BJA

*British Journal of Anaesthesia* 115 (2): 227–33 (2015)

**doi: 10.1093/bja/aev137**
Advance Access Publication Date 21 May 2015
Cardiovascular

# Perioperative myocardial injury in patients receiving cardiac output-guided haemodynamic therapy: a substudy of the OPTIMISE Trial

M. A. Gillies[1,*], A. S. V. Shah[2], J. Mullenheim[3], S. Tricklebank[4], T. Owen[5], J. Antonelli[1], F. Strachan[2], N. L. Mills[2] and R. M. Pearse[6]

[1]Department of Critical Care, [2]BHF Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK, [3]The James Cook University Hospital, Middlesbrough, UK, [4]Guy's and St Thomas' NHS Foundation Trust, London, UK, [5]Lancashire Teaching Hospitals NHS Trust, Preston, UK, and [6]Queen Mary University, London, UK

*Corresponding author. Department of Anaesthesia, Critical Care and Pain Medicine, Royal Infirmary of Edinburgh, Little France Crescent, Edinburgh EH16 4SA, UK. E-mail michael.gillies@ed.ac.uk



## Abstract

**Background:** Evidence suggests that cardiac output-guided haemodynamic therapy algorithms improve outcomes after high-risk surgery, but there is some concern that this could promote acute myocardial injury. We evaluated the incidence of myocardial injury in a perioperative goal-directed therapy trial.

**Methods:** Patients undergoing major gastrointestinal surgery ($n$=723) were randomly assigned to cardiac output-guided haemodynamic therapy (intervention group) or usual care as part of the OPTIMISE trial. At four participating sites, 288 patients were enrolled in a biomarker substudy. Serum high-sensitivity cardiac troponin I (TnI) concentration and N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration were measured before and at 24 and 72 h after surgery.

**Results:** Median preoperative TnI and NT-ProBNP concentrations were 4.3 ng litre$^{-1}$ and 144 pg ml$^{-1}$, respectively. After surgery, 67 (46%) patients in the intervention group and 68 (48%) patients receiving usual care had TnI concentrations above the 99th centile upper reference limit ($P$=0.82). Peak serum TnI concentration was similar in the intervention and usual care groups (median [interquartile range]: 10.0 [5.3–21.5] *vs* 7.8 [5.0–21.8] ng litre$^{-1}$; $P$=0.85), and no differences were observed in serum TnI concentrations over 72 h (repeated-measures ANOVA, $P$=0.51). Likewise, there were no differences in peak NT-proBNP concentration between intervention and usual care groups (645 [362–1169] *vs* 659 [381–1028] pg ml$^{-1}$; $P$=0.86) or in serial NT-proBNP concentrations over 72 h ($P$=0.20).

**Conclusions:** Myocardial injury is common among patients undergoing major gastrointestinal surgery. In this study, the frequency was not affected by cardiac output-guided fluid and low-dose inotropic therapy.

**Key words:** biochemistry; complications, myocardial infarction; fluids, i.v; heart, dopexamine; surgery

Estimates of hospital mortality after inpatient surgery range from 1 to 4%, resulting in at least 2.3 million deaths worldwide each year.[1 2] Postoperative complication rates of up to 10 times this figure have been reported, and these adversely affect long-term survival.[3] There is some evidence to suggest that perioperative haemodynamic therapy algorithms for i.v. fluid and inotrope administration may improve patient outcomes and reduce complications, but this is not standard practice.[4]

Concerns that this treatment approach may increase the incidence of postoperative myocardial injury remain.[4] Ischaemic

**Accepted:** April 3, 2015

**Editor's key points**

- Goal-directed therapies aim to optimize tissue oxygen delivery and so may reduce perioperative complications.
- Both catecholamines and fluid overload might increase the risk of myocardial injury.
- This study found no evidence that perioperative goal-directed therapy increased myocardial injury.
- The mechanisms leading to postoperative elevation of cardiac biomarkers remain unclear.

heart disease is common among patients undergoing major surgery,[5] and pharmacological agents that increase myocardial oxygen demand at times of physiological stress may result in myocardial ischaemia. Cardiac output-guided haemodynamic therapy has been associated with increased mortality in critically ill patients[6] and dopexamine administration with increased incidence of arrhythmia when used in the perioperative period.[7] Concerns also remain that excessive fluid administration, in particular of colloid solutions, could lead to harm associated with fluid overload.[8–10] A recent meta-analysis of perioperative haemodynamic therapy failed to demonstrate any difference in cardiovascular complications between patients exposed to this therapy and those receiving usual care. Two analyses of postoperative troponin concentrations in participants of small, single-centre, perioperative haemodynamic therapy trials (both of which included low-dose dopexamine administration) did not demonstrate differences between the interventions and usual care groups.[11 12]

The recently completed OPTIMISE trial was the largest randomized trial of this intervention in surgical patients to date.[13] In total, 734 high-risk adult patients undergoing major gastrointestinal surgery were randomly assigned to receive cardiac output-guided haemodynamic therapy or usual care. The primary outcome of death or complications at 30 days was not significantly reduced by the intervention, but prespecified subgroup analyses suggest one explanation may have been a lack of statistical power. The OPTIMISE trial demonstrated similar rates of cardiovascular complications between groups at 30 days, but survival analysis suggested an excess of early deaths in the intervention group. Safety data reported cardiovascular events in four patients (1.6%) in this group compared with none in the control group. Despite this, cardiac complications at 30 days were similar between groups. These events may have been related to dopexamine, but evidence to infer causality is not available. This pattern of early serious adverse cardiovascular events raised the possibility of harm associated with the intervention.

As the trial intervention could have been associated with either an increase or a reduction in cardiac complications, we conducted a substudy using biochemical markers to evaluate the incidence of myocardial injury among patients recruited to the OPTIMISE trial, in order to gain better understanding of the safety and efficacy of this treatment.

## Methods

### Ethics, sponsorship, and indemnity

The OPTIMISE trial protocol was approved by a Research Ethics Committee and the Medicines and Healthcare Products Regulatory Agency (MHRA). All patients provided written informed consent to participate. These approvals included blood sampling for the analysis of cardiac biomarkers. The trial sponsor was Queen Mary University of London. Biomarker analysis was performed at the University of Edinburgh.

### Study population

In four participating sites, patients were also enrolled in the OPTIMISE biomarker substudy. High-risk patients undergoing major gastrointestinal surgery were enrolled into the OPTIMISE trial, reported previously.[13] High-risk patients were defined as those aged ≥65 yr or those aged 50–64 yr with one or more of the following: non-elective surgery, acute or chronic renal impairment, diabetes mellitus, or presence of a risk factor for cardiac or respiratory disease. Patients were then randomized to receive either haemodynamic therapy or usual care using a computer-generated dynamic procedure (minimization) with a random component. Perioperative treatment goals were defined for all patients to avoid extremes of clinical practice. All patients received standard measures to maintain oxygen saturation above 94%, haemoglobin above 80 g litre$^{-1}$, core temperature above 37°C, heart rate below 100 min$^{-1}$, and mean arterial pressure between 60 and 100 mm Hg. Patients receiving the trial intervention received non-invasive cardiac output monitoring and stroke volume optimization (LiDCO Ltd, Cambridge, UK) using colloid boluses to achieve a maximal stroke volume. Dopexamine was also administered at a dose of 0.5 μg$^{-1}$ kg$^{-1}$ min$^{-1}$ during and for 6 h after surgery. The dose of dopexamine was reduced if the heart rate increased to 120% of baseline or 100 min$^{-1}$ (whichever was greater) for more than 30 min despite adequate anaesthesia and analgesia. If the heart rate did not decrease despite dose reduction, then the infusion was discontinued.

### Blood sampling and analysis

Blood samples were collected at induction of anaesthesia and then at 24 and 72 h after surgery. Samples were drawn from an arterial or central venous catheter or by venepuncture into a vacuum tube, inverted five times and left for 30 min before centrifugation at 3000 rpm for 10 min. The serum for each patient time point was separated into three eppendorf tubes and stored at –80°C until transfer to a central laboratory for batched analysis.

Serum cardiac troponin I and N-terminal pro-brain natriuretic peptide (NT-proBNP) were selected as biomarkers of cardiac injury. Cardiac troponins are released as a result of myocardial injury or necrosis and have an established role in the diagnosis of myocardial infarction.[14–20] Modern troponin assays now provide a highly sensitive method of detecting myocardial injury.[21 22] Brain natriuretic peptide (BNP) is released by the ventricular wall in response to increased tension associated with volume overload and may also be released as a result of myocardial ischaemia. N-Terminal pro-brain natriuretic peptide is a 76-amino-acid inactive protein cleaved from proBNP. Serum concentrations of NT-proBNP are correlated with pulmonary capillary wedge pressure, perioperative fluid administration, and postoperative fluid balance.[23] Brain natriuretic peptide and NT-proBNP are sensitive tests for acute heart failure and pulmonary oedema.[24 25] They have also been used as prognostic and diagnostic tools for heart failure and cardiac events after surgery.[26 27]

The ARCHITECT$_{STAT}$ high-sensitive cardiac troponin I (TnI) assay (Abbott Laboratories, Abbott Park, IL, USA) has a limit of detection of 1.2 ng litre$^{-1}$ and an interassay coefficient of variation of <10% at 4.7 ng litre$^{-1}$. The mean (SD) concentration for a healthy reference population is 1.6 (3.1) ng litre$^{-1}$, and the 99th percentile upper reference limit (URL) for the whole population is 26 ng litre$^{-1}$ (females, 16 ng litre$^{-1}$; 34 males, ng litre$^{-1}$).

Concentrations of NT-proBNP were measured using the Roche Cobas ProBNP II assay (Roche Diagnostics, Mannheim, Germany). The 97.5th percentile (URL) of a reference population for this assay is 196 pg $ml^{-1}$. Values <125 pg $ml^{-1}$ are typically used to exclude cardiac disease.

### Data collection

Baseline data describing age, sex, ASA Physiological Status (ASA-PS) score, nature and urgency of surgery, anaesthetic technique, and baseline risk factors, and clinical outcome data describing myocardial ischaemia or infarction, major adverse cardiac events (MACE), and death within 180 days were extracted from the OPTIMISE database for patients included in this substudy. A MACE was defined as any of the following: new diagnosis of arrhythmia, cardiogenic pulmonary oedema, myocardial infarction, or cardiorespiratory arrest, as defined in the OPTIMISE Protocol (Supplementary File 1).

### Statistical analysis

The analysis was performed according to a prespecified plan. Serum concentrations of TnI and NT pro-BNP were compared between groups at each time point. For TnI, the area under the concentration–time curve was calculated for each patient and compared between groups. To adjust for skew and outliers, TnI and NT-proBNP concentrations were transformed to natural logarithms. Comparison between groups was made using $\chi^2$, two-way repeated-measures ANOVA (with Bonferroni's correction where appropriate), or Mann–Whitney *U*-test as indicated. Logistic regression analysis was used to test for association between TnI and NT-proBNP and a composite outcome of death or MACE at 30 days and 180 day mortality. Analysis was performed using Stata v12 (StataCorp, College Station, TX, USA) and Prism v5.0 (GraphPad Software Inc., La Jolla, CA, USA). Data are presented as mean (SD) where normally distributed and median (inter-quartile range) where not normally distributed, or as odds ratios (ORs) with 95% confidence intervals (CIs). Significance was set at $P<0.05$.

## Results

Of 734 patients enrolled in the OPTIMISE trial, 288 were entered into this biomarker substudy; 145 in the intervention group and 143 in the usual care group (Table 1). In common with the main trial population, a higher proportion of patients in the usual care group were >65 yr old [125 (87%) *vs* 115 (79%)] or were ASA-PS grade III or IV [75 (52%) *vs* 50 (34%)]. In the biomarker substudy population, there were no differences observed in clinical diagnosis of myocardial infarction, MACE, or mortality at 30 or 180 days between the intervention and usual care groups.

### High-sensitivity cardiac troponin I

Median preoperative TnI concentrations were 4.3 (2.8–7.7) and 4.3 (2.9–7.4) ng $litre^{-1}$ in the intervention and usual care groups, respectively. No differences were observed in the proportion of patients with peak postoperative TnI concentration greater than URL between the intervention (67 of 145, 46%) and the usual care group (68 of 143, 47.6%; $P=0.82$; Fig. 1) or in peak TnI concentration [10.0 (5.3–21.5) *vs* 7.8 (5.0–21.8) ng $litre^{-1}$, respectively; $P=0.85$; Table 2). Serum TnI increased over time ($P<0.001$), but there were no differences in serum concentration between the treatment groups over 72 h (repeated-measures ANOVA, $F$-statistic=0.73; $P=0.49$; Fig. 2). There was no difference in the area under the TnI concentration–time curve between groups ($P=0.95$).

**Table 1** Baseline patient characteristics. Data are presented as *n* (percentage) or mean (SD). Patients may have had more than one baseline risk factor

| Characteristics | Haemodynamic intervention (*n*=145) | Usual care (*n*=143) |
|---|---|---|
| Age (yr) | 69.8 (8.1) | 71.6 (7.5) |
| Sex | | |
| Male | 90 (62.1) | 93 (65) |
| Female | 55 (37.9) | 50 (35) |
| Urgency of surgery | | |
| Elective | 138 (95.2) | 137 (95.8) |
| Emergency | 7 (4.8) | 6 (4.2) |
| Baseline risk factors | | |
| Renal impairment | 8 (5.5) | 4 (2.8) |
| Diabetes mellitus | 23 (15.9) | 25 (17.5) |
| Risk factors for cardiac or respiratory disease | 45 (31) | 54 (37.8) |
| Surgical procedure | | |
| Upper gastrointestinal | 53 (36.6) | 114 (31.2) |
| Lower gastrointestinal | 36 (24.8) | 163 (44.7) |
| Small bowel, pancreas, or both | 53 (36.6) | 84 (23.0) |
| Urological or gynaecological surgery involving gut | 3 (2.1) | 4 (1.1) |
| ASA grade | | |
| I | 8 (5.5) | 5 (3.5) |
| II | 87 (60) | 63 (44.1) |
| III | 49 (33.8) | 72 (50.3) |
| IV | 1 (0.7) | 3 (2.1) |

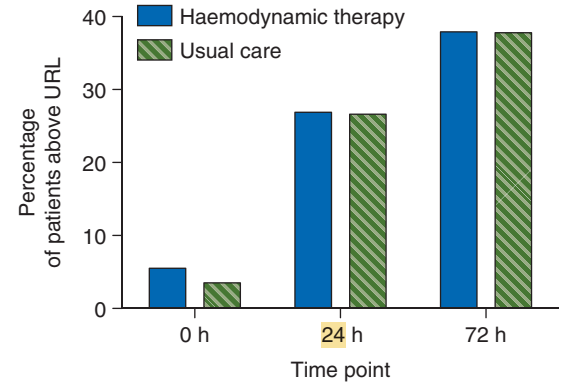


**Fig 1** Proportion of patients with serum high-sensitivity cardiac troponin I (TnI) concentrations above the 99th percentile upper reference limit (URL) before and after surgery.

### N-Terminal pro-brain natriuretic peptide

Median preoperative NT-proBNP concentrations were 162 (80–355) and 139 (84–347) pg $ml^{-1}$ in the intervention and usual care groups, respectively. No differences were observed in the proportion of patients with peak postoperative NT-proBNP concentration greater than URL between the intervention (123, 84.8%) and the usual care group (118, 82.5%; $P=0.60$; Fig. 3) or in peak

Table 2 Clinical outcomes and high-sensitivity cardiac troponin I (TnI) and serum N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations. Data are presented as *n* (percentage) and median (inter-quartile range). URL, upper reference limit

| Outcome | Haemodynamic intervention (*n*=145) | Usual care (*n*=143) | P-value |
|---|---|---|---|
| Myocardial infarction within 30 days | 5 (3.4) | 6 (4.2) | 0.74 |
| Major adverse cardiac event within 30 days | 24 (16.6) | 32 (22.4) | 0.21 |
| Death within 30 days | 5 (3.4) | 5 (3.5) | 0.98 |
| Death within 180 days | 16 (11.0) | 21 (14.7) | 0.36 |
| Postoperative TnI above URL | 67 (46.2) | 68 (47.6) | 0.82 |
| TnI at each time point | | | 0.40 |
| TnI at time 0 (ng litre$^{-1}$) | 4.3 (2.75–7.7) | 4.3 (2.9–7.4) | |
| TnI at 24 h (ng litre$^{-1}$) | 9.3 (5.1–17.0) | 6.9 (4.3–17.8) | |
| TnI at 72 h (ng litre$^{-1}$) | 6.4 (4.1–15.9) | 6.7 (4.0–13.1) | |
| Maximal TnI (ng litre$^{-1}$) | 10.0 (5.3–21.5) | 7.8 (5–21.8) | 0.85 |
| Area under TnI concentration–time curve | 3.58 (2.42, 4.88) | 3.21 (2.23, 5.06) | 0.95 |
| Postoperative NT-proBNP above URL | 123 (84.8) | 118 (82.5) | 0.60 |
| NT-proBNP at each time point | | | 0.42 |
| NT-proBNP at time 0 (pg litre$^{-1}$) | 162 (80–355) | 139 (84–347) | |
| NT-proBNP at 24 h (pg litre$^{-1}$) | 373 (192–857) | 368 (151–672) | |
| NT-proBNP at 72 h (pg litre$^{-1}$) | 338 (22–848) | 434 (0–879) | |
| Maximal NT-proBNP (pg litre$^{-1}$) | 645 (362–1169) | 659 (381–1028) | 0.86 |

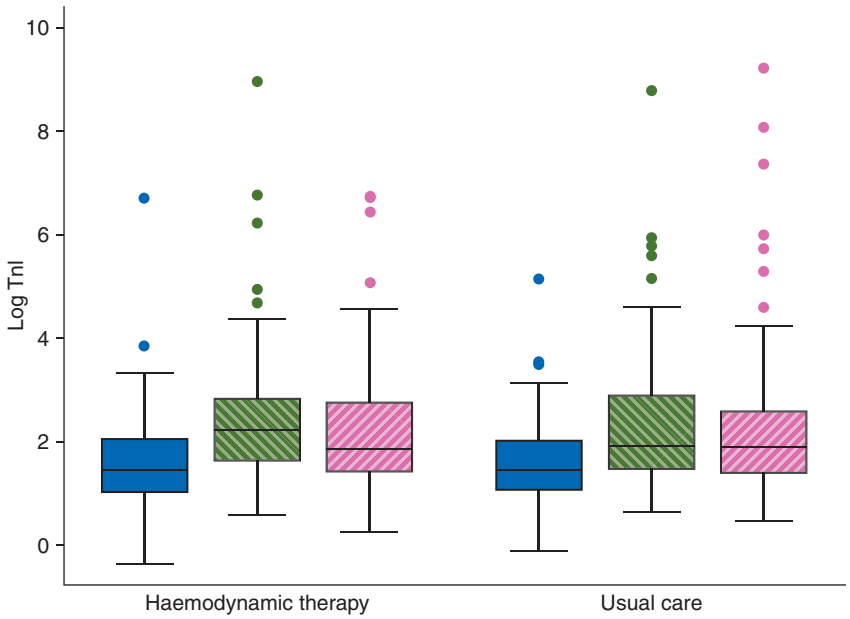


Fig 2 Log serum TnI for each group at each time point. Data are presented as median (inter-quartile range), with outlier values represented as individual points. Log TnI=Log serum troponin I. Blue, time 0; green, time 24 h; pink, time 72 h.

NT-proBNP concentration [645 (362–1169) *vs* 659 (381–1028) ng litre$^{-1}$, respectively; *P*=0.86; Table 2). Serum NT-proBNP increased over time (*P*<0.001), but there were no differences between the treatment groups in concentrations over 72 h (repeated-measures ANOVA, *F*-statistic=0.67; *P*=0.42; Fig. 4).

### Logistic regression analysis

In a logistic regression model adjusted for age, sex, ASA-PS, emergency surgery, and treatment group, peak TnI concentration was not associated with a composite outcome of death or MACE at 30 days (OR, 1.09; 95% CI, 0.90–1.31; *P*=0.37) or death at 180 days (OR, 0.99; 95% CI, 0.75–1.3; *P*=0.92). In the same model, however, peak NT-proBNP concentration was associated with death or MACE at 30 days (OR, 1.36; 95% CI, 1.04–1.76; *P*=0.02) and death at 180 days (OR, 1.46; 95% CI, 1.02–2.10; *P*=0.04).

## Discussion

Biochemical evidence of acute myocardial injury was common after major surgery in the OPTIMISE trial, occurring in almost half of all participants. However, in this analysis, fluid- and

dopexamine-based goal-directed therapy was not associated with any biochemical or clinical evidence of myocardial injury. This study provides some reassurance that early cardiac complications were not attributable to the trial intervention.

Safety issues regarding haemodynamic therapy in the critically ill (in particular, administration of β-adrenergic drugs) are well established,[6] and recent large randomized controlled trials have failed to demonstrate benefit from haemodynamic therapy algorithms in early septic shock.[28 29] Hence, in the critically ill population the risks associated with this therapy may outweigh any benefits. The role of such algorithms in the perioperative setting requires further investigation, and careful consideration of the patients groups most likely to benefit from this approach will be important. It is possible that patients at high risk of ischaemic events have less to benefit from this intervention. Trials of perioperative haemodynamic therapy in vascular surgery, where the incidence of ischaemic heart disease is greater, have not shown benefit[30–32] compared with trials of gastrointestinal surgery, where infectious complications are more common.[33 34]

The incidence of myocardial injury after major surgery is high when quantified using the latest generation of high-sensitivity cardiac troponin I assay. Our findings are consistent with those from a recent study using a high-sensitivity cardiac troponin T assay with 45% of patients having concentrations above the 99th percentile in the perioperative period.[35] Several troponin assays are commercially available, and differences in performance in the perioperative setting have been described.[12] The clinical and biochemical findings of our study concur with findings of two smaller single-centre trials investigating postoperative troponin concentration after haemodynamic therapy[11 12] and of a recently published systematic review, which examined the association between haemodynamic therapy and cardiac complications.[4]

Studies have found that peak postoperative troponin is correlated with outcome.[36 37] The largest of these studies measured troponin T using a fourth generation assay in a cohort of 15 133 patients aged ≥45 yr undergoing inpatient, non-cardiac surgery.[37] The overall mortality in this cohort was low (1.9%), but the investigators found that peak troponin concentration in the first 72 h was strongly associated with increased mortality at 30 days in this group. Our study did not replicate these findings. This may have been attributable to differences in the study populations, smaller sample size, or confounding from the trial intervention. The association between elevated perioperative NT-ProBNP concentrations and outcome is well established, and these findings were also observed in our study cohort.[38]

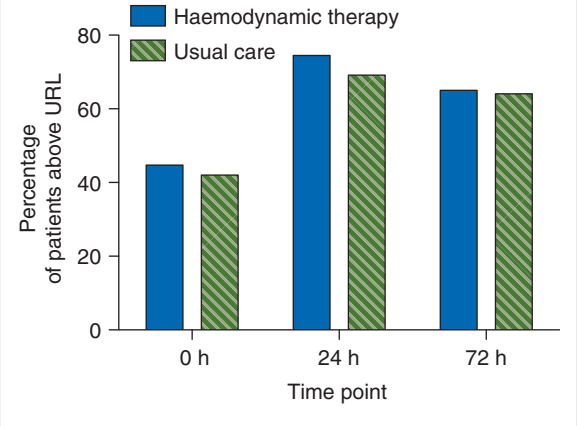


Fig 3 Proportion of patients with serum N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations above the 97th percentile URL before and after surgery.

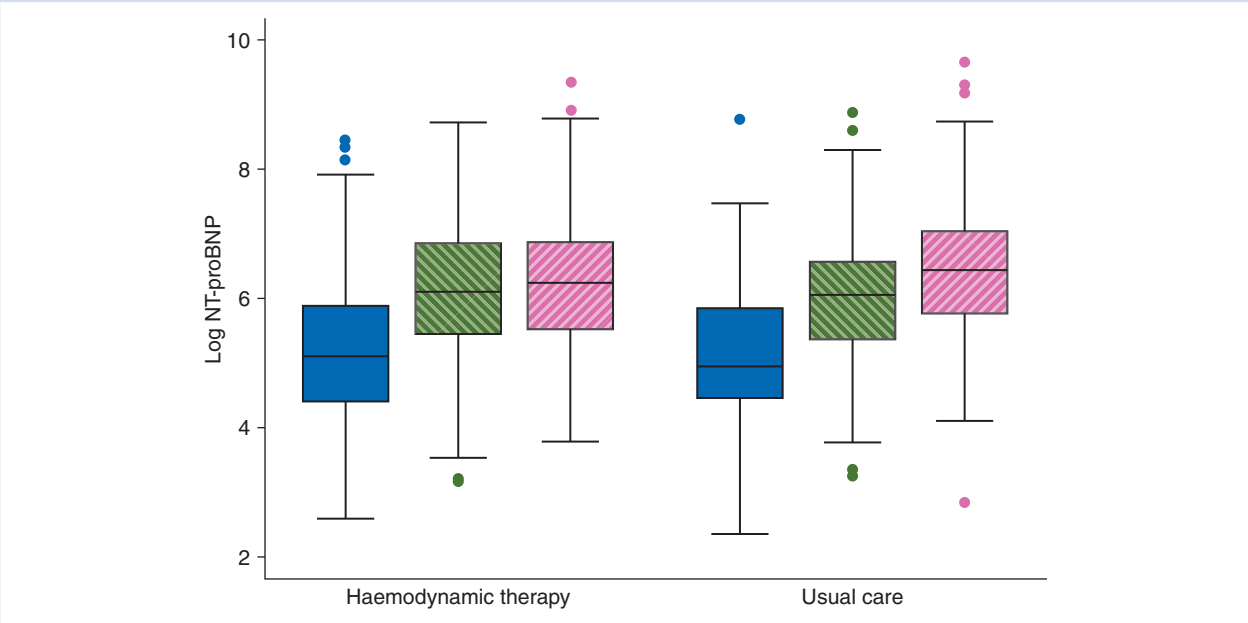


Fig 4 Log serum NT-proBNP for each group at each time point. Data are presented as median (inter-quartile range), with outlier values represented as individual points. Log NT-proBNP=Natural logarithm of serum NT-proBNP. Blue, time 0; green, time 24 h; pink, time 72 h.

Several limitations of our study merit consideration. Although we sought to recruit as many patients as possible at trial sites with the ability to store samples, it is possible that our study was underpowered. A retrospective sample size calculation based on an incidence of myocardial injury of 45%[35] and a relative risk reduction of 33%, with 90% power and an $\alpha$ error of 5%, suggests that a study requires 460 patients to test the hypothesis; hence, a clinically significant effect may have been missed because of lack of statistical power. Another limitation is that we were not able to use the Universal Definition of Myocardial Infarction[39] to differentiate between perioperative myocardial injury and infarction because 12-lead ECGs were not performed routinely in the OPTIMISE trial. The Universal Definition classifies type 1 myocardial infarction, where myocardial necrosis is a consequence of a coronary event, such as plaque rupture, and type 2 myocardial infarction, where necrosis is secondary to an imbalance of myocardial oxygen supply and demand (e.g. arrhythmia or hypotension). The ability to distinguish type 1 from type 2 myocardial infarction may have been relevant to our study, because the intervention may cause tachycardia and tachyarrhythmia that would increase myocardial oxygen demand and result in type 2 myocardial infarction. Myocardial injury after non-cardiac surgery (MINS) is defined as a significant elevation in serum troponin within 30 days of non-cardiac surgery and, although it does not fulfil all of the criteria for a type 2 myocardial infarction, carries prognostic significance.[40] In the VISION study, only 15.8% of patients with MINS had ischaemic symptoms. The findings of our study could have been strengthened if we had been able to distinguish accurately between type 1 myocardial infarction, type 2 myocardial infarction, and MINS.

In this study, we did not observe biochemical evidence of differences in early myocardial injury, heart failure, or fluid overload between groups in the OPTIMISE trial. Concerns remain around the cardiac effects of perioperative haemodynamic therapy in the absence of clear benefit. Whether patients with significant cardiac disease benefit from all the components of this complex intervention remains uncertain. Further studies are needed to understand how haemodynamic interventions in the perioperative period impact on MINS and type 1 or type 2 myocardial infarction. Future studies of perioperative haemodynamic therapy should examine cardiac complications in detail to define which patients benefit most from this intervention.

### Conclusion

Myocardial injury is common among patients undergoing major gastrointestinal surgery, but the frequency was not affected by cardiac output-guided fluid and low-dose inotropic therapy.

## Authors' contributions

M.A.G., R.M.P., N.L.M., and A.S.V.S. were responsible for study design. R.M.P. was chief investigator of the OPTIMISE trial. J.A., M.A.G., R.M.P., T.O., S.T., and J.M. performed patient recruitment and data collection. M.A.G. and A.S.V.S. performed the data analysis with input from R.M.P. and N.L.M. The manuscript was drafted by M.A.G., J.A., R.M.P., N.L.M., and A.S.V.S., and revised after critical review by all authors.

## Supplementary material

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

## Data sharing

The authors are happy to consider data-sharing requests from bona fide researchers; these should be addressed to the senior author at: r.pearse@qmul.ac.uk.

## Acknowlegements

Abbot Diagnostics provided reagent, calibrators, and controls for the cardiac troponin assay at no cost. The biomarker analysis was undertaken by Edwin Carter (BHF Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK) and Alan Reid (Southern General Hospital, Glasgow, UK).

## Declaration of interest

R.M.P. has received an unrestricted research grant and equipment loans from LiDCO Ltd and has performed consultancy work for Edwards Lifesciences, Covidien, and Massimo Inc. R.M.P. is a member of the editorial advisory board of the *BJA*. N.L.M. has acted as a consultant for Abbott Laboratories and Beckman-Coulter. A.S.V.S. has acted as a consultant for Abbott Laboratories. All other authors declare they have no conflicts of interest.

## Funding

National Institute for Health Research (UK) Clinician Scientist Award (to R.M.P.); Chief Scientist Office (Scotland) NHS Research Scheme Fellowship (to M.A.G.); Intermediate Clinical Research Fellowship from the British Heart Foundation (FS/10/024/28266 to N.L.M.).

## References

1. 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
2. Pearse RM, Moreno RP, Bauer P, *et al*. Mortality after surgery in Europe: a 7 day cohort study. *Lancet* 2012; **380**: 1059–65
3. Khuri SF, Henderson WG, DePalma RG, *et al*. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg* 2005; **242**: 326–41; discussion 341–3
4. Grocott MPW, Dushianthan A, Hamilton MA, *et al*. Perioperative increase in global blood flow to explicit defined goals and outcomes after surgery: a Cochrane Systematic Review. *Br J Anaesth* 2013; **111**: 535–48
5. Chassot P-G, Delabays A, Spahn DR. Preoperative evaluation of patients with, or at risk of, coronary artery disease undergoing non-cardiac surgery. *Br J Anaesth* 2002; **89**: 747–59
6. Hayes MA, Timmins AC, Yau E, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994; **330**: 1717–22
7. Takala J, Meier-Hellmann A, Eddleston J, Hulstaert P, Sramek V. Effect of dopexamine on outcome after major abdominal surgery: a prospective, randomized, controlled multicenter study. European Multicenter Study Group on Dopexamine in Major Abdominal Surgery. *Crit Care Med* 2000; **28**: 3417–23
8. Corcoran T, Rhodes JE, Clarke S, Myles PS, Ho KM. Perioperative fluid management strategies in major surgery: a stratified meta-analysis. *Anesth Analg* 2012; **114**: 640–51

9. Challand C, Struthers R, Sneyd JR, *et al*. Randomized controlled trial of intraoperative goal-directed fluid therapy in aerobically fit and unfit patients having major colorectal surgery. *Br J Anaesth* 2012; **108**: 53–62
10. Gillies MA, Habicher M, Jhanji S, *et al*. Incidence of postoperative death and acute kidney injury associated with i.v. 6% hydroxyethyl starch use: systematic review and meta-analysis. *Br J Anaesth* 2014; **112**: 25–34
11. Pearse RM, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett D. The incidence of myocardial injury following postoperative goal directed therapy. *BMC Cardiovasc Disord* 2007; **7**: 10
12. 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
13. Pearse RM, Harrison DA, MacDonald N, *et al*. Effect of a perioperative, cardiac output–guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. *JAMA* 2014; **311**: 2181–90
14. Hamm CW, Ravkilde J, Gerhardt W, *et al*. The prognostic value of serum troponin T in unstable angina. *N Engl J Med* 1992; **327**: 146–50
15. Ohman EM, Armstrong PW, Christenson RH, *et al*. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. *N Engl J Med* 1996; **335**: 1333–42
16. Antman EM, Tanasijevic MJ, Thompson B, *et al*. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996; **335**: 1342–9
17. Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. *N Engl J Med* 2000; **343**: 1139–47
18. Hsieh BP, Rogers AM, Na B, Wu AH, Schiller NB, Whooley MA. Prevalence and prognostic significance of incidental cardiac troponin T elevation in ambulatory patients with stable coronary artery disease: data from the heart and soul study. *Am Heart J* 2009; **158**: 673–9
19. Bonaca M, Scirica B, Sabatine M, *et al*. Prospective evaluation of the prognostic implications of improved assay performance with a sensitive assay for cardiac troponin I. *J Am Coll Cardiol* 2010; **55**: 2118–24
20. Mills NL, Churchhouse AM, Lee KK, *et al*. Implementation of a sensitive troponin I assay and risk of recurrent myocardial infarction and death in patients with suspected acute coronary syndrome. *JAMA* 2011; **305**: 1210–6
21. Keller T, Zeller T, Peetz D, *et al*. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. *N Engl J Med* 2009; **361**: 868–77
22. Reichlin T, Hochholzer W, Bassetti S, *et al*. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med* 2009; **361**: 858–67
23. Parsonage WA, Galbraith AJ, Koerbin GL, Potter JM. Value of B-type natriuretic peptide for identifying significantly elevated pulmonary artery wedge pressure in patients treated for established chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 2005; **95**: 883–5
24. Maisel AS, Krishnaswamy P, Nowak RM, *et al*. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002; **347**: 161–7
25. Januzzi JL Jr, Camargo CA, Anwaruddin S, *et al*. The N-terminal pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *Am J Cardiol* 2005; **95**: 948–54
26. Rodseth RN, Lurati Buse GA, Bolliger D, *et al*. The predictive ability of pre-operative B-type natriuretic peptide in vascular patients for major adverse cardiac events: an individual patient data meta-analysis. *J Am Coll Cardiol* 2011; **58**: 522–9
27. Karthikeyan G, Moncur RA, Levine O, *et al*. Is a pre-operative brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide measurement an independent predictor of adverse cardiovascular outcomes within 30 days of noncardiac surgery? A systematic review and meta-analysis of observational studies. *J Am Coll Cardiol* 2009; **54**: 1599–606
28. ProCESS Investigators; Yealy DM, Kellum JA, Huang MT, *et al*. A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014; **370**: 1683–93
29. ARISE Investigators; ANZICS Clinical Trials Group; Peake SL, Delaney A, Bailey M, *et al*. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med* 2014; **371**: 1496–506
30. Bender JS, Smith-Meek MA, Jones CE. Routine pulmonary artery catheterization does not reduce morbidity and mortality of elective vascular surgery: results of a prospective, randomized trial. *Ann Surg* 1997; **226**: 229–36
31. Valentine RJ, Duke ML, Inman MH, *et al*. Effectiveness of pulmonary artery catheters in aortic surgery: a randomized trial. *J Vasc Surg* 1998; **27**: 203–11
32. Bonazzi M, Gentile F, Biasi GM, *et al*. Impact of perioperative haemodynamic monitoring on cardiac morbidity after major vascular surgery in low risk patients. A randomised pilot trial. *Eur J Vasc Endovasc Surg* 2002; **23**: 445–51
33. Giglio MT, Marucci M, Testini M, Brienza N. Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: a meta-analysis of randomized controlled trials. *Br J Anaesth* 2009; **103**: 637–46
34. Dalfino L, Giglio MT, Puntillo F, Marucci M, Brienza N. Haemodynamic goal-directed therapy and postoperative infections: earlier is better. A systematic review and meta-analysis. *Crit Care* 2011; **15**: R154
35. Kavsak PA, Walsh M, Srinathan S, *et al*. High sensitivity troponin T concentrations in patients undergoing noncardiac surgery: a prospective cohort study. *Clin Biochem* 2011; **44**: 1021–4
36. Lopez-Jimenez F, Goldman L, Sacks DB, *et al*. Prognostic value of cardiac troponin T after noncardiac surgery: 6-month follow-up data. *J Am Coll Cardiol* 1997; **29**: 1241–5
37. Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators; 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
38. Ryding AD, Kumar S, Worthington AM, Burgess D. Prognostic value of brain natriuretic peptide in noncardiac surgery: a meta-analysis. *Anesthesiology* 2009; **111**: 311–9
39. Thygesen K, Alpert JS, White HD, *et al*. Universal definition of myocardial infarction: ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. *Eur Heart J* 2007; **28**: 2525–38
40. 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


*Handling editor: P. S. Myles*