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Review Article

Cardiac biomarkers in the prediction of risk in the non-cardiac surgery setting

B. M. Biccard,[1] P. J. Devereaux[2] and R. N. Rodseth[3]

1 Honorary Associate Professor, 3 Consultant, Perioperative Research Group, Department of Anaesthetics, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa
2 Associate Professor, Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada

Summary

B-Type natriuretic peptides and troponin measurements have potential in predicting risk in patients undergoing non-cardiac surgery. Using the American Heart Association framework for the evaluation of novel biomarkers, we review the current evidence supporting the peri-operative use of these two biomarkers. In patients having major non-cardiac surgery who are risk stratified using clinical risk scores, the measurement of natriuretic peptides and troponin, both before and after surgery, significantly improves risk stratification. However, only pre- and postoperative natriuretic peptide measurement and postoperative troponin measurement have shown clinical utility. It is now important for trials to be conducted to determine whether integrating pre- and postoperative natriuretic peptide and postoperative troponin measurement into clinical practice is able to improve clinical outcomes in patients undergoing non-cardiac surgery.

Correspondence to: B. M. Biccard
Email: biccardb@ukzn.ac.za
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Introduction

Thirty-day mortality following unselected non-cardiac surgery in patients 45 years and older has been reported at 1.9% (95% CI 1.7–2.1%) [1]. In such patients, a postoperative troponin elevation has the largest population-attributable risk for associated 30-day mortality [1]. Considering that annually more than 200 million major surgical procedures [2] are performed globally, it is clear that this equates to a significant public health burden.

The accurate identification of patients at risk of peri-operative morbidity offers many advantages. First, both the patient and the physician can perform an appropriate risk–benefit analysis based on the expected surgical benefit in relation to the surgical risk. Surgery may then be declined, deferred or modified to maximise patient benefit. Second, pre-operative identification of high-risk patients enables physicians to direct their efforts towards those patients most likely to benefit from additional interventions. Finally, postoperative management, monitoring and potential therapies may be individualised according to the patient's predicted risk of postoperative morbidity and mortality.

Any approach used for pre-operative risk stratification must be able accurately and reliably to discriminate patients at high risk of a major cardiovascular

complication and mortality from those at low risk. The most commonly used clinical risk stratification tool, the Revised Cardiac Risk Index (RCRI) [3] is recommended by both the American College of Cardiology/American Heart Association's (ACC/AHA) [4] and the European Society of Cardiology/European Society of Anaesthesiology's (ESC/ESA) guidelines for pre-operative cardiac risk assessment [5]; however, the RCRI misclassifies a substantial number of patients in mixed cohorts of non-cardiac surgical patients [6–8]. There is also evidence to suggest, now, that 'clinically silent' disease, which is reflected by biomarker elevation alone, is associated with increased mortality in non-surgical populations [9]. Furthermore, peri-operative events such as the urgency and extent of the surgical procedure alter patients' risk [10–12]. These dynamic changes in risk are not captured by the RCRI and as a result, the utility of its prediction decreases through the peri-operative period [11].

Evidence from non-surgical populations suggests that biomarkers may improve risk stratification of patients at risk of mortality and cardiovascular events. Out of a number of potential biomarkers, natriuretic peptides (NP; B-type natriuretic peptide (BNP) and N-terminal pro-BNP, NT-proBNP) and troponins hold the most promise [13, 14]. As noted in guidelines published by the AHA/ACC and ESC/ESA, there is mounting evidence that the measurement of NP and troponin significantly improves pre-operative risk stratification in mixed cohorts of non-cardiac surgical patients [1, 15]. In keeping with these observations, the potential utility of these biomarkers for risk stratification in the peri-operative period has been identified in the ESC/ESA peri-operative guidelines [5] and the recently published 'third universal definition' of myocardial infarction (MI) [16]. Measuring these biomarkers before and after surgery may enhance risk prediction, allowing accurate and dynamic risk stratification to occur across the entire peri-operative period [8].

The aim of this review was to evaluate the utility of NPs and troponins in improving peri-operative risk stratification based on accepted risk stratification tools for short- and intermediate-term postoperative mortality and cardiovascular morbidity following non-cardiac surgery.

Cardiac biomarkers in peri-operative risk stratification

Using pre-operative cardiac biomarkers such as troponins (troponin I and T) and NP for pre-operative risk stratification provides significant theoretical advantages over current peri-operative risk stratification models. Elevations in these markers, with some caveats, specifically reflect a cardiac origin. Barring assay variability, they are reproducible and their results are not subjective. This is particularly useful in the peri-operative period where clinical symptomatology of cardiovascular disease may be clouded by peri-operative pain, analgesics and fluid use. Cardiac biomarkers are also able to provide a dynamic picture of individual cumulative cardiac injury, contrasting with static risk factors such as a history of diabetes or cardiac failure.

Converting peri-operative biomarkers from a theoretical construct to a clinical reality

A recent paper advocates a process for evaluating novel biomarkers [17]. The proposed criteria are based on a progressive six-phase evaluation of a novel biomarker before its integration into clinical practice. These steps are as follows: (i) proof of concept; (ii) prospective validation; (iii) demonstration of incremental value; (iv) clinical utility; (v) improved clinical outcome; and (vi) cost-effectiveness [17]. We will discuss the current data on troponin and NP usage for both pre- and postoperative risk assessment in the context of these criteria. Both troponins and NP have well-established proof of concept (stage 1) for cardiovascular complications [16, 18].

Pre-operative risk stratification

Pre-operative natriuretic peptides

The association between pre-operative NPs and major postoperative cardiovascular complications has been extensively validated in prospective studies (stage 2). A meta-analysis of vascular surgical patients found that NP elevation above the optimal discriminatory threshold was significantly associated with 30-day cardiac mortality, non-fatal MI and the composite of cardiac death and MI, which persisted at 180 days postoperatively [19]. A subsequent meta-analysis

confirmed this association in a cohort of mixed non-cardiac surgical patients, where NPs were able to independently predict major cardiovascular complications at 30 days postoperatively [20].

As part of the process of novel biomarker evaluation [21, 22], Choi et al. showed that the addition of a pre-operative NT-proBNP to the RCRI, an established clinical risk index [3], provided incremental value (stage 3) by significantly improving the RCRI's prediction of major adverse cardiac events (i.e. MI, pulmonary oedema and cardiovascular death) [23].

An individual patient data meta-analysis evaluated whether pre-operative NPs could significantly alter the pre-operative risk classification of vascular surgical patients [24]. The meta-analysis found that BNP was associated with a net reclassification improvement (NRI) of 58% for the entire cohort, and 84% ($p < 0.000001$) for patients pre-operatively classified as intermediate risk as per the AHA/ACC guidelines for peri-operative cardiovascular evaluation [4]. A recent individual patient data meta-analysis of pre-operative NPs for non-cardiac surgery confirmed that pre-operative NPs were independently associated with the composite outcome of death and non-fatal MI at 30 and 180 days [15]. In this meta-analysis, the pre-operative NPs were controlled for age, type of surgery (vascular vs non-vascular) and urgency of surgery (urgent/emergency vs elective), in addition to the RCRI [15]. The NRI for mixed non-cardiac surgery was 32%, $p < 0.001$ [15]. The patients in this meta-analysis underwent intermediate and major non-cardiac surgery [15].

These findings show clinical utility (stage 4) because integrating NP into the pre-operative risk stratification models resulted in significantly more patients' being correctly classified before surgery. These papers suggest that patients in low-risk categories could proceed to surgery without further intervention, whereas those in the higher risk category may benefit from further risk investigation. In the vascular surgical dataset, it has been shown that neither the number of RCRI risk factors nor specific RCRI risk factors could improve on NP-based pre-operative risk stratification [25].

In summary, the use of NP for pre-operative risk stratification has shown clinical utility, the fourth level of biomarker evaluation, surpassing the current RCRI clinical standard in pre-operative risk stratification in the process. Thresholds and associated outcomes for pre-operative NP taken from these recent individual patient data meta-analyses are presented in Table 1.

Pre-operative troponins

Two vascular surgical observational studies have reported a very high prevalence of elevated pre-operative troponins, 34% in patients with a history of chronic critical limb ischaemia [26] and 7% in patients undergoing leg amputation for chronic peripheral arterial vascular disease [27]. Both studies suggested that a pre-operative troponin elevation may be useful to risk stratify vascular surgery patients pre-operatively, so demonstrating prospective validation (stage 2).

A prospective observational study of patients with a history of coronary artery disease or at risk of

Table 1 Pre-operative natriuretic peptide thresholds for predicting the composite outcome of 30-day mortality and non-fatal myocardial infarction. Values are number or number (95% CI).

Type of surgery	Type of NP	NP level; pg.ml^{-1}	MACE; %	Likelihood ratio
Vascular [24]	BNP	0–29	1.2 (0.3–2)	0.11
		30–115	6.5 (4.6–8.4)	1.69
		116–371	20.9 (17.7–24.1)	3.6
		≥ 372	36.7 (32.9–40.5)	6.4
Mixed non-cardiac surgery [15]	BNP	0–99	5.3 (3.2–7.2)	0.58
		100–250	11.6 (4.3–18.8)	1.38
		≥ 250	26.9 (17.1–35.5)	3.88
	NT-proBNP	0–300	5.2 (4–6.8)	0.42
		301–900	16.1 (12–20.2)	1.46
		901–3000	26 (18.3–33.7)	2.68
		> 3000	39.5 (26.3–52.6)	4.97

NP, natriuretic peptides; BNP, B-type natriuretic peptide; MACE, major adverse cardiac events; NT-proBNP, N-terminal pro-BNP.

coronary artery disease undergoing major non-cardiac surgery has shown that a pre-operative high-sensitivity troponin T above the upper reference limit (> 14 ng.ml^{-1}) is independently associated with early postoperative MI (OR 3.67, 95% CI 1.65–8.15) and 3-year mortality (HR 2.17, 95% CI 1.19–3.96) [28]. Furthermore, a recent prospective observational study of major non-cardiac surgery found that in comparison with the RCRI, a pre-operative high-sensitivity troponin T of > 14 ng.l^{-1} added incremental value (stage 3) to the pre-operative RCRI ($p = 0.006$) for in-hospital mortality [29].

The role of pre-operative troponins and BNP in risk stratification has been addressed in a prospective observational study [30]. In 788 patients, only pre-operative troponin elevation above the upper reference limit and pre-operative BNP above the optimal discriminatory point were independently associated with major adverse cardiac events, confirming that pre-operative troponin evaluation adds incremental value (stage 3). Both pre-operative BNP and troponin risk stratification significantly improved overall net reclassification 74.6% (95% CI 51.6–97.5%) and 38.5% (95% CI 22.4–54.6%), respectively, suggesting the potential for clinical utility (stage 4). The NRI seen when pre-operative troponin elevation was used for risk stratification seems to have been driven by the correct reclassification of patients without adverse cardiac events. However, pre-operative troponin risk stratification incorrectly classified patients who subsequently did develop major adverse cardiac events (−59%, $p < 0.0001$). Thus, the current evidence suggests that pre-operative troponin evaluation does not have clinical utility when predicting major adverse cardiac events in vascular surgical patients. A major limitation of this study is that it is of a purely vascular surgical cohort.

Current data therefore suggest that a raised pre-operative troponin level may identify patients who are at risk of increased short-term cardiovascular morbidity, mortality and long-term mortality, but it may be an inappropriate additional test for improving pre-operative risk stratification due to its poor specificity. This needs further evaluation in a large prospective observational cohort study of non-cardiac surgery. In summary, using pre-operative BNP for pre-operative risk stratification in elective vascular surgical patients has shown clinical utility, but this is not the case for pre-operative troponins.

Postoperative risk stratification

Postoperative troponins

The low incidence of classic cardiac ischaemic symptoms in patients suffering a peri-operative MI is striking when compared with patients suffering non-operative MIs. Peri-operative studies show that only 14% (95% CI 3–28%) of surgical patients present with chest pain [31] and that 65.3% of patients with a peri-operative MI are entirely asymptomatic [12]. Without anginal symptoms to alert the physician, the postoperative MI has gone largely ignored and its impact on postoperative mortality and morbidity has been underappreciated. In the absence of postoperative troponin screening, the majority of these patients are missed, with a dramatic negative impact on public health.

In the peri-operative period, it is clear that any troponin elevation is associated with an increased risk of death, even in the absence of a defining feature (e.g. ischaemic symptoms, ischaemic ECG changes, evidence of MI on echocardiography) necessary for the diagnosis of MI. A meta-analysis of patients undergoing vascular surgery found an isolated postoperative troponin elevation, without defining MI features, to be associated with an increased risk of 30-day (OR 5.03, 95% CI 2.88–8.79) mortality [32]. In a further meta-analysis of 14 studies, comprising 3318 patients, a troponin level in the elevated range independently predicted mortality (OR 3.4, 95% CI, 2.2–5.2), and the prognostic power was greater within the first year after surgery (OR 6.7, 95% CI 4.1–10.9) than longer durations beyond one year after surgery (OR 1.8, 95% CI 1.4–2.3) [9]. It was also associated with a significantly increased risk for major cardiovascular morbidity [9].

As in non-surgical patients, it appears that the extent of troponin elevation is associated with mortality [12, 33]. In the POISE trial, troponin elevation in the highest quartile without a defining feature for MI was an independent predictor of 30-day postoperative mortality [12]. Similarly, in a meta-analysis, the risk of 30-day mortality was 2.3% in patients with troponin levels in the normal range, 11.6% in patients with elevated troponins but without defining features of an MI and 21.6% in patients with MI ($p = 0.000001$) [32].

An observational study of aortic surgical patients has shown that, in the presence of the RCRI, postoperative troponin elevation is an independent predictor of in-hospital mortality. This confirms that postoperative troponins add incremental value (stage 3) in vascular surgical patients [34].

More recently, the results of the Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Study, a 40 000-patient international multicentre study of patients aged 45 years or older undergoing surgery requiring overnight hospitalisation, have been published [1]. An analysis of the first 15 133 patients in the study found that patients with a peak postoperative troponin T elevation ≤ 0.01 ng.ml^{-1} had a mortality rate of 1%. In contrast, patients with a peak troponin T value of 0.02, 0.03–0.29, and ≥ 0.3 ng.ml^{-1} had mortality rates of 4%, 9.3% and 16.9%, respectively ($p < 0.001$). In summary, postoperative troponin elevation, with and without MI defining features, is associated with a significant increase in mortality risk. It is also clear that the current methods by which we have defined a 'normal' troponin range are inappropriate for postoperative patients. The VISION data show clinical utility (stage 4) as postoperative troponin evaluation significantly improved reclassification for 30-day mortality based on a pre-operative model (25.0%, 95% CI 17.2–32.8%, $p < 0.001$) [1]. Importantly, the highest population-attributable risk for 30-day mortality was accounted for by the elevated postoperative troponin. In this observational study, the pre-operative model was more comprehensive than the RCRI, with a c-index for 30-day mortality of 0.81 [1].

Another important observation from the VISION study was that early postoperative troponin elevation was also an independent predictor of non-vascular deaths following surgery [1]. It is possible that an early postoperative myocardial injury may make a patient susceptible to a fatal complication of a subsequent non-vascular postoperative complication. For example, although pneumonia is a serious complication that can result in death after non-cardiac surgery, it is possible that patients who first experience a myocardial injury may have a higher likelihood of developing pneumonia and/or may have a greater risk of dying if they do develop pneumonia. In the VISION Study, 74.2% of patients who would develop an elevated troponin T measurement did so within the first 24 h after surgery, whereas the median time to develop pneumonia was six days after surgery. A postoperative troponin elevation therefore appears to be a harbinger of an increased risk of vascular mortality, but also portends non-vascular mortality [1]. The likelihood ratios for 30-day mortality following non-cardiac surgery are shown in Table 2.

Table 2 Postoperative troponin thresholds for predicting 30-day mortality after non-cardiac surgery [1]. Values are number or number (95% CI).

Peak troponin T measurement	30-day mortality; %	Likelihood ratio
< 0.01 μg.l^{-1}	1 (0.8–1.2)	0.53 (0.47–0.60)
0.02 μg.l^{-1}	4 (3.7–4.3)	2.22 (1.44–3.42)
0.03-0.29 μg.l^{-1}	9.3 (8.8–9.8)	5.39 (4.57–6.34)
≥ 0.30 μg.l^{-1}	16.9 (16.3–17.5)	10.71 (7.02-16.35)

The current data suggest that the absolute postoperative threshold of troponins is a stronger independent predictor of postoperative MI and intermediate-term survival than the increase in the troponin level between the pre- and postoperative period [28].

Based on the VISION study, a recommendation has been made to conduct postoperative troponin surveillance in high-risk patients [16]. A pharmacoeconomic analysis of routine troponin surveillance in all patients who fulfilled the VISION inclusion criteria, based on a 25% relative risk reduction for vascular mortality and peri-operative MI following the introduction of statin and aspirin therapy in patients who are troponin positive, found routine troponin surveillance to be cost-effective based on South African private healthcare costs (A. Torborg, L. Ryan, G. Kantor, B. M. Biccard, unpublished data).

Postoperative natriuretic peptides

Investigations into the ability of postoperative NP to predict major cardiovascular complications have been undertaken more recently and possibly with a greater understanding of how to conduct and interpret peri-operative biomarker studies. Many studies have prospectively validated (stage 2) the association between postoperative NP and major cardiovascular complications. An individual patient meta-analysis of 18 studies

with just over 2000 patients examined the role of postoperative NPs in predicting postoperative complications. Patients with a postoperative BNP ≥ 245 pg.ml^{-1} or NT-proBNP ≥ 718 pg.ml^{-1} had significantly elevated risk for 30-day mortality or non-fatal MI (OR 4.5, 95% CI 2.75–7.4), mortality (OR 4.2, 95% CI 2.29–7.69) and cardiac failure (OR 18.5, 95% CI 4.55–75.29) [35]. In addition, these postoperative elevations were able to predict long-term outcomes (i.e. ≥ 180 days after surgery). Further analysis of these data has demonstrated that even in patients with a pre-operative NP measurement, the addition of a postoperative NP measurement improved postoperative risk stratification at both 30 days (NRI 20%; $p < 0.001$) and ≥ 180 days (QICu 1320–1300) [15]. This has established postoperative NP measurements as providing clinical utility (stage 4). The likelihood ratios associated with 30-day mortality and non-fatal MI are shown in Table 3 [35].

Similar to postoperative troponin levels, the current data for postoperative NPs suggest that it is the absolute postoperative threshold, rather than the increase in the BNP between the pre- and postoperative period, that is associated with postoperative morbidity and mortality [15].

Natriuretic peptides act as a cumulative marker of myocardial damage sustained during the peri-operative period. This injury may be as a result of ischaemic injury, volume overload [36] or both. It remains, however, unclear what the exact temporal relationship is between postoperative NP elevation and postoperative troponin elevation. In certain circumstances, it is possible that NP elevations may precede troponin elevation, as may occur during fluid overload. In such cases, NP elevations may identify patients at risk of subsequently developing myocardial injury and postoperative troponin elevation [37]. Identification of these at-risk patients may provide a window for therapeutic intervention. It is likely that the more common scenario is postoperative NP elevations that occur together with, or shortly after, a postoperative troponin elevation. In these cases, elevated postoperative NPs may reflect the severity of myocardial injury and may prognosticate short- and long-term outcomes in these patients [38]. Further research is required to understand this relationship and its implications for clinical care.

Table 3 Postoperative natriuretic peptides thresholds for predicting the composite outcome of 30-day mortality and non-fatal myocardial infarction. Values are number or number (95% CI).

Type of surgery	Type of NP	NP level; pg.ml^{-1}	MACE; %	Multilevel likelihood ratio
Mixed non-cardiac surgery [35]	BNP	0–250	6.6 (4.7–9.2)	0.58
		251–400	15.7 (6.4–26.1)	1.37
		> 400	29.5 (20.7–37.8)	2.58
	NT-proBNP	0–300	1.8 (0.8–2.9)	0.16
		301–900	8.7 (5.8–11.7)	0.75
		901–3000	20.9 (16.3–22.5)	1.79
		> 3000	38.4 (30.7–46)	3.28

NP, natriuretic peptides; MACE, major adverse cardiac events; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-BNP.

How postoperative NPs compare with other postoperative risk stratification modalities such as ischaemia monitoring has not been well explored. In a single observational study of 149 patients undergoing vascular surgery, postoperative BNP was not a significant predictor of 30-day mortality or MI (OR 2.1, 95% CI 0.81–5.45; $p = 0.13$), when evaluated together with postoperative ischaemia (defined as any episode of ST-segment depression > 1 mV from baseline lasting ≥ 10 min in duration) (OR 7.1, 95% CI 2.78–18.2; $p < 0.001$) in a multivariate analysis [39].

Biomarkers and peri-operative medicine

Integration of biomarkers into clinical practice may generate their own unique diagnoses in the absence of traditional signs and symptoms. The proposal for a peri-operative clinical entity known as myocardial injury after non-cardiac surgery, which is based on a postoperative troponin elevation with no evidence of a non-ischaemic aetiology (independent of clinical symptoms and signs), is consistent with this concept. Similarly, it cannot, therefore, be assumed that therapies that are known to be efficacious for 'traditional' cardiovascular diseases would have similar efficacy in patients with a 'peri-operative disease' generated by biomarker abnormalities, especially as the surgical period is associated with hypotension and bleeding [40]. A call has therefore been made to conduct trials into therapies for

postoperative cardiovascular complications [41]. Importantly, in patients who have an elevated postoperative troponin, statin and aspirin therapy have been associated with improved survival, although it has been observed that at least a third of patients with a diagnosis of peri-operative MI do not have these medications prescribed at hospital discharge [12]. Troponin surveillance may improve outcome, by identifying patients who require these therapies.

Focusing on the prevention of postoperative cardiovascular complications is important, as an early postoperative troponin elevation is also an independent predictor of non-vascular deaths and all-cause mortality following surgery [1]. It is likely that patients who sustain an early postoperative myocardial injury are less likely to survive a subsequent non-vascular complication, and hence a troponin elevation is also predictive of non-vascular deaths [1].

Limitations

A number of the studies cited in this review have compared the risk stratification performance of the biomarkers with that of the RCRI. This is understandable, given the importance the ACC/AHA [4] and the ESC/ESA [5] have placed on the RCRI in pre-operative risk stratification. However, there are several limitations associated with the RCRI [8]. While it may be an appropriate starting point to demonstrate an improvement in risk stratification based on the RCRI, it is possible that with better clinical risk prediction tools, the performance of the biomarkers presented in this review may not be as robust. Although other risk stratification tools exist, as the RCRI is currently the accepted risk stratification tool, most published studies have used the RCRI as the 'gold standard' to establish the baseline risk against which other risk stratification tools are compared. This has been seen with a number of the studies presented in this article. Fortunately, some of the most robust data for troponins and NPs were evaluated in large cohorts, with baseline risk stratification models that were more comprehensive than the RCRI [1, 15].

Biomarkers are measured on a continuous scale, yet some of studies presented in this review have used single 'threshold' levels. This has the potential to lose a substantial amount of risk stratification data. Fortunately, the individual patient data meta-analysis of BNP in pre- and postoperative risk stratification for non-cardiac surgery [15] and the major paper on postoperative troponin risk stratification [1] have used three or four thresholds and so it is likely that they have not lost substantial predictive accuracy. Despite the potential loss of data in using thresholds with biomarkers, continuous data essentially require physicians to use a website or app that can do the calculation for them because remembering beyond 3–4 estimates of risk is not practical. Currently, there is no preferable troponin assay for peri-operative surveillance; however, based on the loss of information from the receiver-operating characteristic curve, the current datasets that provide the most information are the Roche fourth-generation Elecsys TnT assay [1] and the third-generation enhanced AccuTnI assay [42]. Furthermore, the data supporting the integration of troponins and NPs are predominantly from major non-cardiac surgery cohorts.

The final limitation of the current assessment of the utility of peri-operative biomarkers is the lack of data on the relative importance of biomarkers and cardiopulmonary exercise testing. Both biomarkers and cardiopulmonary exercise testing should be seen as 'complementary' risk stratification tools to an existing clinical risk stratification tool, such as the RCRI. Presently, there are data to suggest that cardiopulmonary exercise testing adds incremental value to the RCRI in the prediction of intermediate-term mortality [43], but insufficient evidence to determine whether biomarkers or cardiopulmonary exercise testing is preferably as a 'complementary' risk stratification tool [44]. Moreover, there is a need for cost consequence analyses to consider the differential in cost between biomarkers and cardiopulmonary exercise testing.

Conclusions

There is compelling evidence, particularly in major non-cardiac surgical patient cohorts, that pre-operative and postoperative NPs and postoperative troponin measurement independently surpass current clinical risk stratification tools, and are able to change risk prediction sufficiently so as to change clinical practice [1, 15, 24, 45].

A critical review of the state of biomarker research in non-surgical patients stresses the importance (yet

lack) of randomised controlled trials that address the utility of biomarker risk stratification to improve patient outcomes through biomarker-directed therapy, management and monitoring [46]. Studies should be undertaken to determine if pre-operative risk stratification using NP is able to improve patient outcomes [17]. Importantly, the fifth stage of integration of a biomarker into clinical practice demands demonstration that biomarker-directed therapy improves clinical outcome. A single study has been conducted in the non-surgical population [47]. In non-surgical patients, standard-of-care heart failure therapy has been compared to BNP-guided heart failure therapy. A more aggressive heart failure therapy regimen driven by targeting the BNP level was generally well tolerated in the elderly and associated with significantly fewer cardiovascular events [47]. We are currently in the process of initiating a peri-operative trial in this field.

In all non-cardiac surgical patients with known cardiovascular risk or undergoing major surgery, we would recommend postoperative troponin monitoring [1, 12]. This is in broad agreement with the recent third universal definition of MI that recommends pre- and postoperative troponin surveillance on high-risk patients undergoing major surgery [16]. Without monitoring early postoperative troponin measurements, physicians would be likely to miss two thirds of the MIs that occur, and asymptomatic MIs carry the same high risk of 30-day mortality as symptomatic MIs [12].

As most of the evidence presented in this study has originated from studies conducted in major non-cardiac surgery populations, it is important that further research be undertaken to confirm these findings in intermediate-risk surgery.

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Competing interests

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