

REVIEW ARTICLE

 Troponin elevations after non-cardiac, non-vascular surgery are predictive of major adverse cardiac events and mortality: a systematic review and meta-analysisS. Ekeloef^{1,*}, M. Alamili¹, P. J. Devereaux^{2,3} and I. Gögenur¹

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Abstract

Background: Patients undergoing non-cardiac, non-vascular surgery are at risk of major cardiovascular complications. In non-cardiac surgery, troponin elevation has previously been shown to be an independent predictor of major adverse cardiac events and postoperative mortality; however, a majority of studies have focused on vascular surgery patients. The aim of this meta-analysis was to determine whether troponin elevation is a predictor of major adverse cardiac events and mortality within 30 days and 1 yr after non-cardiac, non-vascular surgery.

Methods: A systematic review and meta-analysis was conducted in January 2016 according to the Meta-analysis Of Observational Studies in Epidemiology guidelines. Both interventional and observational studies measuring troponin within the first 4 days after surgery were eligible. A systematic search was performed in PubMed, EMBASE, Scopus, and the Cochrane Central Register of Controlled Trials.

Results: Eleven eligible clinical studies ($n=2193$) were identified. A postoperative troponin elevation was a predictor of 30 day mortality, odds ratio (OR) 3.52 [95% confidence interval (CI) 2.21–5.62; $I^2=0\%$], and an independent predictor of 1 yr mortality, adjusted OR 2.53 (95% CI 1.20–5.36; $I^2=26\%$). A postoperative troponin elevation was associated with major adverse cardiac events at 30 days, OR 5.92 (95% CI 1.67–20.96; $I^2=86\%$), and 1 yr after surgery, adjusted OR 3.00 (95% CI 1.43–6.29; $I^2=21\%$).

Conclusions: Postoperative myocardial injury is an independent predictor of major adverse cardiac events and mortality within 30 days and 1 yr after non-cardiac, non-vascular surgery. The meta-analysis provides evidence that supports troponin monitoring as a cardiovascular risk stratification tool.

Key words: cardiovascular diseases; mortality; myocardial ischaemia; perioperative period; postoperative complications; troponin

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Editor's key points

- This pooled analysis has focused on patients having mostly orthopaedic and abdominal surgery.
- Postoperative troponin elevations have prognostic importance.
- Although evidence is lacking, basic cardiac medications for secondary prevention should be considered in this setting.
- Randomized trials of treatments for patients with postoperative troponin elevations are needed.

Worldwide, millions of patients annually undergo major non-cardiac surgery.^{1,2} A significant proportion of the patients suffer from major cardiovascular complications (e.g. non-fatal myocardial infarction, cardiac arrest, cardiovascular death) during the perioperative period and the first years after surgery.³⁻⁵ Perioperative myocardial infarction is the most common cardiovascular complication and is associated with poor outcomes. Moreover, even myocardial injury after non-cardiac surgery that does not fulfil the universal definition of myocardial infarction is independently associated with 30 day mortality.⁵

A recent meta-analysis including 3318 surgical patients concluded that an elevation of postoperative troponin is an independent predictor of mortality, particularly within the first year after non-cardiac surgery.⁶ A majority of the studies in the meta-analysis restricted enrolment to patients undergoing vascular surgery. Hence, >60% of the patients in the meta-analysis underwent major vascular surgery. Likewise, major randomized clinical trials and the VISION cohort study pooled vascular and non-vascular surgery when addressing perioperative cardiovascular risk estimation and cardiovascular optimization.^{4,5,7} Major vascular surgery is, in comparison with other types of non-cardiac surgery, a procedure with a high risk of major cardiovascular complications and is commonly executed in a high-risk population with cardiovascular co-morbidities and manifest systemic atherosclerosis resulting in an increased risk of perioperative myocardial injury.^{3,8,9} Hence, the cardiovascular risk profile of patients undergoing vascular surgery differs from the often more moderate risk profiles of patients undergoing other types of non-cardiac surgery.¹⁰ Moreover, major vascular surgery independently increased the risk of perioperative myocardial infarction in a cohort study enrolling 8351 patients undergoing non-cardiac surgery.³ Major studies have ignored the likelihood that differences between non-cardiac surgical procedures affect the pathogenesis of postoperative cardiovascular morbidity in different degrees and directions.¹¹

In recent years, a substantial number of studies have evaluated the prognostic impact of troponin elevation after non-cardiac, non-vascular surgery.¹²⁻¹⁵ The aim of this meta-analysis was to determine whether postoperative troponin elevation is an independent predictor of mortality or major adverse cardiac events after non-cardiac, non-vascular surgery.

Methods

Eligibility criteria and information source

A systematic review and meta-analysis was executed according to the Meta-analysis Of Observational Studies in Epidemiology guidelines.¹⁶ Study eligibility criteria included the following: a

population limited to adults undergoing non-cardiac, non-vascular surgery; patients had to have at least one troponin measurement within the first 4 days after surgery; one or more patients had to suffer a major cardiac event or die after surgery; and the study had to assess the prognostic impact of postoperative troponin elevation in terms of major adverse cardiac events or mortality within 30 days or 1 yr after surgery or, alternatively, provided data that could be included in the quantitative analyses. Studies on non-cardiac surgery that separately reported the results for non-vascular surgery could be included. Major adverse cardiac events were defined as non-fatal cardiac arrest, emergent coronary revascularization, acute coronary syndrome, stroke, congestive heart failure, atrial fibrillation (new onset or destabilization of pre-existing atrial fibrillation), major arrhythmia, cardiovascular death, and rehospitalization for cardiovascular reasons. Atrial fibrillation and major arrhythmia were determined by documentation in the medical records by the treating unit. We excluded non-English publications, retracted studies, and unpublished studies, including proceedings abstracts.

A literature search was conducted in January 2016 in PubMed, EMBASE, Scopus, and the Cochrane Central Register of Controlled Trials. Reference lists were reviewed manually, and the 'related citations' and 'cited by' features were used for studies fulfilling our eligibility criteria. Duplicates were removed manually. The following search terms were used in the systematic search strategy: nonvascular surgery, non-vascular surgery, non-cardiac surgery, noncardiac surgery, surgical procedures, operative, surgery, operation, cardiovascular events, cardiovascular event, postoperative complication, postoperative complications, perioperative complications, perioperative complication, death, mortality, prognosis, morbidity, cardiac event, cardiac events, human, humans, and troponin. The search terms were fitted to each database individually (MeSH terms, subject heading).

Study selection and data collection

Two reviewers (S.E. and M.A.) independently screened the manuscripts' titles and abstracts for potential eligibility and resolved disagreement through discussion or by consulting a third reviewer (I.G.). All articles selected as potentially eligible during the screening process underwent full-text review by two independent reviewers (S.E. and M.A.) to determine eligibility. Disagreements were resolved using the same procedure as for the screening process. Two independent reviewers (S.E. and M.A.) extracted data from all studies that fulfilled eligibility criteria. Disagreements were resolved using an identical process as for eligibility and screening. Data were extracted on author, year of publication, study design, number of participants, age, type of surgery, priority of surgery, lengths of follow-up, troponin type, troponin assay and manufacturer, cut-off value of myocardial injury in non-cardiac surgery, timing of postoperative measurements of troponin, number of patients with elevated troponin after surgery, definition of major adverse cardiac events, and number of deaths and major adverse cardiac events within 30 days and 1 yr after surgery.

Study quality and risk of bias

Risk of bias within the studies was evaluated according to the following predefined terms: the degree to which the study cohort represented the average patients undergoing non-cardiac, non-vascular surgery in the population;¹⁷ blinding of troponin measurement; preoperative troponin measurement; completeness of follow-up; method of patient follow-up; and

variables adjusted for in the multivariable analysis of mortality and major adverse cardiac events. Moreover, the Newcastle–Ottawa scale was used to assess the quality of the studies.¹⁷ The Newcastle–Ottawa scale rates the studies on selection, outcome, and comparability.¹⁷ Funnel plots were used to explore the existence of publication bias and small sample size bias.¹⁸

Summary measures

The primary outcome was the association between postoperative troponin elevation and mortality within 30 days and 1 yr after surgery. The secondary outcome was the association between postoperative troponin elevation and major adverse cardiac events within 30 days and 1 yr after surgery. We carried out a *post hoc* orthopaedic subgroup analysis on postoperative troponin elevation and 1 yr mortality. We reported the summary measure as odds ratios (OR) with 95% confidence intervals (95% CI). Two of the included studies reported their outcome measures as adjusted hazard ratios.^{12–19} The adjusted hazard ratios and their confidence intervals were converted to ORs and confidence intervals, using the following formula:⁶

$$RR = \frac{1 - e^{HR \cdot \ln(1 - P_0)}}{P_0}$$

The RR was the relative risk of death or major adverse cardiac events within 1 yr after surgery, and P_0 was the proportion of patients without postoperative troponin elevation that died within 1 yr after surgery or had a major adverse cardiac event within 1 yr after surgery. The authors were contacted directly, and they provided the crude data to calculate P_0 .^{12–19} The RR was then converted to OR.²⁰ Crude mortality rates were provided to compute the unadjusted ORs, and their 95% CI on the ln scale was calculated using the following formula: $\ln(\text{OR}_{\text{upper, lower}}) = \ln(\text{OR}) \pm 1.96 \cdot (\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d})$.²¹ The exponential function was used to determine the upper and lower limits on the original scale.

Statistical analysis

The meta-analysis statistics were conducted using Review Manager Version 5.3.²² The pooled ORs were computed with a generic inverse-variance method using random effect models.¹⁸ Moderate statistical heterogeneity was defined by an I^2 -value >30% and a substantial heterogeneity by an I^2 -value >50%.¹⁸ Further investigation of statistical heterogeneity by meta-regression was not performed because <10 studies were included in the pooled analyses.¹⁸

Results

Our search strategy identified 6551 citations in PubMed, EMBASE, Scopus, and the Cochrane Central Register of Controlled Trials. From these, 2685 duplicates were removed, leaving 3866 studies for screening of the title and abstract. After screening of the title and abstract, a total of 199 full-text articles were left. Based on the eligibility criteria, 188 articles were excluded, leaving 11 articles to be included in the systematic review and meta-analysis. No additional article was included after screening reference lists, using the ‘related citations’ and ‘cited by’ features in PubMed (Fig. 1).

Study characteristics

The 11 studies were published between 2009 and 2015. Seven studies were prospective cohort studies,^{12–15 19 23–26} two were

retrospective cohort studies,^{13, 14} and two were randomized controlled trials.^{27 28} From one of the randomized controlled trials, only data on the control group were included.²⁷ In the meta-analysis, 2193 patients were included. Five of 11 studies were in orthopaedic surgery ($n=993$ patients),^{12 19 23–25} one study in neurosurgery ($n=100$ patients),¹⁴ three studies in abdominal surgery ($n=536$ patients),^{26–28} one study in head and neck cancer surgery ($n=378$ patients),¹³ and one study in mixed non-cardiac, non-vascular surgery ($n=186$ patients).¹⁵ The length of follow-up ranged from 30 days to 8 yr (Table 1).

Troponin assessment

All studies assessed troponin within 4 days after surgery. Three studies measured cardiac troponin T,^{12 25 26} seven studies measured cardiac troponin I,^{13–15 19 23 24 28} and one study measured both cardiac troponin T and I.²⁷ The studies used multiple different troponin assays, and the cut-off value defining myocardial injury differed between the studies (Table in web-supplement summarizes the troponin type and assays or manufacture and cut-off values).

Results of individual studies

The proportion of patients with elevated troponin after surgery varied within the range of 6–73% (Table 2). Nine of the 11 studies registered the number of deaths within 30 days after surgery and the proportion varied within the range of 1–18%.^{12–15 23 24 27 28} All-cause mortality within 1 yr varied within the range of 1–27%.^{12 19 23–25} Five of the 11 studies reported the proportion of patients suffering a major adverse cardiac event within 30 days (11–32%) and 1 yr (4–32%) after surgery.^{15 19 23 24 28} The definition of major adverse cardiac events varied within the studies, and two of the studies included cardiovascular death in the definition (Table 3).^{15 19}

Study quality and risk of bias

One of the studies had no description of the inclusion- and exclusion criteria besides including a sample of patients with hip fractures.²⁵ The study populations of four studies were rated only somewhat representative of the average patient undergoing non-cardiac, non-vascular surgery in the community.^{24 26–28} One study recruited patients from the orthopaedic-geriatric unit but excluded patients from nursing homes and patients with moderate–severe dementia.²⁴ Patients with a known history of acute myocardial infarction or acute arrhythmias were excluded in a study involving surgical patients admitted to the intensive care unit.²⁷ Two studies only included moderate-high risk surgical patients.^{26 28} Five of the 11 studies did a blinded troponin measurement^{12 23 25–27} while nine of the 11 studies did a preoperative troponin measurement.^{12 14 15 23–28} The complete follow-up was >95% in all but one study.¹⁵ Direct patient follow-up and review of medical charts were the preferred methods of in-hospital follow-up. All but three studies primarily used medical charts, patient charts and administrative data in their out of hospital follow-up.^{15 19 26} The three studies conducted a structured telephone interview.^{15 19 26} Only five of the 11 studies did an adjusted analysis.^{12 19 23 24 28} The mortality analyses adjusted for more than one variable per 10 events.^{12 19 23 24 28} Three out of four studies adjusted for less than one variable per 10 major adverse cardiac events (detailed table in Supplementary material).^{23 24 28} Funnel plots are provided in the Supplementary material.

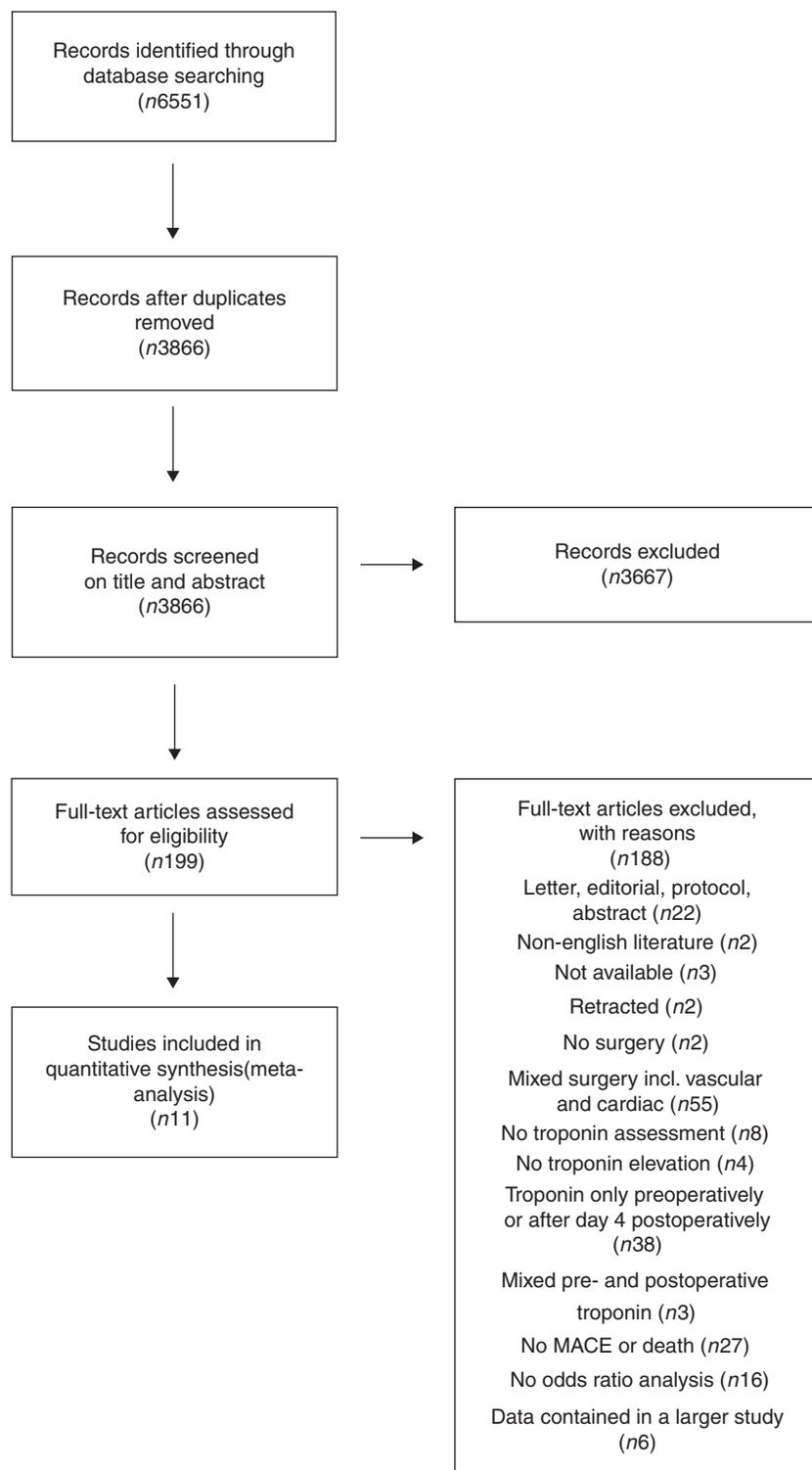


Fig 1 Flow diagram. MACE, major adverse cardiac events.

Table 1 Study characteristics. NA, not assessed

Authors (yr)	Type of Study	No. of patients	Mean age (yr)	Type of Surgery	Priority	Length of follow-up
Ausset and colleagues (2010) ¹⁹	Prospective cohort	355	72	Arthroplasties, hip fracture	Elective, emergency	12 months
Chong and colleagues (2009) ²³	Prospective cohort	102	80	Mixed orthopaedic surgery	Elective, emergency	12 months
Chong and colleagues (2012) ²⁴	Prospective cohort	187	77	Mixed orthopaedic surgery	Elective, emergency	12 months
Garrett and colleagues (2010) ¹⁴	Retrospective cohort	100	55	Neurosurgery	Emergency	30 days
Gillies and colleagues (2015) ²⁸	Randomized controlled trial	288	69.8/71.6	Abdominal surgery	Elective, emergency	180 days
Hietala and colleagues (2014) ¹²	Prospective cohort	200	80	Hip fracture	Emergency	Up to 1000 days
Izhaki and colleagues (2011) ²⁵	Prospective cohort	149	81	Hip fracture	Emergency	Up to 8 yr
Lee and colleagues (2014) ²⁷	Randomized controlled trial	45	NA	Abdominal surgery	Elective	180 days
Nagele and colleagues (2011) ¹³	Retrospective cohort	378	63	Head and neck cancer	NA	2 yr
Noordzij and colleagues (2015) ²⁶	Prospective cohort	203	69	Abdominal surgery	Elective	30 days
Oscarsson and colleagues (2009) ¹⁵	Prospective cohort	186	80	Urological, abdominal, hand and reconstructive surgery, gynaecological, neurosurgery, orthopaedic, spinal, ophthalmological	Emergency	90 days

Table 2 Thirty day and 1 yr all-cause mortality after non-cardiac, non-vascular surgery. The risk of mortality is specified as the odds ratio (95% confidence interval). *High-sensitive cardiac troponin T. aOR, adjusted odds ratio; NA, not assessed; OR, unadjusted odds ratio

Authors (yr)	No. of patients	No. of patients with elevated troponin after surgery [n/N (%)]	30 days no. of deaths n/N (%)	1 yr no. of deaths [n/N (%)]	30 day mortality	1 yr mortality
Ausset and colleagues (2010) ¹⁹	355	21/355 (6)	NA	21/355 (6)	NA	OR 4.58 (1.39–15.03) aOR 1.21 (0.26–5.69)
Chong and colleagues (2009) ²³	102	54/102 (53)	1/102 (1)	21/102 (21)	NA	OR 27.65 (3.54–216.16) aOR 12.0 (1.4–104.8)
Chong and colleagues (2012) ²⁴	187	70/187 (37)	3/187 (2)	16/187 (9)	OR 3.41 (0.30–38.24)	OR 5.3 (1.7–16.6) aOR 4.3 (1.1–16.5)
Garrett and colleagues (2010) ¹⁴	100	21/100 (21)	18/100 (18)	NA	OR 3.09 (1.02–9.41)	NA
Gillies and colleagues (2015) ²⁸	288	135/288 (47)	10/286 (3)	NA	OR 2.78 (0.70–10.91) aOR 3.95 (0.90–17.35)	NA
Hietala and colleagues (2014) ¹²	200	62/200 (31)	18/200 (9)	53/200 (27)	OR 5.38 (1.80–16.12) aOR 3.28 (1.13–10.20)	OR 2.01 (1.04–3.89) aOR 1.85 (0.93–3.94)
Izhaki and colleagues (2011) ²⁵	149	24/149 (16)	NA	6/149 (4)	NA	OR 1.46 (0.52–4.09)
Lee and colleagues (2014) ²⁷	45	33/45 (73)*	5/45 (11)	NA	OR 0.50 (0.07–3.44)	NA
Nagele and colleagues (2011) ¹³	378	57/378 (15)	4/378 (1)	75/378 (20)	OR 5.80 (0.80–42.04)	OR 1.93 (1.02–3.63)
Noordzij and colleagues (2015) ²⁶	202	33/198 (17)	8/198 (4)	NA	OR 5.53 (1.30–23.44)	NA
Oscarsson and colleagues (2009) ¹⁵	186	62/186 (33)	23/186 (12)	NA	OR 3.73 (1.52–9.17)	NA

Postoperative troponin elevation and mortality

The unadjusted association between troponin elevation and 30 day mortality after surgery was estimated in eight studies including 1587 patients.^{12–15 24 26–28} We computed an unadjusted pooled OR of 3.52 (95% CI, 2.21–5.62; $I^2=0\%$),^{12–15 24 26 27} see Fig. 2.

Six studies were included in the unadjusted pooled analysis of the association between postoperative troponin elevation and 1 yr mortality.^{12 13 19 23–25} The studies included 1371 patients. The unadjusted OR was estimated to 2.87 (95% CI, 1.63–5.06; $I^2=50\%$), see Fig. 3a.^{12 13 19 23–25} Four studies enrolling 844

Table 3 Major adverse cardiac events within 30 days and 1 yr after surgery. The risk of major adverse cardiac events is specified as the odds ratio (95% confidence interval). ACS, acute coronary syndrome; AMI, acute myocardial infarction; aOR, adjusted odds ratio; CHF, congestive heart failure; MACE, major adverse cardiac events; NA, not assessed; OR, unadjusted odds ratio

Authors (yr)	No. of patients	No. of patients with elevated troponin after surgery [n/N (%)]	MACE definition	30 days no. of MACE [n/N (%)]	1 yr no. of MACE [n/N (%)]	MACE 30 days	MACE 1 yr
Ausset and colleagues (2010) ¹⁹	355	21/355 (6)	Cardiac death, ACS, coronary revascularization or cardiac surgery, CHF	NA	15/355 (4)	NA	aOR 6.86 (1.61–37.19)
Chong and colleagues (2009) ²³	102	54/102 (53)	Myocardial infarction, CHF, atrial fibrillation, or major arrhythmia	26/102 (25)	33/102 (32)	OR 7.56 (2.36–24.00)	aOR 3.90 (1.40–10.70)
Chong and colleagues (2012) ²⁴	187	70/187 (37)	AMI, CHF, new-onset or rapid atrial fibrillation, major arrhythmia, and cardiac arrest	20/187 (11)	35/187 (19)	OR 8.40 (2.70–26.20) aOR 4.90 (1.30–18.90)	OR 4.30 (2.00–9.30) aOR 1.70 (0.70–4.40)
Gillies and colleagues (2015) ²⁸	288	135/288 (47)	New diagnosis of arrhythmia, cardiogenic pulmonary oedema, AMI, cardiorespiratory arrest	93/288 (32)	NA	OR 1.50 (0.91–2.46) aOR 1.56 (0.93–2.61)	NA
Oscarsson and colleagues (2009) ¹⁵	186	62/186 (33)	AMI, cardiovascular death, or both within 30 days of surgery	26/186 (14)	NA	OR 16.50 (5.38–50.57)	NA

patients computed an adjusted OR predicting 1 yr mortality.^{12 19 23 24} A postoperative troponin elevation was an independent predictor of 1 yr mortality after surgery, with a pooled adjusted OR of 2.53 (95% CI, 1.20–5.36; $I^2=26\%$), see Fig. 3b.^{11 15–17} Five studies ($n=993$ patients) were included in the orthopaedic subgroup analysis on 1 yr mortality.^{12 19 23–25} In orthopaedic surgery, a postoperative troponin elevation was a predictor of 1 yr mortality with an OR of 2.14 (95% CI, 1.12–3.79; $I^2=14\%$).^{12 19 23–25} A forest plot is available in the [Supplementary material](#).

Postoperative troponin elevation and major adverse cardiac events

Table 3 reports the ORs of the association between postoperative troponin elevation and major adverse cardiac events. A pooled unadjusted OR of the risk of major adverse cardiac events within 30 days after surgery was estimated as 5.92 (95% CI, 1.67–20.96; $I^2=86\%$).^{15 23 24 28} Seven hundred and sixty-three patients were included in the analysis. A pooled adjusted OR of the risk of major adverse cardiac events within 1 yr after surgery was estimated as 3.00 (95% CI, 1.43–6.29; $I^2=21\%$), including 654 patients.^{19 23 24}

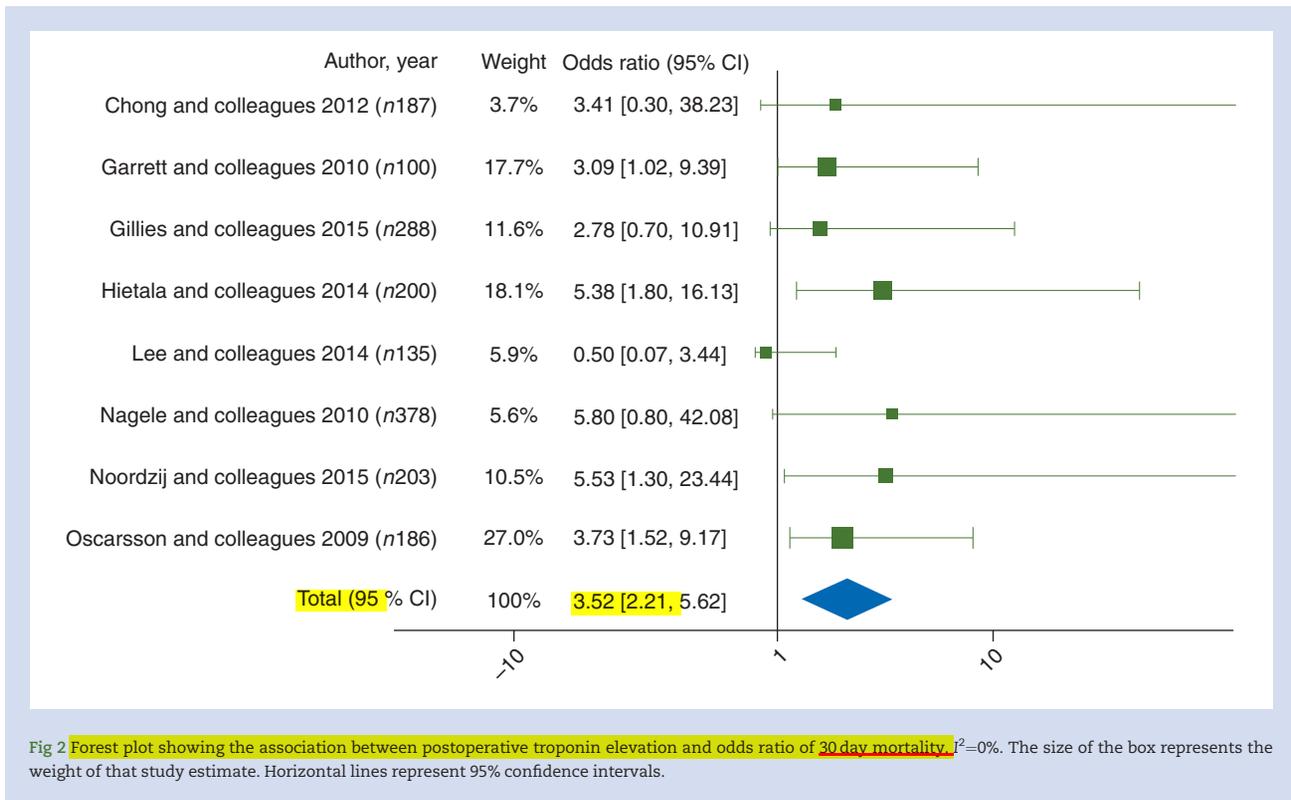
Discussion

This systematic review evaluating the predictive value of postoperative troponin elevation after non-cardiac, non-vascular surgery included 11 studies. The meta-analysis of 30 day mortality showed a strong association with an OR of 3.52 (95% CI, 2.21–5.62), and after 1 yr a postoperative troponin elevation was

an independent predictor of mortality with a pooled adjusted OR of 2.53 (95% CI, 1.20–5.36). The orthopaedic subgroup analysis showed that a postoperative troponin elevation predicted 1 yr mortality with an OR of 2.14 (95% CI, 1.12–3.79; $I^2=14\%$). Postoperative troponin elevation was associated with major adverse cardiac events at 30 days and 1 yr after surgery with a pooled OR of 5.92 (95% CI, 1.67–20.96) and 3.00 (95% CI, 1.43–6.29), respectively.

A meta-analysis published in 2011 reported that an isolated postoperative troponin elevation independently predicted 30 day all-cause mortality after vascular surgery, OR 5.03 (95% CI 2.88–8.79).²⁹ A cohort study including 447 patients undergoing major vascular surgery reported that a troponin elevation independently predicted long-term mortality with an OR of 2.47 (95% CI 1.44–4.23).³⁰ The study had a mean follow-up period of 32.3 (13.8) months. Likewise, our analysis strongly suggests that increased postoperative troponin concentrations in non-vascular surgical patients do, as in vascular surgery, identify a group of vulnerable patients with a significant risk of major adverse cardiac events and postoperative all-cause short- and long-term mortality.

The recent VISION study reported that 84% of the patients suffering myocardial injury in non-cardiac surgery did not experience any ischaemic symptoms and only 35% had evidence of ischaemia on ECG.³¹ A recent cohort study of 8351 patients undergoing non-cardiac surgery reported that 5.0% of the patients had a perioperative myocardial infarction, whereas only 35% of these patients experienced ischaemic symptoms.³ The 30 day mortality rate did not differ between those who did and did not have ischaemic symptoms. In a surgical population,



the diagnosis of perioperative myocardial injury is often possible only by continuous troponin measurements after surgery, because subtle or transient ischaemic signs and absence of symptoms (e.g. as a result of strong analgesics) are common.

Two distinct mechanisms may lead to myocardial injury after surgery: coronary plaque rupture, fissuring, or erosion with subsequent intraluminal thrombosis (type I myocardial infarction) and myocardial ischaemic imbalance (type II myocardial infarction).³² Postmortem studies, preoperative coronary angiography, perioperative Holter, and haemodynamic studies suggest that both mechanisms are in play in the perioperative period.^{33–35} Surgical stress initiates a cascade of inflammation, sympathetic and neuroendocrine hyperactivity, and hypercoagulability.³⁶ This, together with perioperative hypotension (major bleeding, hypovolaemia, and systemic vasodilation), anaemia, transient hypoxia, and tachycardia, results in myocardial hypoperfusion and prolonged imbalance in myocardial oxygen supply and demand, which causes myocardial injury.^{33, 34}

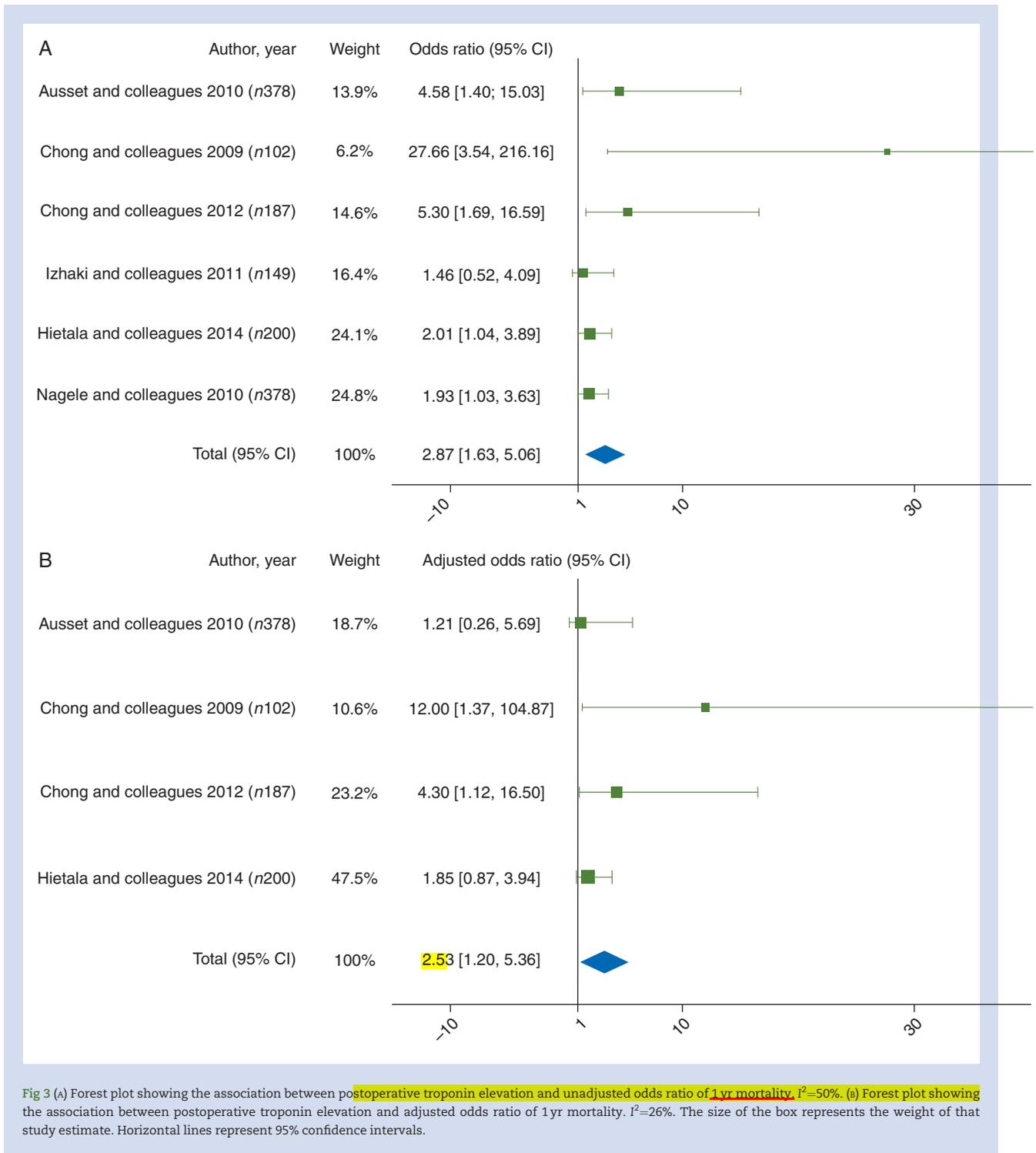
The meta-analysis suggests that a postoperative troponin measurement is useful in risk stratification and provides the physician with important prognostic information after, for example, major abdominal or orthopaedic surgery. Without monitoring perioperative troponins for the first few days after surgery, in patients with known vascular disease or risk factors, the majority of myocardial infarctions and injuries will go undetected.^{3, 31} Although data suggest that postoperative troponin monitoring in patients ≥ 45 yr of age is cost effective, further research is needed to provide better risk stratification and establish the cost consequence for troponin monitoring within specific patient populations.³⁷

Observational studies suggest that optimized perioperative basic quality of care, including prevention of hypoxaemia, pain,

hypothermia, anaemia, hypotension, tachycardia, and hypoglycaemia, may prevent postoperative troponin elevation and major cardiac events.^{19, 38, 39} No medications have been found to prevent postoperative troponin elevation or myocardial infarction safely and efficiently.

Even though the evidence is sparse, basic cardiac medication has been effective for secondary prevention of major cardiac events and death.^{3, 40} An observational study showed that patients with postoperative myocardial infarction who did not receive additional cardiac medication, in terms of anti-platelets, β -blockers, statins, and angiotensin-converting enzyme inhibitors, had a higher risk of major cardiac events within 12 months, hazard ratio 2.80 (95% CI, 1.05–24.2, $P=0.04$), compared with patients who did receive additional cardiac medication.⁴⁰ Likewise, an observational study showed that acetylsalicylic acid and statin use were associated with a reduction in the risk for 30 day mortality among patients with postoperative myocardial infarction, with OR of 0.54 (95% CI, 0.29–0.99) and 0.26 (95% CI, 0.13–0.54), respectively.³ Despite the evidence to support basic cardiac medication for secondary prevention, they are not commonly used.

The meta-analysis was based on a systematic literature search performed in several databases and adhered to the standards of performing and reporting meta-analyses. Authors were contacted directly, and data were provided for the OR calculations. The reviewers had to exclude 16 full-text studies because an OR could not be extracted or calculated. The majority of these studies included small populations with few or no cardiovascular events within the short follow-up period. Fifty-five full-text articles were excluded because they evaluated mixed non-cardiac surgery, including vascular surgery, without reporting extractable subgroup data.



The methodological quality of the included studies was moderate to high. All but one study had complete patient follow-up on >95% of participants. The methodological quality was reduced by three studies that primarily used telephone interviews to follow up on the included patients. In nine of the 11 studies, a preoperative troponin measurement was made to distinguish a continuing baseline troponin elevation from a new postoperative increase. The authors were contacted directly if

the timing of troponin assessment was unclear. The statistical heterogeneity in the pooled OR analyses was moderate to low. An I^2 of 50% was detected in the pooled unadjusted OR analysis of 1 yr mortality and an I^2 of 86% in the pooled unadjusted OR analysis of major adverse cardiac events at 30 days. An investigation of heterogeneity by meta-regression is of questionable value when there are few studies in the analysis;¹⁸ Hence, such an analysis was not performed. The results from the 30 days

major adverse cardiac events analysis should be interpreted with caution because of substantial heterogeneity. Separate pooled analyses of adjusted and unadjusted ORs of 1 yr mortality were undertaken because only four out of the six studies included an adjusted multivariable analysis. The ORs did not differ markedly. The included studies did not assess the same type of troponin, and there was a blinded troponin assessment in <50% of the studies, which could be seen as a limitation. Differences in troponin assays were a potential source of heterogeneity.

We explored **potential publication bias and small sample size bias by funnel plots** (30 day and 1 yr mortality). The funnel plots should be interpreted with caution because of the small number of included studies and log odds ratios, which can cause funnel plots to appear asymmetric.¹⁸ In both funnel plots, we would have expected a broader spectrum of both small positive and negative studies. Especially, the lack of small negative studies could implicate some degree of publication bias. We excluded non-English literature, studies unavailable for purchase, and unpublished studies, including proceedings abstracts, which may contribute to publication bias. We could not perform a sensitivity analysis because the abstracts of the excluded studies lacked sufficient data to compute an OR. In the 1 yr mortality funnel plot, the study by Chong and colleagues²³ seems to induce a small sample size bias, which contributes to the heterogeneity ($I^2=50\%$). However, this was the only small study, and the study only weighted 6.2% in the pooled 1 yr unadjusted mortality analysis.

In conclusion, troponin elevation after non-cardiac, non-vascular surgery is a predictor of major adverse cardiac events and mortality in the ensuing year, with a risk approaching that after major vascular surgery. Physicians should consider monitoring troponin in the first postoperative days in at-risk patients because of the absence of ischaemic symptoms and because ECG changes can be subtle, transient, or both. Postoperative troponin monitoring might serve to identify vulnerable patients who could benefit from cardiovascular optimization.

Authors' contributions

Conception and design: S.E., P.J.D., I.G.

Acquisition of data and analysis: S.E., M.A.

Interpretation of data: S.E., M.A., P.J.D., I.G.

Drafting the article: S.E.

Revising the draft critically for important intellectual content: M.A. P.J.D., I.G.

Final approval of the version to be published; and agreement to be accountable for all aspects of the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: S.E., M.A., P.J.D., I.G.

Declaration of interest

I.G., M.A., and S.E. have no conflict of interest to declare. P.J.D. is part of a group that has a policy of not accepting honoraria or other payments from industry for their own personal financial gain. They do accept honoraria or other payments from industry to support research endeavours and for reimbursement of costs to participate in meetings, such as scientific or advisory committee meetings. Based on study questions he originated and grants he wrote, he has received grants from Abbott Diagnostics, Astra Zeneca, Bayer, Boehringer Ingelheim, Bristol-

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Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

References

- Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* 2008; **372**: 139–44
- Pearse RM, Moreno RP, Bauer P, et al. Mortality after surgery in Europe: a 7 day cohort study. *Lancet* 2012; **380**: 1059–65
- 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
- Devereaux PJ, Mrkobrada M, Sessler DI, et al. Aspirin in patients undergoing noncardiac surgery. *N Engl J Med* 2014; **370**: 1494–503
- 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
- Levy M, Heels-Ansdell D, Hiralal R, et al. Prognostic value of troponin and creatine kinase muscle and brain isoenzyme measurement after noncardiac surgery: a systematic review and meta-analysis. *Anesthesiology* 2011; **114**: 796–806
- Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing noncardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008; **371**: 1839–47
- 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
- Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: the Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur Heart J* 2014; **35**: 2383–431
- Biccard B. Proposed research plan for the derivation of a new cardiac risk index. *Anesth Anal* 2015; **120**: 543–53
- Kehlet H, Mythen M. Why is the surgical high-risk patient still at risk? *Br J Anaesth* 2011; **106**: 289–91
- Hietala P, Strandberg M, Kiviniemi T, Strandberg N, Airaksinen KE. Usefulness of troponin T to predict short-term and long-term mortality in patients after hip fracture. *Am J Cardiol* 2014; **114**: 193–7
- Nagele P, Rao LK, Penta M, et al. Postoperative myocardial injury after major head and neck cancer surgery. *Head Neck* 2011; **33**: 1085–91
- Garrett MC, Komotar RJ, Starke RM, Doshi D, Otten ML, Connolly ES. Elevated troponin levels are predictive of mortality in surgical intracerebral hemorrhage patients. *Neurocrit Care* 2010; **12**: 199–203

15. Oscarsson A, Fredrikson M, Sörliden M, et al. Predictors of cardiac events in high-risk patients undergoing emergency surgery. *Acta Anaesth Scand* 2009; **53**: 986–94
16. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008–12
17. Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003; **7**: iii–x, 1–173
18. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*, version 5.1.0, The Cochrane Collaboration; 2011. Available from: <http://training.cochrane.org/handbook> (accessed 30 July 2016)
19. 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 I elevation. *Anesthesiology* 2010; **113**: 529–40
20. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA* 1998; **280**: 1690–1
21. Bland JM, Altman DG. Statistics notes. The odds ratio. *Br Med J* 2000; **320**: 1468
22. Review Manager. Version 5.3. Informatics and Knowledge Department, The Cochrane Collaboration; 2014. Available from: <http://tech.cochrane.org/revman> (accessed: 30 July 2016)
23. Chong CP, Lam QT, Ryan JE, et al. Incidence of post-operative troponin I rises and 1-year mortality after emergency orthopaedic surgery in older patients. *Age Ageing* 2009; **38**: 168–74
24. Chong CP, Lim WK, Velkoska E, et al. N-terminal pro-brain natriuretic peptide and angiotensin-converting enzyme-2 levels and their association with postoperative cardiac complications after emergency orthopedic surgery. *Am J Cardiol* 2012; **109**: 1365–73
25. Izhaki A, Slesarenko Y, Boaz M, Haimovich Y, Rozenman Y. Cardiac troponin T: an important predictor of late death and myocardial infarction following hip fracture: an eight-year prospective observational cohort study. *Eur J Orthopaed Surg Traumatol* 2011; **21**: 243–9
26. Noordzij PG, van Geffen O, Dijkstra IM, et al. High-sensitive cardiac troponin T measurements in prediction of non-cardiac complications after major abdominal surgery. *Br J Anaesth* 2015; **114**: 909–18
27. Lee GR, Jhanji S, Tarrant H, James S, Pearse RM, Fitzgibbon M. Peri-operative troponin monitoring using a prototype high-sensitivity cardiac troponin I (hs-cTnI) assay: comparisons with hs-cTnT and contemporary cTnI assays. *Ann Clin Biochem* 2014; **51**: 258–68
28. Gillies MA, Shah AS, Mullenheim J, et al. Perioperative myocardial injury in patients receiving cardiac output-guided haemodynamic therapy: a substudy of the OPTIMISE trial. *Br J Anaesth* 2015; **115**: 227–33
29. Redfern G, Rodseth RN, Biccard BM. Outcomes in vascular surgical patients with isolated postoperative troponin leak: a meta-analysis. *Anaesthesia* 2011; **66**: 604–10
30. 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**: 1547–4
31. 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
32. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012; **60**: 1581–98
33. Biccard BM, Rodseth RN. The pathophysiology of peri-operative myocardial infarction. *Anaesthesia* 2010; **65**: 733–41
34. Landesberg G, Beattie WS, Mosseri M, Jaffe AS, Alpert JS. Perioperative myocardial infarction. *Circulation* 2009; **119**: 2936–44
35. Landesberg G. The pathophysiology of perioperative myocardial infarction: facts and perspectives. *J Cardiothorac Vasc Anesth* 2003; **17**: 90–100
36. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth* 1997; **78**: 606–17
37. Torborg A, Ryan L, Kantor G, Biccard BM. The pharmacoeconomics of routine postoperative troponin surveillance to prevent and treat myocardial infarction after non-cardiac surgery. *South Afr Med J* 2014; **104**: 619–23
38. Walsh M, Devereaux PJ, Garg AX, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology* 2013; **119**: 507–15
39. Valentijn TM, Hoeks SE, Martienus KA, et al. Impact of haemoglobin concentration on cardiovascular outcome after vascular surgery. A retrospective observational cohort study. *Eur J Anaesthesiol* 2013; **30**: 664–70
40. Foucrier A, Rodseth R, Aissaoui M, et al. The long-term impact of early cardiovascular therapy intensification for postoperative troponin elevation after major vascular surgery. *Anesth Analg* 2014; **119**: 1053–63

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