ORIGINAL RESEARCH

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Preoperative *N*-Terminal Pro–B-Type Natriuretic Peptide and Cardiovascular Events After Noncardiac Surgery

A Cohort Study

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Background: Preliminary data suggest that preoperative *N*-terminal pro–B-type natriuretic peptide (NT-proBNP) may improve risk prediction in patients undergoing noncardiac surgery.

Objective: To determine whether preoperative NT-proBNP has additional predictive value beyond a clinical risk score for the composite of vascular death and myocardial injury after noncardiac surgery (MINS) within 30 days after surgery.

Design: Prospective cohort study.

Setting: 16 hospitals in 9 countries.

Patients: 10 402 patients aged 45 years or older having inpatient noncardiac surgery.

Measurements: All patients had NT-proBNP levels measured before surgery and troponin T levels measured daily for up to 3 days after surgery.

Results: In multivariable analyses, compared with preoperative NT-proBNP values less than 100 pg/mL (the reference group), those of 100 to less than 200 pg/mL, 200 to less than 1500 pg/mL, and 1500 pg/mL or greater were associated with adjusted hazard ratios of 2.27 (95% CI, 1.90 to 2.70), 3.63 (CI, 3.13 to 4.21), and 5.82 (CI, 4.81 to 7.05) and corresponding incidences of the primary outcome of 12.3% (226 of 1843), 20.8% (542 of 2608), and 37.5% (223 of 595), respectively. Adding NT-proBNP thresholds to clinical stratification (that is, the Revised Cardiac Risk Index [RCRI]) resulted in a net absolute reclassification improvement of 258 per 1000 patients. Preoperative NT-proBNP values were also statistically significantly associated with 30-day all-cause mortality (less than 100 pg/mL [incidence, 0.3%], 100 to less than 200 pg/mL [incidence, 0.7%], 200 to less than 1500 pg/mL [incidence, 1.4%], and 1500 pg/mL or greater [incidence, 4.0%]).

Limitation: External validation of the identified NT-proBNP thresholds in other cohorts would reinforce our findings.

Conclusion: Preoperative NT-proBNP is strongly associated with vascular death and MINS within 30 days after noncardiac surgery and improves cardiac risk prediction in addition to the RCRI.

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Myocardial injury after noncardiac surgery (MINS) is the most common major vascular complication after surgery and is associated with perioperative death (1–3). Accurate preoperative cardiovascular risk prediction is important to facilitate informed decision making about the appropriateness of noncardiac surgery and to guide management decisions. Several guidelines recommend using the Revised Cardiac Risk Index (RCRI) to predict perioperative cardiac risk (4–7). Although the RCRI is easy to use, its accuracy in predicting major perioperative cardiovascular complications is limited (8, 9).

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Supplement

Preliminary evidence suggests that preoperative *N*-terminal pro–B-type natriuretic peptide (NT-proBNP) measurement may improve perioperative cardiovascular risk prediction (10, 11). The VISION (Vascular Events in Noncardiac Surgery Patients Cohort Evaluation) study (ClinicalTrials.gov NCT00512109), an international, prospective cohort study, enrolled adults who had inpatient noncardiac surgery (1, 2). We planned a substudy that included patients with prospectively collected preoperative NT-proBNP measurements. Our objective was to determine whether preoperative NT-proBNP had additional predictive value beyond the RCRI for the composite of vascular death and MINS within 30 days after surgery.

Methods

In this nested substudy within the VISION study, we included patients aged 45 years or older who had inpatient noncardiac surgery with regional or general anesthesia and who consented to participate in the

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VISION NT-proBNP substudy. Patients were excluded if they were previously enrolled in VISION. Between August 2007 and October 2013, a total of 18 920 patients were enrolled in the VISION study in the 16 centers in 9 countries participating in this substudy, of which 10 402 patients were enrolled in this NT-proBNP substudy (**Supplement Table 1**, available at Annals.org). The ethics and institutional review boards at each center approved the study protocol before patient enrollment began.

Study Procedures

The methods for the VISION study have been described (1, 2). Research personnel interviewed and examined patients and reviewed charts at enrollment to obtain baseline variables (for example, comorbid conditions and RCRI variables). The RCRI was calculated after study completion at the statistical analysis stage; study personnel were unaware of this calculation. The RCRI score includes the following variables (worth 1 point each): history of ischemic heart disease, congestive heart failure, cerebrovascular disease, high-risk surgery (that is, intraperitoneal, intrathoracic, or suprainguinal vascular), preoperative insulin use, and preoperative creatinine level greater than 177 μmol/L (2 mg/dL).

All patients had blood drawn before surgery, and samples were refrigerated within 2 hours after collection. Five centers measured NT-proBNP locally, 1 of which measured it in real time. The other 4 sites batched samples before running the assays locally at the same time. Samples collected at the other 11 centers were centrifuged, frozen, and shipped to the Clinical Research Laboratory and Biobank in Hamilton, Ontario, Canada. After the samples were thawed, NT-proBNP was measured subsequently at the same time (12). Each laboratory did its own quality control as part of standard operating procedures; NT-proBNP results were generated with Roche immunoassay analyzers (Roche Diagnostics) in line with laboratory recommendations (13). Health care providers and study personnel were blinded to the NT-proBNP measurements. Patients had troponin T or high-sensitivity cardiac troponin T (Roche Diagnostics) levels measured 6 to 12 hours after surgery and on postoperative days 1, 2, and 3. Patients with postoperative troponin T elevations above the 99th percentile were evaluated for ischemic signs or symptoms and had electrocardiography. Sites were encouraged to perform electrocardiography for several days after noting a troponin elevation.

Research staff contacted patients 30 days after surgery to determine whether any outcome had occurred. If an outcome was reported, relevant documentation was obtained and sent to the study coordination center (Population Health Research Institute, Hamilton, Ontario, Canada). Data were entered in case report forms and submitted and stored in a secure online data management system (iDataFax).

Outcomes

The primary outcome was a composite of vascular death and MINS at 30 days. Myocardial injury after noncardiac surgery includes myocardial infarction (MI) and ischemic myocardial injury that does not satisfy the definition of MI (3, 14). **Supplement Table 2** (available at Annals.org) lists the secondary outcomes and the outcome definitions. Blinded outcome adjudicators evaluated the outcomes, and their decisions were used in all statistical analyses.

Statistical Analysis

A statistical analysis plan was prespecified before analyses were done (**Supplement**, available at Annals.org). We planned a sample size of 10 000 patients a priori. We expected 1000 patients to have a primary event, thereby providing more than 55 events per variable for our multivariable analyses (that is, we could explore NT-proBNP thresholds up to 4000 pg/mL on the basis of the increments outlined in our iterative process to identify prognostically important NT-proBNP thresholds), which would ensure a stable model (15).

We assessed the association between preoperative NT-proBNP and the primary outcome on the basis of categorizing NT-proBNP at iterative thresholds to objectively identify optimal categories (**Supplement Table 3**, available at Annals.org) (2, 16). Cox proportional hazards models were used, in which the dependent variable was vascular death or MINS and the independent variables were the RCRI score and preoperative NT-proBNP values. Patients with missing data for the RCRI calculation were assumed not to have the RCRI risk factor and were included in the analyses. Missing data mainly related to preoperative serum creatinine level. Patients with missing preoperative serum creatinine measurements were younger, had fewer medical comorbid conditions, and more commonly had low-risk surgeries than those who had a preoperative serum creatinine available and had preoperative serum creatinine levels of 177 μmol/L (2 mg/dL) or less.

We compared model performance for the multivariable model including RCRI with and without the NT-proBNP thresholds using the c-statistic corrected for optimism and a bias-corrected calibration curve using 1000 bootstrapped samples (17). We subsequently determined the association between the NT-proBNP thresholds and the secondary outcomes. We assessed the utility of using the NT-proBNP thresholds in addition to the RCRI score for risk prediction by calculating the net absolute reclassification improvement (NARI) (18). The NARI was calculated using 2 approaches: 1) predetermined risk categories (<5%, 5% to 15%, >15% to 30%, and >30%) for vascular death or MINS and 2) a relative change of 25% of predicted risk as a minimally important change (**Supplement Table 4**, available at Annals.org).

Post hoc sensitivity analyses enabled us to assess the association between preoperative NT-proBNP levels and the 30-day composite of vascular death and MINS. First, we did a complete-case sensitivity analysis, excluding patients with any missing RCRI data. We also did a sensitivity analysis using split-sample derivation and validation. Because a validation cohort with more than 100 primary events was large enough to avoid overfitting (that is, a validation cohort based on approximately 10% of the overall cohort), we had a derivation

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Table 1. Baseline Characteristics

Variable	All Patients, *n* (%) (*n* = 10 402)	Preoperative NT-proBNP Threshold			
		<100 pg/mL, *n* (%) (*n* = 5356)	100 to <200 pg/mL, *n* (%) (*n* = 1843)	200 to <1500 pg/mL, *n* (%) (*n* = 2608)	≥1500 pg/mL, *n* (%) (*n* = 595)
Age					
45–64 y	5426 (52.2)	3707 (69.2)	767 (41.6)	793 (30.4)	159 (26.7)
65–74 y	2857 (27.5)	1270 (23.7)	632 (34.3)	805 (30.9)	150 (25.2)
≥75 y	2119 (20.4)	379 (7.1)	444 (24.1)	1010 (38.7)	286 (48.1)
Men	5204 (50.0)	2777 (51.8)	812 (44.1)	1277 (49.0)	338 (56.8)
Diabetes*	2103 (20.2)	932 (17.4)	348 (18.9)	616 (23.6)	207 (34.8)
Hypertension†	5552 (53.4)	2348 (43.8)	1028 (55.8)	1707 (65.5)	469 (79.0)
Congestive heart failure‡	346 (3.3)	36 (0.7)	25 (1.4)	145 (5.6)	140 (23.6)
Coronary artery disease§	1527 (14.7)	374 (7.0)	261 (14.2)	652 (25.0)	240 (40.4)
Peripheral vascular disease	796 (7.7)	211 (3.9)	128 (6.9)	316 (12.1)	141 (23.7)
Cerebrovascular disease	717 (6.9)	203 (3.8)	112 (6.1)	284 (10.9)	118 (19.8)
Preoperative eGFR‖					
<30 mL/min/1.73 m^2 or receiving dialysis	308 (3.1)	26 (0.5)	24 (1.4)	107 (4.2)	151 (25.7)
30–<45 mL/min/1.73 m^2	483 (4.9)	78 (1.5)	67 (3.8)	254 (10.0)	84 (14.3)
45–<60 mL/min/1.73 m^2	1084 (10.9)	325 (6.4)	242 (13.7)	438 (17.3)	79 (13.4)
≥60 mL/min/1.73 m^2	8075 (81.2)	4623 (91.5)	1439 (81.2)	1739 (68.5)	274 (46.6)
Cancer (active or metastatic)	2765 (26.6)	1342 (25.1)	501 (27.2)	766 (29.4)	156 (26.2)
Surgery					
Major vascular	654 (6.3)	203 (3.8)	120 (6.5)	250 (9.6)	81 (13.6)
Major general	1859 (17.9)	922 (17.2)	356 (19.3)	479 (18.4)	102 (17.1)
Major thoracic	277 (2.7)	152 (2.8)	46 (2.5)	71 (2.7)	8 (1.3)
Major urologic/gynecologic	1440 (13.8)	777 (14.5)	242 (13.1)	351 (13.5)	70 (11.8)
Major orthopedic	2632 (25.3)	1239 (23.1)	536 (29.1)	711 (27.3)	146 (24.5)
Major neurologic	524 (5.0)	271 (5.1)	100 (5.4)	131 (5.0)	22 (3.7)
Low-risk	3467 (33.3)	2049 (38.3)	539 (29.2)	702 (26.9)	177 (29.7)
Urgent/emergent	455 (4.4)	159 (3.0)	63 (3.4)	168 (6.4)	65 (10.9)
RCRI score					
0	5899 (56.7)	3553 (66.3)	1053 (57.1)	1159 (44.4)	134 (22.5)
1	3180 (30.6)	1484 (27.7)	584 (31.7)	926 (35.5)	186 (31.3)
2	967 (9.3)	270 (5.0)	167 (9.1)	387 (14.8)	143 (24.0)
≥3	356 (3.4)	49 (0.9)	39 (2.1)	136 (5.2)	132 (22.2)

eGFR = estimated glomerular filtration rate; NT-proBNP = *N*-terminal pro–B-type natriuretic peptide; RCRI = Revised Cardiac Risk Index.
* Missing data from 4 patients.
† Missing data from 2 patients.
‡ Missing data from 9 patients.
§ Missing data from 5 patients.
‖ Missing data from 452 patients.

cohort based on approximately 90% of the overall cohort to maximize statistical power to identify NT-proBNP thresholds through iterative Cox proportional hazards models. We performed 1 analysis split by calendar time and 1 split by randomly selected centers.

A 2-sided *P* value less than 0.05 was used to determine statistical significance unless stated otherwise. Statistical analyses were done using SAS, version 9.4 (SAS Institute), and R, version 3.4.0 (The R Project for Statistical Computing). We followed the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) statement in preparing this manuscript (19).

Role of the Funding Source

The overall VISION study was funded by more than 70 grants and funding sources. Roche Diagnostics provided the NT-proBNP assays and some funding. The Australian and New Zealand College of Anaesthetists Project Grant (grant 13/008) also provided funding for this substudy. No funding entity had a role in data collection, statistical analysis, manuscript writing, or the decision to publish.

RESULTS

Of the 18 920 patients enrolled in VISION during the NT-proBNP substudy's enrollment period, 10 402 were included in the NT-proBNP substudy and the current analyses (**Supplement Figure 1**, available at Annals.org). Approximately 40% of patients came from centers in North America, 30% from Asia-Pacific, and 20% from Europe (**Supplement Table 1**). The mean age was 65 years (SD, 11.1), and 50.0% were men (**Table 1**). Patients had a history of diabetes (20.2%), coronary artery disease (14.7%), congestive heart failure (3.3%), peripheral vascular disease (7.7%), and a cerebrovascular event (6.9%). The most common surgeries were major orthopedic (25.3%), major general (17.9%), and major urology or gynecology (13.8%). A third of the patients (33.3%) had low-risk surgeries; 4.4% of procedures were urgent or emergent.

The primary composite outcome of vascular death (54 events, 0.5%) and MINS (1237 events, 11.9%) occurred in 1269 patients (12.2%) within 30 days after surgery. Characteristics of patients with and without the composite primary outcome are presented in Supple-

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ment Table 5 (available at Annals.org). In the Cox proportional hazards models, compared with the reference group (NT-proBNP <100 pg/mL), NT-proBNP measurements of 100 to less than 200 pg/mL had an adjusted hazard ratio (HR) of vascular death or MINS of 2.27 (95% CI, 1.90 to 2.70) and an incidence of 12.3% (226 of 1843), 200 to less than 1500 pg/mL had an adjusted HR of 3.63 (CI, 3.13 to 4.21) and an incidence of 20.8% (542 of 2608), and 1500 pg/mL or greater had an adjusted HR of 5.82 (CI, 4.81 to 7.05) and an incidence of 37.5% (223 of 595) (Table 2). The Figure shows the cumulative risk for the primary outcome at 30 days according to NT-proBNP thresholds. The incidence of 30-day vascular death or MINS for patients with RCRI scores of 0, 1, 2, and 3 or greater was 7.4% (439 of 5899), 14.1% (449 of 3180), 24.7% (239 of 967), and 39.9% (142 of 356), respectively. The optimism-corrected c-statistic to predict the primary outcome on the basis of the RCRI score was 0.65 (CI, 0.64 to 0.67) and increased to 0.73 (CI, 0.72 to 0.74) when the NT-proBNP thresholds were included. The calibration curve did not show any important miscalibration (Supplement Figure 2, available at Annals.org).

The NT-proBNP thresholds also independently predicted all of the secondary outcomes (Table 2). The addition of these thresholds improved model discrimination to predict the composite of all-cause mortality and MI (optimism-corrected c-statistic for RCRI of 0.69 [CI, 0.66 to 0.71] and for RCRI plus NT-proBNP thresholds of 0.75 [CI, 0.73 to 0.78]). Supplement Table 6 (available at Annals.org) shows the incidence of primary and secondary outcomes in the subset of patients who had elective surgery; these results were similar to the overall cohort. Table 3 shows the reclassification of patients who had and did not have the primary composite outcome according to their predicted risk using RCRI and RCRI plus NT-proBNP thresholds. The percentage of reclassification showed improved risk prediction (that is, patients were classified in more appropriate risk categories) when NT-proBNP values were included for patients with and without events (21.4% and 26.4%, respectively). This resulted in a NARI of 258 per 1000 patients (25.8%). The risk reclassification improvement calculated using a 25% relative change in predicted probabilities showed a NARI of 321 per 1000 patients (32.1%).

Supplement Table 7 (available at Annals.org) reports the results from the post hoc split-sample sensitivity analyses. In the derivation cohort split by time (n = 9391), we identified the same NT-proBNP thresholds (100, 200, and 1500 pg/mL), with similar adjusted HRs for the primary outcome as the ones identified using the overall cohort. In the derivation cohort split by centers (n = 9331), we found similar thresholds (100, 300, and 2000 pg/mL). For both analyses, we assessed the independent association between the primary outcome and the NT-proBNP thresholds and found similar associations, as seen in our main analysis. We assessed the model's performance and found similar discrimination between the whole, derivation, and validation cohorts

Table 2. Incidence of 30-Day Outcomes, by Preoperative NT-proBNP Values*

Variable	All Patients (n = 10 402)	Preoperative NT-proBNP Threshold			
		<100 pg/mL (n = 5356)	100 to <200 pg/mL (n = 1843)	200 to <1500 pg/mL (n = 2608)	≥1500 pg/mL (n = 595)
Composite of vascular death or MINS					
Events, n (incidence [95% CI], %)†	1269 (12.2 [11.6–12.8])	278 (5.2 [4.6–5.8])	226 (12.3 [10.8–13.8])	542 (20.8 [19.2–22.3])	223 (37.5 [33.5–41.3])
Adjusted HR (95% CI)	–	1.00	2.27 (1.90–2.70)	3.63 (3.13–4.21)	5.82 (4.81–7.05)
Composite of all-cause mortality or MI					
Events, n (incidence [95% CI], %)†	446 (4.3 [3.9–4.7])	92 (1.7 [1.4–2.1])	55 (3.0 [2.2–3.8])	205 (7.9 [6.8–8.9])	94 (15.8 [12.8–18.7])
Adjusted HR (95% CI)	–	1.00	1.57 (1.12–2.19)	3.64 (2.83–4.69)	5.35 (3.91–7.34)
MINS					
Events, n (incidence [95% CI], %)†	1237 (11.9 [11.3–12.5])	272 (5.1 [4.5–5.7])	223 (12.1 [10.6–13.6])	529 (20.3 [18.7–21.8])	213 (35.8 [31.9–39.6])
Adjusted HR (95% CI)	–	1.00	2.29 (1.91–2.73)	3.62 (3.12–4.21)	5.70 (4.69–6.92)
MI					
Events, n (incidence [95% CI], %)†	378 (3.6 [3.3–4.0])	82 (1.5 [1.2–1.9])	46 (2.5 [1.8–3.2])	175 (6.7 [5.7–7.7])	75 (12.6 [9.9–15.3])
Adjusted HR (95% CI)	–	1.00	1.47 (1.02–2.10)	3.46 (2.64–4.53)	4.68 (3.32–6.60)
All-cause mortality					
Events, n (incidence [95% CI], %)†	88 (0.8 [0.7–1.0])	14 (0.3 [0.1–0.4])	13 (0.7 [0.3–1.1])	37 (1.4 [1.0–1.9])	24 (4.0 [2.4–5.6])
Adjusted HR (95% CI)	–	1.00	2.41 (1.13–5.14)	4.12 (2.20–7.73)	8.40 (4.10–17.23)
Vascular death					
Events, n (incidence [95% CI], %)†	54 (0.5 [0.4–0.7])	11 (0.2 [0.1–0.3])	8 (0.4 [0.1–0.7])	18 (0.7 [0.4–1.0])	17 (2.9 [1.5–4.2])
Adjusted HR (95% CI)	–	1.00	1.84 (0.74–4.59)	2.41 (1.11–5.21)	6.75 (2.90–15.70)

HR = hazard ratio; MI = myocardial infarction; MINS = myocardial injury after noncardiac surgery; NT-proBNP = *N*-terminal pro–B-type natriuretic peptide; RCRI = Revised Cardiac Risk Index.
* Results based on multivariable Cox regression model including RCRI score (i.e., 0, 1, 2, and ≥3) and NT-proBNP categories.
† Thirty-day cumulative incidences calculated using the Kaplan–Meier estimates of survival with 95% CIs.

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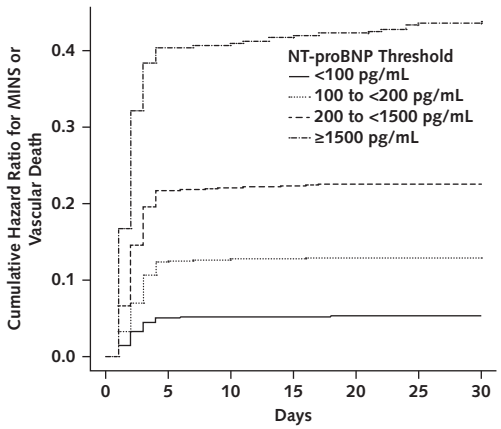
Figure. Kaplan–Meier curve of 30-day risk for MINS or vascular death, by NT-proBNP threshold.



At risk, *n*							
<100 pg/mL	5356	5073	5065	5063	5060	5059	5057
100 to <200 pg/mL	1843	1621	1614	1612	1610	1610	1608
200 to <1500 pg/mL	2608	2080	2068	2063	2054	2050	2048
≥1500 pg/mL	595	384	381	377	374	369	368

MINS = myocardial injury after noncardiac surgery; NT-proBNP = *N*-terminal pro–B-type natriuretic peptide.

in the analyses split by time (c-statistics of 0.73, 0.73, and 0.71, respectively) and centers (c-statistics of 0.73, 0.74, and 0.69, respectively).

We did a sensitivity analysis to compare the results of centers that measured NT-proBNP in their local laboratories with those of centers who shipped samples to the Clinical Research Laboratory and Biobank for measurement. We did not find a meaningful difference in the associations between NT-proBNP thresholds and the primary outcome (**Supplement Table 8**, available at Annals.org) across these 2 cohorts of centers. A complete-case sensitivity analysis excluding patients with missing RCRI data (n = 463) identified the same statistically significant NT-proBNP thresholds (100, 200, and 1500 pg/mL) with no meaningful difference in HRs (**Supplement Table 9**, available at Annals.org). A post hoc analysis demonstrated that the addition of RCRI to NT-proBNP thresholds also improved risk discrimination for the primary outcome (c-statistic of 0.70 for NT-proBNP thresholds alone and 0.73 for the combined RCRI and NT-proBNP model).

DISCUSSION

In this prospective cohort study of 10 402 patients who had inpatient noncardiac surgery, we found that preoperative NT-proBNP concentrations were independently associated with the occurrence of vascular death or MINS at 30 days after surgery. Preoperative NT-proBNP thresholds in addition to the RCRI substantially improved discrimination of patients (optimism-corrected c-statistic increase from 0.65 to 0.73) and perioperative risk stratification (25.8% improved risk reclassification). The preoperative NT-proBNP thresholds also predicted the risk for secondary outcomes. Notably, health care providers were blinded to the NT-proBNP measurements and therefore could not act on the results and potentially alter the relationship between NT-proBNP and primary and secondary outcomes.

In an individual patient data meta-analysis of 1560 patients from 10 cohort studies that measured NT-proBNP levels before noncardiac surgery, a NT-proBNP value of 300 pg/mL or greater was independently associated with the composite of perioperative all-cause mortality or nonfatal MI in a model that included the RCRI (11). In a recent multicenter prospective cohort study, 1347 patients had preoperative NT-proBNP levels measured before major noncardiac surgery (20). Concentrations showed statistically significant independent associations and risk reclassification improvement for death or MINS at 30 days. However, the authors did not use or establish NT-proBNP thresholds. Most stud-

Table 3. Risk Classification Improvement Using NT-proBNP Thresholds*

RCRI and NT-proBNP	RCRI Only				Percentage Reclassification
	<5%	5%–15%	>15%–30%	>30%	
Patients with events, *n*†					21.4%
<5%	0	133	0	0	
5%–15%	0	460	34	8	
>15%–30%	0	229	40	13	
>30%	0	66	165	121	
Patients without events, *n*‡					26.4%
<5%	0	3420	0	0	
5%–15%	0	3820	236	41	
>15%–30%	0	831	127	26	
>30%	0	120	365	147	
Category-based net reclassification					
NARI	258 per 1000 patients				

NARI = Net Absolute Reclassification Index; NT-proBNP = *N*-terminal pro–B-type natriuretic peptide; RCRI = Revised Cardiac Risk Index.
* NARI is calculated as (proportion reclassification for patients with events × event rate) + (proportion reclassification for patients without events × [1 − event rate]). The total is multiplied by 1000 to get the overall NARI.
† A total of 1269 patients.
‡ A total of 9133 patients.

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ies that have evaluated the prognostic capabilities of preoperative NT-proBNP have used a predetermined or dichotomized NT-proBNP threshold (11, 21, 22). Our prospective cohort had a much larger sample size, allowing for greater statistical power to identify several NT-proBNP thresholds and demonstrate improved risk prediction when added to the RCRI.

The 4.3% incidence of all-cause mortality or MI in our cohort was lower than that reported by Rodseth and colleagues (11). Our cohort included 4.4% urgent or emergency surgeries and 6.3% vascular surgeries, compared with 22.7% and 28.8%, respectively, in the Rodseth and colleagues' study. In the overall VISION study, compared with this subcohort, the incidence of MINS was 13.0% versus 11.3%, all-cause mortality was 1.8% versus 0.8%, and vascular mortality was 0.9% versus 0.5%, respectively (1, 2). The lower incidence of these complications in this NT-proBNP cohort compared with the overall VISION cohort may be explained by the lower incidence of urgent or emergency surgeries (4.4% vs. 10.5%, respectively) (1, 2).

The required preoperative blood sample drawn for NT-proBNP prevented enrollment of some patients having urgent or emergency surgery. This may not be a limitation of this study; the utility for preoperative risk stratification may be greatest in the context of elective surgeries. Urgent or emergency surgeries are generally done for organ- or life-threatening conditions, and avoiding delays generally outweighs concerns for preoperative cardiac risk stratification. In our cohort, the incidence of 30-day major cardiac outcomes in patients undergoing elective surgery was similar to that of the overall VISION cohort, confirming that the results can be used to inform cardiac risk for elective cases.

Several national guidelines have proposed the use of NT-proBNP for preoperative risk stratification. The 2014 European Society of Cardiology perioperative guideline noted that NT-proBNP or BNP measurements may be considered for cardiac risk stratification in patients at higher risk, but it did not define "higher risk" or give an NT-proBNP threshold (5). On the basis of the study by Rodseth and colleagues (7), the 2017 Canadian Cardiovascular Society (CCS) perioperative guidelines recommended measuring NT-proBNP or BNP in patients with a baseline risk greater than 5% and to use a NT-proBNP threshold of 300 pg/mL or greater to identify patients at higher risk. Our analyses found that a threshold of 200 pg/mL or greater was associated with a risk greater than 5%. The differences in thresholds are likely due to greater statistical power in our study.

The RCRI is the most validated model for preoperative cardiac risk stratification. Many perioperative guidelines recommend using the RCRI to predict perioperative cardiovascular risk (5–7); however, studies have reported that the RCRI has only moderate discrimination (8). Our results confirm the findings from previous studies that NT-proBNP in addition to the RCRI can improve a patient's cardiac risk reclassification, which is important for several reasons. It is an ethical requirement to accurately inform patients about risk to facilitate optimally informed decisions about the appropriateness of surgery (23). Accurate risk estimation can also affect preoperative management. It can guide choices of surgical and anesthetic approaches (for example, outpatient vs. inpatient surgery, open vs. laparoscopic or endovascular, and general vs. regional anesthesia), decisions regarding further preoperative evaluation (for example, cardiology consultation), and intensity of postoperative surveillance (for example, troponin monitoring, telemetry, and postoperative joint surgical and medical follow-up).

Measurement of troponin levels 48 to 72 hours after major noncardiac surgery in at-risk patients is recommended by the CCS and European Society of Cardiology perioperative guidelines (5, 7). The 2014 American College of Cardiology and American Heart Association perioperative guidelines mentioned uncertainty about postoperative troponin screening in high-risk patients in the absence of a defined management strategy (6). Since the 2014 American College of Cardiology and American Heart Association guidelines, large noncardiac cohort studies have confirmed the utility of systematic troponin monitoring after surgery to detect MINS (2, 24, 25), and new evidence about treatment options for MINS has been published (for example, an international randomized controlled trial of 1754 patients showed the benefits of dabigatran in patients with MINS) (26).

Our study has demonstrated that NT-proBNP can help identify patients who are at higher risk for postoperative cardiac events and may glean the most benefit from perioperative troponin monitoring. The CCS guidelines suggest that troponin monitoring be done in patients with a baseline risk for death or MI of 5% or greater (7). In our cohort, patients with a NT-proBNP less than 200 pg/mL had a risk for death or MI of 3.0% or less, whereas patients with an NT-proBNP between 200 and less than 1500 pg/mL had a risk of 7.9%. Therefore, clinicians could use NT-proBNP to inform decision making about ordering postoperative troponin measurements, with potential cost savings in avoiding such measurements in low-risk patients and to guide management of patients at higher risk for MINS or those who have symptoms.

Our primary outcome was vascular death or MINS. Large prospective cohort studies have shown the prognostic relevance of MINS (27); however, some physicians may not recognize its prognostic relevance because most patients are asymptomatic. To put the prognosis of MINS into perspective, consider the control group outcomes in COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies), a large international trial that included patients with known coronary or peripheral artery disease (28), and MANAGE (Management of myocardial injury After NonCardiac surGEry), a large international trial that included patients with MINS (26). Although COMPASS had substantially longer follow-up than MANAGE (mean of 23 months vs. 16 months, respectively), patients in MANAGE had a risk for vascular death and MI

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greater than 3- and 2-fold higher, respectively, than control patients in COMPASS.

Our study has limitations. Although we confirmed the independent association reported previously between preoperative NT-proBNP and major cardiac events and death after noncardiac surgery (11), we identified new prognostically important NT-proBNP thresholds. These thresholds were derived from our entire cohort and have not been externally validated in a separate cohort study. However, we did 2 split-sample sensitivity analyses (1 by calendar time and 1 by random center selection) to determine whether the results would have differed. In the derivation cohort split by time, we identified the same significant thresholds and similar adjusted HRs as the ones identified using the entire cohort (**Supplement Table 7**). In the derivation cohort split by centers, we found similar thresholds. Both validation cohorts found a similar independent association between NT-proBNP thresholds adjusted for RCRI and our primary outcome with similar model performance.

We did not measure BNP and cannot inform its optimal thresholds for preoperative cardiac risk stratification. Although BNP and NT-proBNP reflect the same cardiac hormonal activity (the prehormone proBNP is cleaved into equal proportions of BNP and NT-proBNP), there is no conversion factor for the comparison between BNP and NT-proBNP values (29). Informing the optimal BNP thresholds in noncardiac surgery will require further investigation; however, this may be challenging because of the instability and shorter half-life of the BNP analyte (12).

Although the RCRI is one of the most validated models for preoperative cardiac risk stratification, it was not designed to predict vascular death and MINS. We systematically measured troponin levels only until day 3 after surgery. Therefore, after that day we may have missed additional MINS events in patients who did not have ischemic symptoms. Optimal use of the RCRI with NT-proBNP measurement will require an online calculator in which clinicians can enter RCRI variables and NT-proBNP and receive an output of the patient's risk for major adverse events.

Preoperative NT-proBNP levels are strongly associated with major cardiac events and death in patients undergoing in-hospital noncardiac surgery. *N*-terminal pro–B-type natriuretic peptide significantly improved discrimination among patients who did and did not have the primary outcome. Clinicians may consider using preoperative NT-proBNP to improve preoperative cardiac risk stratification in patients having in-hospital noncardiac surgery.

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Standing Waves

Should be avoided when marching in groups
The stacked forces grow with the fall of each step
Until a bridge twists off its mooring
And falls to the chasm below.

My friend was a static wave
Until scotch and smoke increased the amplitude
Past the strength of his heart.
The rhythm looked like double jump ropes
Whipping the same spot of hot pavement.

But death is an inexact eraser
Even years after consigning his body to flame
There can still be expectation when a door opens
The particle is gone
But the wave remains.

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