Background. Perioperative mortality after cardiac surgery has decreased in recent years although postoperative morbidity is still significant. Although there is evidence that perioperative goal-directed haemodynamic therapy (GDT) may reduce surgical mortality and morbidity in non-cardiac surgical patients, the data are less clear after cardiac surgery. The objective of this review is to perform a meta-analysis on the effects of perioperative GDT on mortality, morbidity, and length of hospital stay in cardiac surgical patients.

Methods. We conducted a systematic review using Medline, EMBASE, and the Cochrane Controlled Clinical Trials Register. Additional sources were sought from experts. The inclusion criteria were randomized controlled trials, mortality reported as an outcome, pre-emptive haemodynamic intervention, and cardiac surgical population. Included studies were examined in full and subjected to quantifiable analysis, subgroup analysis, and sensitivity analysis where possible. Data synthesis was obtained by using odds ratio (OR) and mean difference (MD) for continuous data with 95% confidence interval (CI) utilizing a random-effects model.

Results. From 4986 potential studies, 5 met all the inclusion criteria (699 patients). The quantitative analysis showed that the use of GDT reduced the postoperative complication rate (OR 0.33, 95% CI 0.15–0.73; \( P = 0.006 \)) and hospital length of stay (MD \(-2.44\), 95% CI \(-4.03\) to \(-0.84\); \( P = 0.003 \)). There was no significant reduction in mortality.

Conclusion. The use of pre-emptive GDT in cardiac surgery reduces morbidity and hospital length of stay.

Keywords: cardiac output; cardiac surgical procedures; haemodynamics; intraoperative; monitoring

Accepted for publication: 16 November 2012

Operative and postoperative mortality after cardiac surgery have decreased in recent years,\(^1\)\(^-\)\(^3\) which highlights the progress in the care of these patients. The incidence of postoperative morbidity, however, is still significant.\(^2\) As a result, up to 10% of patients require a prolonged postoperative care,\(^4\) with longer intensive care unit (ICU) stays and worse long-term outcomes.\(^5\)\(^-\)\(^6\) Patients with complications use a greater amount of resources,\(^7\) and therefore these patients are associated with a higher healthcare cost.

The risk of adverse events increases in patients with certain co-morbidities, such as recent myocardial infarction, poor left ventricular ejection fraction, history of pulmonary disease, or renal dysfunction.\(^4\)\(^-\)\(^8\) The impact of co-morbidities on postoperative morbidity and outcome has also been studied in non-cardiac surgery where the use of haemodynamic manipulations in the perioperative period has been associated with an improved outcome.\(^9\)\(^-\)\(^1\)\(^5\) Fewer studies have been performed specifically for cardiac surgery, and even these are mostly on small sample sizes from single centres.\(^2\)\(^0\)\(^-\)\(^2\)\(^4\)

This systematic review and meta-analysis investigates whether a goal-directed haemodynamic approach to therapy in the perioperative period is associated with improved postoperative outcomes in cardiac surgical patients.

Methods

Search strategy

Three electronic databases (Medline, EMBASE, and the Cochrane Controlled Clinical Trials register) were searched with the following keywords: haemodynamic monitoring, cardiac output, stroke volume, oxygen delivery, GDT, dobutamine, cardiac surgery, cardiac surgical procedures (full electronic search strategy is presented in Supplementary data).
The research strategy ran from 1985 to 31 December 2011. Articles were restricted to randomized clinical trials, English language, and adults and human studies only. In addition to electronic searching, industry representatives were contacted for additional material, and personal archives and communications were searched. All identified review articles and evidence-based guidelines were hand-searched for additional references, and reference lists for identified studies were snowballed for additional articles. The title and abstracts identified from the search strategy were then screened for potential articles by two investigators. After this primary exclusion, full articles were obtained and examined for suitability. When necessary, authors of the selected articles were contacted to obtain missing information for the quantitative analysis.

Study inclusion criteria

Studies were selected according to the following inclusion criteria:

1. Randomized controlled clinical trials (RCTs) evaluating the effect of pre-emptive haemodynamic GDT. All studies had to be prospective, properly randomized to control for selection bias, and had to report hospital mortality as an outcome on an intention-to-treat basis. Only peer-reviewed papers were included. GDT was defined as perioperative monitoring and manipulation of haemodynamic parameters to reach either normal or supra-normal pre-determined values. Therapies could be classified as i.v. fluids, additional inotropic support or both. Haemodynamic intervention had to be pre-emptively started in the perioperative period, which was defined as 24 h before or after operation.

2. Adult (age 18 years or over) patients as participants of the study design.

3. Studies performed in cardiac surgical patients.

Methodological quality of included studies and risk of bias assessment

Eligible studies were graded using the systems described by Jadad and colleagues.25 Non-randomized studies were excluded. This scale is used to describe the study quality by scoring five elements of randomization, implementation, and blinding with a score range of 1 to 5.

To assess risk of bias of selected studies, two reviewers working independently determined the adequacy of concealment of allocation, blinding of participants and healthcare providers, blinding of outcome assessors, extent of loss of follow-up (attrition bias), and risk of selective reporting bias using the Review Manager software (version 5.1, The Cochrane Collaboration, Oxford, UK). Risk was described for every item as ‘low risk’ if the information provided in the study was clear and complete, ‘high risk’ if there was no information about some of the items or the information provided reveal a clear risk of bias, and ‘unclear risk’ when the information provided is incomplete.

Outcome measures

The primary outcome was hospital mortality. The secondary outcome measures were postoperative morbidity and hospital length of stay.

A sensitivity analysis was performed on both the primary and secondary outcomes. This consisted of a correction for quality using the Jadad score, with a score >3 classified as a higher quality study.25 Furthermore, a time-dependent analysis was performed to examine the influence of care evolution and underlying event rates in the last 20 years.

Statistical analysis

The meta-analysis was performed using the Review Manager, version 5.1.4 software (The Cochrane Collaboration, Oxford, UK), with a random-effects model. The results are presented as an odds ratio (OR) for dichotomous data with 95% confidence intervals (CIs) and as mean difference (MD) for continuous data. Significance was set at a P-value of <0.05. All results were checked for statistical heterogeneity presenting the among-study variance χ² and the chi-squared test. Statistical significance was set at a P-value of <0.1 for heterogeneity. Inconsistency was tested using the I² statistic and it was considered significant when it was >40%.

Results

Included trials

A total of 4986 titles were suitable for further review after database searching, snowballing of references, hand searching, and contacting experts and industry representatives. One hundred and three potential articles were selected after thorough examination of titles and abstracts. Further examination led to exclusion of 98 studies from the analysis, because they were not related to early goal-directed therapy, lacked randomization, had a non-prospective study design, or were not performed in cardiac surgical patients (Fig. 1). Five articles were finally included in the analysis.

Description of studies

The five identified studies are described in detail in Table 1. All of them reported mortality and morbidity. Definitions of complications were variable across the studies (reported in Supplementary Appendix 3). Although all the studies also reported ICU and hospital length of stay, these data were reported in different types of central tendency and dispersion measures (Table 2). Data regarding hospital length of stay were obtained from selected authors. None of these five studies used supra-normal targets of resuscitation.

Mortality

Mortality data were available for all five trials on 699 patients. There were no deaths reported in two trials; thus our estimate is based on three trials randomizing 632 patients, 15 of whom died. The overall effect when combining the studies was no reduction in mortality for the
intervention group (pooled OR 0.69; 95% CI 0.19–2.56; \( P=0.58 \)) (Fig. 2). No significant heterogeneity was detected within this comparison (\( I^2=23\% \), \( \chi^2=2.59, df=2, P=0.27 \)).

**Morbidity**

Morbidity data were available for all five trials, reporting data from 699 patients. There was a total of 72 complications, 21 in the EGDT group and 51 in the control group. In the pooled analysis, there was a significant reduction in the overall complication rate (OR = 0.33; 95% CI = 0.15–0.73; \( P=0.006 \)) (Fig. 3). No significant heterogeneity was detected within this comparison (\( I^2=19\% \), \( \tau^2=0.17, \chi^2=4.93, df=4, P=0.29 \)).

**Hospital length of stay**

After contacting authors, hospital length of stay data were available for all five trials, reporting data from 699 patients. In the pooled analysis, there was a significant reduction in the hospital length of stay (MD -2.21; 95% CI -3.84 to -0.57; \( P=0.008 \)) (Fig. 4). Significant heterogeneity was detected within this comparison (\( \tau^2=1.51, \chi^2=8.66, df=4, P=0.07 \), \( I^2=54\% \)). Retrospective exploration of the heterogeneity identified one trial\(^{20}\) that seemed to differ from the others. In this study, the haemodynamic targets of the protocol group were achieved in 56.5% of patients in the protocol group and in 42.1% of patients in the control group. In the post hoc analysis reported by the authors, there was a greater difference in hospital stay between the patients who achieved the targets and those who did not. Exclusion of this trial had no effect on the finding of evidence of a significant difference in length of hospital stay (MD -3.15; 95% CI: -4.27 to -2.02; \( \tau^2=0.00, \chi^2=0.92, df=3, P=0.82, I^2=0\% \)).

**Trial quality**

The Jadad score was 1 for the studies of Smetkin and colleagues,\(^{24}\) 2 for the studies of Kapoor and colleagues\(^{23}\) and Mythen and Webb,\(^{21}\) and 3 for the studies of McKendry and colleagues\(^{22}\) and Pölönen and colleagues.\(^{20}\) Neither of the studies was performed in a double-blind way and all of them were done in a single centre. Neither studies with a Jadad score 3 nor studies with a Jadad score 2 revealed a significant reduction in mortality. The significant reduction in morbidity was irrespective of trial quality.

**Time-dependent analysis**

The control-group mortality was 3.33% for Mythen and Webb,\(^{21}\) 3% for Pölönen and colleagues,\(^{20}\) 2.2% for McKendry and colleagues,\(^{22}\) 0% for Kapoor and colleagues,\(^{23}\) and Smetkin and colleagues.\(^{24}\) The postoperative complications rate over the time was of 20% for Mythen and Webb,\(^{21}\) 6% for Pölönen and colleagues,\(^{20}\) 29% for McKendry and colleagues,\(^{22}\) 13% for Kapoor and colleagues,\(^{23}\) and 20% for Smetkin and colleagues.\(^{24}\) A mean of 17.5% (so ± 8.7) of patients experienced complications (Supplementary Appendix 4).
### Table 1

Randomized clinical trials of goal-directed therapy in cardiac surgical patients. CI, cardiac index; CVP, central venous pressure; SVV, stroke volume variation; $\text{ScvO}_2$, central venous saturation of oxygen; SVI, stroke volume index; SVRI, systemic vascular resistance index; $\text{DO}_2\text{I}$, delivery oxygen index; Hct, haematocrit; MAP, mean arterial pressure; UO, urine output; CABG, coronary artery bypass graft; CPB, cardio-pulmonary bypass.

<table>
<thead>
<tr>
<th>Author/Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>Timing</th>
<th>Monitor</th>
<th>Goals of therapy</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smetkin and colleagues</td>
<td>40 patients (20 EGDT and 20 control group). CABG off-pump. EuroSCORE 2 control group, 2.5 EGDT group</td>
<td>Fluids, inotropes and blood transfusion</td>
<td>Perioperative</td>
<td>PICCOplus cardiac output monitoring and CeVOX (continuous $\text{ScvO}_2$ monitoring)</td>
<td>ITBVI = 850–1000 ml $\text{m}^{-2}$; MAP = 60–100 mm Hg; HR &lt; 90 bpm; Hb ≥ 8 g dl$^{-1}$; CI ≥ 2 litre min$^{-1}$ $\text{m}^{-2}$; $\text{ScvO}_2$ &gt; 60%</td>
<td>CVP = 6–14 mm Hg; MAP = 60–100 mm Hg; HR &lt; 90 bpm</td>
</tr>
<tr>
<td>Kapoor and colleagues</td>
<td>30 patients (13 intervention, 14 control). CABG on CPB. EuroSCORE ≥ 3</td>
<td>Fluids and inotropes</td>
<td>Postoperative</td>
<td>FloTrac™ cardiac output monitoring sensor and PreSep™ catheter (continuous central venous oximetry)</td>
<td>CI 2.5–4.2 ml min$^{-1}$ $\text{m}^{-2}$; CVP 6–8 mm Hg; SVV &lt; 10%; $\text{ScvO}_2$ &gt; 70%; SVI 30–65 ml bet$^{-1}$ $\text{m}^{-2}$; SVRI 1500–2500 dynes s cm$^{-2}$ $\text{m}^{-2}$; $\text{DO}_2\text{I}$ 450–600 ml min$^{-1}$ $\text{m}^{-2}$; Hct &gt; 30%; MAP 90–105 mm Hg; pH 7.35–7.45; $\text{PO}_2$ &gt; 100 mm Hg; $\text{PCO}_2$ 35–45 mm Hg; $\text{SpO}_2$ &gt; 95%; UO &gt; 1 ml kg$^{-1}$ h$^{-1}$</td>
<td>Hct ≥ 30%; MAP 90–105 mm Hg; pH 7.35–7.45; $\text{PO}_2$ &gt; 100 mm Hg; $\text{PCO}_2$ 35–45 mm Hg; $\text{SpO}_2$ &gt; 95%; UO &gt; 1 ml kg$^{-1}$ h$^{-1}$</td>
</tr>
<tr>
<td>McKendry and colleagues</td>
<td>179 patients (89 EGDT and 90 control group). CABG, valve replacement or both on CPB. Parsonnet score 9.7 both groups</td>
<td>Fluids, inotropes and nitrates</td>
<td>Postoperative</td>
<td>Oesophageal Doppler</td>
<td>CI 2.5–4.2 ml min$^{-1}$ $\text{m}^{-2}$; CVP 6–8 mm Hg; SVV &lt; 10%; $\text{ScvO}_2$ &gt; 70%; SVI 30–65 ml bet$^{-1}$ $\text{m}^{-2}$; SVRI 1500–2500 dynes s cm$^{-2}$ $\text{m}^{-2}$; $\text{DO}_2\text{I}$ 450–600 ml min$^{-1}$ $\text{m}^{-2}$; Hct &gt; 30%; MAP 90–105 mm Hg; pH 7.35–7.45; $\text{PO}_2$ &gt; 100 mm Hg; $\text{PCO}_2$ 35–45 mm Hg; $\text{SpO}_2$ &gt; 95%; UO &gt; 1 ml kg$^{-1}$ h$^{-1}$</td>
<td>Standard care</td>
</tr>
<tr>
<td>Pöllönen and colleagues</td>
<td>403 patients (9 excluded; 196 EGDT group; 197 control group). CABG, valve replacement or other surgery on CPB</td>
<td>Fluid and inotropes</td>
<td>Postoperative</td>
<td>Thermidilution pulmonary artery catheter</td>
<td>$\text{ScvO}_2$ &gt; 70% and Lactate ≤ 2 mmol litre$^{-1}$ up to 8 h post-op</td>
<td>Standard care</td>
</tr>
<tr>
<td>Mythen and colleagues</td>
<td>60 patients (30 protocol group, 30 control group). CABG, valve replacement or both on CPB</td>
<td>Fluids</td>
<td>Perioperative</td>
<td>Oesophageal Doppler</td>
<td>Maximum SV, increase of CVP &lt; 3 mm Hg</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

### Table 2

Length of stay (LOS) in days for hospital and intensive care unit for early goal-directed therapy group (EGDT) vs control group among different studies. *Median with interquartile range. † Mean with range.

<table>
<thead>
<tr>
<th>Author/Study</th>
<th>LOS ICU (days)</th>
<th>LOS hospital (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EGDT</td>
<td>Control</td>
</tr>
<tr>
<td>Smetkin and cols.</td>
<td>0.8 (0.8–1.0)</td>
<td>1.0 (0.9–1.6)</td>
</tr>
<tr>
<td>Kapoor and cols.</td>
<td>2.6 ± 0.9</td>
<td>4.9 ± 1.8</td>
</tr>
<tr>
<td>McKendry and cols.</td>
<td>2.5</td>
<td>3.2</td>
</tr>
</tbody>
</table>
Assessment of publication bias

Given the small number of studies, a funnel plot was drawn for every comparison to explore the possibility of publication bias. Funnel plots are available in the Supplementary data. The measure of precision used is the standard error (SE) of the log OR of dichotomous data, and the SE of the MD for continuous data. The symmetry of such funnel plots was assessed visually. The funnel plot related to mortality included only the three studies included in the analysis, so it is not possible to draw strong conclusions from this plot. The plots related to morbidity and length of hospital stay reveal a clear asymmetry that could be consistent with publication bias.

Discussion

This meta-analysis and systematic review represents the most up-to-date evaluation of the issue of haemodynamic optimization in cardiac surgical patients, in which a quality...
assessment was performed and related to the outcome of the studies, in terms of mortality and morbidity. This analysis suggests that early goal-directed haemodynamic therapy reduces postoperative complications and hospital length of stay after cardiac surgery.

The use of early goal-directed haemodynamic therapy to improve outcomes in non-cardiac surgery has been demonstrated in several randomized controlled trials and in a recent meta-analysis. Numerous studies, with different types of goals, monitoring devices, and interventions have been conducted in different types of populations. Some of these studies did not show any benefit on mortality, and furthermore, some studies found an increased mortality rate in the intervention group. In our meta-analysis, we did not find any improvement in mortality with GDT. This may be related to the relatively low mortality in cardiac surgery compared with high-risk non-cardiac surgery and to the relatively small number of studies and therefore patients. As the mortality in the ‘standard-care group’ is low, these studies may not have sufficient statistical power to study an effect on mortality. A meta-analysis by Kern and colleagues, using 21 studies with critically ill patients after high-risk surgery, severe trauma, and septic shock, found significant mortality reductions when patients were treated early to achieve optimal goals before the development of organ failure, when there were control-group mortalities >20% and when therapy produced differences in oxygen delivery between the control and protocol groups.

Another explanation for the lack of effect on mortality could be the comparability of haemodynamics achieved in the control and protocol group, irrespective of the treatment. In the study of McKendry and colleagues, 44% of patients in the control group achieved the haemodynamic goals and in the case of Polonen and colleagues it was 42%. In the study of Mythen, there were no significant differences between the two groups for DO$_2$I.

The rate of complications is related to several factors associated with the type of surgery performed, the expertise of the operative team, the co-morbid status of the patient, and the provision of the right postoperative care to reduce the risk. The available data highlight the fact that while mortality is low in cardiac surgery, the rate of complications is still high, even in the studies with zero mortality.

This review corroborates the fact that early goal-directed haemodynamic therapy may reduce the risk of postoperative complications. These results are similar to recent meta-analyses of non-cardiac patients. Briendz and colleagues carried out a meta-analysis demonstrating that postoperative acute renal injury was significantly reduced by perioperative haemodynamic optimization and, on the other hand, Giglio and colleagues conducted another meta-analysis confirming that goal-directed therapy can reduce major and minor gastrointestinal complications in the perioperative period of major surgery (general, vascular, or trauma surgery). Recently, Dalfino and colleagues revealed that GDT reduced postoperative hospital-acquired infections in high-risk surgical population.

An increased length of stay and more costly care usually accompanies postoperative complications. It is not therefore a surprise that a lower incidence of postoperative morbidity is often accompanied by a shorter length of hospital stay. This study shows that there is a significant reduction in the length of hospital stay in the intervention group, which suggests that this technique is an effective method to drive down additive costs in cardiac surgery.

There are several critical issues to be addressed before valid conclusions can be drawn from the present meta-analysis. In the present review, no RCT obtained a Jadad score higher than 3. This is explained by the fact that it is very difficult to have a properly double-blind study when the two groups need to have therapy targeted to different protocols. In addition, all the studies are single-centre and performed on a limited sample size. Biased effect estimates may be originated by suboptimal quality or RCTs, because less rigorous studies overestimate an intervention’s effect and result in ‘false-positive’ conclusion. A second limitation is the small number of available studies in cardiac surgery. In order to reduce publication bias, an effort was made to identify, retrieve, and include all reports, grey and published, that met pre-defined inclusion criteria and to regain unpublished data by contacting the authors of included studies. In addition, funnel plots were drawn to assess this possible bias. We acknowledge that the asymmetry in the funnel plot could be explained by other factors such as methodological heterogeneity between studies; the possibility of publication bias given the asymmetry of the plots and the small number of studies cannot be totally excluded.

A third limitation is the heterogeneity between studies. Although the incidence of postoperative complications is reported across the studies, the definition on each complication may differ significantly, limiting the applicability of some of our findings. In fact, although there was no evidence of statistical heterogeneity regarding mortality and morbidity, these results have to be taken with caution given the small number of studies and the small sample size of some studies. There are many possible sources of clinical and methodological heterogeneity between studies such as the surgical team expertise, patient’s characteristics, therapeutic goals, protocol for achieving these goals, type of fluids given, type of inotrope used, timing of the intervention, duration of the intervention, and monitor utilized. In spite of the fact that we tried to control some confounding factors by subgroup analyses, we were not able to adjust our analysis for all of them. The differences in therapeutic goals are an important source of heterogeneity. Only three studies included flow-based goals such as cardiac index (CI) or stroke volume index (SVI), and the same studies used similar arterial pressure values as a goal even though in the case of Kapoor and colleagues a mean arterial pressure of 90–105 mm Hg is higher compared with the standards in this particular population. Three studies used also
markers of tissular perfusion or oxygen consumption such as SvO₂ or lactate concentration. Only one study included DO₂I as a goal, and one study was based in a process of maximization of stroke volume. Although some studies have pointed out some superiority of flow-based goals and supra-normal values of DO₂I, this evidence is based in non-cardiac surgical patients. On the other hand, recent data suggest no superiority of a liberal red blood cell transfusion strategy (to maintain a haematocrit ≥30%) after cardiac surgery compared with a restrictive strategy (haematocrit ≥24%). Thus, it has to be admitted that there is still not enough evidence to suggest a critical value of DO₂I as the goal after cardiac surgery.

In conclusion, this meta-analysis, within the limitations of existing data, suggests that goal-directed haemodynamic therapy is an effective tool to reducing the incidence of post-operative complications after cardiac surgery and shortening hospital length of stay.

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

Declaration of interest
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