NRI).[27] The category-free NRI measures the correctness of patient reclassification after adding the biomarker as a predictor of outcome in addition to Lee's index. A correct reclassification occurs when the predicted probability of Lee's RCRI + additional biomarker(s) is greater than Lee's RCRI alone among patients with outcome events and/or when the predicted probability is less than Lee's RCRI alone among patients without outcome events. The NRI is determined as the net improvement among events plus the net improvement among nonevents, where net improvement is the difference between those correctly versus those incorrectly reclassified. NRI values range from −2 to 2, with positive values indicating overall improvement when adding the biomarker.

Statistical analyses were performed on SAS v9.4 and JMP 12.2.0 (SAS Institute Inc., Cary, NC). Graphs were constructed on GraphPad Prism 6.01 (GraphPad Software Inc., La Jolla, CA).

RESULTS

The study population consisted of 572 patients from the VINO trial in whom preoperative hs-cTnT and NT-proBNP were measured (original VINO sample size: n = 625). All patients had several cardiac risk factors, and more than half had been diagnosed previously with coronary artery disease; the distribution within the RCRI and ASA PS are listed in Table 1.

Before surgery, hs-cTnT was detectable in 563 of 572 patients (98.5%) with 240 patients having elevated hs-cTnT ≥14 ng/L (42%), whereas contemporary cTnI was detectable in only 74 of 569 patients (13%). Baseline NT-proBNP was detectable in all patients, with 191 having elevated NT-proBNP >300 ng/L (33%). At baseline, hs-cTnT and NT-proBNP were positively correlated (Spearman's ρ = 0.54).

Table 1. Preoperative Characteristics of the Study Population

	Preoperative Biomarker Status				
	hs-cTnT < 14 ng/L NT-proBNP < 300 ng/L n = 279 (48.8%)	hs-cTnT > 14 ng/L NT-proBNP < 300 ng/L n = 102 (17.8%)	hs-cTnT < 14 ng/L NT-proBNP > 300 ng/L n = 53 (9.3%)	hs-cTnT > 14 ng/L NT-proBNP > 300 ng/L n = 138 (24.1%)	Total n = 572 (100%)
Mean age (y, SD)	60.1 (9.4)	65.8 (8.5)	66.2 (8.6)	70.5 (10.1)	64.9 (10.7)
Male sex (n, %)	153 (54.8)	76 (74.5)	32 (60.4)	94 (68.1)	355 (62.1)
Race (n, %)					
White	221 (79.2)	83 (82.2)	45 (84.9)	112 (81.8)	461 (80.1)
Black	56 (20.1)	18 (17.8)	8 (15.1)	25 (18.2)	107 (18.8)
Other	2 (0.7)	0	0	0	2 (0.4)
Smoking history (n, %)	218 (78.1)	71 (69.6)	47 (88.7)	94 (69.1)	430 (75.4)
Current smoker (n, %)	90 (32.3)	22 (21.5)	22 (41.5)	32 (23.2)	166 (29.0)
Pack-years (median, IQR)	37.5 (20; 50)	32 (19; 60)	40 (25; 55.5)	40 (20; 60)	40 (20;60)
Diabetes (n, %)	83 (29.9)	40 (39.6)	13 (24.5)	71 (51.8)	207 (36.8)
Insulin dependent (n, %)	24 (29.3)	16 (40.0)	4 (30.8)	38 (53.5)	82 (14.3)
Hypertension (n, %)	208 (74.8)	90 (88.2)	48 (90.6)	116 (84.1)	462 (80.1)
Hypercholesterolemia (n, %)	176 (63.1)	66 (64.7)	34 (64.2)	97 (71.3)	373 (65.4)
Chronic renal failure (n, %)	17 (6.2)	8 (7.9)	3 (5.7)	31 (22.6)	59 (10.4)
On hemodialysis (n, %)	1 (0.4)	1 (0.4)	0	4 (2.9)	6 (1.0)
eGFR (median, IQR)	90 (75;101)	79 (62; 94)	75 (57; 90)	60 (46; 82)	80 (61; 95)
COPD (n, %)	35 (12.5)	11 (10.8)	12 (22.6)	19 (13.8)	77 (13.5)
Coronary artery disease (n, %)	126 (45.3)	60 (58.8)	31 (58.5)	105 (76.1)	322 (56.4)
Previous MI (n, %)	57 (20.4)	27 (26.5)	20 (37.7)	50 (36.8)	154 (27.0)
Previous PCI/stent (n, %)	82 (29.7)	34 (33.7)	15 (28.3)	62 (45.9)	193 (34.2)
Previous CABG (n, %)	28 (10.1)	18 (17.6)	9 (17.0)	44 (31.9)	99 (17.4)
Congestive heart failure (n, %)	21 (7.5)	8 (7.8)	8 (15.1)	32 (23.4)	69 (12.1)
Peripheral vascular disease (n, %)	84 (30.2)	26 (26.0)	16 (30.2)	63 (46.0)	189 (33.3)
Carotid disease (n, %)	17 (6.2)	13 (12.9)	4 (7.5)	14 (10.2)	48 (8.5)
Stroke/TIA (n, %)	34 (12.2)	11 (10.8)	12 (22.6)	23 (16.8)	80 (14.0)
Atrial fibrillation (n, %)	18 (6.5)	6 (5.9)	8 (15.4)	36 (26.3)	68 (11.9)
Lee's revised cardiac risk index					
I	104 (37.5)	32 (31.4)	15 (28.8)	24 (17.4)	175 (30.8)
II	121 (43.7)	50 (49.0)	23 (44.2)	56 (40.6)	250 (43.9)
III	48 (17.3)	17 (16.7)	12 (23.1)	39 (28.3)	116 (20.4)
IV	4 (1.4)	3 (2.9)	2 (3.8)	19 (13.8)	28 (4.9)
ASA status (n, %)					
II	61 (21.9)	18 (17.8)	5 (9.4)	8 (5.8)	92 (16.1)
III	211 (75.9)	79 (78.2)	47 (88.7)	119 (86.2)	456 (80.0)
IV	6 (2.2)	4 (4.0)	1 (1.9)	11 (8.0)	22 (3.9)
hs-cTnT (ng/L; median, IQR)	8.6 (6.3; 10.5)	18.2 (15.7; 22.4)	10.0 (7.7; 11.8)	23.7 (18.6; 34.8)	12.0 (8.3; 19.3)
NT-proBNP (ng/L; median, IQR)	66 (35; 112)	122 (70; 179)	479 (360; 718)	936 (493; 1926)	140 (60; 421)

Abbreviations: ASA, American Society of Anesthesiologists; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; hs-cTnT, high-sensitivity cardiac troponin T; IQR, interquartile range; MI, myocardial infarction; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Prediction of Perioperative Myocardial Injury and Infarction

Within the first 3 postoperative days 30 of 572 patients (5.2%) developed an acute MI. Postoperative MI was more frequent among patients with RCRI level 4 and ASA PS IV and in patients with isolated or dual preoperative cardiac biomarker elevation (Table 2).

Lee's RCRI, ASA PS, as well as preoperative hs-cTnT and NT-proBNP concentrations, were associated individually with postoperative MI (Table 3A). After we adjusted for age, sex, eGFR, and preexisting coronary artery disease, elevated hs-cTnT (≥14 ng/L) before surgery was associated with an adjusted odds ratio (aOR) for acute MI of 2.26 (95% confidence interval [CI] 0.93–5.83, P = .07), whereas elevated NT-proBNP (>300 ng/L) was associated with an aOR of 1.55 (95% CI 0.66–3.36, P = .31). In a sensitivity analysis (Table 3B) comparing the association of individual predictors in patients with or without known coronary artery disease, elevated hs-cTnT before surgery was associated with an aOR of 6.04 (95% CI 0.94–38.90, P = .06) for postoperative MI, whereas NT-proBNP had no discernible effect. In patients with known coronary artery disease, elevated hs-cTnT and NT-proBNP before surgery were associated with aORs of 1.55 (95% CI 0.54–4.43, P = .41) and 1.84 (95% CI 0.70–4.87, P = .22) for postoperative MI.

Of note, among the 74 patients who had a detectable contemporary cTnI concentration before surgery, 7 (10%) developed acute MI (10%; aOR 2.07; 95% CI 0.79–4.81, P = .13). Using receiver operating characteristic curve analyses, we found the optimal NT-proBNP concentration cutoff (which maximizes the sum of sensitivity + 1 − specificity) for prediction of acute MI was 108 ng/L.

Lee's RCRI and ASA PS had mediocre discriminatory ability in correctly predicting postoperative MI: AUROC was 0.590 and 0.608 for acute MI, respectively (Figure 1). Compared with RCRI, hs-cTnT and NT-proBNP on a continuous scale each improved discrimination: 0.690 and 0.699 for acute MI. The addition of hs-cTnT (cutoff 14 ng/L)

Table 2. Postoperative Study Outcomes

	Myocardial Infarction (n = 30)	Unadjusted Odds Ratio (95% CI)
Lee's RCRI (n, %)		
I (n = 175)	5 (2.9%)	1 (ref.)
II (n = 250)	15 (6.0%)	2.18 (0.83–6.80)
III (n = 116)	4 (3.5%)	1.23 (0.30–4.73)
IV (n = 28)	5 (17.9%)	7.40 (1.92–28.52)
Missing (n = 3)	1	
ASA status (n, %)		
II (n = 92)	2 (2.2%)	1 (ref.)
III (n = 456)	22 (4.9%)	2.29 (0.66–14.46)
IV (n = 22)	5 (22.7%)	13.24 (2.62–97.87)
Missing (n = 2)	1	
Preoperative biomarker profile, n (%)		
hs-cTnT <14 ng/L and NT-proBNP <300 ng/L (n=279)	6 (2.2%)	1 (ref.)
hs-cTnT >14 ng/L and NT-proBNP <300 ng/L (n = 102)	8 (7.8%)	3.87 (1.31–12.04)
hs-cTnT <14 ng/L and NT-proBNP >300 ng/L (n = 53)	3 (5.7%)	2.73 (0.56–10.71)
hs-cTnT >14 ng/L and NT-proBNP >300 ng/L (n = 138)	13 (9.6%)	4.81 (1.85–13.96)

Abbreviations: ASA, American Society of Anesthesiologists; CI, confidence interval; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; RCRI, Revised Cardiac Risk Index.

and NT-proBNP (cutoff 300 ng/L) to RCRI significantly improved the prediction of postoperative MI (Figure 2), the AUROC increased from 0.590 to 0.716 when both biomarkers were added to RCRI ($P = .02$) with a 0.66 improved event classification (NRI 0.66, 95% CI 0.32–0.99, $P < .001$).

Sensitivity, specificity, positive, and negative predictive value to predict postoperative MI for hs-cTnT were 0.70, 0.60, 0.09, and 0.97 and for NT-proBNP were 0.53, 0.68, 0.08, and 0.96 (Table 4).

Use of the empirically obtained "optimal" cutoff value of 108 ng/L for NT-proBNP markedly improved the sensitivity compared with 300 ng/L (0.87 vs 0.53) while also improving the net reclassification index from 0.66 to 0.71 (95% CI 0.37-1.04) for postoperative MI.

DISCUSSION

The goal of this study was to determine whether cardiac biomarkers hs-cTnT and NT-proBNP could improve preoperative cardiac risk prediction compared with standard risk indices such as RCRI and ASA PS. In our high-risk population, classical risk indices (ie, Lee's RCRI and ASA PS) had mediocre ability to predict postoperative MI. Preoperatively measured cardiac biomarkers hs-cTnT and NT-proBNP outperformed Lee's RCRI or ASA PS either alone or when added to the risk indices. A joint elevation of both biomarkers indicated patients with the greatest risk for postoperative cardiac morbidity (4- to 5-fold increase). Although both

Table 3A. Association of Predictors With Postoperative MI

		Univariate Analysis			Multiple Regression Analysis		
Outcome	Variable	OR	95% CI	*P* Value	aOR	95% CI	*P* Value
Postoperative MI	Lee's RCRI (overall)	1.56	(1.02–2.37)	.04	1.53	(1.00–2.33)	.05
	ASA physical status (overall)	4.26	(1.67–10.81)	.003	4.17	(1.60–10.64)	.003
	hs-cTnT baseline (continuous)	1.02	(1.01–1.03)	.01	0.99	(0.98–1.00)	.13
	hs-cTnT baseline > 14 ng/L (yes versus no)	3.58	(1.61–7.97)	.001	2.26	(0.93–5.83)	.07
	NT-pro BNP baseline (continuous)	1.00	(1.00–1.00)	.03	1.00	(1.00–1.00)	.34
	NT-pro BNP baseline >300 ng/L	2.42	(1.16–5.08)	.02	1.55	(0.66–3.63)	.31

Table 3B. Sensitivity Analysis Comparing Individual Predictors in Patients With or Without Known CAD

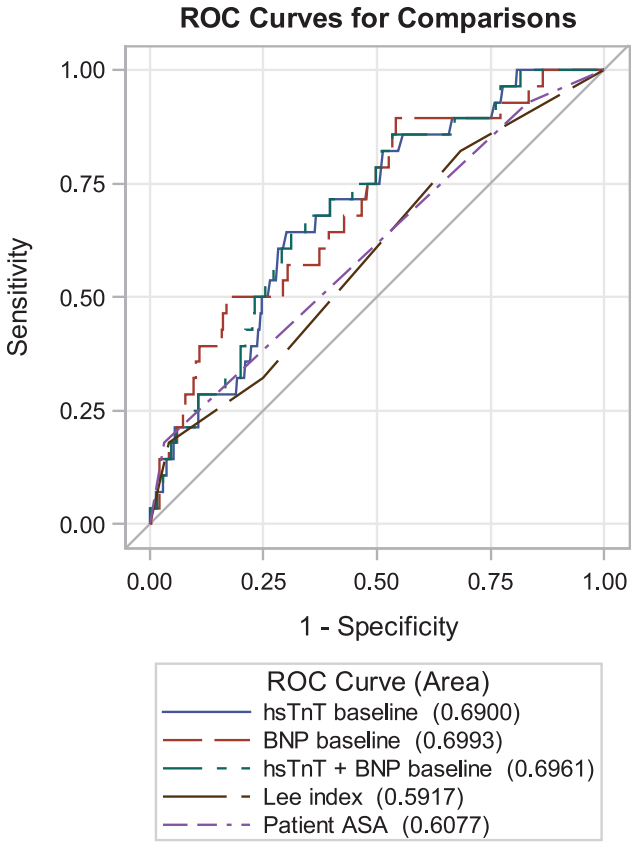
	No CAD			CAD		
Variable	aOR	95% CI	*P* Value	aOR	95% CI	*P* Value
Lee's RCRI	1.0	(0.24–4.10)	1.00	1.07	(0.59–1.97)	.82
hs-cTnT baseline > 14 ng/L	6.04	(0.94–38.90)	.06	1.55	(0.54–4.43)	.41
NT-pro BNP baseline >300 ng/L	0.56	(0.05–6.31)	.64	1.84	(0.70–4.87)	.22

Abbreviations: aOR, adjusted odds ratio; CAD, coronary artery disease; CI, confidence interval; hs-cTnT, high-sensitivity cardiac troponin T;MI, myocardial infarction; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; RCRI, Revised Cardiac Risk Index.
The multiple regression model adjusted for age, sex, eGFR, coronary artery disease in Table 3A and for age, sex, eGFR in Table 3B.

Table 4. Sensitivity, Specificity, Negative, and Positive Predictive Value of hs-cTnT and NT-proBNP

	MI	No MI	Odds Ratio (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Likelihood Ratio
hs-cTnT >14 ng/L	21	217	3.47 (1.56–6.98)	0.70 (0.51–0.85)	0.60 (0.56–0.64)	0.09 (0.06–0.13)	0.97 (0.95–0.99)	1.74
hs-cTnT <14 ng/L	9	323						
NT-proBNP >300 ng/L	16	173	2.42 (1.16–5.09)	0.53 (0.34–0.72)	0.68 (0.64–0.72)	0.08 (0.05–0.13)	0.96 (0.94–0.98)	1.67
NT-proBNP <300 ng/L	14	367						
NT-proBNP >108 ng/L	26	293	5.48 (1.89–15.90)	0.87 (0.69–0.96)	0.46 (0.41–0.50)	0.08 (0.05–0.11)	0.98 (0.96–1.00)	1.60
NT-proBNP <108 ng/L	4	247						

Abbreviations: CI, confidence interval; hs-cTnT, high-sensitivity cardiac troponin T; NPV, negative predictive value; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; PPV, positive predictive value.



Variable	AUC	95% CI	Versus Lee's Index AUC (*P* Value)
RCRI	0.590	(0.490–0.690)	–
ASA status	0.608	(0.525–0.690)	.78
hs-cTnT	0.690	(0.598–0.782)	.18
NT-proBNP	0.699	(0.600–0.799)	.14
hs-cTnT + NT-proBNP	0.696	(0.603–0.789)	.15

Abbreviations: ASA, American Society of Anesthesiologists; CI, confidence interval; hs-cTnT, high-sensitivity cardiac troponin T; NPV, negative predictive value; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; RCRI, Revised Cardiac Risk Index; ROC, receiver operating characteristics.

Figure 1. Area under the ROC curves for postoperative acute MI.

biomarkers hs-cTnT and NT-proBNP were significant predictors of adverse cardiac events, the stronger discriminator was hs-cTnT. The use of a lower NT-proBNP cutoff value of 108 ng/L determined from our data increased sensitivity compared with a 300 ng/L cutoff.

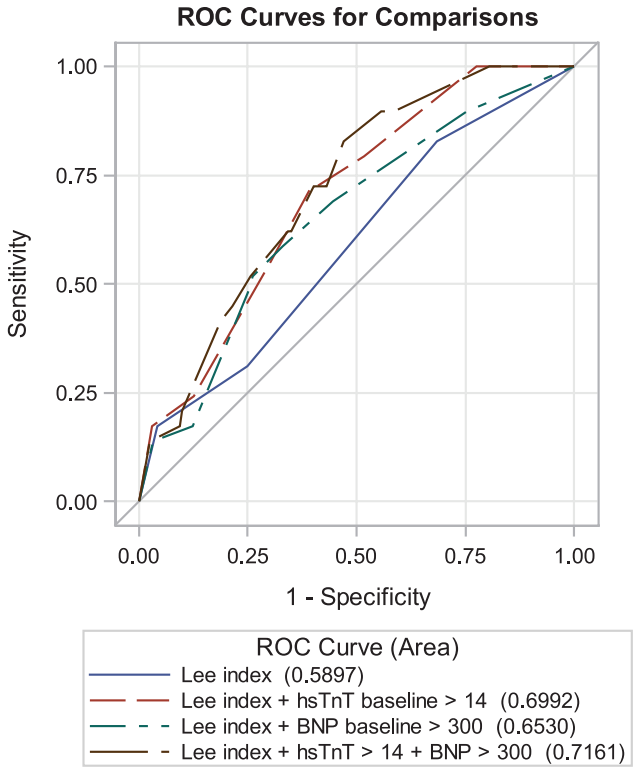
BNP and NT-proBNP have been used for many years to diagnose and stratify patients with acute and chronic heart failure.[28] In perioperative medicine, several studies have shown that preoperative BNP and NT-proBNP values are associated with postoperative cardiac events after major noncardiac surgery.[15–18,20,21,29–32] High-sensitivity cardiac troponin assays now allow the detection of more subtle episodes of cardiac injury.[9,11] Baseline hs-cTnT is a strong predictor of cardiac morbidity and mortality in the general adult population.[12,33,34] Several perioperative studies, including one from this cohort, have shown that baseline hs-cTnT alone can predict postoperative myocardial injury and infarction as well as long-term mortality.[14,19,35] We observed that the 99th percentile of the upper reference limit of the hs-cTnT assay (14 ng/L) appeared to be a good cutoff to identify the patients at greatest risk for subsequent postoperative cardiac morbidity and mortality.

We enrolled a high-risk patient population: many patients either suffered from coronary artery disease or were at high risk for coronary artery disease from a combination of several risk factors (diabetes, hypertension, renal disease, stroke, etc.). It should therefore come as no surprise most patients had either an elevated NT-proBNP or hs-cTnT value before surgery. At the outset of this study, it was unclear whether both cardiac biomarkers would identify the same high-risk patients, that is, if both cardiac biomarkers would be elevated jointly. Although we observed a modest correlation of 0.54, many patients had either an isolated hs-cTnT or NT-proBNP elevation, which indicates predominantly distinct patient subpopulations.

Despite the significant improvement in postoperative cardiac risk prediction by cardiac biomarkers compared with risk indices, the overall level of discrimination still is modest, which is in line with earlier evidence from other studies.[36,37] In our population, hs-cTnT had a sensitivity of 70% and a specificity of 60% for acute postoperative MI. The low positive predictive value (20%) but very high negative predictive value (>90%) indicates the potential utility of preoperative cardiac biomarkers as "rule out" markers, that is, patients with a normal biomarker value have a very low risk of developing postoperative cardiac events. However, the negative predictive value of a test is influenced by the low prevalence of postoperative MI. The pattern of low positive but high negative predictive value may, however, change when hs-cTn assays are used for postoperative event detection, which should result in a larger number of events.[38]

An interesting inconsistency, however, relates to the fact that a high negative predictive value of a test with strong "rule-out" features would be expected to mostly correct the nonevents. Our study showed that hs-cTnT and NT-proBNP had corrective effects for both events and nonevents, and it is unclear why. A possible explanation may lie in the fact that the negative predictive value, like other epidemiological test metrics such as sensitivity and specificity, is determined in isolation, that is, for each test or biomarker individually. The net reclassification index, however, is asking whether the addition of a biomarker to RCRI—when we already know the RCRI—can improve risk prediction beyond the RCRI. Thus, these may be 2 separate questions and explain the inconsistency.

Our study has several limitations. First, the study population comprised a targeted group of high-risk patients who may not be representative of a general surgical population. In a general surgical population, one would expect a greater number of healthy patients with fewer cardiac risk factors and therefore fewer patients with an elevated hs-cTnT or NT-proBNP. On the one hand, this would probably result in less efficient and more expensive screening; on the other hand, if elevated hs-cTnT or NT-proBNP levels were found, it may improve the identification of increased cardiovascular risk in these patients. Second, although both biomarkers



Area Under Receiver Operating Characteristics (ROC) Curve, Postoperative Acute MI

Variable	AUC	95% CI	Versus RCRI AUC (*P* Value)
RCRI	0.590	(0.490, 0.690)	–
RCRI + hs-cTnT > 14	0.699	(0.615, 0.783)	.025
RCRI + NT-proBNP >300	0.653	(0.553, 0.753)	.15
RCRI + hs-cTnT > 14 + NT-proBNP >300	0.716	(0.636, 0.796)	.015

Benefit of Adding Additional Predictor(s) of Postoperative Acute MI to Lee's RCRI

	RCRI		RCRI + hs-cTnT >14		RCRI + NT-proBNP >300		RCRI + hs-cTnT > 14 + NT-proBNP >300	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Intercept	–	–	–	–	–	–	–	–
RCRI	1.56 (1.02, 2.37)	.04	1.36 (0.89– 2.08)	.15	1.38 (0.89–2.12)	.15	1.31 (0.84–2.02)	.23
hsTnT >14 ng/L	–	–	3.63 (1.56– 8.45)	.003	–	–	3.15 (1.26– 7.86)	.014
NT-proBNP >300 ng/L	–	–	–	–	2.27 (1.04–4.96)	.04	1.43 (0.61–3.35)	.41
Category-free NRI[a]			0.66 (0.32, 0.99), *P* < .001 • 45% of MIs were correctly reclassified • 21% of non-MIs were correctly reclassified		0.46 (0.09, 0.84), *P* = .015 • 10% of MIs were correctly reclassified • 36% of non-MIs were correctly reclassified		0.66 (0.32, 0.99), *P* < .001 • 45% of MIs were correctly reclassified • 21% of non-MIs were correctly reclassified	

Abbreviations: AUC, are under the curve; CI, confidence interval; hs-cTnT, high-sensitivity cardiac troponin T; MI, myocardial infarction; NPV, negative predictive value; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; OR, odds ratio; RCRI, Revised Cardiac Risk Index; ROC, receiver operating characteristic.

[a]Correct reclassification occurs when the addition of a biomarker to RCRI leads to improved classification of events (MIs) and nonevents (no MI observed) of patients.

Figure 2. Addition of cardiac biomarkers to Lee's RCRI for prediction of postoperative acute MI.

were associated with postoperative cardiac morbidity, they could not identify all patients who experienced these outcomes. Third, despite enrolling a high-risk patient population, event rates were low and thus the precision of our findings modest. In addition, we used a standard non-high sensitivity cardiac troponin assay to define events. Without doubt, this assay reduced the number of events detected postoperatively and thus may have exaggerated or diminished the ability of biomarkers to predict events. Fourth, on the basis of our previous research, we decided not to use sex-specific cutoffs for hs-cTnT,[14] but future work may find that using sex-specific cutoffs may improve

risk prediction.[39] The sample size of our study limited the robustness of the findings and several associations became statistically nonsignificant after adjustment for several covariates, indicating limited statistical power. Finally, our study used a contemporary, nonhigh-sensitivity cTn assay, the current standard of care in the United States, but not a high-sensitivity cTn assay to diagnose study outcomes. As we show in a related analysis, the use of hs-cTnT more than doubles the diagnosis of postoperative MI. hs-cTn assays have become the standard-of-care in many countries worldwide, but these assay have not yet been cleared by the Food and Drug Administration.

An important consideration is in regards to the RCRI. The RCRI originally was devised to predict MACE (major adverse cardiac events), including MI, pulmonary edema, ventricular fibrillation or primary cardiac arrest, and complete heart block. Like most subsequent studies, our study did not assess pulmonary edema, ventricular fibrillation, or complete heart block that jointly comprised more than half of the observed events in the original RCRI derivation.[6] Second, neither RCRI nor ASA PS were designed to measure postoperative cardiac troponin elevation, a condition that has recently been termed MINS (myocardial injury after noncardiac surgery)[40] and that has independently been associated with adverse long-term outcomes.[41–45]

In conclusion, the addition of cardiac biomarkers hs-cTnT and NT-proBNP to RCRI improved preoperative prediction of adverse cardiac events after major noncardiac surgery. The use of a lower NT-proBNP cutoff value of 108 ng/L provides increased sensitivity and improved risk prediction compared with a 300-ng/L cutoff. Recently, experts presented a compelling case for a new revision of the RCRI.[46,47] Perhaps the inclusion of preoperative cardiac biomarkers may further improve the identification of patients at risk for adverse postoperative cardiac outcomes. ■

DISCLOSURE

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