Prediction of Perioperative Cardiac Events through Preoperative NT-pro-BNP and cTnI after Emergent Non-Cardiac Surgery in Elderly Patients

Jinling Ma1, Qian Xin2, Xiujie Wang3, Meng Gao1, Yutang Wang1, Jie Liu4

1 Department of Geriatric Cardiology, Chinese PLA General Hospital, Beijing, China, 2 Department of Cardiology, Chinese PLA General Hospital, Beijing, China, 3 Department of Radiology, Zhaoyuan People’s Hospital, Shandong, China, 4 Emergency Department, Chinese PLA General Hospital, Beijing, China

These authors contributed equally to this work.

Abstract

Objectives
Clinical risk stratification has an important function in preoperative evaluation of patients at risk for cardiac events prior to non-cardiac surgery. The aim of this study was to determine whether the combined measurement of pre-operative N-terminal pro-brain natriuretic peptide (NT-pro-BNP) and cardiac troponin I (cTnI) could provide useful prognostic information about postoperative major adverse cardiac events (MACE) within 30 days in patients aged over 60 years undergoing emergent non-cardiac surgery.

Methods
The study group comprised 2519 patients aged over 60 years that were undergoing emergent non-cardiac surgery between December 2007 and December 2013. NT-pro-BNP and cTnI were measured during hospital admission. The patients were monitored for MACE (cardiac death, non-fatal myocardial infarction, or cardiac arrest) during the 30-day postoperative follow-up period.

Results
MACE occurred in 251 patients (10.0%). Preoperative NT-pro-BNP and cTnI level were significantly higher in the individuals that experienced MACE than in those who did not (P < 0.001). The confounding factors of age, sex, co-morbidities and preoperative medications were adjusted in a multivariate logistic regression analysis. This analysis showed that preoperative NT-proBNP level > 917 pg/mL (OR 4.81, 95% CI 3.446–6.722, P < 0.001) and cTnI ≥ 0.07 ng/mL (OR 8.74, 95% CI 5.881–12.987, P < 0.001) remained significantly and independently associated with MACE after the adjustment of the confounding factors. Kaplan-Meier event-free survival curves demonstrated that patients with preoperative
simultaneous NT-proBNP level > 917 pg/mL and cTnT ≥0.07 ng/mL had worse event-free survival than individual assessments of either biomarker.

**Conclusion**

Preoperative plasma NT-proBNP and cTnI are both independently associated with an increased risk of MACE in elderly patients after emergent non-cardiac surgery. The combination of these biomarkers provides better prognostic information than using either biomarker separately.

**Introduction**

Clinical risk stratification has an important function in preoperative evaluation of patients at risk for cardiac events prior to non-cardiac surgery [1]. However, emergency surgery patients often have limited preoperative physical activity that can provide accurate assessment of cardiac risk [2]. Multiple studies have demonstrated that preoperative N-terminal pro-brain natriuretic peptide (NT-pro-BNP) is a valuable predictor of perioperative cardiovascular complications after non-cardiac surgery [2–13]. The guidelines of the European Society of Cardiology and the European Society of Anesthesiology for preoperative cardiac risk assessment have recommended the consideration of preoperative NT-pro-BNP measurement in high-risk non-cardiac surgery patients [14]. Moreover, accumulating evidence support that troponins reflect minor myocardial injury, thereby providing prognostic information [15,16]. The availability of powerful cardiovascular biomarkers, such as troponins and NT-pro-BNP, offer the opportunity for further refinement of clinical scores [17].

In the present study, we evaluated the value of preoperative NT-pro-BNP and cardiac troponin I (cTnI) levels in a cohort of patients undergoing emergent non-cardiac surgery. Ageing patients have increased risk of perioperative cardiac events because of multiple comorbidities [12]. This prospective observational study aimed to determine whether or not the combined measurement of pre-operative NT-pro-BNP and cTnI can provide useful prognostic information about postoperative major adverse cardiac events (MACE) within 30 days in patients aged over 60 years undergoing emergent non-cardiac surgery.

**Methods**

**Study population**

Consecutive patients aged 60 years and over presenting for emergent non-cardiac surgery (defined as surgery that must be performed within 24 h after admission) under general anesthesia between December 2007 and December 2013 in Chinese PLA General Hospital and Zhaoyuan People’s Hospital were prospectively included in the study. Prior to surgery, patient characteristics, as well as medical and demographic details were documented. These emergent non-cardiac surgeries include abdominal, gynecological, urological, reconstructive, orthopedic, and vascular surgeries. We excluded patients who had severe degree of valvular heart disease and those who were receiving hemodialysis or peritoneal dialysis for renal failure. Patients who are unable to provide informed consent were also excluded. A total of 2519 patients were enrolled in this study.
The written informed consents were obtained from all subjects or their designated relatives. The study was approved by the Ethics Committee of the Chinese PLA General Hospital (Beijing, China) and Zhaoyuan People’s Hospital (Shandong, China).

Measurement of plasma NT-pro-BNP and cTnI
Peripheral blood samples for NT-pro-BNP and cTnI were obtained upon admission at the hospital through direct vein puncture. NT-proBNP and cTnI were measured by electrochemiluminescence immunoassay on the Dimension Vista 500 Intelligent Laboratory System (Siemens Healthcare Diagnostics, Deerfield, Illinois, United States). An increased level of cTnI was defined as ≥ 0.07 ng/mL.

Follow-up
After surgery, the patients were followed up for 30 days by a research assistant. No patients were lost during follow-up. The patients were monitored for MACE, namely, cardiac death, non-fatal myocardial infarction (MI), or cardiac arrest, during the perioperative period. Non-fatal MI was defined according to the new universal definition of MI. This definition was the typical increase/decrease of troponin together with the evidence of myocardial ischemia with at least one of the following: symptoms of ischemia, ECG changes indicative of new ischemia or new Q waves; or imaging evidence of new regional wall motion abnormality [18]. Cardiac death was defined as death secondary to MI, arrhythmia, or heart failure. Cardiac arrest was defined as a cardiopulmonary event that led to the initiation of cardiopulmonary resuscitation and advanced cardiac life support protocols.

Statistical analysis
Normally distributed continuous data were expressed as mean ± SD and compared using Student’s t test. Non-normally distributed continuous data were expressed as median with the inter-quartile range and compared using the Mann Whitney U test. The categorical variables were presented as proportions (percentages). Categorical variables were compared with $\chi^2$ tests. Logistic regression analysis was used to predict the prevalence of MACE, with adjustments for age, sex, co-morbidities, history, and medication. The results are presented as adjusted odds ratios (OR) and their 95% confidence interval (CI). A Kaplan-Meier analysis was performed to assess event-free survival. The event-time curve was separated into four curves according to the discriminatory preoperative NT-pro-BNP and cTnI and these curves were compared by log-rank test. All data were processed using the PASW (version 18.0; SPSS, Chicago, IL, USA). A P value <0.05 was considered statistically significant.

Results
A total of 2519 consecutive patients undergoing emergency surgery between December 2009 and December 2013 were included in this study. The mean age of the subjects was 77.3 ± 8.4 years, and men comprised 52.1% of the group. Of the patients, 1078 (42.8%) underwent abdominal surgery, 807 (32.0%) orthopedic surgery, 212 (8.4%) urological surgery, and 422 (16.8%) other surgery, respectively.

During the 30-day postoperative follow-up period, a total of 251 (10.0%) patients experienced MACE, including 223 nonfatal myocardial infarctions, 11 nonfatal cardiac arrests, and 17 cardiac deaths. The preoperative baseline characteristics of the study population according to the occurrence of MACE during follow-up are presented in Table 1. The preoperative NT-pro-BNP and cTnI level were significantly higher in the individuals that experienced MACE.
than in those who did not ($P < 0.001$). Moreover, age and chronic renal insufficiency were significantly higher in patients with perioperative MACE than in those without (Table 1). No significant difference was observed in the proportion of subjects with preoperative medications. According to the preoperative NT-pro-BNP, the population was divided into two groups: NT-pro-BNP $> 917$ pg/mL ($n = 1131, 8.3\%$) and $\leq 917$ pg/mL ($n = 1388, 91.7\%$) (Fig. 1).

![Kaplan-Meier event-time curve according to preoperative NT-pro-BNP levels.](https://doi.org/10.1371/journal.pone.0121306.g001)
The confounding factors of age, sex, co-morbidities, and preoperative medications were adjusted in a multivariate logistic regression analysis. This analysis showed that preoperative NT-pro-BNP > 917 pg/mL (OR 4.81, 95% CI 3.446–6.722, P < 0.001) and cTNI/C21 > 0.07 ng/mL (OR 8.74, 95% CI 5.881–12.987, P < 0.001) remained significantly and independently associated with MACE (Table 2).

Kaplan-Meier event-free survival curves demonstrated that patients with preoperative NT-pro-BNP level > 917 pg/mL had worse event-free survival compared with those with NT-pro-BNP levels ≤ 917 pg/mL during the 30-day postoperative follow-up period (Fig. 1).

To determine the potential utility of simultaneous cTnI and NT-pro-BNP assessment, the patients were divided into four groups based on cTnI and NT-pro-BNP cut-off points. Patients with elevated levels of both cTnI and NT-pro-BNP had a significantly increased risk (P < 0.001) (Fig. 2). Thus, the assessment of both cTnI and NT-pro-BNP was more effective at identifying a high-risk subgroup than individual assessments of either biomarker.

**Table 2. Risk factors associated with MACE in a multivariable logistic regression analysis.**

| Risk factors                                      | P Value  | OR       | 95% CI       |
|--------------------------------------------------|----------|----------|--------------|
| Age, years                                       | <0.001   | 1.08     | 1.006–1.096  |
| Male (%)                                         | 0.1587   | 1.24     | 0.920–1.666  |
| Co-morbidities, n (%)                            |          |          |              |
| Hypertension                                     | 0.8116   | 0.94     | 0.585–1.523  |
| Hypertipidaemia                                  | 0.1762   | 1.37     | 0.867–2.177  |
| Diabetes                                         | 0.3010   | 0.81     | 0.543–1.208  |
| Atrial fibrillation                              | 0.1953   | 1.37     | 0.850–2.210  |
| COPD                                             | 0.4847   | 1.15     | 0.773–1.719  |
| Malignancy                                       | 0.9665   | 1.01     | 0.619–1.650  |
| Chronic renal insufficiency                      | <0.001   | 3.95     | 2.526–6.185  |
| Co-morbidities, n (%)                            |          |          |              |
| Previous myocardial infarction                   | 0.5089   | 1.20     | 0.695–2.081  |
| Previous congestive heart failure                | 0.6578   | 0.88     | 0.497–1.554  |
| Preoperative NT-pro-BNP > 917 pg/mL              | <0.001   | 4.81     | 3.446–6.722  |
| Preoperative cTNI ≥ 0.07 ng/mL                    | <0.001   | 8.74     | 5.881–12.987 |
| Preoperative medications, n (%)                  |          |          |              |
| Beta-blockers                                    | 0.8714   | 1.03     | 0.749–1.406  |
| Statins                                          | 0.4513   | 1.14     | 0.808–1.614  |
| Calcium channel blocker                          | 0.1407   | 0.75     | 0.517–1.098  |
| Diuretes                                         | 0.4283   | 1.16     | 0.799–1.696  |
| ACEI/ARB                                         | 0.6061   | 0.91     | 0.642–1.295  |

COPD: chronic obstructive pulmonary disease; ACE: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker.

doi:10.1371/journal.pone.0121306.002

The confounding factors of age, sex, co-morbidities, and preoperative medications were adjusted in a multivariate logistic regression analysis. This analysis showed that preoperative NT-pro-BNP > 917 pg/mL (OR 4.81, 95% CI 3.446–6.722, P < 0.001) and cTNI ≥ 0.07 ng/mL (OR 8.74, 95% CI 5.881–12.987, P < 0.001) remained significantly and independently associated with MACE (Table 2).

Kaplan-Meier event-free survival curves demonstrated that patients with preoperative NT-pro-BNP level > 917 pg/mL had worse event-free survival compared with those with NT-pro-BNP levels ≤ 917 pg/mL during the 30-day postoperative follow-up period (Fig. 1).

To determine the potential utility of simultaneous cTnI and NT-pro-BNP assessment, the patients were divided into four groups based on cTnI and NT-pro-BNP cut-off points. Patients with elevated levels of both cTnI and NT-pro-BNP had a significantly increased risk (P < 0.001) (Fig. 2). Thus, the assessment of both cTnI and NT-pro-BNP was more effective at identifying a high-risk subgroup than individual assessments of either biomarker.

**Discussion**

It is very important to determine the risk of cardiac complications before emergent non-cardiac surgery in elderly patients who already possibly had heart disease, various comorbidities, and whose response to transfusion or fluid therapy is weakened. Furthermore, an emergency population does not have the luxury of intense preoperative cardiovascular workup compared with an elective population because delay to surgery can be detrimental to the outcome [5].
This study provides a comprehensive analysis of the prognostic value of preoperative NT-pro-BNP, alone or in combination with cTnI, in a cohort of patients undergoing emergent non-cardiac surgery. This study demonstrated that preoperative NT-pro-BNP levels are associated with increased risk of MACE during the 30-day postoperative follow-up period in the enrolled elderly patients. Perioperative cardiovascular risks may increase as NT-pro-BNP concentrations increase. After multivariate adjustment for age, sex, co-morbidities, and preoperative medications, logistic regression analysis showed that both pre-operative NT-pro-BNP and cTnI levels are independent predictors of adverse cardiac events. This study demonstrated that a single pre-operative measurement of NT-pro-BNP provides useful information for use in risk stratification. Furthermore, the combined use of NT-pro-BNP and cTnI provided incremental prognostic information that enhances the prediction of increased risk of perioperative MACE. Therefore, a simultaneous increase in both markers identifies patients with high probability of postoperative cardiac events. Simultaneous assessment of the two biomarkers would be more useful in predicting postoperative cardiac events than using either biomarker separately.

In agreement with our results, previously published studies have suggested that an independent association exists between elevated preoperative NT-pro-BNP levels and increased risks of adverse perioperative cardiovascular outcomes [2–5, 19–26]. Measuring NT-pro-BNP in adults having major non-cardiac surgery significantly improves the preoperative risk stratification and can easily be incorporated into clinical practice. This procedure allows physicians to plan prophylactic strategies in patients identified as high risk [27]. The results from these investigations suggest that NT-pro-BNP is useful in predicting perioperative adverse outcome. In the present study, NT-pro-BNP remained an independent correlate of perioperative cardiac events, even when cTnI was included in the multivariable analysis. Previous studies have used different thresholds, from 201 pg/mL to 3980 pg/mL for preoperative NT-pro-BNP assays, to represent abnormal values [7,11,12,20–22]. Although there is no consensus of what the normal NT-pro-BNP values are, we identified 917 pg/mL as the optimal cut-off value to predict the 30-day MACE according to another study.9 The cutoff point with the best specificity and sensitivity in relation to the primary outcome was 917 pg/mL for preoperative NT-pro-BNP [9].

During the perioperative period, 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 [28,29]. Moreover, a number of other stressors that can lead to myocardial...
dysfunction exist, such as hypoxia, activation of the sympathetic system, and an increase in plasma pro- and anti-inflammatory cytokines [30]. These factors can increase the risk for postoperative complications.

Previous studies have found that troponin increase occur silently and is a prognostic marker of cardiovascular complications and death after non-cardiac surgery [31–34]. cTnI is unique to myocardium, cTnT can be re-expressed in skeletal muscle in response to injury [35]. An increase in specific cardiac biomarkers, as it is the case for natriuretic peptides and troponins, always indicates that the heart is under a stress condition or even actually injured [36]. Our data further confirmed a significant association between cTnI and post-operative cardiac events that is incremental to NT-pro-BNP. The combination of both biomarkers is associated with a substantially higher risk compared with either biomarker alone. The combination of both biomarkers may further improve the identification of patients with increased myocardial wall tension and minor myocardial damage, even in the absence of ischemic symptoms. Our study suggests that the combined use of preoperative NT-pro-BNP and cTnI may be a superior short-term prognostic marker after emergent non-cardiac surgery in elderly patients. Moreover, to improve perioperative risk stratification in noncardiac surgery and going beyond established clinical scores with the use of cardiac biomarkers, prospective studies are needed, specifically aimed at evaluating the independence of troponin and NP predictive value even in mid- and long-term periods [37].

This study has several limitations that should be considered. First, the patient mean age was 77.3 ± 8.4 years in our patient cohort. Therefore, these characteristics may limit the generalizability of our findings to those ages. Second, long-term follow-up after discharge was not performed. The study did not prioritize the long-term follow-up because most postoperative cardiovascular events develop in the early postoperative periods [38, 39]. Third, clearance of NT-pro-BNP is largely dependent on excretion from the kidney [40]. NT-pro-BNP level and its prognostic ability can be affected by renal failure [26, 41]. In this study, we did not exclude patients with renal dysfunction, which may have decreased the specificity of NT-pro-BNP in predicting cardiac complications and mortality. In addition, in the present study, NT-proBNP was measured by electrochemiluminescence immunoassay, which is thought to measure only nonglycoNT-proBNP. Glycosylated proBNP is a major molecular form in human plasma and glycosylated NT-proBNP is underestimated by the NT-proBNP assay system currently being used [40]. Under these conditions, correct interpretation of the NT-proBNP levels and clinical application may require careful consideration. Fourth, a consensus concerning the reference range of perioperative NT-pro-BNP values has not been achieved. We identified 917 pg/mL as the optimal cut-off value. This value was in accordance to the basis of our experience and another study [9]. The optimal discriminatory (or ‘cut-off’) point requires further investigation. Fifth, differences in pre-operative risk factors other than those included in the multivariate model may have affected the MACE results, such as the type of surgery, scope of operation and scores of serious illness. Thus, we should interpret our results very carefully. Finally, this study was performed at two different hospitals. Most of the patients were from North China; thus, our findings may not be completely representative of the population of other locations. Further prospectively multiple center studies with a large number of patients in various surgery are required to form stronger conclusions. Although caution is necessary for the interpretation of our data, we consider it improbable that these limitations have influenced our main findings.

In conclusion, the present study demonstrated that elevated levels of preoperative plasma NT-pro-BNP and cTnI are both independently associated with an increased risk of MACE in a real-life cohort of elderly patients undergoing emergent non-cardiac surgery. Thus, the combination of preoperative NT-pro-BNP and cTnI measurements provide better prognostic information than using either biomarker separately. Patients at high risk should be considered for
less invasive procedures and must receive optimized perioperative care. Further research with a larger number of patients having various types of surgeries is needed to confirm the clinical utility of these prognostic tests.

Author Contributions
Conceived and designed the experiments: JLM QX XJW YTW. Performed the experiments: JLM QX XJW. Analyzed the data: JLM XJW MG. Contributed reagents/materials/analysis tools: JLM MG JL. Wrote the paper: JLM.

References
1. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof EL, Fleischmann KE, et al. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines; 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; Society for Vascular Surgery. 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. J Am Coll Cardiol. 2009; 54: e13–e118. doi:10.1016/j.jacc.2009.07.010 PMID: 19926002
2. Farzi S, Stojakovic T, Marko T, Sankin C, Rehak P, Gumpert R, et al. Role of N-terminal pro B-type natriuretic peptide in identifying patients at high risk for adverse outcome after emergent non-cardiac surgery. Br J Anaesth. 2013; 110: 554–560. doi:10.1093/bja/aes454 PMID: 23248094
3. Rodseth RN, Lurati Buse GA, Bolliger D, Burkhart CS, Cuthbertson BH, Gibson SC, et al. The predictive ability of pre-operative B-type natriuretic peptide in vascular patients for major adverse cardiac events: an individual patient data meta-analysis. J Am Coll Cardiol. 2011; 58: 522–529. doi:10.1016/j.jacc.2011.04.018 PMID: 21777751
4. Karthikeyan G, Moncur RA, Levine O, Heels-Ansdell D, Chan MT, Alonso-Coello P, et al. Is a pre-operative brain natriuretic peptide or N-terminal pro-B-Type natriuretic peptide measurement an independent predictor of adverse cardiovascular outcomes within 30 days of noncardiac surgery? A systematic review and meta-analysis of observational studies. J Am Coll Cardiol. 2009; 54: 1599–1606. doi: 10.1016/j.jacc.2009.06.028 PMID: 19833258
5. Chong CP, Ryan JE, van Gaal WJ, Lam QT, Sinnappu RN, Rurrell LM, et al. Usefulness of N-terminal pro—Brain natriuretic peptide to predict postoperative cardiac complications and long-term mortality after emergency lower limb orthopedic surgery. Am J Cardiol. 2010; 106: 865–872. doi: 10.1016/j.amjcard.2010.05.012 PMID: 20816130
6. Feringa HH, Schouten O, Dunkelgrun M, Bax JJ, Boersma E, Elhendy A, et al. Plasma N-terminal pro-B-type natriuretic peptide as long-term prognostic marker after major vascular surgery. Heart. 2007; 93: 226–231. PMID: 16914484
7. Feringa HH, Bax JJ, Elhendy A, de Jonge R, Lindemans J, Schouten O, et al. Association of plasma N-terminal pro-B-type natriuretic peptide with postoperative cardiac events in patients undergoing surgery for abdominal aortic aneurysm or leg bypass. Am J Cardiol. 2006; 98: 111–115. PMID: 16784932
8. Goei D, Hoeks SE, Boersma E, Winkel TA, Dunkelgrun M, Flu WJ, et al. Incremental value of high-sensitivity C-reactive protein and N-terminal pro-B-type natriuretic peptide for the prediction of postoperative cardiac events in noncardiac vascular surgery patients. Coron Artery Dis. 2009. 20: 219–224. doi: 10.1097/MCA.0b013e3283219e47 PMID: 19322079
9. Borges FK, Furtado MV, Rossini AP, Bertoluci C, Gonzalez VL, Bertoldi EG, et al. Prognostic value of perioperative N-terminal pro-B-type natriuretic peptide in noncardiac surgery. Arq Bras Cardiol. 2013. 100: 561–570. doi: 10.5935/abc.20130090 PMID: 23657264
10. Biccard BM, Naidoo P, de Vasconcellos K. What is the best pre-operative risk stratification tool for major adverse cardiac events following elective vascular surgery? A prospective observational cohort study evaluating pre-operative myocardial ischaemia monitoring and biomarker analysis. Anaesthesia. 2012; 67: 389–395. doi: 10.1111/j.1365-2044.2011.07020.x PMID: 22324824
11. Yun KH, Jeong MH, Oh SK, Choi JH, Rhee SJ, Park EM, et al. Preoperative plasma N-terminal pro-Brain natriuretic peptide concentration and perioperative cardiovascular risk in elderly patients. Circ J. 2008. 72: 195–199. PMID: 18219153
12. Oscarsson A, Fredriksson M, Sörliden M, Anskär S, Eintrei C. N-terminal fragment of pro-B-type natriuretic peptide is a predictor of cardiac events in high-risk patients undergoing acute hip fracture surgery. Br J Anaesth. 2009; 103: 206–212. doi: 10.1093/bja/aep139 PMID: 19525907
13. Rodseth RN, Padayachee L, Biccard BM. A meta-analysis of the utility of preoperative brain natriuretic peptide in predicting early and intermediate-term mortality and major adverse cardiac events in vascular surgical patients. Anaesthesia. 2008; 63:1226–1233. doi: 10.1111/j.1365-2044.2008.05574.x PMID: 18673363

14. Poldermans D, Bax JJ, Boersma E, De Hert S, Eekhout E, Fowkes G, et al. Guidelines for preoperative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery. Eur Heart J. 2009; 30: 2769–2812. doi: 10.1093/eurheartj/ehp337 PMID: 19713421

15. Latini R, Masson S, Anand IS, Missov E, Carlson M, Vago T, et al. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. Circulation. 2007. 116:1242–1249. PMID: 17698733

16. Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, et al. A sensitive cardiac troponin T assay in stable coronary artery disease. N Engl J Med. 2009; 361:2538–2547. doi: 10.1056/NEJMo0805299 PMID: 19940289

17. Karakas M, Koenig W. Improved peri-operative risk stratification in non-cardiac surgery: going beyond established clinical scores. Eur Heart J. 2013; 34:796–798. doi: 10.1093/eurheartj/eht014 PMID: 23359389

18. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. J Am Coll Cardiol. 2007; 50: 2173–2195. PMID: 18036459

19. Schutt RC, Cevik C, Phy MP. Plasma N-terminal prohormone brain natriuretic peptide as a marker for postoperative cardiac events in high-risk patients undergoing noncardiac surgery. Am J Cardiol. 2009; 104:137–140. doi: 10.1016/j.amjcard.2009.03.005 PMID: 19576335

20. Mahla E, Baumann A, Rehak P, Watzinger N, Vicenzi MN, Maier R, et al. N-terminal pro-brain natriuretic peptide identifies patients at high risk for adverse cardiac outcome after vascular surgery. Anesthesiology. 2007; 106: 1088–1095. PMID: 17525582

21. Yeh HM, Lau HP, Lin JM, Sun WZ, Wang MJ, Lai LP. Preoperative plasma N-terminal pro-brain natriuretic peptide as a marker of cardiac risk in patients undergoing elective non-cardiac surgery. Br J Surg. 2005; 92:1041–1045. PMID: 15997451

22. Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, et al. Increased perioperative N-terminal pro-B type natriuretic peptide levels predict atrial fibrillation after thoracic surgery for lung cancer. Circulation. 2007; 115:1339–1344. PMID: 17339553

23. Goel D, van Kuijk JP, Flu WJ, Hoeks SE, Chonchol M, Verhagen HJ, et al. Usefulness of repeated N-terminal pro-B-type natriuretic peptide measurements as incremental predictor for long-term cardiovascular outcome after vascular surgery. Am J Cardiol. 2011; 107: 609–614. doi: 10.1016/j.amjcard.2010.10.021 PMID: 21185000

24. Rajagopalan S, Croal BL, Reeve J, Bachoo P, Brittenden J. N-terminal pro-Btype natriuretic peptide is an independent predictor of all-cause mortality and MACE after major vascular surgery in medium-term follow-up. Eur J Vasc Endovasc Surg. 2011; 41: 657–662. doi: 10.1016/j.ejvs.2010.12.017 PMID: 21390158

25. Choi JH, Cho DK, Song YB, Hahn JY, Choi S, Gwon HC, et al. Preoperative NT-proBNP and CRP predict perioperative major cardiovascular events in non-cardiac surgery. Heart. 2010; 96: 56–62. doi: 10.1136/hrt.2009.181386 PMID: 19861299

26. Goel D, Schouten O, Boersma E, Welten GM, Dunkelgrun M, Lindemans J, 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; 101:122–126. PMID: 18157978

27. Rodseth RN, Biccard BM, Le Manach Y, Sessler DI, Lurati Buse GA, Thabane L, et al. The prognostic value of pre-operative and post-operative B-type natriuretic peptide in patients undergoing noncardiac surgical procedures: B-type natriuretic peptide and N-terminal fragment of pro-B-type natriuretic peptide: a systematic review and individual patient data meta-analysis. J Am Coll Cardiol. 2014; 63:170–180. doi: 10.1016/j.jacc.2013.08.1630 PMID: 24076282

28. Poldermans D, Hoeks SE, Feringa HH. Pre-operative risk assessment and risk reduction before surgery. J Am Coll Cardiol. 2008; 51:1913–1924. doi: 10.1016/j.jacc.2008.03.005 PMID: 18482658

29. Schouten O, Bax JJ, Poldermans D. Preoperative cardiac risk assessment in vascular surgery patients: seeing beyond the perioperative period. Eur Heart J. 2008; 29: 283–284. doi: 10.1093/eurheartj/ehm521 PMID: 18245116

30. Sun JZ, Maguire D. How to prevent perioperative myocardial injury: the conundrum continues. Am J Heart. 2007; 154: 1021–1028. PMID: 18035070

31. Chong CP, Lam Q, Ryan JE, Sinnappu RN, Lim WK. Incidence of post-operative troponin I rises and one year mortality after emergency orthopaedic surgery in older patients. Age Ageing. 2009; 38:168–174. doi: 10.1093/ageing/afn231 PMID: 19008306
32. Ausset S, Auroy Y, Lambert E, Vest P, Plotton C, Rigal S, et al. Cardiac troponin I release after hip surgery correlates with poor long-term cardiac outcome. Eur J Anaesth. 2008; 25:158–164. PMID: 17666156
33. Ausset S, Minville V, Marquis C, Fourcade O, Rosencher N, Benhamou D, et al. Postoperative myocardial damages after hip fracture repair are frequent and associated with a poor cardiac outcome: a three-hospital study. Age Ageing. 2009; 38: 488–489. doi: 10.1093/ageing/afp040 PMID: 19411672
34. Weber M, Luchner A, Seeberger M, Mueller C, Liebetrau C, Schlitt A, et al. Incremental value of highsensitive troponin T in addition to the revised cardiac index for peri-operative risk stratification in non-cardiac surgery. Eur Heart J. 2013; 34: 853–862. doi: 10.1093/eurheartj/ehs445 PMID: 23257946
35. Rittoo D, Jones A, Lecky B, Neithercut D. Elevation of cardiac troponin T, but not cardiac troponin I, in patients with neuromuscular diseases: implications for the diagnosis of myocardial infarction. J Am Coll Cardiol. 2014; 63: 2411–2420. doi: 10.1016/j.jacc.2014.03.027 PMID: 24747102
36. Clerico A, Emdin M, Passino C. Cardiac biomarkers and risk assessment in patients undergoing major non-cardiac surgery: time to revise the guidelines? Clin Chem Lab Med. 2014; 52: 959–963. doi: 10.1515/cclm-2013-0900 PMID: 24501160
37. Clerico A, Passino C, Emdin M. Surgery casualties: do not leave hearts behind enemy lines. J Am Coll Cardiol. 2014; 63:181–183. doi: 10.1016/j.jacc.2013.09.015 PMID: 24076286
38. McFalls EO, Ward HB, Moritz TE, Apple FS, Goldman S, PIERPONT G, 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. doi: 10.1093/eurheartj/ehm620 PMID: 18245121
39. Owens CD, Ridker PM, Belkin M, Hadman AD, Pomposelli F, Logero F, 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. PMID: 17123769
40. Nakagawa Y, Nishikimi T, Kuwahara K, Yasuno S, Kinoshita H, Kuwabara Y, et al. The effects of superflux (high performance) dialyzer on plasma glycosylated Pro-B-Type Natriuretic Peptide (proBNP) and glycosylated N-Terminal proBNP in end stage renal disease patients on dialysis. PLoS One. 2014; 9: e92314. doi: 10.1371/journal.pone.0092314 PMID: 24667631
41. De Filippi C, van Kimmenade RR, Pinto YM. Amino-terminal pro-B-type natriuretic peptide testing in renal disease. Am J Cardiol. 2008; 101: 82–88. doi: 10.1016/j.amjcard.2007.11.029 PMID: 18243865