BJA

British Journal of Anaesthesia 114 (6): 909–18 (2015)

doi: 10.1093/bja/aev027
Advance Access Publication 3 March 2015
Clinical Practice

CLINICAL PRACTICE

High-sensitive cardiac troponin T measurements in prediction of non-cardiac complications after major abdominal surgery†

P. G. Noordzij[1,*], O. van Geffen[1], I. M. Dijkstra[2], D. Boerma[3], A. J. Meinders[4], T. C. D. Rettig[1], F. D. Eefting[5], D. van Loon[2], E. M. W. van de Garde[6] and E. P. A. van Dongen[1]

[1]Department of Anaesthesia, Intensive Care and Pain Medicine, [2]Department of Clinical Chemistry, [3]Department of Surgery, [4]Department of Internal Medicine, [5]Department of Cardiology, and [6]Department of Clinical Pharmacy, St Antonius Hospital, Koekoekslaan 1, 3430 EM, Nieuwegein, The Netherlands

*Corresponding author. E-mail: p.noordzij@antoniusziekenhuis.nl

Abstract

Background: Postoperative non-cardiac complication rates are as high as 11–28% after high-risk abdominal procedures. Emerging evidence indicates that postoperative cardiac troponin T elevations are associated with adverse outcome in non-cardiac surgery. The aim of this study was to determine the relationship between postoperative high-sensitive cardiac troponin T elevations and non-cardiac complications in patients after major abdominal surgery.
Methods: This prospective observational single-centre cohort study included patients at risk for coronary artery disease undergoing elective major abdominal surgery. Cardiac troponin was measured before surgery and at day 1, 3, and 7. Multivariable logistic regression analysis was performed to examine the adjusted association for different cut-off concentrations of postoperative myocardial injury and non-cardiac outcome.
Results: In 203 patients, 690 high-sensitive cardiac troponin T measurements were performed. Fifty-three patients (26%) had a non-cardiac complication within 30 days after surgery. Hospital mortality was 4% (8/203). An increase in cardiac troponin T concentration ≥100% compared with baseline was a superior independent predictor of non-cardiac postoperative clinical complications (adjusted odds ratio 4.3, 95% confidence interval 1.8–10.1, $P<0.001$) and was associated with increased length of stay (9 days, 95% confidence interval 7–11 *vs* 7 days, 95% confidence interval 6–8, $P=0.004$) and increased hospital mortality (12 *vs* 2%, $P=0.028$).
Conclusions: A postoperative high-sensitive cardiac troponin T increase ≥100% is a strong predictor of non-cardiac 30 day complications, increased hospital stay and hospital mortality in patients undergoing major abdominal surgery.
ClinicalTrials.gov Identifier: NCT02150486.

Key words: coronary artery disease; general surgery; postoperative complications; troponin T

† This article is accompanied by Editorial Aev068.
Accepted: December 4, 2014

Editor's key points

- Increases in cardiac troponin T (cTnT) are associated with worse cardiac outcomes after major surgery.
- This study investigated postoperative cTnT and outcome in high-risk patients undergoing abdominal surgery.
- A doubling of cTnT was associated with increased non-cardiac complications, length of stay and mortality.
- A doubling of cTnT compared with baseline was more predictive than absolute values.
- Increased cTnT appears to predict both cardiac and non-cardiac outcomes after major surgery.

Successful recovery from major abdominal surgery is frequently disturbed by the emergence of postoperative complications. Despite the development of new surgical techniques and improvements in anaesthesia management and postoperative care, complication rates in the literature remain as high as 11–28% after high-risk abdominal procedures.[1–3] The occurrence of an adverse event after surgery has a major impact on a patient's personal and economic life, because it often disables their physical well-being and leads to a prolonged recovery during and after hospital admission. For decades, doctors and researchers have been trying to unfold the pathophysiological mechanisms of postoperative complications. In this regard, many studies have focused on perioperative myocardial ischaemia, because it is a leading cause of postoperative morbidity and mortality after non-cardiac surgery.[4–7]

Postoperative cardiac troponin (cTn) measurements are an important test for the detection of myocardial ischaemia. Recent findings indicate that elevated cTn concentrations can be present in >10% of patients after major non-cardiac surgery.[8 9] Currently, mild elevations in postoperative cTn concentrations are often dismissed as non-relevant in the absence of additional signs of myocardial ischaemia (e.g. clinical symptoms or abnormal findings on electrocardiography); however, emerging evidence indicates that such cTn elevations, referred to as myocardial injury, are associated with adverse outcome.[8–13] In the Vascular Events In Non-cardiac Surgery Patients Cohort Evaluation (VISION) trial, peak postoperative fourth-generation cTnT concentrations in >15 000 patients after major non-cardiac surgery were associated with increased 30 day mortality.[8] In the VISION trial, patients with cTnT concentrations >20 ng litre^{-1} already had a more than two-fold increased risk of postoperative death.[8] An interesting finding of that study was that peak cTnT concentrations equally predicted death after surgery as a result of cardiovascular and non-cardiovascular causes. Based on these results, one might argue that myocardial injury is at least partly involved in the aetiology of important complications after abdominal surgery, such as anastomotic dehiscence, pneumonia, or wound infection.

The present study was initiated to gain further insight into the possible influence of asymptomatic myocardial injury on non-cardiac outcome in patients after major abdominal surgery.

Methods

Study design

The MICOLON (Myocardial Injury and Complications after major abdominal surgery) study is a prospective, single-centre, observational cohort study on the association between fifth generation high-sensitive cTnT concentrations and non-cardiac outcome after major abdominal surgery in patients at risk for coronary artery disease. Recruitment took place between June, 2012 and February, 2014 at St Antonius Hospital, Nieuwegein, The Netherlands, an 880-bed teaching hospital. The local medical ethics committee approved the study protocol.

Patient eligibility

Patients were eligible to enter the study if they were to undergo elective major abdominal surgery with an expected postoperative mortality rate >3%,[14] were aged 45 yr or older and had at least one of the following major cardiac risk factors: diabetes mellitus, peripheral artery disease (i.e. intermittent claudication or history of vascular surgery except arteriovenous shunt and vein-stripping procedures), history of hospitalization for congestive heart failure, history of myocardial infarction, stable angina pectoris, history of coronary artery bypass grafting or percutaneous coronary angioplasty, renal insufficiency (defined as preoperative creatinine >150 μmol litre^{-1}), history of cerebral vascular event, aortic valve stenosis (defined as aortic valve area <1 cm^2), atrial fibrillation, moderate or poor left ventricular function (defined as left ventricular ejection fraction <55%), or two of the following minor risk factors for coronary artery disease: age >70 yr, hypertension, hypercholesterolaemia, history of transient ischaemic attack, chronic obstructive pulmonary disease, smoking, or low functional capacity (capable of physical activity of 4 metabolic equivalents or less). Patients were excluded from study participation if they had no signed informed consent.

Study procedure

Patients eligible for the study were identified at the outpatient preoperative anaesthesia clinic. Patients were examined and screened for cardiac risk factors by an anaesthesia resident or a dedicated screening nurse. Results of preoperative laboratory tests, data on patient characteristics, and preoperative use of cardiovascular drugs (i.e. statin, β-blocker, platelet inhibitor, calcium antagonists, angiotensin-converting enzyme inhibitor, and angiotensin receptor blocker) were noted. Before any study procedure, written informed consent was obtained from all patients. During the study period, blood was collected for plasma cTnT measurements after induction of general anaesthesia (baseline) and on the first, third, and seventh postoperative day. All plasma samples were frozen and stored at −20°C at the hospital's laboratory until analysis. Cardiac troponin T batch analysis was performed every 3 weeks with the use of a fifth generation Elecsys Troponin T high-sensitive assay on an automated Cobas 6000 platform (Roche Diagnostics, Mannheim, Germany). The limit of detection of this high-sensitive assay was determined at 3 ng litre^{-1} with a 99th percentile upper reference limit of 14 ng litre^{-1}.[15] In addition, plasma creatinine concentrations were measured in each sample with an enzymatic method on the same automated platform (Roche Diagnostics). An estimated glomerular filtration rate (eGFR) was calculated from plasma creatinine values using the Modification of Diet in Renal Disease (MDRD-4) formula.[16] During the entire study period, daily routine quality control samples for cTnT and creatinine ensured comparable patient data across different reagent lots. After analysis, the samples were stored at −80°C.

Surgical procedures were performed under general anaesthesia or a combination of general and epidural anaesthesia. Anaesthesia management was left to the discretion of the attending anaesthetist. According to hospital protocol, patients undergoing

gastric–oesophageal, pancreatic, or hepatic surgery and patients aged ≥80 yr or with an ASA grade ≥III were admitted to an intensive care unit after surgery for at least 24 h. To improve postoperative recovery, all patients were treated according to the current Enhanced Recovery After Surgery (ERAS) guidelines (http://www.erassociety.org/index.php/eras-guidelines/eras-society-guidelines, accessed 23 January, 2015).

During the postoperative period, research personnel performed patient visits, reviewed medical charts, and noted complications. During this period, research personnel were blinded to the cTnT results. At 30 days after surgery, cTnT results were reported to the researchers, and a follow-up telephone interview was conducted with all patients who were discharged from the hospital at that time. For the purpose of this interview, a set of standardized questions were used regarding the occurrence of a non-cardiac complication. If a complication had occurred, medical details were retrieved from the treating physicians. Information from routine postoperative clinic visits was used if patients could not be reached by telephone. Follow-up was completed for 99.5% (202/203) of patients alive at 30 days after surgery. Noted end-points were judged by an event committee (D.B. and A.J.M.) that was blinded to the cTnT results.

Interpretation of cardiac troponin T results

Fifth generation high-sensitive cTnT assays facilitate troponin T measurements at very low concentrations (i.e. ≥3 ng litre^{-1}) because of greater analytical sensitivity and precision compared with fourth generation assays. In this study, we used an hs-cTnT assay to determine a baseline value in each study patient before surgery. This is important because the presence of cTnT has previously been established in apparently healthy individuals and patients with stable cardiac disease.[17 18] Postoperative cTnT measurements were interpreted according to peak concentrations (i.e. highest postoperative cTnT concentration) and changes compared with baseline (i.e. absolute and relative differences in cTnT concentration between peak concentration and baseline). Results on postoperative peak cTnT concentrations and increases in cTnT compared with baseline were subsequently used to determine the optimal cut-off value for the association between cTnT elevations and adverse non-cardiac outcome.

End-point definition

The primary end-point of the study was the occurrence of any of the following non-cardiac events within 30 days after surgery: mortality, defined as death without cardiovascular origin; sepsis, defined as systemic inflammatory response syndrome (SIRS)[19] in response to a proven or suspected microbial infection; pneumonia, defined as purulent sputum or isolation of a pathogen from sputum culture or blood culture and clinical symptoms (e.g. dyspnoea, fever, cough) or a consolidation or pleural effusion on chest radiograph; respiratory failure, defined as non-cardiac hypoxia or hypercapnia leading to intensive care unit (re)admission for respiratory support [e.g. (non)invasive ventilation or high-concentration oxygen therapy]; anastomotic dehiscence, defined as presence of luminal contents through drain or wound site causing local inflammation or SIRS, or leak detected on imaging studies in combination with clinical signs of SIRS; intestinal ischaemia, defined as signs of superficial or transmural bowel ischaemia on imaging studies and clinical symptoms (e.g. abdominal pain or tenderness) or SIRS; wound infection, defined as purulent drainage from superficial incision or deliberate opening of superficial incision by surgeon and clinical signs of local inflammation (e.g. pain, tenderness, swelling, redness); or bleeding, defined as abnormal postoperative bleeding needing surgical (i.e. reoperation) or endovascular (i.e. coiling) treatment. Other study parameters were length of hospital stay and hospital mortality.

Statistics

Data were analysed using IBM SPSS Statistics 22.0 software. Continuous data are presented as the mean (SD) if normally distributed. In the case of abnormal distribution, the median and interquartile range (IQR) are presented. The Kolmogorov–Smirnov test was used to test for normal distribution. To compare variables between groups, the χ^2 test was used for dichotomous variables and Student's *t*-test or median test for continuous variables, when appropriate. Receiver operating characteristic curves were used to assess the diagnostics accuracy for non-cardiac events of postoperative peak cTnT concentrations and cTnT changes compared with baseline. Optimal cut-off values were derived from receiver operating characteristic curve analyses and prior literature reports.[8 17–19] Sensitivity, specificity, and positive and negative predictive values were calculated for different cTnT cut-off concentrations. Univariate analyses were performed to examine the crude associations of preoperative and perioperative characteristics and primary end-points. Multivariate analysis was performed to examine the adjusted association of different cTnT cut-off concentrations and primary outcome. To do so, a multivariable logistic regression model was constructed, considering all variables that were imbalanced between the arms ($P \leq 0.10$) in Table 1. A variable was retained in the model as a confounder if it changed the odds ratio (OR) of myocardial injury and primary outcome by >10%. *P*-values <0.05 were considered significant in all analyses. Cardiac troponin T measurements that were performed after the occurrence of any postoperative adverse event were not included in the risk analyses.

To determine optimal sample size, a power analysis was performed before study commencement. Based on prior literature reports, we estimated the incidences of elevated cTnT concentrations and 30 day complications to be at least 10 and 15%, respectively. Based on the assumption that patients with elevated cTnT concentrations have a two-fold increased risk of a postoperative non-cardiac complication, the number of study patients needed was 437 (power=80%, α=0.05). After 100 patients were included, an interim analysis revealed that elevated cTnT concentrations were present in at least 25% of patients and that patients with cTnT elevations had a three-fold increased risk of adverse outcome. As a result, at least 187 study patients were needed to test accurately our hypothesis that cTnT elevation is associated with adverse postoperative non-cardiac outcome in patients undergoing major abdominal surgery.

Results

Study population and outcome

A total of 210 patients were eligible for study participation and signed informed consent. Seven patients (3.3%) were excluded from the analysis for the following reasons: in two patients, surgery was cancelled; one patient was discharged from the hospital on the first postoperative day and only baseline cTnT measurements were performed; in one patient, surgery was cancelled after laparotomy was performed because of metastatic disease; and in three patients, postoperative blood samples were not collected for logistical reasons. The remaining 203 patients were included in the analysis. Baseline characteristics of all study patients are shown in Table 1. A majority of patients underwent

Table 1 Baseline characteristics of patients with and without adverse 30 day outcome. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; RCRI, Revised Cardiac Risk Index; POSSUM, Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity; TIA, transient ischaemic attack. Coronary artery disease is the composite of patients with angina pectoris or a history of myocardial infarction, coronary artery bypass grafting, or percutaneous coronary angioplasty. Data are presented as mean (interquartile range) unless stated otherwise. *Estimated operative mortality according to POSSUM

	All (*n*=203)	No event (*n*=150)	Event (*n*=53)	*P*-value
Male gender [*n* (%)]	128 (63)	90 (60)	38 (72)	0.13
Age (yr)	69 (62–77)	69 (62–76)	69 (60–78)	0.52
BMI (kg m^{-2})	26 (24–30)	27 (25–31)	25 (23–29)	0.05
Medical history [*n* (%)]				
Current smoking	35 (17)	25 (17)	10 (19)	0.72
Diabetes mellitus	59 (29)	46 (31)	13 (25)	0.40
COPD	66 (33)	47 (32)	19 (36)	0.55
Hypertension	148 (73)	114 (76)	34 (64)	0.10
Hypercholesterolaemia	95 (47)	72 (48)	23 (43)	0.56
Congestive heart failure	15 (7)	12 (8)	3 (6)	0.58
Coronary artery disease	49 (24)	34 (23)	15 (28)	0.41
Prior myocardial infarction	38 (19)	25 (17)	13 (25)	0.21
Peripheral artery disease	14 (7)	10 (7)	4 (8)	0.83
Prior CVA or TIA	29 (14)	17 (11)	12 (23)	0.04
Atrial fibrillation	28 (14)	18 (12)	10 (19)	0.21
Normal left-ventricular function	191 (94)	142 (95)	49 (93)	0.62
eGFR [ml min^{-1} (1.73 $m)^{-2}$]	91 (77–113)	92 (75–112)	99 (81–123)	0.12
Malignancy	137 (67.5)	99 (66.0)	38 (71.7)	0.45
Medications [*n* (%)]				
Platelet inhibitor	61 (30.0)	46 (30.7)	15 (28.3)	0.75
Statin	93 (45.8)	70 (46.7)	23 (43.4)	0.68
β-Blocker	80 (29.4)	62 (41.3)	18 (34.0)	0.35
Calcium antagonist	32 (15.8)	27 (18.0)	5 (9.4)	0.14
ACE inhibitor/ARB	86 (43)	63 (42)	23 (44)	0.78
Risk scores				
ASA	II (II–III)	II (II–III)	II (II–III)	0.83
RCRI	2 (1–2)	2 (1–2)	2 (1–2)	0.30
POSSUM* (%)	5.0 (1.9–11.3)	4.9 (1.9–11.2)	6.4 (3.6–13.0)	0.12
Type of surgery [*n* (%)]				
Colorectal	104 (51)	82 (55)	22 (42)	0.10
Gastric–oesophageal	43 (21)	21 (14)	22 (42)	<0.001
Pancreatic	21 (10)	14 (9)	7 (13)	0.43
Gastric bypass	19 (9)	18 (12)	1 (2)	0.03
Hepatic	9 (4)	8 (5)	1 (2)	0.30
Other	7 (3)	7 (5)	0	0.11
Surgery duration (min)	135 (90–180)	120 (80–180)	180 (95–240)	0.01
Operative blood loss (ml)	100 (20–288)	60 (20–250)	150 (50–400)	0.05

colorectal surgery. Fifty-three patients (26%) were diagnosed with at least one non-cardiac complication within 30 days after surgery. Postoperative sepsis (13%), pneumonia (10%), and anastomotic dehiscence (10%) occurred most frequently. Sepsis was associated with anastomotic dehiscence in 48% (13/27) of patients and pneumonia in 33% (9/27) of patients. More than half of the patients with sepsis also had respiratory insufficiency. The median length of postoperative stay was 8 days (IQR 5–13). Hospital mortality was 4% (8/203), and the median time between surgery and death was 20 days (IQR 6–33).

Preoperative cTnT concentrations and 30 day non-cardiac complications

Six-hundred and ninety cTnT measurements were performed in 203 patients. Cardiac troponin T samples were available at baseline and at day 1, 3, and 7 in, respectively, 97.5 (198/203), 99.5 (202/203), 97.3 (183/188), and 88.4% (107/121) of study patients admitted to the hospital at that time. Before surgery, 31% (61/198) of patients had a cTnT concentration ≥14 ng $litre^{-1}$, which was associated with advanced age, decline in renal function, and severe systemic disease (Fig. 1). Cardiac troponin T concentrations before surgery were not significantly different between patients with and without a postoperative non-cardiac complication (12 ng $litre^{-1}$, IQR 7–15 *vs* 9 ng $litre^{-1}$, IQR 6–16, *P*=0.44). Twenty-eight per cent (17/61) of patients with elevated preoperative cTnT concentrations had a non-cardiac adverse event *vs* 26% (35/137) with normal cTnT concentrations (*P*=0.73).

Postoperative cTnT concentrations and 30 day non-cardiac complications

In patients with a non-cardiac postoperative complication, peak postoperative cTnT concentrations were higher before any event

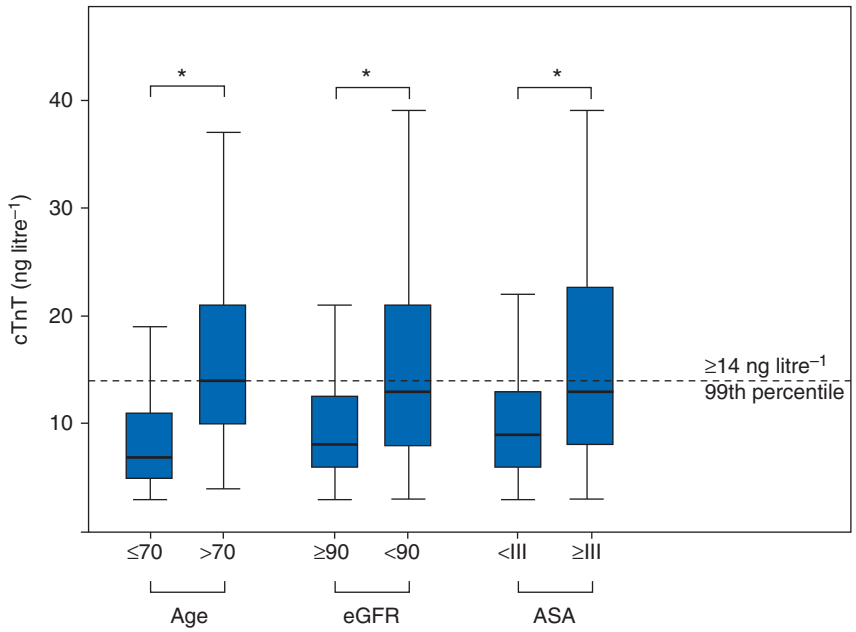

Fig 1 Differences in median preoperative cardiac troponin T (cTnT) concentrations according to age (in years), renal function and physical status. eGFR, estimated glomerular filtration rate (in millilitres per minute per 1.73 m^2). *P<0.001.

compared with patients without a non-cardiac complication (20 ng litre^{-1}, IQR 11–34 *vs* 13 ng litre^{-1}, IQR 8–22, *P*=0.004). The first elevated postoperative cTnT measurement was noted at day 1 or 3 in 91% of patients. A cTnT ≥14 ng litre^{-1} was present in 64% (34/53) of patients with adverse outcome compared with 48% (72/150) of patients with uneventful recovery (*P*=0.043; Fig. 2A). None of the patients with a cTnT ≥14 ng litre^{-1} experienced symptoms of myocardial ischaemia. There was a weak linear relationship between postoperative cTnT concentrations and a decline in eGFR (*r*=0.11, *P*=0.02). Increasing age had no linear relationship with postoperative cTnT concentrations (*r*=0.01, *P*=0.91).

Absolute and relative increases in postoperative cTnT concentrations compared with baseline were higher in patients with adverse non-cardiac 30 day outcome than in patients with uneventful recovery (5 ng litre^{-1}, IQR 2–16 *vs* 3 ng litre^{-1}, IQR 0–6, *P*=0.002; and 43%, IQR 25–184% vs 25%, IQR 0–60%, *P*=0.001, respectively). A non-cardiac postoperative complication was preceded by a cTnT increase ≥85% in 35% of patients with adverse non-cardiac outcome compared with 13% of patients without a non-cardiac 30 day complication (*P*=0.001; Fig. 2C). Details on sensitivity, specificity, and positive and negative predictive values of different cTnT cut-off concentrations are presented in Table 2. In multivariable analysis, a cTnT increase ≥100% correctly differentiated between a complicated and a non-complicated postoperative course in 80% of patients, with respect to non-cardiac 30 day events. This performance was superior to other cTnT cut-off concentrations presented in Table 2. The corresponding area under the receiver operating characteristic curve was 0.78 (95% CI 0.70–0.87).

Multivariable analysis for cTnT increase ≥100% and 30 day non-cardiac complications, length of stay, and hospital mortality

Patients with a cTnT increase ≥100% had a four-fold increased risk (95% CI 1.6–10.1) for a non-cardiac 30 day complication independent of other risk factors (Table 3). Postoperative sepsis, anastomotic dehiscence, respiratory insufficiency, wound infection, and bleeding occurred more frequently in patients who suffered from a cTnT increase ≥100% after surgery (Fig. 3). After adjustment for age, gender, and a postoperative decline in renal function, a cTnT increase ≥100% was associated with a history of cerebral vascular event or transient ischaemic attack (adjusted OR 3.6, 95% CI 1.3–10.0) and pancreatic surgery (adjusted OR 3.4, 95% CI 1.1–11.2). The association between an increase in cTnT ≥100% and adverse non-cardiac 30 day outcome was observed throughout important patient subgroups, such as patients with preoperative or postoperative mild renal dysfunction (adjusted OR 6.5, 95% CI 1.2–34.6 and adjusted OR 4.7, 95% CI 1.5–14.4, respectively). As shown in Fig. 4, an increase in cTnT ≥100% before the occurrence of any event was associated with a significant longer hospital stay (9 days, 95% CI 7–11 *vs* 7 days, 95% CI 6–8, *P*=0.004) compared with patients without an increase in cTnT ≥100%. Hospital mortality was higher in patients with an increase in cTnT ≥100% compared with patients without an increase in cTnT ≥100% [12% (4/33) *vs* 2% (4/165), *P*=0.028].

Discussion

This observational cohort study used fifth generation high-sensitive cTnT measurements to diagnose myocardial injury after major abdominal surgery in patients with risk factors for coronary artery disease and reports several new findings. First, myocardial injury after major abdominal surgery is common and associated with adverse non-cardiac 30 day outcome. Second, a relative increase in cTnT is superior to an absolute increase or peak postoperative cTnT concentration in predicting non-cardiac complications. Third, an increase in cTnT ≥100% is a superior independent predictor of non-cardiac 30 day complications after major abdominal surgery compared with other cut-off

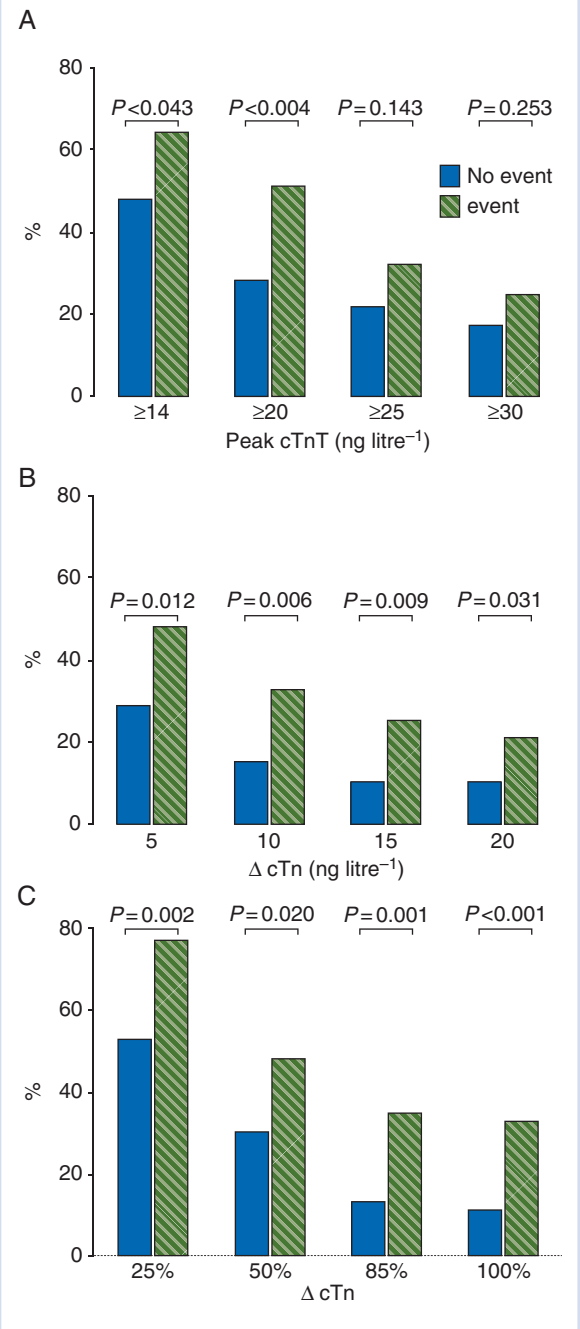

Fig 2 Association between postoperative myocardial injury and non-cardiac complications for peak concentration (A), absolute increase (B), and relative increase (C) of cardiac troponin T (cTnT).

concentrations and is associated with increased length of stay and hospital mortality.

The impact of perioperative myocardial infarction on fatal and non-fatal outcome after major non-cardiac surgery has previously been established.[4–7] In recent years, several studies have shown that many patients sustain myocardial injury during the surgical period that does not fulfil the diagnostic criteria for myocardial infarction. These patients are characterized by mild postoperative cTn elevations, often without ischaemic features, and are at risk for increased mortality at 30 days and 1 yr after surgery.[8–13] Landesberg and colleagues[10] were among the first to show that even small elevations in postoperative cardiac biomarker concentrations were predictive of adverse outcome. Patients undergoing major vascular surgery with mild myocardial injury had a more than two-fold increased risk of long-term mortality after adjustment for important confounders. Beattie and colleagues[11] performed a large retrospective single-centre cohort analysis in patients undergoing major non-cardiac surgery. A postoperative cTn measurement was performed in >10 000 patients and was independently associated with 30 day mortality when elevated. This association was strengthened in patients with incremental concentrations of postoperative cTn. The relationship between peak postoperative cTn concentrations and 30 day mortality after major non-cardiac surgery was confirmed by Devereaux and colleagues[8] in a prospective international cohort study. In addition, the results of that study showed that minor cTn elevations, which were below the commonly used threshold value of the assay used, were already associated with adverse outcome. Recently, Van Waes and colleagues[12] illustrated that the implementation of routine postoperative cTn measurements identified patients at risk for postoperative mortality and improved risk stratification after surgery. The results of our study confirm that postoperative cTn measurements can be used for risk stratification to identify patients at risk for adverse outcome after major non-cardiac surgery. Additionally, we demonstrate that in a population at risk for coronary artery disease a considerable variation in baseline cTnT concentrations can be present. This implies that an elevated postoperative cTnT measurement can be the consequence of a postoperative increase and a continuation of an already increased baseline value. The latter finding explains the observed increase in discriminative value of relative changes in cTnT concentrations compared with absolute peak concentrations.

Although previous studies have shown an association between elevated postoperative cTn concentrations and major adverse cardiac outcome, this has not been established for non-cardiac complications. In the present study, patients with an increase in cTnT ≥100% were at increased risk for postoperative respiratory insufficiency, sepsis, anastomotic dehiscence, wound infection, and bleeding. Of all patients with a non-cardiac complication, almost half had postoperative sepsis. In patients with postoperative sepsis, the primary diagnosis was anastomotic dehiscence in a majority of patients. The exact pathophysiological mechanism of a major non-cardiac complication, such as anastomotic dehiscence, and whether or not causality exists with myocardial injury, remains unclear. During the perioperative period, patients are characterized by an increased state of coagulation, high concentrations of circulating stress hormones, and enhanced platelet reactivity.[20–22] Although the aetiology of postoperative cTn elevations is not fully elucidated, it is assumed that this is similar to acute myocardial injury in the non-surgical population.[23] Regional myocardial injury leads to stunning of the myocardium, with diastolic dysfunction and a reduced cardiac output. During the first postoperative days, this may result in important changes in peripheral blood supply, with impaired healing of local tissue and an increased risk of anastomotic dehiscence or wound infection. However, if causality exists between myocardial injury and non-cardiac complications, one would expect that preoperative use of cardioprotective drugs, such as a platelet inhibitor, β-blocker, or statin, may benefit patients and improve postoperative outcome. In our study population, the incidence of non-cardiac postoperative complications was 24% (35/144) in patients using a platelet

Table 2 Sensitivity, specificity, PPV, and NPV of different cTnT cut-off concentrations and the association with non-cardiac complications. CI, confidence interval; cTnT, cardiac troponin T; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value. *Odds ratios were adjusted for age, gender, BMI, postoperative decline in renal function, and type of surgery

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*
cTnT						
Peak ≥14 ng litre^{-1}	64	52	32	80	1.9 (1.0–3.7)	1.7 (0.7–4.1)
Peak ≥20 ng litre^{-1}	51	72	39	81	2.7 (1.4–5.1)	2.2 (1.0–5.1)
Peak ≥25 ng litre^{-1}	32	78	34	77	1.7 (0.8–3.4)	1.1 (0.5–2.5)
Peak ≥30 ng litre^{-1}	25	83	33	76	1.6 (0.7–3.3)	1.1 (0.5–2.7)
Increase ≥5 ng litre^{-1}	48	71	37	79	2.3 (1.2–4.4)	2.3 (1.1–5.2)
Increase ≥10 ng litre^{-1}	32	85	44	78	2.7 (1.3–5.7)	2.3 (1.0–5.6)
Increase ≥15 ng litre^{-1}	25	90	46	77	2.9 (1.3–6.6)	2.4 (0.9–6.1)
Increase ≥20 ng litre^{-1}	21	90	44	76	2.5 (1.1–6.0)	2.1 (0.8–5.7)
Increase ≥25%	77	47	34	85	3.0 (1.5–6.2)	3.3 (1.4–7.8)
Increase ≥50%	48	70	36	79	2.1 (1.1–4.1)	2.4 (1.1–5.1)
Increase ≥85%	35	87	49	79	3.5 (1.7–7.5)	3.7 (1.5–8.8)
Increase ≥100%	33	89	52	79	3.9 (1.8–8.6)	4.0 (1.6–10.1)

Table 3 Univariate and multivariate association between clinical characteristics and non-cardiac complications. CI, confidence interval; cTnT, cardiac troponin T; CVA, cerebrovascular accident; OR, odds ratio; TIA, transient ischaemic attack. *Adjusted for age, gender, gastric–oesophageal surgery, BMI >25 kg m^{-2}, and postoperative renal decline. †Postoperative renal decline, per 1 μmol litre^{-1} increase in plasma creatinine

	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Variables				
Δ cTnT ≥100%*	3.9 (1.8–8.6)	0.001	4.0 (1.6–10.1)	0.003
Gastric–oesophageal surgery	4.4 (2.1–8.9)	<0.001	5.4 (2.4–12.5)	<0.001
BMI >25 kg m^{-2}	0.5 (0.2–0.9)	0.02	0.3 (0.1–0.7)	0.003
Postoperative renal decline†	1.0 (1.0–1.0)	0.05	1.0 (1.0–1.0)	0.02
Prior CVA or TIA	2.3 (1.0–5.2)	0.05		
Gastric bypass surgery	0.1 (0.0–1.1)	0.06		
Surgery duration >120 min	1.6 (1.1–2.3)	0.02		
Operative blood loss >100 ml	2.1 (1.1–4.0)	0.03		

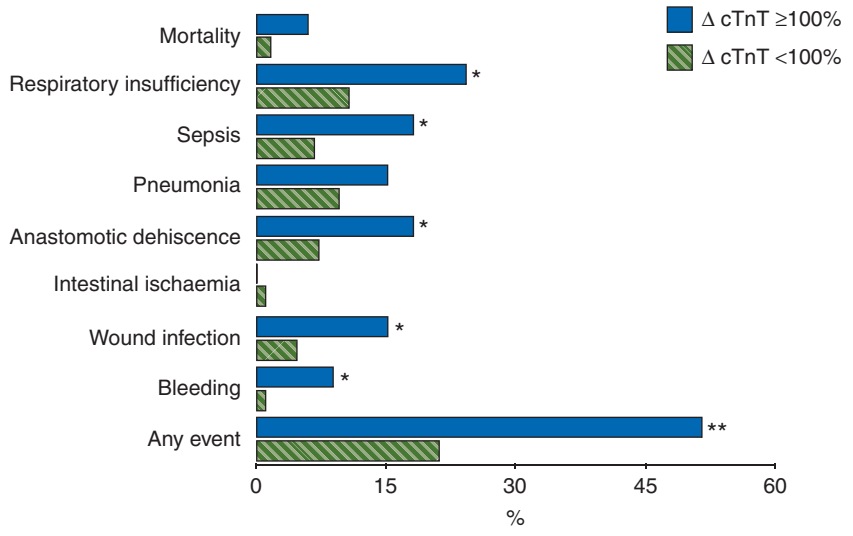

Fig 3 Incidences of 30 day complications in patients with and without a cTnT increase ≥100%. cTnT, cardiac troponin T. *P<0.05, **P<0.001.

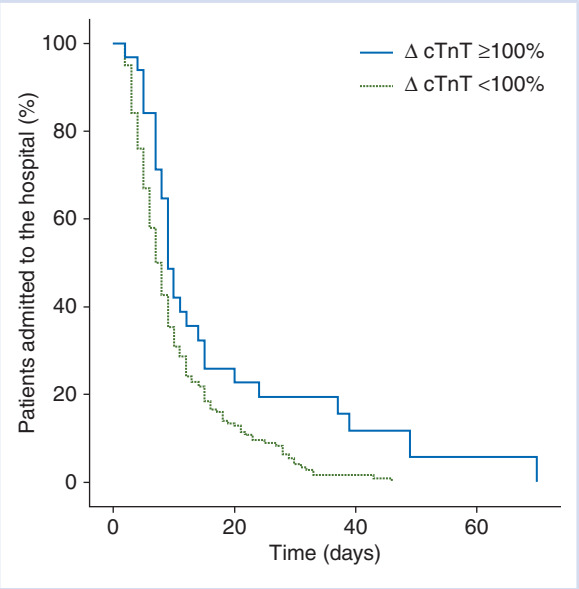

Fig 4 Length of hospital stay for patients with and without a cTnT increase ≥100% before any event. cTnT, cardiac troponin T.

inhibitor, β-blocker, or statin *vs* 31% (18/59) in patients who did not (*P*=0.36). Of all cardiac drugs listed in Table 1, the occurrence of an increase in cTnT ≥100% was reduced by preoperative statin therapy (adjusted OR 0.31, 95% CI 0.12–0.76), but this was not associated with a reduction in non-cardiac postoperative complications [25% (23/93) in statin users *vs* 27% (30/110) in non-users, *P*=0.68]. Based on these results, one might argue that causality between myocardial injury and non-cardiac complications is non-existent. Instead, similar to the myocardium, other organs, such as the gastrointestinal tract, may be disposed to ischaemic injury as a result of perioperative inflammation, local vasoconstriction, and hypercoagulation. Irrespective of myocardial injury, this may result in local changes in tissue perfusion and reduced tissue regeneration, with increased risk of multi-organ disease and non-cardiac complications, such as anastomotic dehiscence, pneumonia, or wound infection. However, the present study was not primarily designed to investigate whether the risk of postoperative non-cardiac complications could be modified by a preoperative intervention to reduce cTnT elevations, and therefore, no definite conclusions can be drawn from these results.

Currently, there is no accepted guideline on the appropriate postoperative change in cTnT necessary to diagnose myocardial injury. Based on the results of fourth generation cTnT assays in a large international cohort study, a peak postoperative cTnT ≥30 ng litre^{-1} has recently been suggested as the optimal cut-off concentration for myocardial injury in predicting 30 day mortality.[9] As a result of greater analytical sensitivity, fifth generation high-sensitive assays can detect cTnT over a low range of concentrations and facilitate reliable quantification of cTnT in healthy patients and patients with stable coronary artery disease.[17 18] Using the published 99th percentile of ≥14 ng litre^{-1}, 31% of patients in this study had an elevated cTn concentration before surgery. Cardiac troponin T concentrations ≥14 ng litre^{-1} were associated with patient characteristics that are common in the surgical population, such as increased age and mild renal insufficiency. Given this, and the fact that myocardial injury is often characterized by minor changes in postoperative cTnT concentration, a definition that is based on a significant increase in cTnT concentration compared with baseline might be preferable to postoperative peak concentrations.

Previous studies have assessed the biological and analytical variability of cTnT concentrations in healthy subjects and determined reference change values necessary to define a significant increase in cTnT concentration indicative of myocardial injury. A publication by Vasile and colleagues[17] reported that a short-term change of 85% is necessary to distinguish an increase in cTnT concentration because of myocardial injury from biological and analytical variation. In a study with similar design, performed in patients with suspected stable coronary artery disease undergoing coronary angiography, Nordenskjöld and colleagues[18] demonstrated that individual variation of cTnT was comparable to the biological variation in healthy individuals. A change in hs-cTnT concentration >50% was suggested by the authors to diagnose acute myocardial injury. In our study population, a postoperative increase in cTnT of at least 50 and 85% were present in 35 and 19% of patients, respectively. The negative predictive values of the different cTnT cut-off concentrations presented in Table 2 varied between 76 and 85%, meaning that patients with a 'negative' test result had a ~80% chance of an uncomplicated postoperative recovery, irrespective of what cTnT cut-off concentration was applied.

The positive predictive value of a two-fold increase in cTnT was substantially higher compared with other cut-off concentrations for myocardial injury and can be useful to identify patients after major abdominal surgery at risk for non-cardiac complications. The data presented in Table 2 support the fact that using different cut-off criteria will involve some trade-offs between sensitivity and specificity. Multivariable analyses showed that a diagnostic cut-off for a postoperative increase in cTnT ≥100% was superior in differentiation between uneventful and complicated recovery, with respect to non-cardiac 30 day complications. However, using this cut-off in daily practice will lead to a substantial number of patients in whom myocardial injury might be falsely ruled out based on too small an observed increase in cTnT, and one might argue that this approach is too conservative. In our opinion, a conservative approach in diagnosing myocardial injury seems justified at the moment, because a specific strategy for asymptomatic postoperative cTn elevation is lacking, and possible treatment benefit or harm in patients with myocardial injury remains unknown.[24]

The results of our study confirm that postoperative cTn measurements can be used for risk stratification after major non-cardiac surgery, as has been demonstrated previously by others.[8–13] Regarding non-cardiac 30 day outcome, the positive predictive value of a two-fold postoperative increase in cTnT can provide the physician with important prognostic information after abdominal surgery and may aid clinical decision making in patients who experience a delayed recovery without apparent cause. Although a clear therapeutic strategy for patients with cTn elevations is currently lacking, serial postoperative cTn measurements can be used as a marker to improve postoperative care. In a recent study by Ausset and colleagues,[25] postoperative cTn was measured during the first 3 days in patients after major orthopaedic surgery. After an in-depth analysis of factors that were possibly associated with myocardial injury (i.e. hypoxaemia, anaemia, hypotension, tachycardia, and hyperglycaemia) an improvement programme with simple therapeutic interventions was initiated to enhance postoperative care. The authors reported a 56% reduction in the incidence of myocardial injury and a 75% reduction in the incidence of major adverse cardiac events at 1 yr after implementation of the quality-of-care

protocol. Based on these results, gastrointestinal surgeons may choose to use postoperative cTn monitoring after major surgery to identify patients at risk for adverse outcome or as a simple benchmark tool for future interventions that affect the quality of perioperative care. In this respect, we recommend using a fifth generation high-sensitive cTn assay and interpretation of postoperative cTn results compared with baseline.

This study is one of the first to demonstrate an association between high-sensitive cTnT elevations and adverse non-cardiac 30 day outcome after major abdominal surgery. The strengths of this study include a preoperative cTnT measurement in 98% of patients and interpretation of postoperative cTnT concentrations with respect to pre-existing elevations. In each postoperative blood sample the plasma creatinine concentration was measured, and the association between postoperative cTnT concentrations and adverse outcome was adjusted for a decline in eGFR. Cardiac troponin T measurements that were performed after the occurrence of any postoperative event were not included in the analyses, and only one patient was lost to follow-up. A model that used an increase in cTnT ≥100% had good discrimination with respect to non-cardiac events.

We recognize that our study has several limitations. First, this study was performed in a selective group of patients at risk for coronary artery disease who were undergoing high-risk abdominal surgery and may not be representative of the general surgical population. Second, although we aimed to include patients undergoing high-risk abdominal surgery, patients undergoing a gastric bypass procedure had relatively few postoperative complications and no hospital mortality. This may have influenced our results.

Conclusion

A postoperative increase in cTnT ≥100% compared with baseline is a strong predictor of major non-cardiac 30 day complications, increased hospital stay, and hospital mortality in patients undergoing abdominal surgery. Our data suggest that one in two patients with a two-fold increased postoperative cTnT concentration will suffer from a major non-cardiac complication within 30 days after surgery. Postoperative monitoring of cTnT concentrations can be used to identify patients at increased risk for adverse non-cardiac outcome after major abdominal surgery. Whether or not causality is present between cTnT elevations and adverse non-cardiac outcome and whether this risk is modifiable by future interventions remain to be elucidated.

Authors' contributions

P.G.N. leading investigator, design of study, acquisition of data, analysis and interpretation of data, primary author of paper; O. v.G. primary investigator, acquisition of data, critical revision of article; I.M.D. primary investigator, acquisition of data, interpretation of data, critical revision of article; D.B. member event committee; interpretation of data; critical revision of article; A.J.M. member event committee, interpretation of data, critical revision of article; T.C.D.R., acquisition of data, interpretation of data, critical revision of article; F.D.E. interpretation of data, critical revision of article; D.V.L. design of study, critical revision of article; E.M.W.v.d.G. analyses and interpretation of data, critical revision of article; E.P.A.v.D. design of study, interpretation of data, critical revision of article.

Declaration of interest

None declared.

Funding

Institutional and departmental sources.

References

1. Paun BC, Cassie S, MacLean AR, Dixon E, Buie WD. Postoperative complications following surgery for rectal cancer. *Ann Surg* 2010; **251**: 807–18
2. Peeters KC, Tollenaar RA, Marijnen CA, *et al*. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. *Br J Surg* 2005; **92**: 211–16
3. Arozullah AM, Khuri SF, Henderson WG, Daley J. Development and validation of a multifactorial risk index for predicting postoperative pneumonia after major noncardiac surgery. *Ann Int Med* 2001; **135**: 847–57
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. Eagle KA, Rihal CS, Mickel MC, Holmes DR, Foster ED, Gersh BJ. Cardiac risk of noncardiac surgery: influence of coronary artery disease and type of surgery in 3368 operations. *Circulation* 1997; **96**: 1882–7
6. Badner NH, Knill RL, Brown JE, Novick TV, Gelb AW. Myocardial infarction after noncardiac surgery. *Anesthesiology* 1998; **88**: 572–8
7. Devereaux PJ, Xavier D, Pogue J, *et al*. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. *Ann Intern Med* 2011; **154**: 523–8
8. Devereaux PJ, Chan MT, Alonso-Coello P, *et al*. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2012; **307**: 2295–304
9. Botto F, Alonso-Coello P, Chan MT, *et al*. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. *Anesthesiology* 2014; **120**: 564–78
10. Landesberg G, Shatz V, Akopnik I, *et al*. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. *J Am Coll Cardiol* 2003; **42**: 1547–54
11. Beattie WS, Karkouti K, Tait G, *et al*. Use of clinically based troponin underestimates the cardiac injury in non-cardiac surgery: a single-centre cohort studying 51,701 consecutive patients. *Can J Anesth* 2012; **59**: 1013–22
12. Van Waes JA, Nathoe HM, de Graaff JC, *et al*. Myocardial injury after noncardiac surgery and its association with short-term mortality. *Circulation* 2013; **127**: 2264–71
13. Levy M, Heels-Ansdell D, Hiralal R, *et al*. Prognostic vale of troponin and creatinine kinase muscle and brain isoenzyme measurement after noncardiac surgery. *Anesthesiology* 2011; **114**: 796–806
14. Noordzij PG, Poldermans D, Schouten O, Bax JJ, Schreiner FA, Boersma E. Postoperative mortality in The Netherlands: a population based analysis of surgery-specific risk in adults. *Anesthesiology* 2010; **112**: 1105–15
15. Giannitsis E, Kurtz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. *Clin Chem* 2010; **56**: 254–61
16. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate

from serum creatinine: a new prediction equation. *Ann Intern Med* 1999; **130**: 461–70
17. Vasile VC, Saenger AK, Kroning JM, Jaffe AS. Biological and analytical variability of a novel high-sensitivity cardiac troponin T assay. *Clin Chem* 2010; **56**: 1086–90
18. Nordenskjöld AM, Ahlström H, Eggers KM, *et al*. Short- and long-term individual variation in cardiac troponin in patients with stable coronary artery disease. *Clin Chem* 2013; **59**: 401–9
19. Bone RC, Balk RA, Cerra FB, *et al*. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. 1992. *Chest* 2009; **136**(5 Suppl): e28
20. Gibbs NM, Crawford GP, Michalopoulos N. Postoperative changes in coagulant and anticoagulant factors following abdominal aortic surgery. *J Cardiothorac Vasc Anesth* 1992; **6**: 680–5
21. Sametz W, Metzler H, Gries M, *et al*. Perioperative catecholamine changes in cardiac risk patients. *Eur J Clin Invest* 1999; **29**: 582–7
22. Rosenfeld BA, Faraday N, Campbell D, *et al*. Perioperative platelet reactivity and the effects of clonidine. *Anesthesiology* 1993; **79**: 255–61
23. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002; **105**: 1135–43
24. Chong CP, Van Gaal WJ, Ryan JE, Profitis K, Savige J, Lim WK. Does cardiology intervention improve mortality for post-operative troponin elevations after emergency orthopaedic–geriatric surgery? A randomised controlled study. *Injury* 2012; **43**: 1193–8
25. Ausset S, Auroy Y, Verret C, *et al*. Quality of postoperative care after major orthopedic surgery is correlated with both long-term cardiovascular outcome and troponin Ic elevation. *Anesthesiology* 2010; **113**: 529–40

Handling editor: J. P. Thompson