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Preoperative NT-proBNP and CRP Predict Perioperative Major Cardiovascular Events in Noncardiac Surgery

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Running title: NT-proBNP and CRP predict perioperative event

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Abstract

Objective: To investigate whether simple and non-invasive measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP) and/or C-reactive protein (CRP) can predict perioperative major cardiovascular event (PMCE).

Design: Prospective, single center, cohort study.

Setting: A 1900-bed tertiary-care university hospital in Seoul, Korea

Design and Patients: The predictive power of NT-proBNP, CRP, and Revised Cardiac Risk Index (RCRI) for the risk of PMCE (myocardial infarction, pulmonary edema, or cardiovascular death) were evaluated from a prospective cohort of 2054 elective major noncardiac surgery patients. Optimal cut-off values were derived from receiver operating characteristic curve (ROC) analysis.

Main outcome measurement: PMCE (myocardial infarction, pulmonary edema, or cardiovascular death) within postoperative 30 days.

Results: PMCE developed in a total of 290 patients (14.1%). Each increasing quartile of NT-proBNP or CRP level was associated with a greater risk of PMCE after adjustment for traditional clinical risk factors. The relative risk (RR) of highest versus lowest quartile was 5.2 for NT-proBNP ($p<0.001$) and 3.7 for CRP ($p<0.001$). Both NT-proBNP (cut-off = 301 ng/L) and CRP (cut-off = 3.4 mg/L) predicted PMCE better than RCRI (cut-off = 2) by ROC analysis ($p<0.001$). Moreover, the predictive power of RCRI (adjusted RR = 1.5) could be improved significantly by addition of CRP and NT-proBNP to RCRI (adjusted RR = 4.6) ($p<0.001$).

Conclusions: High preoperative NT-proBNP or CRP is a strong and independent predictor of perioperative major cardiovascular event in non-cardiac surgery. The predictive power of current clinical risk evaluation system would be strengthened by these biomarkers.

Keywords: perioperative cardiovascular event, natriuretic peptides, CRP

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Perioperative major cardiovascular events (PMCE) such as acute myocardial infarction, pulmonary edema, or primary cardiovascular death are important causes of morbidity in patients undergoing a major noncardiac surgery.[1] A number of clinical risk indices using scoring system have been developed, but the predictive power is still insufficient.[2-5] Moreover, the results of preoperative myocardial stress test were not consistently predictive of risk.[6-8] A simple and strongly predictive non-invasive test is clinically warranted.

We hypothesized that the pathophysiology of cardiovascular disease including inflammation, myocardial ischemia, or increased ventricular filling pressures would be important in the development of PMCE. Then cardiovascular biomarkers reflecting this pathophysiology would be useful for the prediction of perioperative risk.[9] Based on abundant clinical data, practical availability, and background pathophysiology,[10-12] we reasoned that N-terminal pro-brain natriuretic peptide (NT-proBNP) and C-reactive protein (CRP), representative biomarkers of hemodynamic stress and inflammation, respectively, would be predictive of PMCE. We investigated the predictive power of preoperative NT-proBNP and CRP and compared it with a well-validated clinical risk index for perioperative cardiovascular risk in a large prospective cohort of patients undergoing elective major non-cardiac surgery.

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Methods

Patients

We enrolled patients who were referred to consulting cardiology physician for the evaluation of preoperative cardiovascular risk if the following criteria were fulfilled; 1) candidates for elective major non-cardiac surgery and aged more than 21 years old, and 2) at least one of cardiovascular risk factors such as hypertension, diabetes, angina, history of revascularization, heart failure, or stroke, or 3) abnormal preoperative electrocardiography with pathological Q wave or non-sinus rhythm. Major non-cardiac surgery was defined by procedures performed in the operating room requiring general, spinal, or epidural anesthesia, after exclusion of very low risk surgeries such as dermatologic, ophthalmologic, nasal, or auditory procedures.

We prospectively enrolled 2304 consecutive patients from November 2004 to April 2008. The following patients were excluded; surgery was not done within 2 weeks (N=118), significant myocardial ischemia or who required open heart surgery (N=29). To avoid bias in the NT-proBNP results from renal insufficiency, 103 patients with preoperative serum creatinine ≥2.0 mg/dL (≥176.8 µmol/L) were also excluded.[13] The remaining 2054 patients had undergone non-cardiac surgery within 2 weeks and constituted the study cohort (Figure 1).

Data collection

Clinical perioperative cardiovascular risk was assessed according to the Revised Cardiac Risk Index (RCRI) modified by Lee, a well-validated and widely used risk prediction index.[1,4,5,8,14] Briefly, RCRI calculates perioperative risk by sum of points. Each risk factor, including high-risk surgical procedures, history of ischemic heart disease, pulmonary edema, cerebrovascular disease, insulin-dependent diabetes, and serum creatinine > 2.0 mg/dL, is assigned one point. The risk of major cardiac event including myocardial infarction, pulmonary edema, primary cardiac arrest and complete heart block predicted by RCRI was known to be 0.4% to 11% according to RCRI score of 0 to ≥ 3.

Patient's clinical history and functional capacity were evaluated according to the

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ACC/AHA guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery.[8] Basic laboratory tests including electrocardiography, chest X-ray, NT-proBNP, and CRP were evaluated within 2 weeks before surgery. Additional non-invasive tests were performed by physician's discretion. Electrocardiography and serum troponin I were evaluated at the end of the day of surgery and 24 hours later. Chest X-ray was taken on the next day. Any abnormal signs or symptoms suggesting pulmonary edema or myocardial ischemia was followed by meticulous evaluation of perioperative cardiac status with repeated cardiac serum markers and electrocardiography. If active pulmonary edema or ongoing myocardial ischemia was found, the patient was transferred to the cardiovascular team and treated appropriately. Patients were followed up by the consulting physician until discharge or up to 30 days in-hospital after surgery. In case of mortality, the cause of death was decided on the consensus of the surgeon, anaesthesiologist, and cardiovascular consulting physician.

Primary endpoint was perioperative major cardiovascular event (PMCE), which was defined by any single or combined event of secondary endpoints including myocardial infarction, development of pulmonary edema, or primary cardiovascular death. Myocardial infarction was defined by a rise in postoperative troponin I above the 99th percentile of upper reference limit (0.78 ng/mL, Roche Diagnostics, Switzerland). Diagnosis of pulmonary edema required a formal reading of chest X-ray by a radiologist consistent with the complication. Primary cardiovascular death was defined by sudden death that could not be explained by any other non-cardiovascular postoperative complications. All clinical events were collected by research nurse and investigated by physicians. This study protocol was approved by the institutional review board of Samsung Medical Center.

Statistics

Perioperative risk predictors (RCRI, CRP, and NT-proBNP) were treated as continuous variables or ordered categorical variables. Logarithmically transformed values of NT-proBNP and CRP were also used to minimize distribution skewness and kurtosis. Dose-response relationship between risk predictors and clinical outcome were investigated by Jonckheere-Terpstra test for trend. The predictive power of each risk predictor was also quantitatively evaluated with relative risk per 1-SD increase of RCRI and logarithmically transformed biomarker levels. Receiver-operating characteristic (ROC)

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analysis was performed to calculate sensitivity, specificity, area under the curve, and the optimal cut-off. The predictive power of each method was compared using Hanley and McNail method.[15] Relative risk was calculated by Zhang and Yu's method.[16] Relative risk was also calculated for the risk predictors with values categorized by optimal cut-off levels, or combination of these cut-off levels in an additive manner. Independent predictors of PMCE in univariate analysis were included in multivariate logistic models with forward conditional methods. A p value < 0.05 (2-sided) was considered significant. SPSS version 13.0 was used mostly. ROC curves were compared using Medcalc version 9.6.

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Results

Clinical characteristics

Preoperative clinical characteristics of the study population are shown in Table 1. Briefly, most patients had good functional status without overt heart failure (functional class I or II in 94.6% and no heart failure in 97.0%). A history of angina was found in 13.2%, including 8.0% of myocardial infarction. Percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) had been performed before non-cardiac surgery in 14.8%. Two-dimensional echocardiography was performed in most patients (93.6%), revealing abnormal left ventricular wall motion in 19.9% of patients. Evidence of myocardial ischemia which was defined by positive non-invasive test or significant coronary artery stenosis was found in 21.6%. Preoperative beta-blocker or statin was used in 17.3% and 14.8%, respectively.

Perioperative clinical evaluation

Most patients received general anesthesia (97.1%). Ninety-three patients (4.5%) underwent urgent surgery within 24 hours after consultation because of altered clinical situation. These cases were not excluded from the analysis (Table 2).

Clinical outcomes

Perioperative major cardiovascular event (PMCE) had developed in 290 (14.1%) patients. Individual patients may have had more than one event, and all events were counted as an incidence. There were 102 (5.0%) acute myocardial infarction, 248 (12.1%) pulmonary edema, and 20 (1.0%) deaths, which were similar to previous studies evaluated patients with risk of cardiovascular disease.[1] Five patients died due to postoperative disease progression or surgical complication (0.2%), and 15 deaths were determined to be primary cardiovascular death (0.7%), which included 3 (0.2%) acute myocardial infarction, 2 (0.1%) stress induced cardiomyopathy,[17] 4 (0.2%) aortic aneurysm rupture or dissection, 1 (0.1%) stroke, and 5 (0.2%) sudden death of unknown cause (Figure 1) (Table 3).

Predictive power of perioperative risk predictors

We evaluated the continuous values of three risk predictors against perioperative events. Not only increasing score of a clinical predictor, RCRI, but also increasing quartile of

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biomarker levels, NT-proBNP and CRP, was associated with a greater risk of PMCE ($p<0.001$) (Figure 2).

Next we investigated whether the risk predictors are related to clinical outcomes independently each other. Each 1-SD increase in RCRI (1 to 2) (adjusted relative risk (RR) = 1.26 [95% CI = 1.10–1.44]), log CRP (2.7 to 15.1 mg/L) (1.74 [1.55–1.95]), or log NT-proBNP (135 to 601 ng/L) (2.17 [1.91–2.45]) was associated with 1.3- to 2.2-fold increased rate of PMCE, even after adjustment for other risk predictors and traditional clinical risk factors. By subgroup analysis, CRP and NT-proBNP were also significantly associated with all secondary endpoints, whereas RCRI was not associated with AMI or primary cardiovascular death. Each 1-SD increase in log CRP or log NT-proBNP was also associated with 1.6- to 2.3-fold increased risk of PMCE (Table 4).

Augmentation of predictive power of clinical risk index by addition of biomarkers

Risk predictors categorized by optimal cut-off levels were used to test whether the predictive power could be increased by the combination of multiple risk factors. RCRI cut-off (≥2) was associated with 1.5-fold increased risk of PMCE after adjustment for age, sex, and traditional clinical risk factors (adjusted RR = 1.50 [95% CI =1.17–1.91]). The risk of PMCE based on CRP cut-off (≥3.4 mg/L) and NT-proBNP cut-off (≥301 ng/L) were much higher, 2.7-fold and 3.9-fold, respectively (CRP cut-off, 2.75 [2.16–3.45]; NT-proBNP cut-off, 3.89 [3.15–4.14]) (Table 4). Higher CRP and NT-proBNP values were also associated with 2.5- to 5.4-fold increased risk of secondary endpoints including AMI, pulmonary edema, and primary cardiovascular death ($p<0.05$), whereas higher RCRI was not associated with AMI or primary cardiovascular death (Table 4).

The addition of biomarkers to RCRI increased the relative risk of RCRI for clinical events 3-fold. For PMCE, the adjusted RR of RCRI increased from 1.50 [95% CI = 1.17–1.91] to 4.55 [3.69–5.52] after addition of CRP and NT-proBNP. The relative risks for secondary endpoints including AMI, pulmonary edema, and primary cardiovascular death also increased 3- to 7-fold (Table 4). The increase of predictive power of RCRI by addition of biomarkers to RCRI was again calculated using ROC analysis. For PMCE,

AUC (area under curve) of combination of RCRI cut-off (≥2) and NT-proBNP cut-off

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(≥301 ng/L), 0.735 [0.714–0.754], and AUC of combination of RCRI cut-off and CRP cut-off (≥3.4 mg/L), 0.694 [0.673–0.715], were significantly higher than AUC of RCRI cut-off, 0.592 [0.570–0.615], ($p<0.001$, each). AUC of combination of RCRI cut-off and NT-proBNP cut-off and CRP cut-off, 0.772 [0.752–0.790], was even much higher than AUC of RCRI cut-off ($p<0.001$) (Figure 3 panel A). The increase in AUC by addition of biomarker cut-offs to RCRI cut-off was also evident in all secondary endpoints including AMI, pulmonary edema, and primary cardiovascular death (Figure 3 panel B-D).

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Discussion

Our study showed that the predictive power of a current perioperative clinical risk index could be strengthened significantly by the simple addition of cardiovascular biomarkers, NT-proBNP and CRP. Our findings can be summarized that the average sensitivity of predicting perioperative major cardiovascular event increased from 59% to 77% after addition of biomarkers to clinical risk prediction system.

Predictive power of biomarker versus clinical risk index

The Revised Cardiac Risk Index modified by Lee (RCRI), which has been shown to be superior to other perioperative risk indices was selected as the clinical risk predictor in our study.[2-5] The results showed that a single cardiovascular biomarker, NT-proBNP or CRP, is superior to clinical risk indices for the prediction of perioperative events. In addition, both NT-proBNP and CRP were significantly associated not only with all clinical events but also with all subsidiary events including AMI, pulmonary edema, and primary cardiovascular death, whereas RCRI was not associated with primary cardiovascular death. Furthermore, NT-proBNP and CRP were not only useful for risk prediction but also shown to improve the predictive power of clinical risk index. The addition of NT-proBNP and CRP to the clinical risk index increased the adjusted relative risk 3-fold.

Role of NT-proBNP and CRP in the pathophysiology of perioperative cardiovascular events

The pathophysiology of perioperative myocardial infarction has been explained by responses to perioperative surgical stress represented by a catecholamine surge with associated hemodynamic stress, systemic inflammation, and hypercoagulability.[18,19] High NT-proBNP was associated not only with a high risk of pulmonary edema but also with AMI and primary cardiovascular death in our study. This could be explained by the release of NT-proBNP or B-natriuretic peptide (BNP) from subclinical ischemic or injured myocardial tissue regardless of hemodynamic stress.[12,20] Our results strongly suggest that NT-proBNP could be marker of myocardial ischemia or generalized cardiac impairment in perioperative situations as well as non-surgical situations. The predictive power of CRP was also better than the clinical risk index in this study. However the high CRP levels did not predict clinical events beyond NT-proBNP. Previous population

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based studies showed that the value of CRP in cardiovascular risk prediction was moderate or less than traditional risk factors.[21,22] A recently published study showed that NT-proBNP was better than CRP for the prediction of sudden cardiac death.[23] Relatively high CRP level in perioperative condition might lead to greater contribution of CRP for the risk prediction in our study.

Limitations

This study was performed at single center. Only patients who had undergone formal preoperative cardiovascular consultation were included. However, given the strength of our results and wide variability in the predictive power of risk indices which highly depend on study population, it is unlikely that enrollment of more patients would have changed the main results of our study.[1] Long-term follow-up after discharge was not performed, although most postoperative cardiovascular events is known to develop in early postoperative periods.[24,25] Exclusion of patients with renal dysfunction might have affected the predictive power of RCRI, which includes renal function evaluation.[13,26] Therefore, our results cannot be generalized to patients with renal dysfunction. The presence of preoperative infection or the use of antibiotics, which might affect the level of CRP or the severity of perioperative systemic inflammation, was not used as an exclusion criterion. The relationship between infection and perioperative cardiovascular disease is little known and requires further investigation. The use of preoperative beta-blocker or statin was less than 20% and was not associated with clinical events in our study. The benefit of beta-blocker or statin is currently in debate even in high risk patients, and large prospective trials are needed to confirm it.[6,27,28]

In conclusion, our results demonstrate that high preoperative NT-proBNP and CRP levels are strong and independent predictors of perioperative cardiovascular event following non-cardiac surgery. Furthermore, the predictive power of the current clinical perioperative risk index could be strengthened significantly by the addition of these biomarkers. Evaluation of preoperative NT-proBNP and CRP is a practical, simple, and reasonable strategy to improve perioperative risk prediction strategies with minimal clinical burden and cost.

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Conflict of interest: None declared.

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References

1. Devereaux PJ, Goldman L, Cook DJ, *et al.* Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. *Cmaj*. 2005;**173**:627-34.
2. Goldman L, Caldera DL, Nussbaum SR, *et al.* Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med*. 1977;**297**:845-50.
3. Detsky AS, Abrams HB, Forbath N, *et al.* Cardiac assessment for patients undergoing noncardiac surgery. A multifactorial clinical risk index. *Arch Intern Med*. 1986;**146**:2131-4.
4. Lee TH, Marcantonio ER, Mangione CM, *et al.* Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;**100**:1043-9.
5. Kertai MD, Boersma E, Klein J, *et al.* Optimizing the prediction of perioperative mortality in vascular surgery by using a customized probability model. *Arch Intern Med*. 2005;**165**:898-904.
6. Poldermans D, Bax JJ, Schouten O, *et al.* Should major vascular surgery be delayed because of preoperative cardiac testing in intermediate-risk patients receiving beta-blocker therapy with tight heart rate control? *J Am Coll Cardiol*. 2006;**48**:964-9.
7. Falcone RA, Nass C, Jermyn R, *et al.* The value of preoperative pharmacologic stress testing before vascular surgery using ACC/AHA guidelines: a prospective, randomized trial. *J Cardiothorac Vasc Anesth*. 2003;**17**:694-8.
8. Fleisher LA, Beckman JA, Brown KA, *et al.* ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *J Am Coll Cardiol*. 2007;**50**:e159-241.

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9. Kistorp C, Raymond I, Pedersen F*, et al.* N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. *Jama*. 2005;**293**:1609-16.
10. Zethelius B, Berglund L, Sundstrom J*, et al.* Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. *N Engl J Med*. 2008;**358**:2107-16.
11. Timpson NJ, Lawlor DA, Harbord RM*, et al.* C-reactive protein and its role in metabolic syndrome: mendelian randomisation study. *Lancet*. 2005;**366**:1954-9.
12. Morrow DA, de Lemos JA, Blazing MA*, et al.* Prognostic value of serial B-type natriuretic peptide testing during follow-up of patients with unstable coronary artery disease. *Jama*. 2005;**294**:2866-71.
13. Goei D, Schouten O, Boersma E*, et al.* Influence of renal function on the usefulness of N-terminal pro-B-type natriuretic peptide as a prognostic cardiac risk marker in patients undergoing noncardiac vascular surgery. *Am J Cardiol*. 2008;**101**:122-6.
14. Laine C, Williams SV, Wilson JF. In the clinic. Preoperative evaluation. *Ann Intern Med*. 2009;**151**:ITC1-16.
15. Stephan C, Wesseling S, Schink T*, et al.* Comparison of eight computer programs for receiver-operating characteristic analysis. *Clin Chem*. 2003;**49**:433-9.
16. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *Jama*. 1998;**280**:1690-1.
17. Hahn JY, Gwon HC, Park SW*, et al.* The clinical features of transient left ventricular nonapical ballooning syndrome: comparison with apical ballooning syndrome. *Am Heart J*. 2007;**154**:1166-73.
18. Poldermans D, Hoeks SE, Feringa HH. Pre-operative risk assessment and risk reduction before surgery. *J Am Coll Cardiol*. 2008;**51**:1913-24.
19. Schouten O, Bax JJ, Poldermans D. Preoperative cardiac risk assessment in vascular surgery patients: seeing beyond the perioperative period. *Eur Heart J*. 2008;**29**:283-4.
20. Sabatine MS, Morrow DA, de Lemos JA*, et al.* Acute changes in circulating natriuretic peptide levels in relation to myocardial ischemia. *J Am Coll Cardiol*. 2004;**44**:1988-95.
21. van der Meer IM, de Maat MP, Kiliaan AJ*, et al.* The value of C-reactive protein

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in cardiovascular risk prediction: the Rotterdam Study. *Arch Intern Med*. 2003;**163**:1323-8.

22. Pradhan AD, Manson JE, Rossouw JE*, et al.* Inflammatory biomarkers, hormone replacement therapy, and incident coronary heart disease: prospective analysis from the Women's Health Initiative observational study. *Jama*. 2002;**288**:980-7.
23. Korngold EC, Januzzi JL, Jr., Gantzer ML*, et al.* Amino-terminal pro-B-type natriuretic peptide and high-sensitivity C-reactive protein as predictors of sudden cardiac death among women. *Circulation*. 2009;**119**:2868-76.
24. McFalls EO, Ward HB, Moritz TE*, et al.* Predictors and outcomes of a perioperative myocardial infarction following elective vascular surgery in patients with documented coronary artery disease: results of the CARP trial. *Eur Heart J*. 2008;**29**:394-401.
25. Owens CD, Ridker PM, Belkin M*, et al.* Elevated C-reactive protein levels are associated with postoperative events in patients undergoing lower extremity vein bypass surgery. *J Vasc Surg*. 2007;**45**:2-9; discussion 9.
26. McCullough PA, Duc P, Omland T*, et al.* B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. *Am J Kidney Dis*. 2003;**41**:571-9.
27. Devereaux PJ, Yang H, Yusuf S*, et al.* Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet*. 2008;**371**:1839-47.
28. Bangalore S, Wetterslev J, Pranesh S*, et al.* Perioperative beta blockers in patients having non-cardiac surgery: a meta-analysis. *Lancet*. 2008;**372**:1962-76.

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Tables

Table 1. Baseline Clinical Characteristics

	Frequency (%) or median with interquartile range
Age (years)	68 (61 – 73)
Male gender	1247 (60.7)
Functional class III or IV	112 (5.5)
Diabetes	355 (17.3)
Diabetes treated with insulin	71 (3.5)
Hypertension	1247 (60.7)
Previous or current heart failure	62 (3.0)
Previous stroke	188 (9.3)
Angina	270 (13.2)
Previous myocardial infarction	165 (8.0)
Previous revascularization*	304 (14.8)
Creatinine (mg/dL)	0.9 (0.7 – 1.1)
NT-proBNP (ng/L)	109.3 (47.0 – 352.8)
C-reactive protein (mg/L)	2.0 (0.7 – 8.0)
Electrocardiography	2054 (100)
Pathological Q waves	111 (5.4)
Atrial fibrillation	164 (8.0)
Left bundle branch block	14 (0.7)
Echocardiography	1923 (93.6)
Left ventricular ejection fraction ≤40%	95 (4.6)
Abnormal left ventricular wall motion	408 (19.9)
Preoperative noninvasive test[†]	765 (37.2)
Overall positive result for ischemia	188 (9.2)
Preoperative Invasive test	544 (26.5)
Significant coronary artery disease by invasive test	359 (17.5)
Any evidence of myocardial ischemia[§]	444 (21.6)

Data are shown as frequency (%) or median with interquartile range, as appropriately.
*Previous revascularization includes percutaneous coronary intervention in 222 cases and bypass surgery in 82 cases.

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†Preoperative noninvasive test includes SPECT in 577 cases, Treadmill test in 113 cases, and stress echocardiography in 47 cases.

§Positive non-invasive test or coronary artery stenosis of more than 50% was defined as any evidence of myocardial ischemia.

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Table 2. Surgical Procedure and Perioperative Risk

	Frequency (%)
Vascular surgery	531 (25.9)
Aorta	160 (7.8)
Suprainguinal vascular	98 (4.8)
Infrainguinal vascular	158 (7.7)
Carotid endarterectomy	97 (4.7)
Other vascular	18 (0.9)
Non-vascular surgery	1520 (74.4)
Thorax	85 (4.1)
Abdomen	501 (24.4)
Head and neck	178 (8.7)
Orthopedic	439 (21.4)
Prostate	82 (4.0)
Neurosurgery	55 (2.7)
Other surgery	182 (8.9)
General anesthesia	1994 (97.1)
Urgent surgery	93 (4.5)
RCRI (median, interquartile range)	1 (0–2)
RCRI = 0	555 (27.0)
RCRI = 1	846 (41.2)
RCRI = 2	579 (28.2)
RCRI = 3	69 (3.4)
RCRI = 4	5 (0.2)
High risk surgery by RCRI*	844 (41.1)

Data are shown as frequency (percent).

*Defined by intraperitoneal, intrathoracic, or suprainguinal vascular surgery according to RCRI (Revised Cardiac Risk Index modified by Lee).

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Table 3. Clinical Outcome

	Frequency (%)
Perioperative major cardiovascular event (PMCE)	290 (14.1)
Acute myocardial infarction	102 (5.0)
Revascularization	26 (1.3)
Percutaneous coronary intervention	24 (1.2)
Coronary artery bypass surgery	2 (0.1)
New or aggravated heart failure	248 (12.1)
Primary cardiovascular death*	15 (0.7)
Acute myocardial infarction	3 (0.2)
Stress induced cardiomyopathy	2 (0.1)
Aortic disease	4 (0.2)
Stroke	1 (0.1)
Unknown	5 (0.2)
Death due to postoperative complication or disease progression	5 (0.2)
All death	20 (1.0)

Data are shown as frequency (percent).

*Death that was not caused by postoperative complication or underlying non-cardiovascular disease progression.

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Table 4. Clinical Outcomes According to the Risk Predictors

	PMCE		AMI		PE		CV Death	
	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
Per 1-SD increase*								
RCRI	1.26 (1.10-1.44)	0.001	1.18 (0.88-1.56)	0.27	1.30 (1.13-1.49)	<0.001	0.53 (0.29-1.00)	0.05
CRP	1.74 (1.55-1.95)	<0.001	1.58 (1.28-1.93)	<0.001	1.86 (1.64-2.10)	<0.001	2.16 (1.32-3.51)	0.002
NT-proBNP	2.17 (1.91-2.45)	<0.001	1.55 (1.28-1.88)	<0.001	2.27 (1.97-2.62)	<0.001	2.30 (1.48-3.56)	<0.001
Optimal cut-off of each risk predictors†								
RCRI	1.50 (1.17-1.91)	0.002	1.14 (0.70-1.86)	0.59	1.52 (1.17-1.96)	0.002	0.38 (0.08-1.71)	0.21
CRP	2.75 (2.16-3.45)	<0.001	2.62 (1.66-4.08)	<0.001	2.97 (2.28-3.81)	<0.001	5.38 (1.50-18.78)	0.010
NT-proBNP	3.89 (3.15-4.74)	<0.001	2.54 (1.68-3.79)	<0.001	4.72 (3.72-5.89)	<0.001	5.39 (1.86-15.30)	0.002
Combination of best cutoff of each predictors§								
RCRI or CRP or NT-proBNP≥ cutoff§	4.55 (3.69-5.52)	<0.001	3.24 (2.10-4.92)	<0.001	5.64 (4.49-6.96)	<0.001	7.71 (2.48-23.32)	<0.001

Investigate independent association of each risk predictors with clinical outcomes were shown as adjusted relative risk (RR) with 95% confidence intervals (CI) , all three risk predictors were included in the logistic regression analysis with forward conditional method. Analysis was adjusted with all significant univariate risk factors including age and sex. PMCE, perioperative major cardiovascular event; AMI, acute myocardial infarction; PE, pulmonary edema; CV Death, primary cardiovascular death.

*Measured in linear values, 1-SD increase from mean corresponded to 1 to 2 for RCRI, 135 ng/L to 601 ng/L for NT-proBNP, and 2.7 mg/L to 15.1 mg/L for CRP, respectively.
†Optimal cut-off values were ≥2 for RCRI, ≥301 ng/L for NT-proBNP, and ≥3.4 mg/L for CRP.

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§Defined by at least two of three risk predictors are higher than cutoff values.

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Figure Legends

Figure 1. Study flowchart

Figure 2. Clinical outcomes according to the risk predictors

PMCE, perioperative major cardiovascular event; AMI, acute myocardial infarction; PE, pulmonary edma; CV death, primary cardiovascular death. * p<0.001 by Jonckheere-Terpstra test for trend.

Figure 3. ROC analysis of perioperative risk predictors

The predictive power of each combination of categorized risk predictor in an additive manner was investigated. Risk predictors were categorized according to the optimal cut-off levels derived from ROC analysis, which were 2 for RCRI, 301 ng/L for BNP, and 3.4 mg/L for CRP. AUCs with 95% CI are shown below each panel. *p<0.05 by Hanley and McNail methods.

Panel A. ROC for PMCE. *p<0.001 for all, except RCRI + NT-proBNP versus RCRI + NT-proBNP + CRP (p=0.001), and RCRI + CRP versus RCRI + NT-proBNP (p=0.010).

Panel B. ROC for AMI. *p<0.001 for all, except RCRI + NT-proBNP versus RCRI + NT-proBNP + CRP (p=0.026), RCRI + CRP versus RCRI + NT-proBNP + CRP (p=0.002), and RCRI + CRP versus RCRI + NT-proBNP (p=0.590).

Panel C. ROC for pulmonary edema. *p<0.001 for all, except RCRI + CRP versus RCRI + NT-proBNP (p=0.004), and RCRI + NT-proBNP versus RCRI + NT-proBNP + CRP (p=0.001).

Panel D. ROC for primary cardiovascular death. *RCRI versus CRP, p=0.021; RCRI versus RCRI + NT-proBNP, p=0.012; RCRI versus RCRI + NT-proBNP + CRP, p=0.002; RCRI + CRP versus RCRI + NT-proBNP + CRP, p=0.021.

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Figure 1. Study flowchart

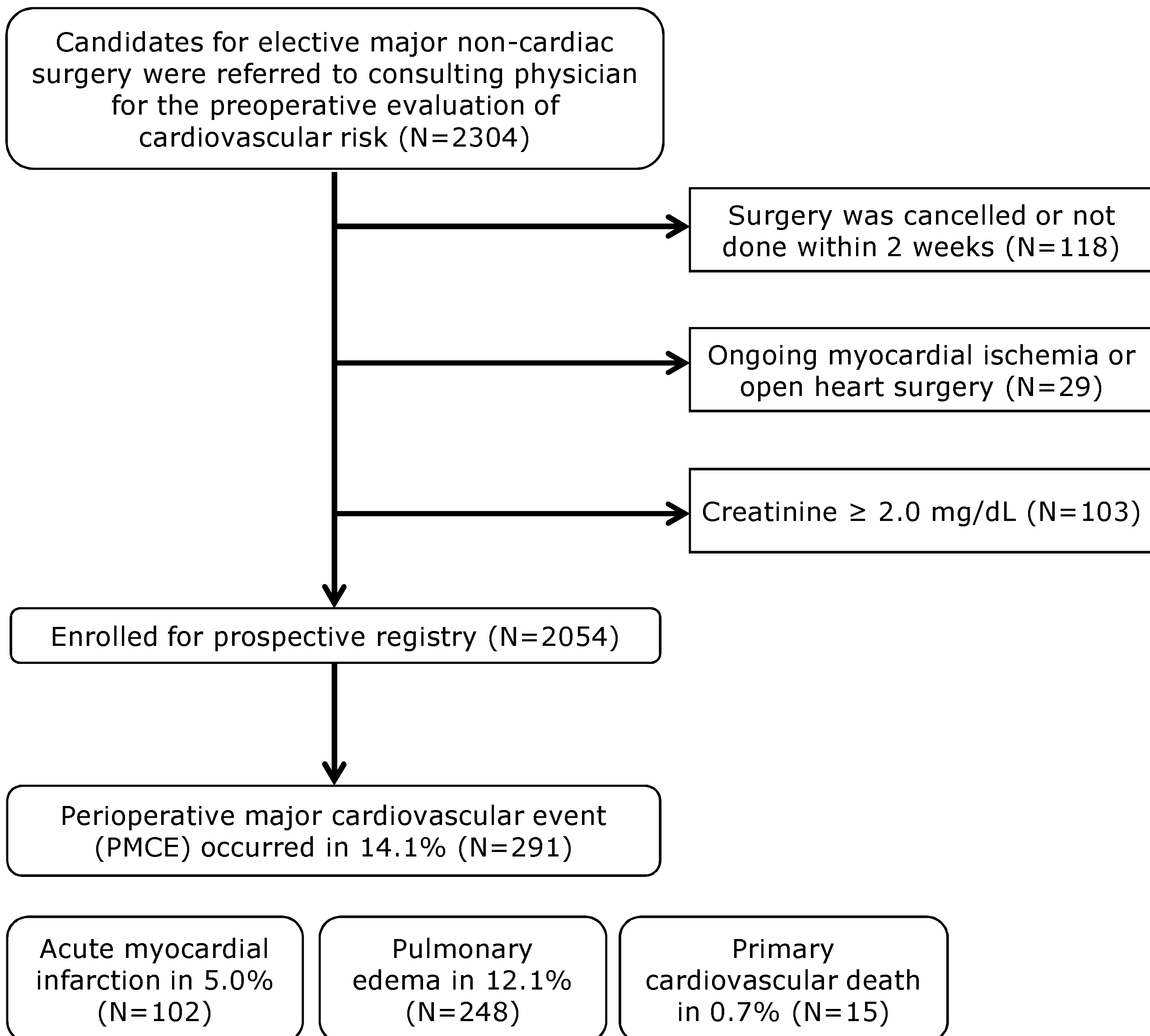

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Figure 2. Clinical outcomes according to the risk predictors

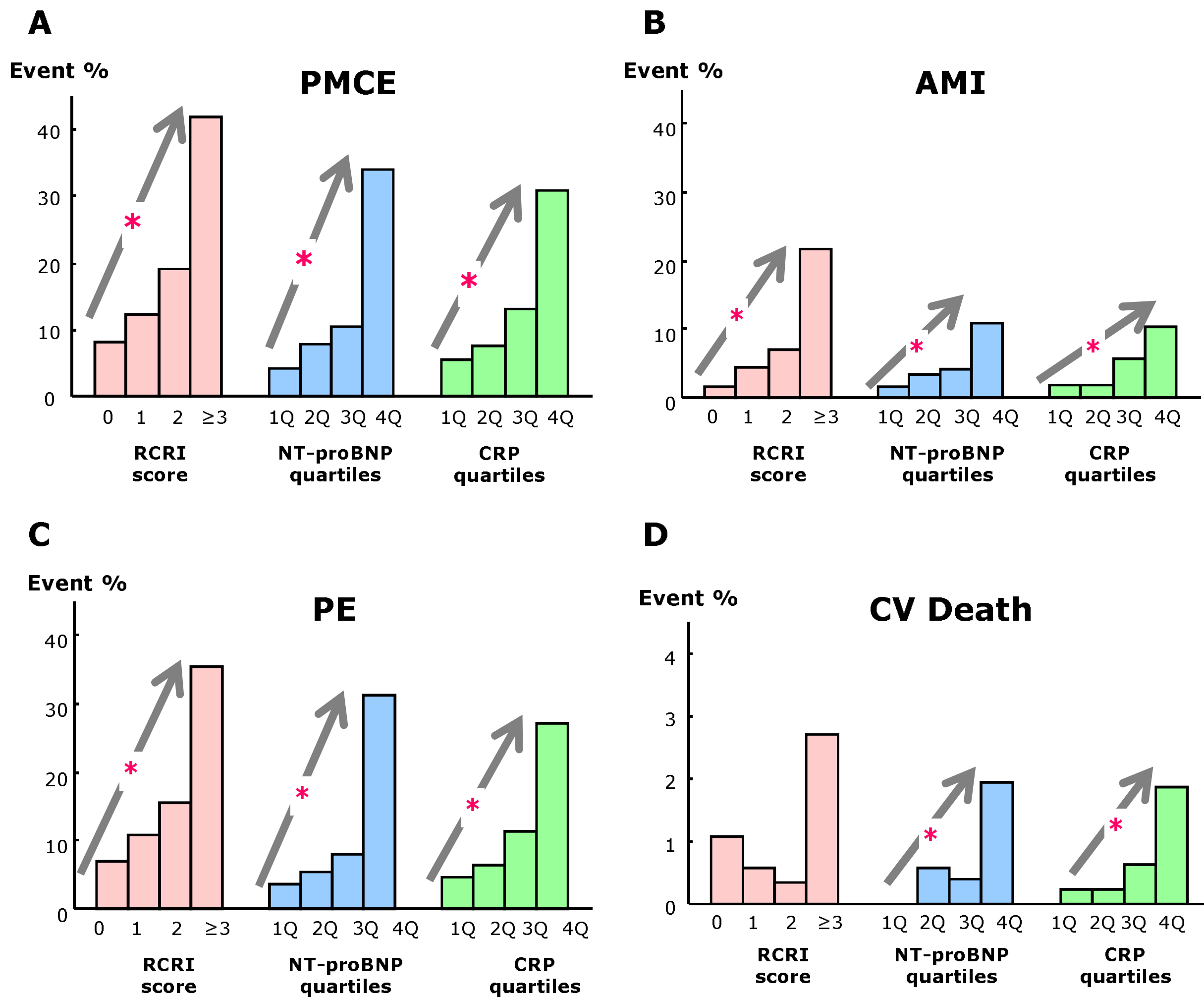

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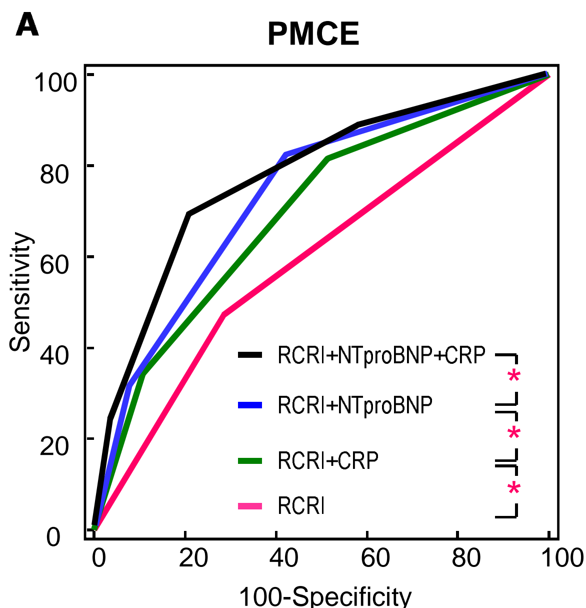
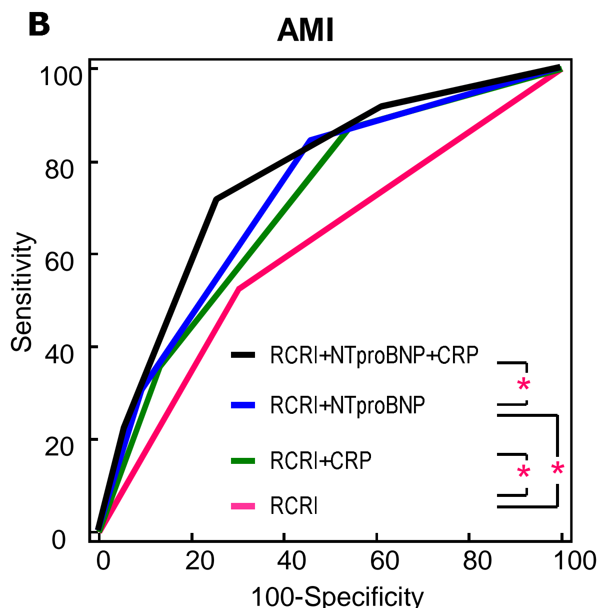
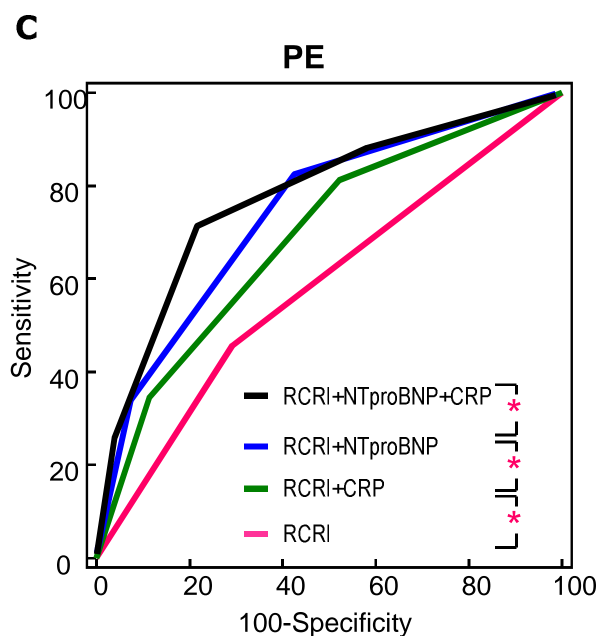
Figure 3. ROC analysis of perioperative risk predictors

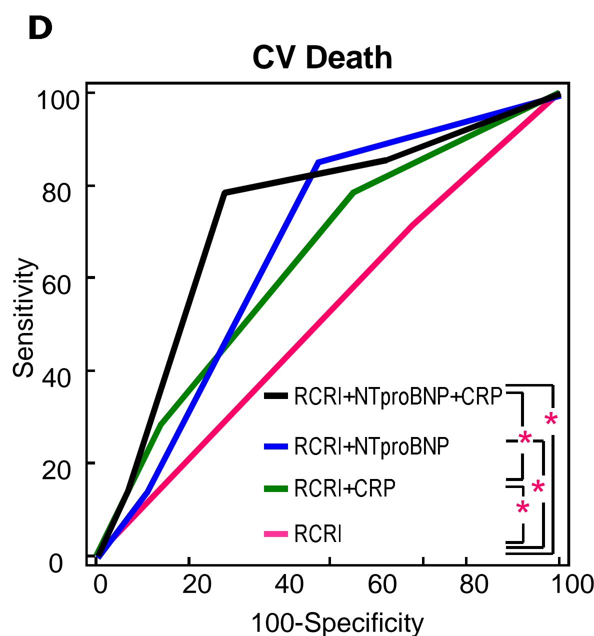




RCRI+NTproBNP+CRP	0.772±0.017 [95% CI 0.752–0.790]
RCRI+NTproBNP	0.735±0.018 [95% CI 0.714–0.754]
RCRI+CRP	0.694±0.019 [95% CI 0.673–0.715]
RCRI	0.592±0.019 [95% CI 0.570–0.615]

RCRI+NTproBNP+CRP	0.761±0.029 [95% CI 0.741–0.780]
RCRI+NTproBNP	0.720±0.030 [95% CI 0.700–0.740]
RCRI+CRP	0.705±0.031 [95% CI 0.685–0.726]
RCRI	0.611±0.031 [95% CI 0.589–0.633]





RCRI+NTproBNP+CRP	0.777±0.018 [95% CI 0.758–0.796]
RCRI+NTproBNP	0.738±0.019 [95% CI 0.718–0.758]
RCRI+CRP	0.689±0.020 [95% CI 0.668–0.710]
RCRI	0.582±0.020 [95% CI 0.560–0.604]

RCRI+NTproBNP+CRP	0.737±0.077 [95% CI 0.717–0.757]
RCRI+NTproBNP	0.678±0.080 [95% CI 0.657–0.699]
RCRI+CRP	0.639±0.080 [95% CI 0.617–0.660]
RCRI	0.515±0.077 [95% CI 0.492–0.537]

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