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Perioperative increase in global blood flow to explicit defined goals and outcomes following surgery (Review)

Grocott MPW, Dushianthan A, Hamilton MA, Mythen MG, Harrison D, Rowan K, Optimisation Systematic Review Steering Group

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[Intervention Review]

Perioperative increase in global blood flow to explicit defined goals and outcomes following surgery

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ABSTRACT

Background

Studies have suggested that increasing whole body blood flow and oxygen delivery around the time of surgery reduces mortality, morbidity and the expense of major operations.

Objectives

To describe the effects of increasing perioperative blood flow using fluids with or without inotropes or vasoactive drugs. Outcomes were mortality, morbidity, resource utilization and health status.

Search methods

We searched CENTRAL (*The Cochrane Library* 2012, Issue 1), MEDLINE (1966 to March 2012) and EMBASE (1982 to March 2012). We manually searched the proceedings of major conferences and personal reference databases up to December 2011. We contacted experts in the field and pharmaceutical companies for published and unpublished data.

Selection criteria

We included randomized controlled trials with or without blinding. We included studies involving adult patients (aged 16 years or older) undergoing surgery (patients having a procedure in an operating room). The intervention met the following criteria. 'Perioperative' was defined as starting up to 24 hours before surgery and stopping up to six hours after surgery. 'Targeted to increase global blood flow' was defined by explicit measured goals that were greater than in controls, specifically one or more of cardiac index, oxygen delivery, oxygen consumption, stroke volume (and the respective derived indices), mixed venous oxygen saturation (SVO_2), oxygen extraction ratio (0_2ER) or lactate.

Data collection and analysis

Two authors independently extracted the data. We contacted study authors for additional data. We used Review Manager software.

Main results

We included 31 studies of 5292 participants. There was no difference in mortality: 282/2615 (10.8%) died in the control group and 238/2677 (8.9%) in the treatment group, RR of 0.89 (95% CI 0.76 to 1.05, P = 0.18). However, the results were sensitive to analytical methods and the intervention was better than control when inverse variance or Mantel–Haenszel random-effects models were used, RR of 0.72 (95% CI 0.55 to 0.95, P = 0.02). The results were also sensitive to withdrawal of studies with methodological limitations. The rates of three morbidities were reduced by increasing global blood flow: renal failure, RR of 0.71 (95% CI 0.57 to 0.90); respiratory failure, RR of 0.51 (95% CI 0.28 to 0.93); and wound infections, RR of 0.65 (95% CI 0.51 to 0.84). There were no differences in the rates of nine other morbidities: arrhythmia, pneumonia, sepsis, abdominal infection, urinary tract infection, myocardial infarction, congestive cardiac failure or pulmonary oedema, or venous thrombosis. The number of patients with complications was reduced by the intervention, RR of 0.68 (95% CI 0.58 to 0.80). Hospital length of stay was reduced in the treatment group by a mean of 1.16 days (95% CI 0.43 to 1.89, P = 0.002). There was no difference in critical care length of stay. There were insufficient data to comment on quality of life and cost effectiveness.

Authors' conclusions

It remains uncertain whether increasing blood flow using fluids, with or without inotropes or vasoactive drugs, reduces mortality in adults undergoing surgery. The primary analysis in this review (mortality at longest follow-up) showed no difference between the intervention and control, but this result was sensitive to the method of analysis, the withdrawal of studies with methodological limitations, and is dominated by a single large RCT. Overall, for every 100 patients in whom blood flow is increased perioperatively to defined goals, one can expect 13 in 100 patients (from 40/100 to 27/100) to avoid a complication, 2/100 to avoid renal impairment (from 8/100 to 6/100), 5/100 to avoid respiratory failure (from 10/100 to 5/100), and 4/100 to avoid postoperative wound infection (from 10/100 to 6/100). On average, patients receiving the intervention stay in hospital one day less. It is unlikely that the intervention causes harm. The balance of current evidence does not support widespread implementation of this approach to reduce mortality but does suggest that complications and duration of hospital stay are reduced.

PLAIN LANGUAGE SUMMARY

Perioperative increase in global blood flow to explicit defined goals and outcomes following surgery

Death and serious complications commonly occur following major surgery and are a significant public health problem. These outcomes might be prevented by using fluids and drugs to maintain the supply of oxygen and other nutrients to vital organs. Global blood flow, adjusted to maintain specific targets, might serve as a proxy in determining whether administered fluid and drugs maintain critical nutrient supply. In this Cochrane review of 31 studies conducted in 5292 patients undergoing major surgery, the use of fluids, with or without additional drugs, to achieve defined targets associated with increased total blood flow did not reduce mortality. There was a reduction in the number of patients with complications and the length of time patients stayed in hospital (by 1.2 days). However, the quality of the studies in this area was mediocre.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Protocol to increase global blood flow compared to control for surgical patients

Protocol to increase global blood flow compared to control for surgical patients

Patient or population: Surgical patients
Settings: Hospital
Intervention: Protocol to increase global blood flow
Comparison: Control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Protocol to increase global blood flow				
Mortality (Longest follow-up)	**11 per 100**	**10 per 100** (8 to 11)	**RR 0.89** (0.76 to 1.05)	5292 (31 studies)	⊕⊕⊖⊖ **low** [1,2]	P=0.18
Mortality (Hospital or 28-day)	**7 per 100**	**6 per 100** (5 to 7)	**RR 0.81** (0.65 to 1.00)	5292 (31 studies)	⊕⊕⊖⊖ **low** [1,2]	P=0.06
Number of patients with complications	**40 per 100**	**27 per 100** (23 to 32)	**RR 0.68** (0.58 to 0.80)	1841 (17 studies)	⊕⊕⊖⊖ **low** [1,2]	P<0.00001
Length of hospital stay		The mean length of hospital stay in the intervention groups was **1.16 lower** (1.89 to 0.43 lower)		4729 (27 studies)	⊕⊕⊖⊖ **low** [1,2]	P=0.002

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Majority of studies are unblinded due to the nature of the intervention and hence we have suggested "unclear risk for most of the studies".
[2] Most studies had small number of patients.

BACKGROUND

Description of the condition

It has been known for many years that patients undergoing surgery are more likely to have serious complications or die if they have limited physiological reserve (Boyd 1959; Clowes 1960). Post hoc analysis of patients undergoing major surgery revealed that survivors had a higher cardiac index and lower systemic vascular resistance than those who died (Shoemaker 1972; Shoemaker 1973). Commonly monitored vital signs (heart rate, arterial blood pressure, central venous pressure, temperature, haemoglobin concentration) were found to be poor predictors of mortality when compared with the flow related variables cardiac output and total body oxygen delivery (DO_2) (Shoemaker 1979; Shoemaker 1993). In particular, survivors of major surgical procedures were found to have higher values for cardiac output or DO_2. More recent studies have shown mixed results for the impact of oxygen transport on postoperative morbidity and mortality (Kusano 1997; Peerless 1998; Polonen 1997).

Description of the intervention

New therapeutic options and monitoring techniques that became available in the 1970s, particularly the introduction of the pulmonary artery flow directed catheter (PAC) (Ganz 1971; Swan 1970), opened up the possibility of measuring and then manipulating an individual's cardiovascular system. It was hypothesized that targeting goals for cardiac output and DO_2 in all patients to the values manifested by the survivors of surgery would improve outcome (Bland 1978).

How the intervention might work

An important principle of this intervention is that the perioperative manipulation to augment cardiac output and DO_2 would lead to an improved tissue perfusion and oxygenation. This physiological improvement would lead to better survival and fewer postoperative complications in patients undergoing major surgery.

Why it is important to do this review

It is almost 30 years since the initial uncontrolled data were presented suggesting that perioperative manipulation of flow related cardiovascular variables might improve outcomes in higher risk surgical patients (Shoemaker 1982). Since then, a number of randomized trials have been undertaken in patients in the perioperative period which have investigated this issue. However, these trials differ in:

- the case mix of the patients recruited (different operation severities, comorbidities and, therefore, expected mortalities);
- the techniques used to measure cardiac output (pulmonary artery catheter (PAC) thermodilution, Doppler velocimetry);
- the specific goals targeted (cardiac output, DO_2, maximum stroke volume);
- the techniques used to achieve the goals (fluids, fluids plus inotropes or vasoactive drugs);
- the management of the control arm.

In addition, some of the studies were not blinded and many had small sample sizes leading to limited statistical power. Despite this, a number of non-systematic reviews have attempted to combine studies in order to draw general conclusions from the studies (Boyd 1996; Boyd 1999; Forst 1997; Ivanov 1997; Leibowitz 1997). However, these reviews have identified varying numbers of trials and have not been undertaken systematically, using scientifically rigorous techniques for literature searching or for abstraction and analyses of data. Three previous systematic reviews have addressed this question (Heyland 1996; Kern 2002; Poeze 2005) and reported improved outcomes. They do not include recently published studies and did not focus exclusively on perioperative data. Among recent systematic reviews and meta-analyses, one study included patients with trauma and sepsis (Hamilton 2011) while other studies analysed renal function (Brienza 2009) and gastrointestinal complications (Giglio 2009) as primary outcomes.

The time is now ripe for a systematic review of the literature to address the important question: does perioperative administration of fluids, with or without vasoactive drugs, targeted to increase global blood flow in adults undergoing surgery reduce mortality, morbidity and resource utilization?

OBJECTIVES

To describe the effects of perioperative (24 hours before surgery up to six hours after surgery) administration of fluids, with or without vasoactive drugs, that were targeted to increase global blood flow (relative to control) as defined by explicit measured goals on outcomes following surgery (mortality, morbidity, resource utilization and health status).

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs), with or without blinding, that were available as full published papers. We applied no language restrictions .

Types of participants

We included adults (aged 16 years or older) undergoing surgery in an operating theatre.

Types of interventions

Perioperative administration (initiated within 24 hours before surgery and lasting up to six hours after surgery) of fluids, with or without inotropes or vasoactive drugs, to increase blood flow (relative to control) against explicit measured goals: cardiac output (CO), cardiac index (CI), oxygen delivery (DO_2) or oxygen delivery index (DO_2I), oxygen consumption or oxygen consumption index (VO_2), stroke volume (SV) or stroke volume index, mixed venous oxygen saturation (SVO_2), oxygen extraction ratio (O_2ER) and lactate.

Types of outcome measures

Primary outcomes

1. Mortality (at longest available follow-up)

Secondary outcomes

1. Mortality: all reported time frames e.g. hospital or 28 day, six months.

2. Morbidity:
2.1. rates of overall complications;
2.2. rates of renal impairment, arrhythmia, respiratory failure or acute respiratory distress syndrome (ARDS), infection, myocardial infarction, congestive heart failure or pulmonary oedema, and venous thrombosis.

3. Resource utilization: length of intensive care (ICU) stay, length of hospital stay, cost.

4. Health status: e.g., six month functional health status, quality of life scores.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library (*2012, Issue 1), see Appendix 1; MEDLINE via OvidSP (1966 to March 2012), see Appendix 2; and EMBASE via OvidSP (1982 to March 2012), see Appendix 3. For searching in MEDLINE we combined our topic-specific key words with the Cochrane highly sensitive search strategy for identifying RCTs (Higgins 2011). We modified this filter for use in EMBASE. We used specific keywords to identify potential studies (Appendix 4).

Searching other resources

We searched the proceedings of the following major, relevant European and North American conferences from the year 2011 backwards, without finding eligible studies.

- American College of Surgeons (2011 to 1996).
- American Society of Anesthesiologists (2011 to 1995).
- American Thoracic Society (2011 to 1997*) (* = not available for searching prior to 1997).
- Association of Surgeons of Great Britain and Ireland (2011 to 1996).
- European Society of Anaesthesiologists (2011 to 1995).
- European Society of Intensive Care Medicine (2011 to 1983).
- International Anesthesia Research Society (2011 to 1994).
- Society of Critical Care Medicine (2011 to 1986).

We checked the reference lists of potentially eligible studies and previously published systematic reviews. We also searched the personal reference databases of the authors and the Steering Group for this review. We contacted experts in the field and relevant pharmaceutical companies and asked for published and unpublished reports.

Data collection and analysis

Selection of studies

Two independent authors (MG and MH for 2001 to 2006, AD and AV for 2006 to 2012) identified titles and abstracts of potentially eligible studies. We resolved any disagreement by discussion. We obtained the full texts of potentially eligible studies. We abstracted the study characteristics including: study design; patient population; interventions; and outcomes (see Appendix 5; Appendix 6; Table 1). Review authors were not involved in the selection of studies they had authored.

Data extraction and management

Two authors (MG and MH for 2001 to 2006, AD and AV for 2006 to 2012) independently extracted data. We achieved consensus by resolving any disparity in data collection by discussion. In the absence of appropriate published data, we made at least three attempts to contact authors of eligible studies to obtain any required data. Some studies were conducted by the authors of this review (MGM). They were not involved in the data extraction or risk of bias assessment.

Assessment of risk of bias in included studies

We performed the risk of bias assessment according to the Cochrane risk of bias tool (Higgins 2011). From this tool, we used the following seven domains to assess the methodological quality of included studies. This is summated in a graph and a summary table.

1. Random sequence generation (selection bias): describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

2. Allocation concealment (selection bias): describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.

3. Blinding of participant and personnel (performance bias): describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.

4. Blinding of outcome assessment (detection bias): describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blindness was effective.

5. Incomplete outcome data (attrition bias): describe the completeness of the outcome data for each main outcome, including attrition and exclusion from the analysis. State whether attrition and exclusions were reported, the number in each intervention group (compared with total randomized participants), reasons for attrition and exclusions, and any re-inclusions in analysis performed by the review authors.

6. Selective reporting (reporting bias): state how the possibility of selective outcome reporting was examined by the review authors, and what was found.

7. Other sources of bias: state any important concerns about bias not addressed in the other domains in the tool.

Measures of treatment effect

We based analyses of outcomes on intention-to-treat. We calculated a weighted treatment effect across all RCTs using Review Manager (RevMan 5.1). We expressed measures of treatment effect, such as mortality and complications, as relative risks (RR) and 95% confidence intervals (CI). We used mean differences (standard deviation) for continuous variables such as length of hospital or ICU stay. We explored the robustness of these estimates by

comparing both fixed-effect and random-effects models for the primary outcome.

Unit of analysis issues

We included studies with different treatment groups, interventions and outcomes. Consequently, we performed subgroup analyses of these differences. Many studies reported the number of complications, arrhythmias and infections as total numbers, leaving unclear what the denominators were for these episodes. We have not analysed variables for which the denominator was unknown.

Dealing with missing data

We contacted the authors of the studies for further information and the analysis was performed with the best available information when there was no response.

Assessment of heterogeneity

We assessed inconsistencies and variability in the outcomes among the studies by the I^2 statistic. Variations of > 40% in the outcomes may not be explained by sampling variation. We assumed substantial heterogeneity when the I^2 statistic exceeded 40% (Higgins 2011).

Assessment of reporting biases

We assessed graphical evidence of reporting biases using contour enhanced funnel plots with a subsequent Harbord or Egger's test (Egger 1997; Harbord 2006).

Data synthesis

We performed statistical analysis using Review Manager 5.1 (RevMan 5.1). We applied the intention-to-treat method for all analyses. We used both fixed-effect and random-effects models for the primary outcome analysis and the fixed-effect model for the secondary outcomes. We used relative risks (95% CI) for dichotomous outcomes and mean difference (standard deviation (SD) of the mean or 95% CI) for continuous variables.

Subgroup analysis and investigation of heterogeneity

Due to the heterogeneous nature of the selected studies, we conducted subgroup analyses in the following areas.

1. The urgency of surgery (elective or emergency).
2. The type of surgery (general, vascular, cardiac, other).
3. The timing of the intervention (perioperative, intraoperative, postoperative).
4. The type of intervention (fluids, fluids with vasoactive agents).
5. The intervention goals (CO, SV, oxygen indices).

Sensitivity analysis

We analysed mortality, both over the longest follow-up and hospital or 28 day mortality, with fixed-effect and random-effects models. In addition, we excluded studies with fewer than 100 participants. The intervention in the protocol group varied. The control group in some studies had explicit blood flow goals to standardize care. Further, some studies did not fully control for co-interventions, for instance admission to critical care. We performed sensitivity analysis excluding these studies.

RESULTS

Description of studies

All included studies were RCTs of surgical participants. Compared to controls, the intervention group had a separate protocol to optimise global blood flow, measured by cardiac output (CO) or oxygen delivery.

Results of the search

The initial electronic search identified 18,951 potential studies (Figure 1). After removal of duplicated studies, the search yielded 10,462 studies. No additional studies were identified by contacting experts in the field or relevant pharmaceutical companies or by searching the personal reference databases of the authors or Steering Group. No additional studies were identified following screening of reference lists of potentially eligible studies and previously published systematic reviews.

Figure 1. Study flow diagram.

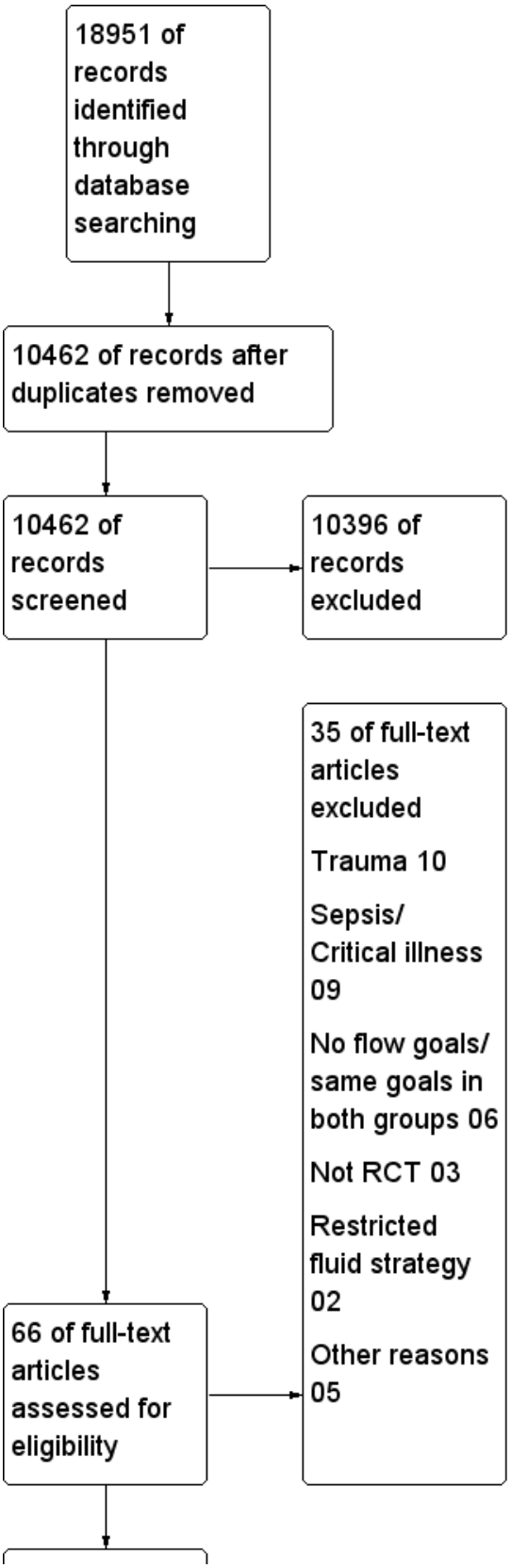
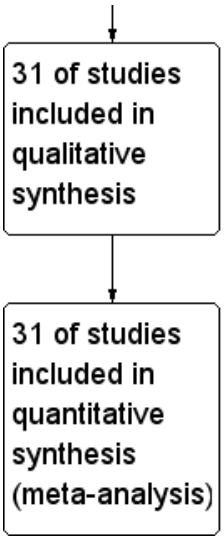


Figure 1. (Continued)



We identified 66 potentially eligible studies following screening of the abstracts of studies. Of those 66 studies, 35 potentially eligible studies did not meet the study inclusion criteria for the reasons summarized in Characteristics of excluded studies.

The remaining 31 fully published studies (5292 participants) met the inclusion criteria. We have summarized the Included studies in Characteristics of included studies; Appendix 5; and Appendix 6. We contacted study authors for additional data where necessary.

Included studies

We included 31 studies in the review (see Characteristics of included studies). The studies were conducted in Europe (20), USA (seven), India (one), Brazil (one), Japan (one) and Canada (one). Most studies (24 studies) recruited participants having elective surgery. The studies were published between 1988 and 2011 (Appendix 5; Appendix 6).

Excluded studies

We excluded 35 studies (Characteristics of excluded studies). We excluded studies that included trauma patients (10) and septic or critically ill patients (nine) unless all patients underwent surgery.

Risk of bias in included studies

We evaluated the risk of bias of included studies with the Cochrane tool (Higgins 2011). This was performed by two authors (AD, AV) independently and we resolved any disparity by discussion and the involvement of a third person (MG). We present the methodological quality in a summary table and a graph (Figure 2; Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

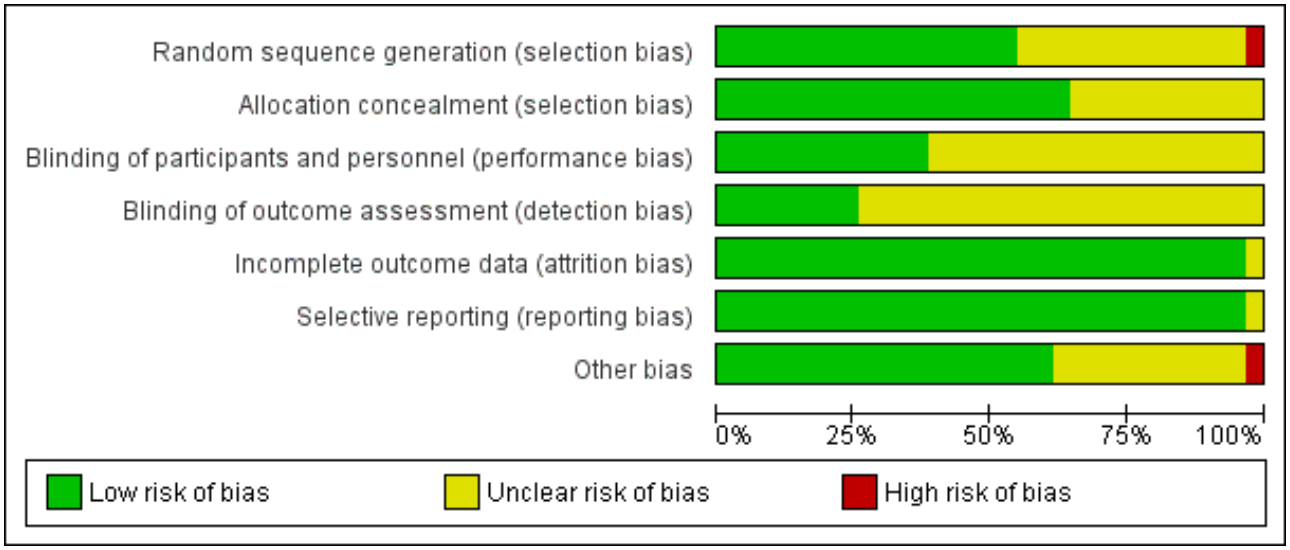


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

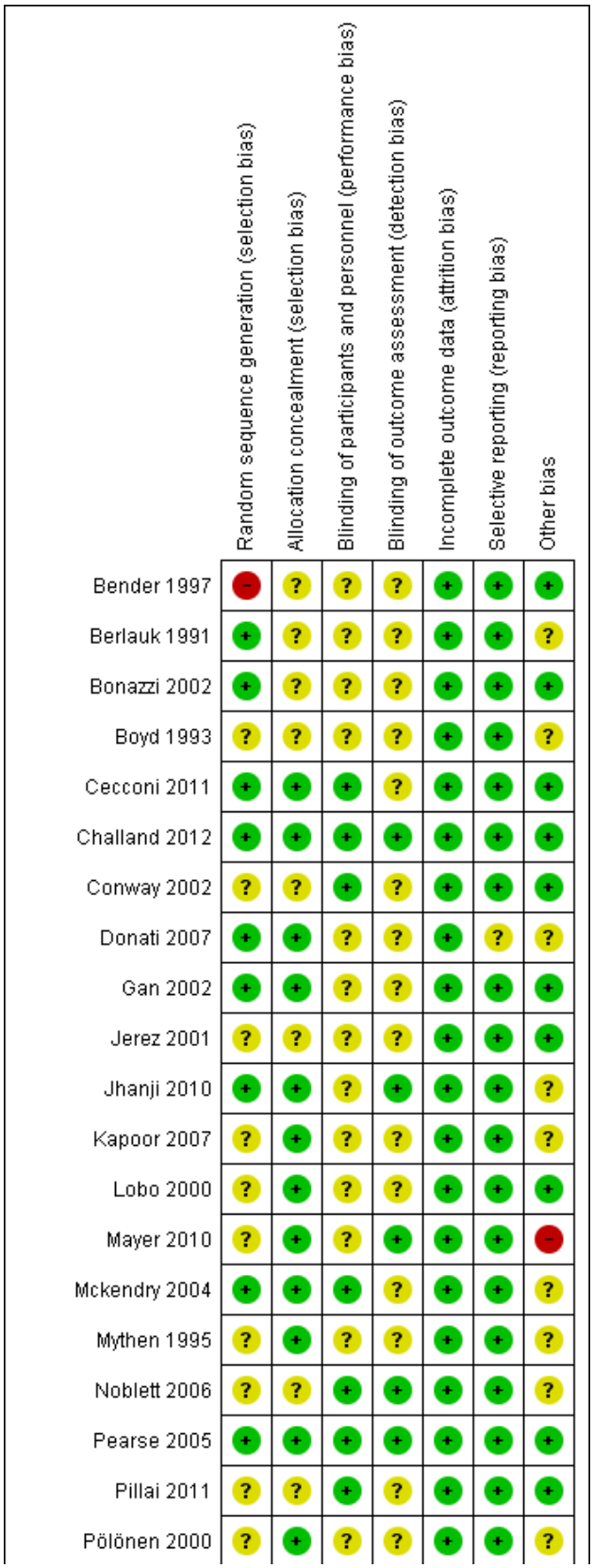
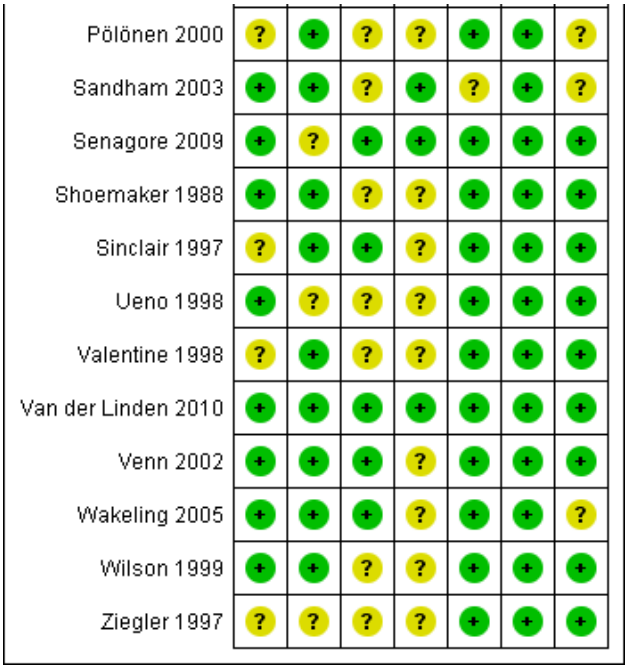


Figure 3. (Continued)



Allocation

All included studies randomly allocated participants. The method of randomization was described in 25 studies (80%): (Bender 1997; Berlauk 1991; Bonazzi 2002; Cecconi 2011; Challand 2012; Donati 2007; Gan 2002; Jhanji 2010; Kapoor 2007; Lobo 2000; Mayer 2010; Mckendry 2004; Mythen 1995; Pearse 2005; Pölönen 2000; Sandham 2003; Senagore 2009; Shoemaker 1988; Sinclair 1997; Ueno 1998; Valentine 1998; Van der Linden 2010; Venn 2002; Wakeling 2005; Wilson 1999). However, in seven studies (Kapoor 2007; Lobo 2000; Mayer 2010; Mythen 1995; Pölönen 2000; Sinclair 1997; Valentine 1998) it was unclear whether the sealed envelope technique allocated participants sequentially. In one study (Bender 1997) participants were allocated by a surgical intensivist, which may have introduced selection bias. We assessed as adequate the random allocation in 17 studies (55%) (Berlauk 1991; Bonazzi 2002; Cecconi 2011; Challand 2012; Donati 2007; Gan 2002; Jhanji 2010; Mckendry 2004; Pearse 2005; Sandham 2003; Senagore 2009; Shoemaker 1988; Ueno 1998; Van der Linden 2010; Venn 2002; Wakeling 2005; Wilson 1999).

We assessed the methods of allocation concealment as adequate for 20 studies (65%) (Cecconi 2011; Challand 2012; Donati 2007: Gan 2002; Jhanji 2010; Kapoor 2007; Lobo 2000; Mayer 2010; Mckendry 2004; Mythen 1995; Pearse 2005; Pölönen 2000; Sandham 2003; Shoemaker 1988; Sinclair 1997; Valentine 1998; Van der Linden 2010; Venn 2002; Wakeling 2005; Wilson 1999).

Blinding

We assessed blinding of personnel or participants as adequate in only 12 studies (39%), reflecting the nature of the intervention (Cecconi 2011; Challand 2012; Conway 2002; Mckendry 2004; Noblett 2006; Pearse 2005; Pillai 2011; Senagore 2009; Sinclair 1997; Van der Linden 2010; Venn 2002; Wakeling 2005). We assessed blinding of outcome assessment as adequate in eight studies (26%) (Challand 2012; Jhanji 2010; Mayer 2010; Noblett 2006; Pearse 2005; Sandham 2003; Senagore 2009; Van der Linden 2010).

Incomplete outcome data

Attrition bias was detected in one study (Sandham 2003) where a large number of participants were lost to follow-up, which may have introduced attrition bias.

Selective reporting

All anticipated outcomes were reported by the included studies.

Other potential sources of bias

In Mayer 2010, the second author has been found to have fabricated results in some clinical studies. We recognized this as a potential high risk.

Exclusion of participants after randomization was noted in seven studies (Berlauk 1991; Kapoor 2007; Mayer 2010; Mckendry 2004; Noblett 2006; Pölönen 2000; Wakeling 2005), which may have induced selection bias.

To test the effect of publication bias, we produced a contour-enhanced funnel plot for the primary outcome (Figure 4), the subsequent Harbord test showing a significant small-studies effect: regression bias -0.72 (95% CI -0.08 to -1.39) (Figure 5). Similarly, the rate of complications (Figure 6; Figure 7) showed evidence of a small studies effect. No other outcome demonstrated small study effects (Harbord 2006).

Figure 4. Contour-enhanced funnel plot: mortality.

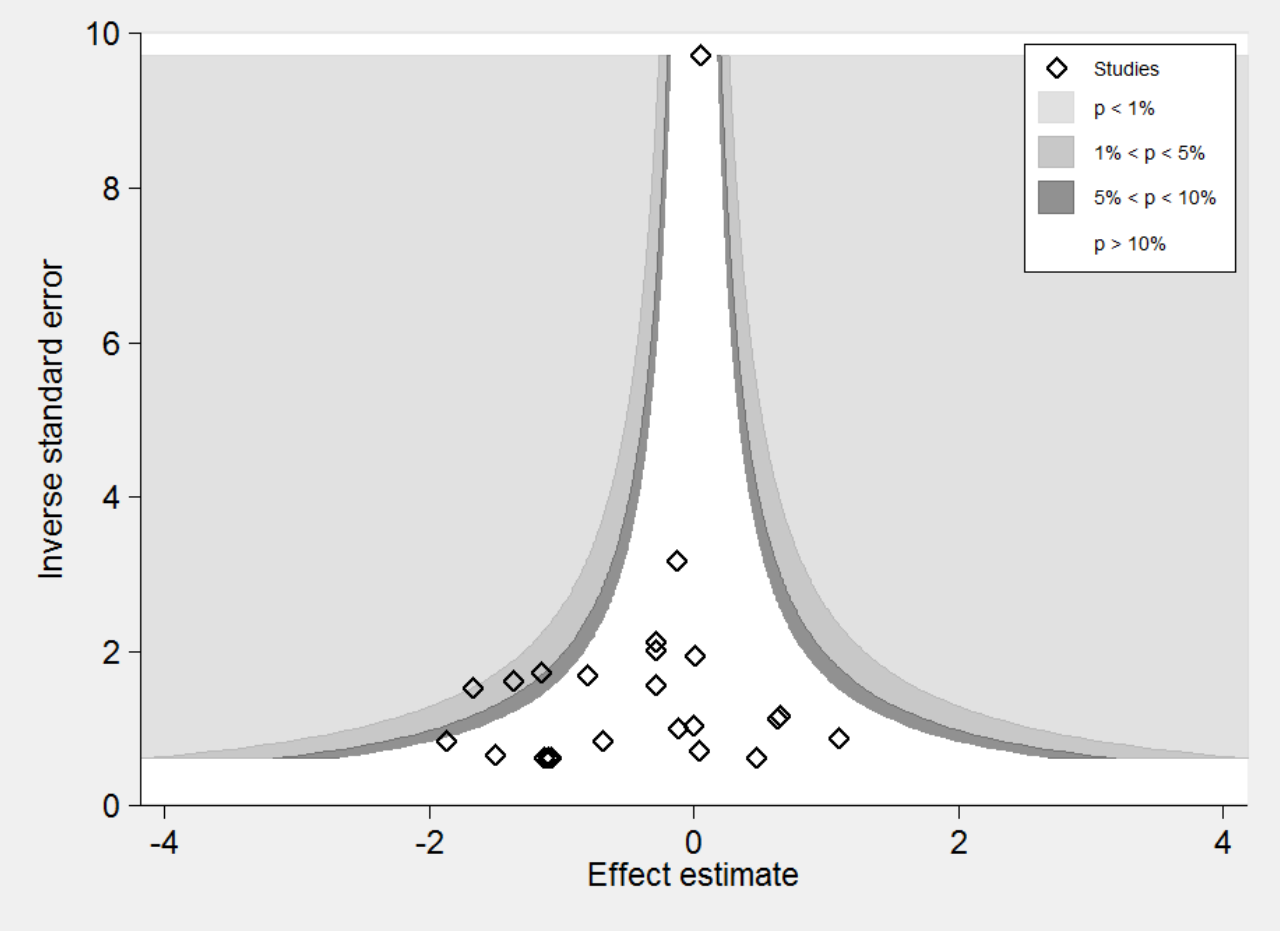


Figure 5. Galbraith plot, Harbord analysis, mortality. The regression slope is -0.72 (-0.08 to -1.39).

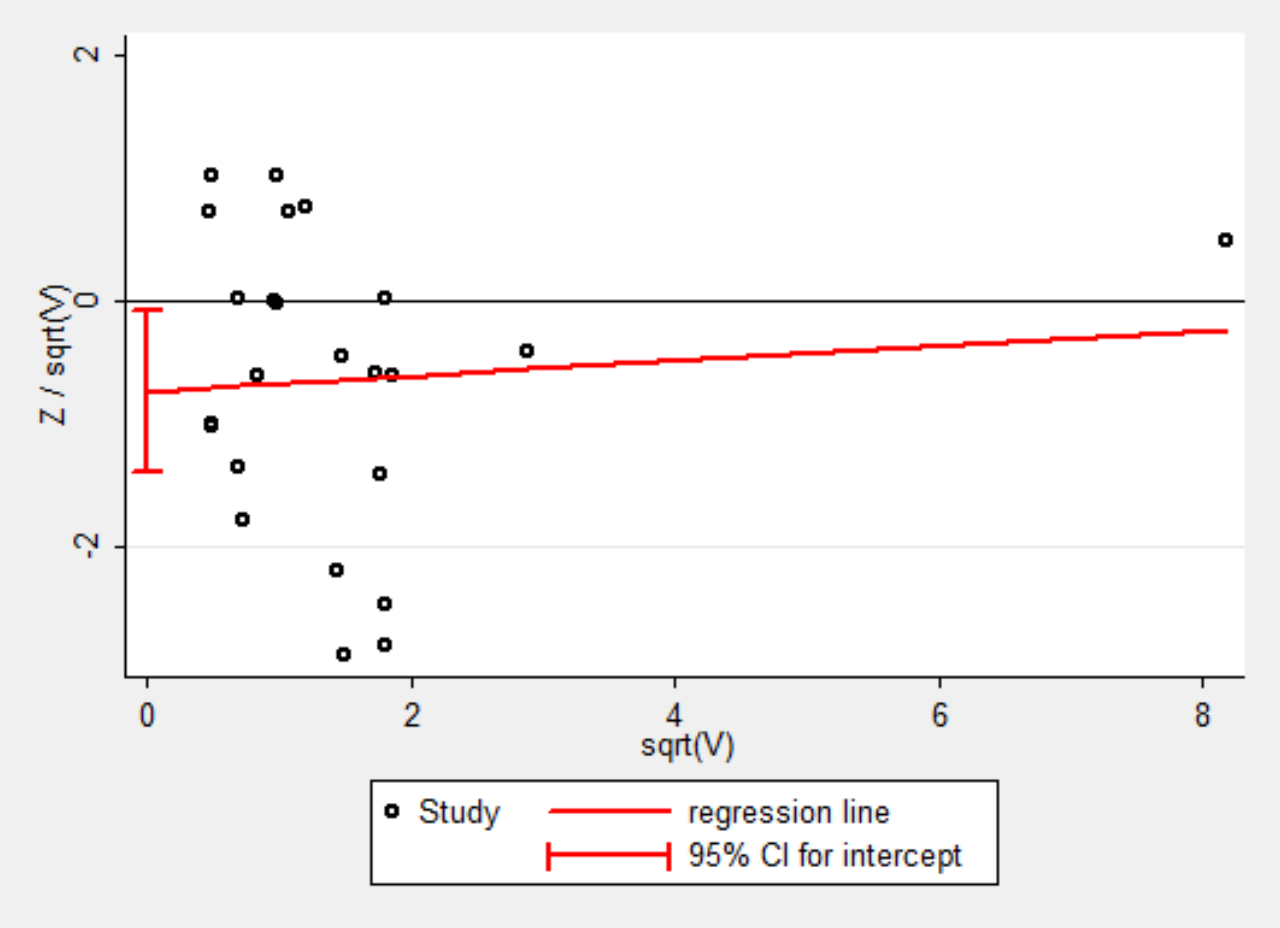


Figure 6. Contour-enhanced funnel plot for rate of complications.

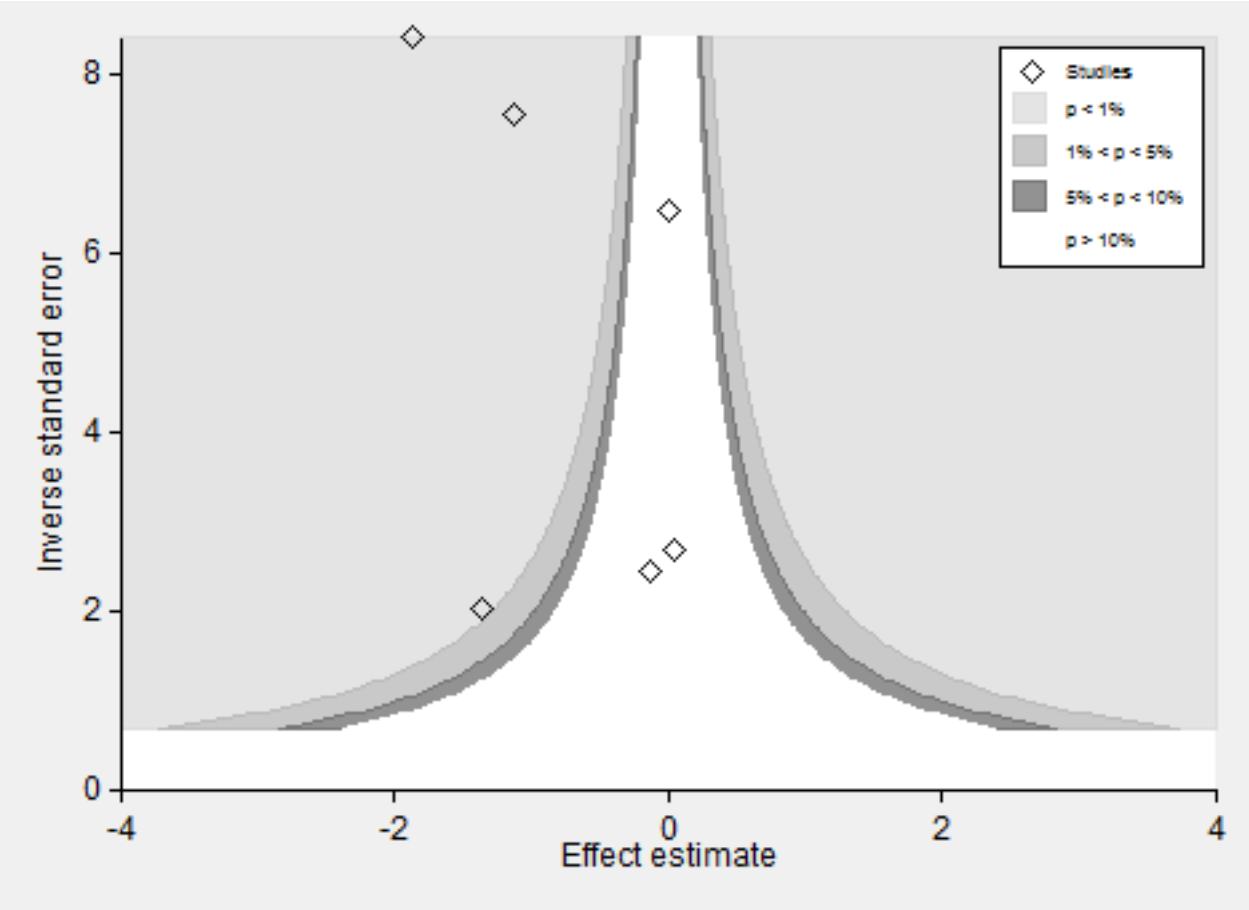
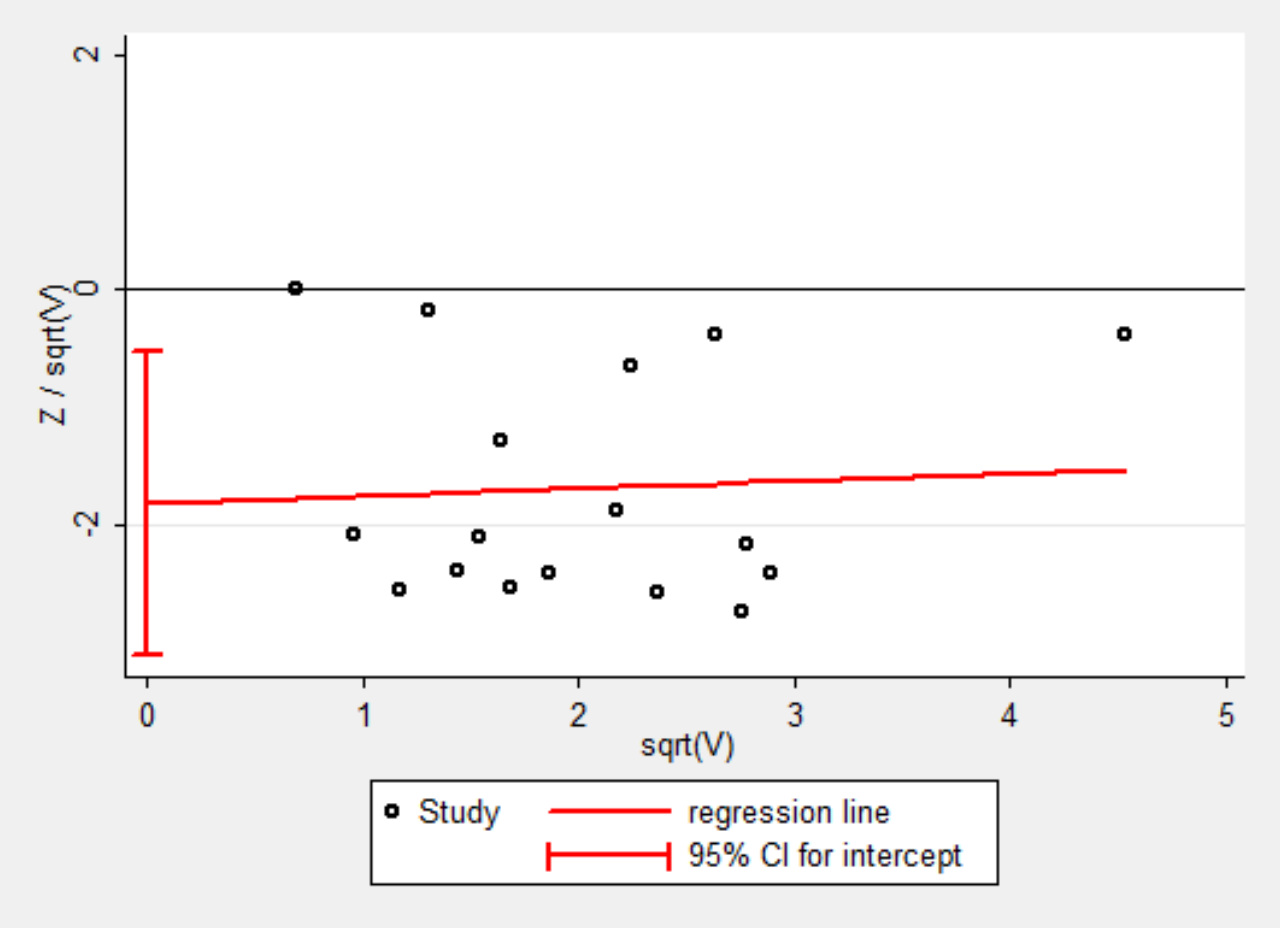


Figure 7. Galbraith plot of Harbord analysis for rate of complications.



Effects of interventions

See: **Summary of findings for the main comparison** Protocol to increase global blood flow compared to control for surgical patients

Data Synthesis

Mortality

1.1 Long-term mortality

Thirty studies reported mortality data and further information was obtained from authors for one study (Pillai 2011). A number of different definitions were used and some papers reported more than one definition. Using data from the longest reported follow-up, the overall mortality was 238/2677 (8.9%) in the intervention group and 282/2615 (10.8%) in the control group, RR of 0.89 (95% CI 0.76 to 1.05, P = 0.18, I^2 = 15%) (Analysis 1.1). The results were sensitive to analytical methods, becoming statistically significant with two methods: the inverse variance random-effects model, RR of 0.72 (95% CI 0.55 to 0.95, P = 0.02, I^2 = 15%); the Mantel–Haenszel random-effects model, RR of 0.72 (95% CI 0.55 to 0.95, P = 0.02, I^2 = 16%) (Appendix 7).

1.2 Hospital or 28 day mortality

Hospital or 28 day mortality was reported in 30 studies and further information was obtained from one study (Pillai 2011). Pooled hospital or 28 day mortality was 146/2677 (5.4%) in the intervention group and 192/2615 (7.3%) in the control group, RR of 0.81 (95% CI 0.65 to 1.00, P = 0.06, I^2 = 1%) (Analysis 1.2). The results were sensitive to analytical methods, becoming significant with three methods: the inverse variance random-effects model, RR of 0.79 (95% CI 0.63 to 0.99, P = 0.04, I^2 = 1%); the Mantel–Haenszel fixed-effect model, RR of 0.77 (95% CI 0.63 to 0.95, P = 0.01, I^2 = 2%) and random-effects model, RR of 0.78 (95% CI 0.62 to 0.99, P = 0.04, I^2 = 2%) (Appendix 8).

Morbidity

We analysed seven categories of morbidity using the investigators' definitions. No two studies used the same list of morbidities following surgery (Table 1). In most cases no specific criteria were listed for morbidities. No two studies used the same criteria.

2.1 Renal impairment

We accepted the rate of renal impairment reported by study authors: we did not apply a single definition across studies. Data on renal impairment were available for 21 studies (Bender 1997; Berlauk 1991; Bonazzi 2002; Boyd 1993; Cecconi 2011; Challand 2012; Donati 2007; Gan 2002; Jhanji 2010; Kapoor 2007; Lobo 2000; Mayer 2010; Mckendry 2004; Mythen 1995; Pölönen 2000; Sandham 2003; Shoemaker 1988; Valentine 1998; Venn 2002; Wakeling 2005; Wilson 1999). The intervention reduced the rate of

renal impairment, RR of 0.71 (95% CI 0.57 to 0.90, P = 0.004, I^2 = 20%) (Analysis 2.1).

2.2 Arrhythmia

Arrhythmia was reported in 16 studies (Bender 1997; Berlauk 1991; Bonazzi 2002; Cecconi 2011; Kapoor 2007; Lobo 2000; Mayer 2010; Mckendry 2004; Pearse 2005; Sandham 2003; Senagore 2009; Shoemaker 1988; Valentine 1998; Venn 2002; Wilson 1999; Ziegler 1997). However, we excluded three studies for which there were unit-of-analysis issues: two studies (Bender 1997; Berlauk 1991) reported the number of events; one of these studies and one other (Bender 1997; Valentine 1998) reported for both the intraoperative and postoperative periods. One study (Shoemaker 1988) reported transient dysrhythmias ("almost always premature ventricular complexes") during insertion of pulmonary artery (PA) catheters. This was reported as a combined percentage (12%) for both control and protocol PA catheter groups. We were unable to identify the exact rate of arrhythmias for each group separately and therefore excluded this study from the analysis. For the 12 studies (Bonazzi 2002; Cecconi 2011; Kapoor 2007; Lobo 2000; Mayer 2010; Mckendry 2004; Pearse 2005; Sandham 2003; Senagore 2009; Venn 2002; Wilson 1999; Ziegler 1997) that we were able to analyse, there was no significant difference between groups in development of an arrhythmia, RR of 0.84 (95% CI 0.67 to 1.06, P = 0.14, I^2 = 0%) (Analysis 2.2).

2.3 and 2.4 Infection

Infections were reported several ways in 20 studies (Bender 1997; Boyd 1993; Cecconi 2011; Gan 2002; Jhanji 2010; Lobo 2000; Mayer 2010; Mckendry 2004; Mythen 1995; Pearse 2005; Pillai 2011; Sandham 2003; Senagore 2009; Shoemaker 1988; Sinclair 1997; Valentine 1998; Van der Linden 2010; Venn 2002; Wakeling 2005; Wilson 1999). The number of participants who had infections was reported in nine studies (Bender 1997; Jhanji 2010; Lobo 2000; Mythen 1995; Pillai 2011; Sinclair 1997; Valentine 1998; Van der Linden 2010; Wakeling 2005). The number of participants with infections was unaffected by the intervention, RR of 0.88 (95% CI 0.69 to 1.12, P = 0.29, I^2 = 0%) (Analysis 2.3).

The types of infection (such as pneumonia) were reported separately in 15 studies (Bender 1997; Boyd 1993; Cecconi 2011; Gan 2002; Lobo 2000; Mayer 2010; Mythen 1995; Pillai 2011; Sandham 2003; Shoemaker 1988; Sinclair 1997; Valentine 1998; Van der Linden 2010; Venn 2002; Wilson 1999). Nine studies (Boyd 1993; Cecconi 2011; Gan 2002; Mayer 2010; Pearse 2005; Sandham 2003; Shoemaker 1988; Venn 2002; Wilson 1999) reported more than one infective complication per participant. It was not possible to add the total number of infections as the exact denominator was unknown. We therefore analysed each infection separately. There was no difference in the rates of: pneumonia, RR of 0.78 (95% CI 0.61 to 1.00, P = 0.05, I^2 = 0%); sepsis, RR of 0.68 (95% CI 0.26 to 1.77, P = 0.43, I^2 = 6%); abdominal infections, RR of 0.53 (95% CI 0.23 to 1.22, P = 0.14, I^2 = 0%); or urinary tract infections, RR of 0.54 (95% CI 0.26 to 1.15, P = 0.11, I^2 = 0%). The intervention significantly reduced the rate of wound infections, RR of 0.65 (95% CI 0.50 to 0.84, P = 0.001, I^2 = 22%) (Analysis 2.4). Two studies (Mckendry 2004; Senagore 2009) reported on the total number of infections and we were unable to include these studies due to unit-of-analysis issues.

2.5 Respiratory failure or acute respiratory distress syndrome (ARDS)

Respiratory failure or ARDS was reported in nine studies (Boyd 1993; Donati 2007; Gan 2002; Mayer 2010; Mythen 1995; Pearse 2005; Shoemaker 1988; Ueno 1998; Wilson 1999). One study (Wilson 1999) also included the number of participants with prolonged ventilation, which we were unable to analyse due to unit-of-analysis issues. The intervention significantly reduced the rate of respiratory failure, RR of 0.51 (95% CI 0.28 to 0.93, P = 0.03, I^2 = 0%) (Analysis 2.5).

2.6 Myocardial infarction

Myocardial infarction was reported in 15 studies (Bender 1997; Berlauk 1991; Bonazzi 2002; Boyd 1993; Cecconi 2011; Kapoor 2007; Mayer 2010; Mckendry 2004; Pearse 2005; Sandham 2003; Shoemaker 1988; Valentine 1998; Venn 2002; Wilson 1999; Ziegler 1997). There was no significant difference in myocardial infarction, RR of 1.01 (95% CI 0.71 to 1.45, P = 0.95, I^2 = 0%) (Analysis 2.6).

2.7 Congestive cardiac failure or pulmonary oedema

Congestive heart failure or pulmonary oedema was reported in 14 studies (Bender 1997; Berlauk 1991; Bonazzi 2002; Boyd 1993; Lobo 2000; Mayer 2010; Pearse 2005; Sandham 2003; Shoemaker 1988; Sinclair 1997; Valentine 1998; Venn 2002; Wakeling 2005; Wilson 1999). There was no significant difference, RR of 1.00 (95% CI 0.81 to 1.24, P = 0.98, I^2 = 0%) (Analysis 2.7).

2.8 Venous thrombosis

Venous thrombosis was reported in 10 studies (Boyd 1993; Cecconi 2011; Lobo 2000; Mayer 2010; Pearse 2005; Sandham 2003; Senagore 2009; Shoemaker 1988; Venn 2002; Wilson 1999). There was no difference, RR of 1.04 (95% CI 0.39 to 2.77, P = 0.93, I^2 = 0%) (Analysis 2.8).

2.9 Complications

More than one method was used to pool complications. The number of participants with complications was reported by 19 studies (Bender 1997; Berlauk 1991; Bonazzi 2002; Cecconi 2011; Challand 2012; Conway 2002; Donati 2007; Jerez 2001; Jhanji 2010: Lobo 2000; Mayer 2010; Mythen 1995; Noblett 2006; Pearse 2005; Shoemaker 1988; Sinclair 1997; Ueno 1998; Wakeling 2005; Wilson 1999). The number of complications per participant was reported by three studies (Boyd 1993; Jerez 2001; Shoemaker 1988). The number of participants with individual complications or the number of individual complications was reported by 27 studies (Bender 1997; Berlauk 1991; Bonazzi 2002; Boyd 1993; Cecconi 2011; Challand 2012; Conway 2002; Donati 2007; Gan 2002; Jhanji 2010; Kapoor 2007; Lobo 2000; Mayer 2010; Mckendry 2004; Mythen 1995; Noblett 2006; Pearse 2005; Pölönen 2000; Sandham 2003; Senagore 2009; Shoemaker 1988; Ueno 1998; Valentine 1998; Venn 2002; Wakeling 2005; Wilson 1999; Ziegler 1997).

We did not pool data for the number of complications because of this variation and the associated unit-of-analysis issues. Further, six studies (Bonazzi 2002; Boyd 1993; Gan 2002; Kapoor 2007; Mckendry 2004; Pillai 2011) that reported the number of participants with complications also reported the individual complications separately, therefore pooling of these would again lead to unit-of-analysis issues. Two studies (Bender 1997; Valentine 1998) reported the number of participants with complications separately for the intraoperative and postoperative periods. We

were unable to combine these outcomes due to unit-of-analysis issues. We therefore pooled 17 studies (Berlauk 1991; Cecconi 2011; Challand 2012; Conway 2002; Donati 2007; Jerez 2001; Jhanji 2010; Lobo 2000; Mayer 2010; Mythen 1995; Noblett 2006; Pearse 2005; Shoemaker 1988; Sinclair 1997; Ueno 1998; Wakeling 2005; Wilson 1999). The number of participants with complications was reduced by the intervention, RR of 0.68 (95% CI 0.58 to 0.80, P < 0.00001, I^2 = 34%) (Analysis 2.9).

Health status

No study reported health status.

Resource use

3.1 Postoperative hospital stay

Postoperative length of hospital stay was reported in 28 studies (Bender 1997; Berlauk 1991; Bonazzi 2002; Boyd 1993; Cecconi 2011; Challand 2012; Conway 2002; Donati 2007; Gan 2002; Jhanji 2010; Kapoor 2007; Lobo 2000; Mayer 2010; Mckendry 2004; Mythen 1995; Noblett 2006; Pearse 2005; Pillai 2011; Pölönen 2000; Sandham 2003; Senagore 2009; Shoemaker 1988; Sinclair 1997; Valentine 1998; Van der Linden 2010; Venn 2002; Wakeling 2005; Wilson 1999). This was reported as the mean (SD) by seven studies (Bender 1997; Berlauk 1991; Donati 2007; Gan 2002; Kapoor 2007; Pearse 2005; Shoemaker 1988), mean (range) by one study (Mythen 1995), mean (95% CI) by two studies (Pillai 2011; Venn 2002), mean (SEM) by one study (Valentine 1998) and median (range or interquartile range (IQR)) by 15 studies (Bonazzi 2002; Boyd 1993; Cecconi 2011; Challand 2012; Conway 2002; Jhanji 2010; Lobo 2000; Mayer 2010; Mckendry 2004; Noblett 2006; Pölönen 2000; Sandham 2003; Sinclair 1997; Van der Linden 2010; Wakeling 2005). We excluded one study from this analysis (Senagore 2009), for which we were unable to get further information. We obtained additional details for five studies (Jhanji 2010; Mythen 1995; Noblett 2006; Wakeling 2005; Wilson 1999). We used the statistical equation by Hozo 2005 to convert the median (range/IQR) to mean (SD). We estimated the SD as IQR/1.35, SEM × √(n) or 95% CI / 1.96. Four studies (Berlauk 1991; Jhanji 2010; Shoemaker 1988; Venn 2002) had two groups in either of the intervention or control groups and these were numerically combined using equation 7.7a in Higgins 2011. The intervention significantly reduced the postoperative length of hospital stay, mean 1.16 days (95% CI 0.43 to 1.89, P = 0.002). We used the random-effects model as the I^2 = 87% (Analysis 3.1).

3.2 Postoperative intensive care stay

Postoperative length of critical care stay was reported by 14 studies (Bender 1997; Berlauk 1991; Boyd 1993; Jerez 2001; Jhanji 2010; Kapoor 2007; Lobo 2000; Mayer 2010; Mythen 1995; Pearse 2005; Pölönen 2000; Shoemaker 1988; Valentine 1998; Wilson 1999). This was reported as the mean (SD) by six studies (Bender 1997; Berlauk 1991; Jerez 2001; Kapoor 2007; Mayer 2010; Shoemaker 1988), mean (range) by one study (Mythen 1995), mean (SEM) by one study (Valentine 1998) and median (range/IQR) by five studies (Boyd 1993; Jhanji 2010; Lobo 2000; Pearse 2005; Pölönen 2000). We were able to obtain additional information for three studies (Jhanji 2010; Mythen 1995; Wilson 1999). Numerical conversion to mean (SD) was performed according to the previous paragraph. There was no difference in postoperative length of critical care stay, mean difference of 0.45 days (95% CI -0.03 to 0.94, P = 0.06). We used the random-effects model as the I^2= 87% (Analysis 3.2).

Three studies (Bender 1997; Berlauk 1991; Shoemaker 1988) reported cost (USD), none of which found a statistical difference. Three other studies (Boyd 1993; Mythen 1995; Wilson 1999) reported cost in separate publications from the original report (two reported GBP (Guest 1997; Mythen 1994); one reported EUR (Fenwick 2002)). Two of these (Fenwick 2002; Guest 1997) reported that the intervention significantly reduced cost. The third (Mythen 1994) reported cost for a subgroup of patients included in the trial and these data were not analysed by treatment groups. Only one study reported means and SDs (Berlauk 1991) and only one study reported means and SEMs (Bender 1997) for cost data. In view of the variety of currencies and statistical descriptors we did not attempt to pool these data.

Subgroup mortality analyses

Timing of intervention

The intervention was commenced in the preoperative period in nine studies (Bender 1997; Berlauk 1991 ; Bonazzi 2002; Boyd 1993; Sandham 2003; Shoemaker 1988; Valentine 1998; Wilson 1999; Ziegler 1997), in the intraoperative period in 15 studies (Cecconi 2011; Challand 2012; Conway 2002; Donati 2007; Gan 2002; Lobo 2000; Mayer 2010; Mythen 1995; Noblett 2006; Pillai 2011; Senagore 2009; Sinclair 1997; Van der Linden 2010; Venn 2002; Wakeling 2005) and in the postoperative period in nine studies (Boyd 1993; Jerez 2001; Jhanji 2010; Kapoor 2007: Mckendry 2004; Pearse 2005; Pölönen 2000; Ueno 1998). In one study (Berlauk 1991) participants were randomized to two intervention groups (a preoperative and an intraoperative group) with a shared control group. In another study (Boyd 1993) the intervention was initiated either preoperatively or postoperatively depending on when the participants came to the attention of the investigators. There was no evidence that this had any effect on the chances of being recruited into the study and therefore we did not consider that this had potential to confound the randomization process. Further, one study (Lobo 2000) had both intraoperative and postoperative interventions. Timing of the intervention did not interact with mortality: preoperative, RR of 0.96 (95% CI 0.79 to 1.17, P = 0.69, I^2 = 63%); intraoperative, RR of 0.67 (95% CI 0.40 to 1.13, P = 0.13, I^2 = 0%); postoperative, RR of 0.73 (95% CI 0.50 to 1.06, P = 0.10, I^2 = 0%) (Analysis 1.4).

Type of intervention

The intervention involved fluids alone in 10 studies (Challand 2012; Conway 2002; Gan 2002; Mythen 1995; Noblett 2006; Pillai 2011; Senagore 2009: Sinclair 1997; Venn 2002; Wakeling 2005) and fluids in combination with vasoactive drugs in 20 studies (Bender 1997; Berlauk 1991; Bonazzi 2002; Boyd 1993; Cecconi 2011; Donati 2007; Jerez 2001; Kapoor 2007; Lobo 2000; Mayer 2010; Mckendry 2004; Pearse 2005; Pölönen 2000; Sandham 2003; Shoemaker 1988; Ueno 1998; Valentine 1998; Van der Linden 2010; Wilson 1999; Ziegler 1997). One study (Jhanji 2010) had two intervention groups; one group had fluid alone and the other had fluids and dopexamine. These groups were analysed separately. There was no difference in mortality between groups according to the intervention provided: fluids alone, RR of 0.80 (95% CI 0.46 to 1.39, P = 0.43, I^2 = 0%); fluids in combination with vasoactive drugs, RR of 0.90 (95% CI 0.76 to 1.07, P = 0.23, I^2 = 41%) (Analysis 1.5).

Type of goal

Fourteen studies (Bender 1997; Berlauk 1991; Bonazzi 2002; Boyd 1993; Kapoor 2007; Lobo 2000; Mayer 2010; Pearse 2005; Sandham 2003; Shoemaker 1988; Ueno 1998; Valentine 1998; Van der Linden 2010; Wilson 1999) used CO and oxygen transport goals; four studies (Donati 2007; Jerez 2001; Pölönen 2000; Ziegler 1997) used mixed venous oxygen saturation, oxygen extraction and lactate; and 13 studies (Cecconi 2011; Challand 2012; Conway 2002; Gan 2002; Jhanji 2010; Mckendry 2004; Mythen 1995; Noblett 2006; Pillai 2011; Senagore 2009; Sinclair 1997; Venn 2002; Wakeling 2005) used stroke volume (SV) goals. Mortality was not reduced for any of the three subgroups: CO and oxygen transport, RR of 0.91 (95% CI 0.75 to 1.09, P = 0.91, I^2 = 58%); mixed venous oxygen saturations, oxygen extraction and lactate, RR of 0.83 (95% CI 0.50 to 1.38, P = 0.47, I^2 = 0%); SV, RR of 0.84 (95% CI 0.51 to 1.41, P = 0.51, I^2 = 0%) (Analysis 1.6).

Mode of surgery

Twenty-four studies (Bender 1997; Berlauk 1991; Bonazzi 2002; Cecconi 2011; Challand 2012; Conway 2002; Donati 2007; Gan 2002; Jhanji 2010; Jerez 2001; Kapoor 2007; Lobo 2000; Mayer 2010; Mythen 1995; Noblett 2006; Pillai 2011; Pölönen 2000; Senagore 2009; Ueno 1998; Valentine 1998; Van der Linden 2010; Wakeling 2005; Wilson 1999; Ziegler 1997) recruited participants having only elective procedures; two studies were exclusively of urgent or emergency surgery (Sinclair 1997; Venn 2002) and five had a mix of urgent or emergency and elective operations (Boyd 1993; Mckendry 2004; Pearse 2005; Sandham 2003; Shoemaker 1988). None of the studies in this latter group were able to provide separate data to allow comparison between elective and urgent or emergency groups. Intervention significantly reduced the mortality of participants in RCTs of elective surgery, RR of 0.68 (95% CI 0.48 to 0.94, P = 0.02, I^2 = 0%); mortality was unchanged for emergency or urgent operations, RR 0.of 68 (95% CI 0.23 to 2.06, P = 0.50, I^2 = 0 %) (Analysis 1.7).

Type of surgery

Six studies (Bender 1997; Berlauk 1991; Bonazzi 2002; Valentine 1998; Van der Linden 2010; Ziegler 1997) were exclusively of participants undergoing vascular surgery. Five additional studies (Boyd 1993; Lobo 2000; Pearse 2005; Sandham 2003; Wilson 1999) included participants undergoing vascular surgery, but in only one of these were group-specific mortality data available (Boyd 1993). Five studies were of patients undergoing cardiac surgery (Jerez 2001; Kapoor 2007; Mckendry 2004; Mythen 1995; Pölönen 2000). Fifteen studies were exclusively of patients undergoing general (non-vascular, non-cardiac) surgery (Cecconi 2011; Challand 2012; Conway 2002; Donati 2007; Gan 2002; Jhanji 2010; Mayer 2010; Noblett 2006; Senagore 2009; Shoemaker 1988; Sinclair 1997; Ueno 1998; Venn 2002; Wakeling 2005). Five additional studies included patients undergoing general surgery (Boyd 1993; Lobo 2000; Pearse 2005; Sandham 2003; Wilson 1999) but in only one of these were group-specific mortality data available (Boyd 1993). There was no interaction between type of surgery and the intervention; vascular, RR of 0.78 (95% CI 0.34 to 1.79, P = 0.56, I^2 = 18%); cardiac, RR of 0.81 (95% CI 0.48 to 1.35, P = 0.42, I^2 = 0%); and general surgery, RR of 0.66 (95% CI 0.41 to 1.07, P = 0.09, I^2 = 0%) (Analysis 1.8).

Sensitivity analyses

We performed sensitivity analyses of the analysis method used to generate relative risks for mortality (Appendix 7; Appendix 8). The results were dependant upon both the analytical method and whether a random-effects model or fixed-effect model was used. There was no difference in mortality when small studies (fewer than 100 participants) were excluded (Analysis 1.3), consistent with Analysis 1.1. The effect of small studies was significant in the Harbord analysis, with a regression slope of -0.72 (95% CI -0.08 to -1.39). Participants were more likely to die in studies that recruited fewer than 100 participants, RR of 1.84 (95% CI 1.02 to 3.33, P = 0.04).

In some studies the fluid and drug management in the control group was comparable with the intervention in other studies. For instance, four studies (Jerez 2001; Lobo 2000 ; Pölönen 2000; Ueno 1998) had fluid and inotropes administered in response to measures of blood flow (CI or DO_2I) in the control groups. Shoemaker 1988 had one control group with DO_2I driven measures. We performed a sensitivity analysis excluding these studies and the control group from Shoemaker 1988 (Analysis 4.1; Analysis 4.2; Analysis 4.3; Analysis 4.4; Analysis 4.5; Analysis 4.6; Analysis 4.7; Analysis 4.8; Analysis 4.9; Analysis 4.10; Analysis 4.11; Analysis 4.12). The findings were consistent with the primary analyses (Analysis 1.1; Analysis 1.2; Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 2.5; Analysis 2.6; Analysis 2.7; Analysis 2.8; Analysis 2.9; Analysis 3.1; Analysis 3.2).

In some studies, fluid and inotrope administration were not the only systematic differences between the control and intervention groups. Five studies (Bender 1997; Bonazzi 2002; Sandham 2003; Valentine 1998; Wilson 1999) did not control for the insertion and presence of a pulmonary artery flow catheter. Three studies (Cecconi 2011; Kapoor 2007; Mayer 2010) did not control for the presence of other flow sensors (FloTrac or Vigileo) and one study (Venn 2002) did not control for the insertion or presence of an oesophageal doppler probe. In one study (Shoemaker 1988) one control group was not matched for the insertion and presence of a pulmonary artery flow catheter. We also performed sensitivity analyses excluding these studies for all outcome measures (Analysis 5.1; Analysis 5.2; Analysis 5.3; Analysis 5.4; Analysis 5.5; Analysis 5.6; Analysis 5.7; Analysis 5.8; Analysis 5.9; Analysis 5.10; Analysis 5.11; Analysis 5.12). With these studies excluded the intervention reduced mortality (longest follow-up), RR of 0.65 (95% CI 0.48 to 0.89, P = 0.007, I^2 = 0%) (Analysis 5.1) and hospital or 28 day mortality, RR of 0.66 (95% CI 0.47 to 0.92, P = 0.01, I^2 = 0%) (Analysis 5.2). The rates of renal failure and ARDS were no longer significantly different. The number of participants with complications and their length of hospital stay were not altered in this analysis, remaining significantly different between groups.

This meta-analysis was dominated by one study (Sandham 2003). In this study a large number of participants were lost to follow-up. We performed sensitivity analyses for the outcomes of mortality (longest follow-up and hospital or 28 day mortality) excluding this study and assuming the possibility that all patients who were lost to follow-up died. The results were not sensitive to these analyses (Analysis 6.1; Analysis 6.2).

DISCUSSION

Summary of main results

The key finding of this review is that the perioperative administration of fluids, with or without vasoactive drugs, targeted to increase global blood flow defined by explicit measured goals reduced postoperative complications and length of stay but did not reduce mortality, using the inverse variance method. The exclusion of larger studies (> 100 participants) resulted in mortality being reduced by the intervention (RR 0.51, 95% CI 0.29 to 0.90, P = 0.02). Mortality was also significantly reduced when we used random-effects models (Mantel-Haenszel and inverse variance, RR 0.72, 95% CI 0.55 to 0.95, P = 0.02), but not fixed-effect models (Mantel-Haenszel RR 0.85, 95% CI 0.73 to 1.00, P = 0.05; inverse variance RR 0.89, 95% CI 0.76 to 1.05, P = 0.18; or Peto odds ratio 0.83, 95% CI 0.69 to 1.00, P = 0.05). We calculated similar results for hospital and 28 day mortality. When control group care was managed using a protocol that included explicit goals less than the intervention group (in contrast to 'usual care'), mortality was not reduced (longest follow-up inverse variance RR 0.94, 95% CI 0.79 to 1.12, P = 0.45; hospital or 28 day inverse variance RR 0.84, 95% CI 0.67 to 1.07, P = 0.14). When studies with intervention groups that were less well controlled for the intervention (for example pulmonary artery catheters were not matched to intervention groups) were excluded, there was a significant reduction in mortality at the longest follow-up (inverse variance RR 0.65, 95% CI 0.48 to 0.89, P = 0.007) and hospital or 28 day mortality (inverse variance RR 0.66, 95% CI 0.47 to 0.92, P = 0.01). It is notable that the sensitivity analyses are of limited value as they tend to reflect the inclusion or exclusion of the single largest study (Sandham 2003).

The limited data indicate that for every 100 patients exposed to treatment, one can expect 13 in 100 (from 40/100 to 27/100) to avoid a complication, 2/100 to avoid renal impairment (from 8/100 to 6/100), 5/100 to avoid respiratory failure (from 10/100 to 5/100), and 4/100 to avoid postoperative wound infection (from 10/100 to 6/100), with no effect on other types of morbidity (myocardial infarction, arrhythmia, congestive cardiac failure or pulmonary oedema, venous thrombosis, and the number of patients with infections). These results were unchanged following sensitivity analyses that excluded studies where the control group care was managed using a protocol that included explicit goals that were less than the intervention group (in contrast to 'usual care'). When studies using intervention groups that were less well controlled (control groups not matched to intervention groups) were excluded only the number of patients with complications was reduced, by 12/100 (from 36/100 to 24/10).

The hospital length of stay was reduced by about one day, from 12.4 to 11.2 days, and was not sensitive to exclusion of studies where the control group care was managed using a protocol that included explicit goals that were less than the intervention group (in contrast to 'usual care') or studies using intervention groups that were less well controlled. There was no difference in critical care stay in the intervention group. This was sensitive to exclusion of studies using intervention groups that were less well controlled and the reduction was less than a day (from 4 to 3.3 days). There were insufficient data to conduct a meta-analysis of cost and no data available describing quality of life.

A stratified meta-analysis to address secondary hypotheses, determined a priori, suggested that mortality was reduced in the intervention group when study participants underwent elective surgery.

The predefined analysis plan, using mortality from the longest available follow-up, increased the weight attributed to the two largest studies that both reported one-year follow-up. Only one other study reported follow-up beyond 60 days. In this group of studies a proportion of the operations were for cancer resection, therefore introducing a possible competing cause of mortality.

Overall completeness and applicability of evidence

Our systematic review pooled data from 31 studies with 5292 participants (Bender 1997; Berlauk 1991; Bonazzi 2002; Boyd 1993; Cecconi 2011; Challand 2012; Donati 2007: Conway 2002; Gan 2002; Jerez 2001; Jhanji 2010; Kapoor 2007; Lobo 2000; Mayer 2010; Mckendry 2004; Mythen 1995; Noblett 2006; Pearse 2005; Pillai 2011; Pölönen 2000; Sandham 2003; Senagore 2009; Shoemaker 1988; Sinclair 1997; Ueno 1998; Valentine 1998; Van der Linden 2010; Venn 2002; Wakeling 2005; Wilson 1999; Ziegler 1997). Study inclusion criteria were tightly defined and the meta-analysis was rigorously conducted according to a predefined analysis plan addressing specific hypotheses. The meta-analysis combined data from a group of predominantly underpowered single centre studies. However, the included studies reflect international practice, although the majority of included studies are from major teaching centres. The pooled studies included adults (age > 16 years) undergoing several types of surgery, including abdominal, urology, gynaecology, orthopaedic, cardiac, thoracic and vascular. Therefore, the included studies represent the population for whom the intervention might be considered.

Quality of the evidence

The quality of outcome data reporting in the included studies was variable. Mortality was reported over a variety of time frames and other outcomes were either limited or inconsistent between studies, precluding meaningful analyses in many cases. Diverse criteria and descriptions for morbidities, along with infrequent use of validated metrics, limited the precision of treatment effect estimates and the confidence that can be attached to them. Furthermore, pooling of different types of morbidity was inconsistent, limiting assessment of the overall 'morbidity load'.

Most studies tested a complex package of care (for example fluids, inotropes, monitor, goals, critical care environment) rather than a single clearly-defined intervention. Heterogeneity in the components of such a complex intervention may contribute to study heterogeneity within a systematic review. Study heterogeneity may reduce the precision of treatment effect estimates and reduce the generalizability of the results of meta-analyses (Louis 1991). By definition, it is not easy to define precisely the 'active ingredients' of a complex intervention (MRC 2000). However, hypothesis-generating subgroup analyses indicated that there were insufficient data to distinguish statistically between many of the prespecified subgroups, and highlighted the limited quantity of data in some areas for example emergency surgery.

Several possible sources of bias arose in this meta-analysis. The primary analysis was sensitive to the analytical methods used, the exclusion of larger studies, and the exclusion of studies that inadequately controlled for the intervention. Larger studies are less

likely to be affected by bias (Kjaergard 2001) and the inclusion of lower quality studies can alter the interpretation of the benefit of interventions in meta-analysis (Moher 1998).

Statistical heterogeneity was generally absent (I^2 less than 40%). Except for some analyses such as hospital length of stay, there was evidence of significant statistical heterogeneity. We used random-effects models in all cases where I^2 exceeded 40%. In all analyses of mortality, the point estimate of effect was less than 0.90, suggesting that the intervention was probably not harmful.

The sensitivity of our results to the methods of analysis indicates that the results of this study are far from clear-cut. Further research is essential in this area both to address the overall objective of this review and to focus on specific questions.

The studies included in this review are typical of studies in critical care research in general in that the majority of studies are underpowered and from single centres (Langham 2002) and about half the studies are small (< 100 participants). Future studies in this area should test an explicitly framed hypothesis, be adequately powered, methodologically rigorously and blinded (where possible). Reporting of outcomes should be standardized (to allow comparison between studies and to facilitate the conduct of future meta-analyses) and inclusive (morbidity, health status, resource usage).

Potential biases in the review process

The possibility of publication bias cannot be excluded. We found no evidence of this from contact with experts and industry but some of the identified published abstracts have yet to be published as full peer-reviewed papers. Harbord's regression test was significant at P = 0.03, suggesting small study effects. Language bias is possible because of the electronic databases and conferences we searched. Flaws in the original study designs are a significant potential source of bias. The meta-analysis includes 5292 participants but the unit of analysis is the study (or study subgroup) and the sample size (31 studies) is relatively small. The results of the subgroup analyses should be considered as hypothesis-generating only and are largely influenced by inclusion or exclusion of a single study (Sandham 2003).

Agreements and disagreements with other studies or reviews

This review represents the best up-to-date summary of the literature. We framed a tightly defined question and used explicit inclusion criteria for studies and a predefined analysis plan. Our primary result does not agree with previous reviews (Boyd 1999; Brienza 2009; Giglio 2009; Hamilton 2011; Heyland 1996; Ivanov 1997 Kern 2002; Poeze 2005), which have been uniformly supportive of this intervention. This may be explained by the precision of the question we addressed (for example other reviews included trauma patients not having surgery) and the analytical methods used. The results of our systematic review do, however, agree with the results of the largest study in this area (Sandham 2003). However, it is of concern that the Sandham study dominates the review primary analysis both in terms of number of patients (1994/5292) and weight (67%), and that the Sandham study was one of the studies where the intervention group was less well controlled (control groups not matched to intervention groups).

Research should focus on answering these questions. Sandham et al showed that a large multicentre study can be conducted in this area and several such studies are currently ongoing, in particular a large multicentre study anticipated to recruit about 700 participants (Pearse 2009). Future research will hopefully disentangle the complex package of care that forms the intervention (for example fluids, inotropes or vasoactive agents, monitor, goals, critical care environment) and thereby identify which components are effective in different clinical contexts.

AUTHORS' CONCLUSIONS

Implications for practice

Clinicians should base their decision whether to manipulate perioperative global blood flow on the magnitude of reductions in postoperative morbidities and length of hospital stay rather than upon the assumption that mortality will be reduced. For every 100 patients exposed to the intervention one can expect 13/100 to avoid having complications (from 40 to 27 per 100); 2/100 to avoid renal impairment (from 8 to 6 per 100); 5/100 to avoid respiratory failure (from 10 to 5 per 100); and 4/100 to avoid postoperative wound infection (from 10 to 6 per 100). Patients remain in hospital about one day less and there is no increase in harm. This intervention should be considered where the relevant resources are available and implementation will not otherwise harm the patient (for example delay in definitive care).

Implications for research

A specific limitation of this review is the large number of studies that were published more than 10 years and the limited amount of data that represent current practice and outcomes. A specific group that particularly merits further study, in view of the high incidence of mortality and morbidity and limited available data, is patients undergoing emergency surgery.

Future studies in this area should test an explicitly framed hypothesis, be adequately powered (and preferably multicentre), methodologically rigorous, and include blinded interventions where possible. Reporting of outcomes should be standardized (to allow comparison between studies and to facilitate the conduct of future meta-analyses) and inclusive (morbidity, health status, resource usage).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bender 1997

Methods	RCT Single centre
Participants	104 patients Elective surgery Vascular surgery
Interventions	Two groups Preoperative

Bender 1997 *(Continued)*

	Fluids and Inotropes
	Pulmonary artery catheter
	Goals = CI
Outcomes	Hospital mortality
	Hospistal length of stay (HLOS)
	ICU length of stay (ICULOS)
	Cost
	Pulmonary oedema
	Acute myocardial infarction
	Arrhythmia
	Acute renal failure
	Wound infection
	Haemorrhage
	Sepsis
	Graft thrombosis or infection
	Groin haematoma
Notes	Number of arrhythmia episodes were reported in both intra and postoperative periods, but not clear it occurred in same patients or different patients. Number of patients with complications only reported in postoperative period.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Patients were "assigned randomly to one of two groups by the surgical intensivist"
Allocation concealment (selection bias)	Unclear risk	Method of concealment is not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not detailed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not detailed
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data are reported
Selective reporting (reporting bias)	Low risk	Published report included main outcome measures

Bender 1997 *(Continued)*

Other bias	Low risk	No other specific bias identified

Berlauk 1991

Methods	RCT Single centre
Participants	89 patients Elective surgery Vascular surgery
Interventions	3 groups Preoperative Fluids and inotropes Pulmonary artery catheter Goals = CI
Outcomes	Hospital mortality HLOS ICULOS Cost Acute renal failure Congestive cardiac failure Graft thrombosis Acute myocardial infarction Arrhythmia
Notes	3 Groups, where group-1 had PA catheter driven protocol initiated in surgical intensive care unit (SICU) 12 hours before surgery, group-2 had PA catheter driven protocol initiated 3 hours before surgery and group-3 control group without protocol. Arrhythmia episodes were reported, not clear of denominator. The analysis is combined for groups 1 and 2.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization for all study groups was generated by a random number generator (Statworks)"
Allocation concealment (selection bias)	Unclear risk	Method of concealment is not described
Blinding of participants and personnel (performance bias)	Unclear risk	Not detailed

Berlauk 1991 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not detailed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Report included all expected outcomes
Other bias	Unclear risk	Two patients were excluded from group 1 due to not having surgery. This may have induced selection bias.

Bonazzi 2002

Methods	RCT Single centre
Participants	100 patients Elective surgery Vascular surgery
Interventions	2 groups Preoperative Fluids and inotropes Pulmonary artery catheter Goals = CI, DO_2I
Outcomes	Hospital mortality HLOS Arrythmias Myocardial infarction Congestive heart failure Renal failure
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer generated random number was obtained by phone call to the statistical centre of the hospital"

Bonazzi 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment is not presented
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not detailed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not detailed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Published report included all expected outcomes
Other bias	Low risk	No other sources of bias identified

Boyd 1993

Methods	RCT Single centre
Participants	107 patients 2 groups Elective and emergency surgery General surgery Vascular surgery
Interventions	Preoperative and postoperative Fluids and inotropes Pulmonary artery catheter Goals = DO_2I
Outcomes	28 day mortality HLOS ICULOS (Cost reported separately) Respiratory failure, acute renal failure, sepsis, cardiorespiratory arrest, pulmonary oedema, pleural fluid, wound infection, disseminated intravascular coagulation, acute myocardial infarction, abdominal abscess, haemorrhage, gastric outlet obstruction, cerebrovascular accident, pulmonary embolism, chest infection, psychosis, distal ischaemias

Boyd 1993 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly allocated to a protocol or control limb of the study". No information provided regarding random sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not presented in the paper
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Neither the anaesthesiologist nor the surgeon was aware of a patient's allocation". However its not clear if the investigators were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not sure, see quote above
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All anticipated outcomes were reported
Other bias	Unclear risk	The study was funded by a pharmaceutical company

Cecconi 2011

Methods	RCT Single centre
Participants	2 groups 40 patients Elective Total hip arthroplasty under regional anaesthesia
Interventions	Intraoperative Fluids and inotropes FloTrac sensor/Vigileo Goal = SV, DO_2I
Outcomes	Mortality Complications Renal failure

Cecconi 2011 *(Continued)*

	Arrhythmias
	Infections
	Anaemia
	Pulmonary embolism
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomized with concealed envelope technique"
Allocation concealment (selection bias)	Low risk	Concealed envelope technique
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients enrolled and the clinical teams caring for the patients were blinded"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not detailed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All anticipated outcomes were reported
Other bias	Low risk	No other bias identified

Challand 2012

Methods	RCT
	Single centre
Participants	2 Groups
	179 patients
	Elective
	Major colorectal surgery
Interventions	Intraoperative
	Fluids
	Oesophageal doppler

Challand 2012 *(Continued)*

	Goal = SV
Outcomes	Surgical readiness for discharge Total postop days flatus passed, bowel movement, tolerance of food Any deviation from postoperative course Serious postop complications Critical care admission Readmission <30 days Mortality
Notes	Patients were initially screened with CPET and was classified into two groups (aerobically fit and unfit as defined by anaerobic threshold) with subsequent randomization into control and intervention arms.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization by "random block allocation using sequentially numbered opaque sealed envelopes"
Allocation concealment (selection bias)	Low risk	As per quote above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Group allocation, ODM readings and algorithm -guided colloid administration were concealed from other staff in the operating theatre by screens"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The investigator had no involvement in perioperative decision-making or postoperative care"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All anticipated outcomes were reported
Other bias	Low risk	No other sources of bias identified

Conway 2002

Methods	RCT 2 centres
Participants	2 groups 57 patients

Conway 2002 *(Continued)*

	Elective surgery
	General surgery
Interventions	Intraoperative
	Fluids
	Oesophageal Doppler
	Goals = SV, FTc
Outcomes	Hospital mortality
	HLOS
	ICULOS
	Tolerating food
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Prior to induction of anaesthesia, patients were individually randomized into doppler or control" . Although the study was randomized, the method of random sequence generation was not presented
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned in the paper
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Medical and nursing staff were unaware of randomization"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See quote above, blinding of outcome assessment was not explained
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Published report included all expected outcomes
Other bias	Low risk	No other source of bias identified

Donati 2007

Methods	RCT
	Multicentre study
Participants	135 patients

Donati 2007 *(Continued)*

	Elective abdominal surgery
Interventions	Intraoperative Fluids and inotropes Goals = Oxygen extraction (0_2ER)
Outcomes	New postoperative organ failure Number of organ failures during ICU stay ICULOS HLOS Hospital mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was based on a permuted- block algorithm"
Allocation concealment (selection bias)	Low risk	"Patients were randomized to one of the two groups of treatment by a telephone system"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not explained
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not explained
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	All anticipated outcomes were reported
Other bias	Unclear risk	No other sources of bias identified

Gan 2002

Methods	RCT Single centre
Participants	100 patients Elective surgery

Gan 2002 *(Continued)*

	General surgery
Interventions	Intraoperative Fluids Oesophageal Doppler Goals = SV, FTc
Outcomes	Hospital mortality HLOS Cost renal dysfunction, respiratory support for >24 hours, cardiovascular (hypotension, pulmonary oedema, arrhythmia), chest infection, severe PONV requiring rescue antiemetics, coagulopathy, wound infection, food tolerance
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The patients were randomized into either protocol or control group using a random number generator in sealed envelopes"
Allocation concealment (selection bias)	Low risk	"See quote above"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"While the data were collected by independent dedicated research personnel not involved in the intra-operative management of patients, we were unable to blind the anaesthesiologists as to the treatment group"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See quote above
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	The anticipated outcomes were published
Other bias	Low risk	The study appears free from other sources of bias

Jerez 2001

Methods	RCT Single centre
Participants	390 patients

Jerez 2001 *(Continued)*

	Elective surgery
	Cardiac surgery
Interventions	Postoperative
	Fluids and Inotropes
	Pulmonary artery catheter
	Goals = SVO_2, CI
Outcomes	Hospital mortality
	Organ failures
Notes	Published in Spanish

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Se trata de un estudio prospectivo, intervencional, aleatorizado y controlado" "This is a prospective, interventional, randomized controlled study". However the method of sequence generation was not mentioned
Allocation concealment (selection bias)	Unclear risk	See quote above
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not detailed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not detailed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Published report include all expected outcomes
Other bias	Low risk	The study seems free from other sources of bias

Jhanji 2010

Methods	RCT
	Single centre
Participants	135 patients (3 arms)
	45 patients in each arm
	Elective

Jhanji 2010 *(Continued)*

	Gastrointestinal surgery
Interventions	Postoperative 3 arms to the study (arm-1 CVP group fluid optimisation according to CVP, arm-2 SV fluid optimization according to SV, third arm had fluids and continuous dopexamine infusion) LidCO Goals = SV
Outcomes	Microvascular flow and oxygenation Complications Infections Acute kidney injury Cardiac complications Critical care free days HLOS Hospital mortality
Notes	The 3rd arm with continuous dopexamine infusion is not included in the analysis as the control group was not matched

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were randomly allocated to one of three treatment groups by computer-generated random sequence in blocks of nine"
Allocation concealment (selection bias)	Low risk	"The study group allocations were placed in serially numbered opaque envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Only the member of the research team who delivered the intervention was aware of the study group allocation"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Clinical outcomes data for each patient were collected by a member of the research team who was unaware of study group allocation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Published report includes all expected outcomes
Other bias	Unclear risk	Study was supported by pharmaceutical company

Kapoor 2007

Methods	RCT Single centre
Participants	30 patients 2 groups Coronary artery bypass surgery
Interventions	Postoperative Fluids and Inotropes FloTrac Goals = CI, SVV
Outcomes	Hospital mortality HLOS ICULOS Duration of ventilation Duration of inotropic days Arrhythmia Renal failure
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were divided randomly into two groups, namely control and EGDT groups, by sealed envelope technique"
Allocation concealment (selection bias)	Low risk	See quote above
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not detailed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not detailed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Report included all expected outcomes

Kapoor 2007 *(Continued)*

Other bias	Unclear risk	Three patients excluded after allocation. There is a possibility of selection bias

Lobo 2000

Methods	RCT Single centre
Participants	37 patients 2 groups Elective surgery General surgery Vascular surgery
Interventions	Intra and postoperative Fluids and inotropes Pulmonary artery catheter Goals = DO_2I
Outcomes	28 day and 60 day mortality HLOS ICULOS Sepsis, shock, septic shock, cardiogenic shock, nosocomial infection, acute pancreatitis, postoperative fistula, arrhythmia, cerebrovascular accident, deep vein thrombosis, gastrointestinal bleeding, hypothermia, sepsis-related organ failure assessment (SOFA) score, bronchopneumonia, urinary tract infection, wound infection. ventilator days, organ dysfunction
Notes	Both groups had PAC and protocol group aimed to achieve supranormal DO_2I

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomized at the preoperative stage by means of sealed opaque envelopes"
Allocation concealment (selection bias)	Low risk	See quote above
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not detailed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not detailed

Lobo 2000 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Published report included all expected outcomes
Other bias	Low risk	No other potential source of bias identified

Mayer 2010

Methods	RCT Single centre
Participants	60 patients 2 groups Elective surgery Major abdominal surgery
Interventions	Intraoperative Fluid and Inotropes FloTrac/Vigileo Goal = CI, SV (SVI,SVV)
Outcomes	HLOS Complications ICULOS Mortality
Notes	The second author for this study is currently under investigation for research misconduct in relation to published studies of fluid therapy.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomized preoperatively either into a standard protocol group or an enhanced goal directed haemodynamic monitoring group using a closed envelope system"
Allocation concealment (selection bias)	Low risk	See quote above
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Both groups were managed by the same physicians on the same wards who were not involved in the intraoperative management, data collection or group allocation of the study"

Mayer 2010 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All data collected by a study nurse blinded to the study design and group allocation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missed outcome data
Selective reporting (reporting bias)	Low risk	All anticipated outcomes are reported
Other bias	High risk	The second author for this study is currently under investigation for research misconduct in relation to published studies of fluid therapy.

Mckendry 2004

Methods	RCT Single centre
Participants	174 patients Elective surgery Emergency surgery Cardiac surgery
Interventions	Postoperative Fluids and inotropes Oesophageal Doppler Goals = SVI
Outcomes	Hospital mortality HLOS ICULOS Atrial fibrillation requiring treatment, pneumothorax, Cerebrovascular accident, chest infection or sternal wound infection, GI bleed, acute renal failure, pleural effusion, infected leg wound, aortic regurgitation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomized by a priori computer generated sequence"
Allocation concealment (selection bias)	Low risk	"The study nurse opened the serially numbered, sealed opaque envelopes on arrival of patients"

Mckendry 2004 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Both patients and staff on the general wards to which patients were sent after discharge from intensive care were unaware of the group assignment"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not detailed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Published report includes all expected outcomes
Other bias	Unclear risk	Possibility of selection bias as 4 patients were excluded after allocation

Mythen 1995

Methods	RCT Single centre
Participants	60 patients 2 groups Elective surgery Cardiac surgery
Interventions	Intraoperative Fluids Oesophageal Doppler Goals = SV
Outcomes	Hospital mortality HLOS ICULOS (cost reported separately) Knaus organ failure criteria, chest infection, pleural effusion, disorientation, respiratory failure, nausea and vomiting, cerebrovascular accident, paralytic ileus, pericardial effusion.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Mythen 1995 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"Patients were randomized according to the contents of a sealed envelope to either a control group or a protocol group"
Allocation concealment (selection bias)	Low risk	See quote above
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not detailed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not detailed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All anticipated outcomes are reported
Other bias	Unclear risk	The study was funded by a pharmaceutical company

Noblett 2006

Methods	RCT Single centre
Participants	103 patients 2 groups Elective surgery General surgery
Interventions	Intraoperative Fluids Goals = SV, FTc
Outcomes	Hospital mortality HLOS ICULOS Surgical fitness for discharge, return of gastrointestinal function, flatus, bowel movement, food tolerance, readmission rate, cytokine markers of the systemic inflammatory response
Notes	
Risk of bias	

Noblett 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Double blind randomized controlled trial"; the method of randomization not mentioned
Allocation concealment (selection bias)	Unclear risk	See above quote, the method of allocation concealment not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Doppler probe insertion and monitoring, and trial fluid administration were carried out by a medically qualified researcher who had no involvement in postoperative patient care or decision making"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See quote above
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	All outcomes data were presented
Other bias	Unclear risk	Five patients excluded after allocation may have induced selection bias

Pearse 2005

Methods	RCT
	Single centre
Participants	122 patients
	Elective surgery
	Emergency surgery
	Vascular surgery
	General surgery
	Urology surgery
Interventions	Postoperative
	Fluids and inotropes
	LidCO
	Goals = DO_2I
Outcomes	Hospital, 28 and 60 day mortality
	HLOS
	ICULOS

Pearse 2005 *(Continued)*

	Number of patients with complications, infection (pneumonia, abdominal, urinary tract, CVC, wound), respiratory (pleural effusion, pneumothorax, pulmonary embolism, ARDS), cardiovascular (arrhythmia, pulmonary oedema, MI, stroke), abdominal (*C. diff*, diarrhoea, acute bowl obstruction, upper GI bleed, paralytic ileus, anastomotic leak, intra-abdominal hypertension), postoperative massive haemorrhage
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were assigned to GDT or control groups by computer-generated random sequence"
Allocation concealment (selection bias)	Low risk	"Study group assignments were placed in serially numbered opaque envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"These treatments were administered by a member of the research team who was the only individual aware of study group allocation"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	All potential outcomes data were presented
Other bias	Low risk	No other sources of bias

Pillai 2011

Methods	Randomized controlled study
Participants	66 patients Patients undergoing radical cystectomy
Interventions	2 groups Oesophageal Doppler Goal = SV, FTc
Outcomes	Length of hospital stay ICU admission Wound dehiscence wound infection GI function (ileus, time to flatus, bowel opening)

Pillai 2011 *(Continued)*

	Postop nausea and vomiting
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"All patients were randomized into a control arm, which received standard intraoperative fluids at the discretion of the consultant anaesthetist, and an intervention arm which received additional fluid from a researcher via a oesophageal doppler determined protocol" . However the method of random sequence was not mentioned
Allocation concealment (selection bias)	Unclear risk	See above quote, allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Anaesthetic and surgical teams were blinded to the randomization"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment was not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	All potential outcomes data were presented
Other bias	Low risk	No other sources of bias

Pölönen 2000

Methods	RCT Single centre
Participants	393 patients 2 groups Elective surgery Cardiac surgery
Interventions	Postoperative Fluids and Inotropes Pulmonary artery catheter Goals = SVO_2, lactate
Outcomes	28 day, 6 month and 12 month mortality

Pölönen 2000 *(Continued)*

	HLOS ICULOS Organ dysfunctions: central nervous system (haemiplegia, stroke, Glasgow coma scale (GCS <10), circulatory (vasoactive medication or intraaortic counterpulsation to treat hypotension or low cardiac output), respiratory (need for mechanical or assisted ventilation), renal (low urine output or increased creatinine), hepatic (increased liver enzymes or bilirubin), gastrointestinal (macroscopic bleeding or paralytic ileus), haematological (low white cell or platelet count) ICU readmission
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomized the day before surgery by sealed envelope technique"
Allocation concealment (selection bias)	Low risk	See quote above
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Although study was randomized, it was not blinded and the data of the oxygen transport measurements of both groups were open to those taking care of patients during the study period"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See quote above
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Published report included all expected outcomes
Other bias	Unclear risk	10 patients were excluded after allocation may have induced selection bias

Sandham 2003

Methods	RCT Multicentre
Participants	1994 patients Elective surgery Emergency surgery General surgery Thoracic surgery Vascular surgery

Sandham 2003 *(Continued)*

	Hip fracture surgery
Interventions	Preoperative Fluids and inotropes Pulmonary artery catheter Goals = DO_2I, CI
Outcomes	Hospital, 6 month and 12 month mortality HLOS Myocardial infarction, congestive heart failure, supraventricular tachycardia, pulmonary embolism, renal insufficiency, hepatic insufficiency, sepsis from central venous catheter (CVC) or pulmonary artery catheter (PAC), wound infection, pneumonia, adverse events related to PAC or CVC: pulmonary infarction, haemothorax, pulmonary haemorrhage, pneumothorax, arterial puncture
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was carried out by computer-generated sequence, stratified according to type of surgery and according to ASA class and blocked according to centre"
Allocation concealment (selection bias)	Low risk	"Assignments were concealed in opaque sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not blinded as it was not feasible
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss of patients follow-up at 6 months in both groups
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Unclear risk	Supported by a healthcare company

Senagore 2009

Methods	RCT Single centre
Participants	64 patients

Senagore 2009 *(Continued)*

	3 arms study
	Elective
	Laparoscopic colectomy
Interventions	Intraoperative
	Fluids
	Oesophageal doppler
	Goals = SV increase 10%
Outcomes	Hospital Mortality
	HLOS
	Arrhythmia
	infections
Notes	This is a 3-arm study with a control group in the first arm and goal directed groups in arms 2 and 3, where patients received lactated Ringer's solution and 6% HES

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed after EDM insertion via a established random number table"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not presented
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"A separate anaesthesia team monitored the EDM readings and administered boluses, whereas the clinical anaesthesia was blinded to this process"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See quote above
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	No other sources of bias identified

Shoemaker 1988

Methods	RCT
	Single centre

Shoemaker 1988 *(Continued)*

Participants	88 patients Elective surgery Emergency surgery General surgery
Interventions	Preoperative Fluids and inotropes Pulmonary artery catheter Goals = CI, DO_2I
Outcomes	Hospital mortality HLOS ICULOS Cost Respiratory failure, renal failure, sepsis and septic shock, hepatic failure, cardiac arrest, pulmonary oedema, pleural effusion, wound infection, disseminated intravascular coagulation (DIC), acute myocardial infarction, evisceration, abdominal abscess, haemorrhage, pancreatitis, gastric outlet obstruction, urinary tract infection, cerebral infarct, pulmonary embolism, ventilator days
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The remaining 88 patients were prospectively allocated to one of the three groups designated by cards arranged according to a random numbers table by an outside person and placed in opaque sealed envelopes"
Allocation concealment (selection bias)	Low risk	See quote above
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not detailed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not detailed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	All anticipated outcomes were reported
Other bias	Low risk	No other sources of bias identified

Sinclair 1997

Methods	RCT Single centre
Participants	40 patients Emergency surgery Hip fracture surgery
Interventions	Intraoperative Fluids oesophageal Doppler Goals = SV
Outcomes	Hospital mortality HLOS None, "time declared fit for medical discharge"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"After consent had been obtained, the patients were individually randomized before induction of anaesthesia by a sealed envelope technique to either protocol or control groups"
Allocation concealment (selection bias)	Low risk	See quote above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The anaesthetist was blinded to the doppler measurements but was aware of the fluid volumes given as fluid challenges to the protocol group" " postoperative management was carried out on the orthopaedic ward with both medical and nursing staff blinded to the randomization"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not detailed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	No other sources of bias identified

Ueno 1998

Methods	RCT Single centre
Participants	34 patients Elective surgery Liver surgery
Interventions	Postoperative Fluids and inotropes Pulmonary artery catheter Goals = CI, DO_2I, VO_2I
Outcomes	Hospital mortality Bleeding, peritoneal infection, adult respiratory distress syndrome, hyperbilirubinaemia, liver failure.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The patients were randomly assigned to either group N or group S by the stratified block randomization method"
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not detailed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"All measurements were obtained and recorded by one of the authors"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	All anticipated outcomes were reported
Other bias	Low risk	No other sources of bias identified

Valentine 1998

Methods	RCT Single centre

Valentine 1998 *(Continued)*

Participants	120 patients Elective surgery Vascular surgery
Interventions	Preoperative Fluids and inotropes Pulmonary artery catheter Goals = CI
Outcomes	Hospital mortality HLOS ICULS Myocardial infarction, arrhythmia, congestive heart failure, pneumonia, non-cardiogenic pulmonary insufficiency, acute renal insufficiency, catheter sepsis. ventilator days
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomized into two groups by means of a sealed envelope"
Allocation concealment (selection bias)	Low risk	See quote above
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not detailed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not detailed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	All expected outcomes were published
Other bias	Low risk	No other sources of bias identified

Van der Linden 2010

Methods	RCT

Van der Linden 2010 *(Continued)*

	Single centre
Participants	37 patients 3-arm study High risk (ASA II-III) Peripheral artery bypass grafting
Interventions	Intraoperative Fluids and Inotropes (dobutamine) FloTrac Vigileo monitor Goal = CI
Outcomes	Mortality HLOS Complications (infections)
Notes	The study comprised of 3 groups. Group 1: controls, Group 2: goal directed therapy and Group 3: goal directed therapy with different anaesthetic compared to group 1 and 2. As Group 3 was not matched with controls this was not included in the analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned to three groups using computer generated random code"
Allocation concealment (selection bias)	Low risk	"The assignment was concealed in an envelope"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The attending anaesthesiologist was blinded for the data displayed by the Vigileo monitor. Cardiac index data in these patients were recorded by an independent observer who was not involved in the patients treatment"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data were analysed blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	No other potential sources of bias identified

Venn 2002

Methods	RCT Single centre
Participants	90 patients Emergency surgery Hip fracture surgery
Interventions	Intraoperative Fluids Oesophageal Doppler Goals = SV
Outcomes	Hospital mortality HLOS Time to medical fitness for discharge, deep haemorrhage requiring >2 unit blood transfusion, haematemesis, chest infection, wound infection, cellulitis, pancreatitis, pulmonary embolus, cerebrovascular accident, myocardial infarction, cardiac failure, rapid atrial fibrillation, hypotension, impaired renal function, pseudo-obstruction
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were individually randomized into 3 groups, through the use of a set of computer generated random numbers and an opaque sealed envelope technique"
Allocation concealment (selection bias)	Low risk	See above quote
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The anaesthetist was unaware of the central venous pressure or oesophageal doppler ultrasonography measurements" "Post operative management was performed by the orthopaedic medical team and nursing staff who were all unaware of the patient's randomization"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See above quote
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	All expected outcomes were presented
Other bias	Low risk	No other potential sources of bias identified

Wakeling 2005

Methods	RCT Single centre
Participants	134 patients Elective surgery General surgery
Interventions	Intraoperative Fluids Oesophageal Doppler Goals = SV
Outcomes	Hospital and 6 month mortality HLOS Time until fit for discharge, bowel recovery (flatus, bowels opening, full diet), quality of recovery score, postoperative morbidity survey (POMS), quality of life questionnaires (European organisation for the research and treatment of cancer (EORTC) - QLQ-C30 and QLQ-CR38)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomized and allocated according to the sequentially numbered, sealed opaque envelope technique"
Allocation concealment (selection bias)	Low risk	See quote above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The surgical teams, nursing staff and patients themselves were blinded" "The anaesthetists was blinded to the oesophageal doppler measurements"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment was not explained
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	All anticipated outcomes were reported
Other bias	Unclear risk	Three patients in each group did not receive allocated intervention, this may have induced selection bias

Wilson 1999

Methods	RCT single centre
Participants	138 patients 3 groups Elective surgery General surgery Vascular surgery
Interventions	Preoperative Fluids and inotropes Pulmonary artery catheter Goals = DO_2I
Outcomes	Hospital mortality HLOS ICULOS (Costs reported separately) Respiratory (prolonged weaning, adult respiratory distress syndrome (ARDS), pleural effusion, secondary ventilation, sputum retention), cardiovascular (myocardial infarction, arrhythmia, cardiac arrest, pulmonary embolus, cerebrovascular accident, transient ischaemic attack, cardiac failure), gastrointestinal (infarction, haemorrhage), acute renal failure, coagulopathy, infection (bacteraemia, sepsis syndrome, septic shock, respiratory sepsis, urinary sepsis, abdominal sepsis, wound sepsis, line sepsis, other sepsis), surgical (anastomotic breakdown, deep haemorrhage, wound haemorrhage)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random sequence was generated from a Unix computer program"
Allocation concealment (selection bias)	Low risk	"Allocation was concealed until trial entry by sealed opaque envelope"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	" We were unable to effect true blinding between patients in the control and treatment groups"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See quote above
Incomplete outcome data (attrition bias)	Low risk	No missing data

Wilson 1999 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	All anticipated outcome data were reported
Other bias	Low risk	No other potential sources of bias

Ziegler 1997

Methods	RCT Single centre
Participants	72 patients Elective surgery Vascular surgery
Interventions	Preoperative Fluids and inotropes Pulmonary artery catheter Goals = SVO_2
Outcomes	Hospital mortality ICULOS Hypotension, congestive heart failure, myocardial infarction, arrhythmia, oliguria, graft thrombosis, cerebrovascular accident.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence was not presented
Allocation concealment (selection bias)	Unclear risk	This was not presented
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not detailed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not detailed
Incomplete outcome data (attrition bias)	Low risk	No missing data

Ziegler 1997 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	No other sources of bias identified

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alia 1999	Severe sepsis, septic shock
Balogh 2003	Trauma
Benes 2010	Patients not had surgery also included in the analysis
Bishop 1995	Trauma
Blow 1999	Trauma
Chang 2000	Trauma, not RCT
Chytra 2007	Trauma
Durham 1996	Established critical illness
Flancbaum 1998	Retrospective, not RCT
Fleming 1992	Trauma
Forget 2010	Pulse pressure variation is not a surrogate of global blood flow
Gattinoni 1995	Established critical illness
Gutierrez 1992	pHi guided
Hayes 1994	Established critical illness
Ivatury 1996	Trauma
Jammer 2010	Restricted goal directed fluid administration
Jorgensen 2009	Not RCT
Lobo 2006	Same flow goal in each group
Miller 1998	Trauma
Muller 1999	No explicit flow goal
Pargger 1998	pHi guided
Rivers 2001	Severe sepsis and septic shock

Study	Reason for exclusion
Scalea 1990	Trauma
Schilling 2004	Same flow goal in each group
Schultz 1985	No explicit flow goals
Stewart 2009	Retrospective study
Stone 2003	No explicit flow goals
Szakmany 2005	Intrathoracic blood volume goal
Takala 2000	No explicit flow goals
Tuchschmidt 1992	Septic shock
Velmahos 2000	Trauma
Wenkui 2010	Restricted fluid regimen
Yu 1993	Established critical illness
Yu 1995	Established critical illness
Yu 1998	Established critical illness

Characteristics of ongoing studies *[ordered by study ID]*

Pearse 2009

Trial name or title	Optimization of perioperative cardiovascular management to improve surgical outcome
Methods	Randomized controlled study
Participants	Adults undergoing major abdominal surgery
Interventions	
Outcomes	28 day mortality, postoperative complications, postoperative morbidity survey score, LOHS, critical care free days, cost
Starting date	2009
Contact information	ISRCTN04386758
Notes	Ongoing study

DATA AND ANALYSES

Comparison 1. Mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All studies (longest follow-up)	31	5292	Risk Ratio (IV, Fixed, 95% CI)	0.89 [0.76, 1.05]
2 All studies (hospital or 28 day)	31	5292	Risk Ratio (IV, Fixed, 95% CI)	0.81 [0.65, 1.00]
3 Participant numbers	31	5292	Risk Ratio (IV, Fixed, 95% CI)	0.89 [0.76, 1.05]
3.1 >100	16	4428	Risk Ratio (IV, Fixed, 95% CI)	0.94 [0.79, 1.12]
3.2 <100	15	864	Risk Ratio (IV, Fixed, 95% CI)	0.51 [0.29, 0.90]
4 Time intervention started	31		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
4.1 Pre-operative	9	2786	Risk Ratio (IV, Fixed, 95% CI)	0.96 [0.79, 1.17]
4.2 Intra-operative	15	1202	Risk Ratio (IV, Fixed, 95% CI)	0.67 [0.40, 1.13]
4.3 Post-operative	9	1341	Risk Ratio (IV, Fixed, 95% CI)	0.73 [0.50, 1.06]
5 Type of intervention	31		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
5.1 Fluids and Inotropes	21	4354	Risk Ratio (IV, Fixed, 95% CI)	0.90 [0.76, 1.07]
5.2 Fluids	11	983	Risk Ratio (IV, Fixed, 95% CI)	0.80 [0.46, 1.39]
6 Goals of intervention	31	5292	Risk Ratio (IV, Fixed, 95% CI)	0.89 [0.76, 1.05]
6.1 CO, DO2	14	3060	Risk Ratio (IV, Fixed, 95% CI)	0.91 [0.75, 1.09]
6.2 Lactate, SVO2, O2ER	4	990	Risk Ratio (IV, Fixed, 95% CI)	0.83 [0.50, 1.38]
6.3 SV	13	1242	Risk Ratio (IV, Fixed, 95% CI)	0.84 [0.51, 1.41]
7 Mode of surgery	31	5292	Risk Ratio (IV, Fixed, 95% CI)	0.89 [0.76, 1.05]
7.1 Elective	24	2677	Risk Ratio (IV, Fixed, 95% CI)	0.68 [0.48, 0.94]
7.2 Emergency	2	130	Risk Ratio (IV, Fixed, 95% CI)	0.68 [0.23, 2.06]
7.3 Elective and Emergency	5	2485	Risk Ratio (IV, Fixed, 95% CI)	0.99 [0.81, 1.20]
8 Type of surgery	27		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
8.1 Vascular	7	580	Risk Ratio (IV, Fixed, 95% CI)	0.78 [0.34, 1.79]
8.2 Cardiac	5	1047	Risk Ratio (IV, Fixed, 95% CI)	0.81 [0.48, 1.35]
8.3 General	16	1374	Risk Ratio (IV, Fixed, 95% CI)	0.66 [0.41, 1.07]

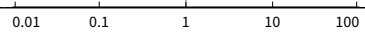
Analysis 1.1. Comparison 1 Mortality, Outcome 1 All studies (longest follow-up).

Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Bender 1997	1/51	1/53		0.36%	1.04[0.07,16.18]
Berlauk 1991	1/68	2/21		0.49%	0.15[0.01,1.62]
Bonazzi 2002	0/50	0/50			Not estimable
Boyd 1993	3/53	12/54		1.86%	0.25[0.08,0.85]
Cecconi 2011	0/20	0/20			Not estimable
Challand 2012	7/89	7/90		2.69%	1.01[0.37,2.76]
Conway 2002	0/29	1/28		0.27%	0.32[0.01,7.59]
Donati 2007	2/68	2/67		0.73%	0.99[0.14,6.79]
Gan 2002	0/50	0/50			Not estimable
Jerez 2001	16/181	21/209		7.09%	0.88[0.47,1.63]
Jhanji 2010	9/90	6/45		2.89%	0.75[0.28,1.98]
Kapoor 2007	0/15	0/15			Not estimable
Lobo 2000	3/19	9/18		2.1%	0.32[0.1,0.98]
Mayer 2010	2/30	2/30		0.76%	1[0.15,6.64]
Mckendry 2004	4/89	2/85		0.97%	1.91[0.36,10.16]
Mythen 1995	0/30	1/30		0.27%	0.33[0.01,7.87]
Noblett 2006	0/51	1/52		0.27%	0.34[0.01,8.15]
Pearse 2005	7/62	9/60		3.2%	0.75[0.3,1.89]
Pillai 2011	1/32	0/34		0.27%	3.18[0.13,75.38]
Pölönen 2000	4/196	9/197		2.02%	0.45[0.14,1.43]
Sandham 2003	163/997	155/997		66.85%	1.05[0.86,1.29]
Senagore 2009	1/42	0/22		0.27%	1.6[0.07,37.83]
Shoemaker 1988	1/28	18/60		0.71%	0.12[0.02,0.85]
Sinclair 1997	1/20	2/20		0.51%	0.5[0.05,5.08]
Ueno 1998	0/16	2/18		0.31%	0.22[0.01,4.34]
Valentine 1998	3/60	1/60		0.54%	3[0.32,28.03]
Van der Linden 2010	0/20	0/17			Not estimable
Venn 2002	3/30	8/60		1.73%	0.75[0.21,2.62]
Wakeling 2005	0/67	1/67		0.27%	0.33[0.01,8.04]
Wilson 1999	3/92	8/46		1.66%	0.19[0.05,0.67]
Ziegler 1997	3/32	2/40		0.91%	1.88[0.33,10.55]
Total (95% CI)	**2677**	**2615**		**100%**	**0.89[0.76,1.05]**
Total events: 238 (Protocol), 282 (Control)					
Heterogeneity: $Tau^2=0$; $Chi^2=29.55$, df=25(P=0.24); $I^2=15.41\%$					
Test for overall effect: Z=1.35(P=0.18)					

Analysis 1.2. Comparison 1 Mortality, Outcome 2 All studies (hospital or 28 day).

Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Bender 1997	1/51	1/53		0.61%	1.04[0.07,16.18]
Berlauk 1991	1/68	2/21		0.83%	0.15[0.01,1.62]
Bonazzi 2002	0/50	0/50			Not estimable
Boyd 1993	3/53	12/54		3.14%	0.25[0.08,0.85]

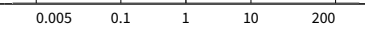
Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Cecconi 2011	0/20	0/20			Not estimable
Challand 2012	3/89	4/90		2.13%	0.76[0.17,3.29]
Conway 2002	0/29	1/28		0.46%	0.32[0.01,7.59]
Donati 2007	2/68	2/67		1.23%	0.99[0.14,6.79]
Gan 2002	0/50	0/50			Not estimable
Jerez 2001	16/181	21/209		11.95%	0.88[0.47,1.63]
Jhanji 2010	9/90	6/45		4.88%	0.75[0.28,1.98]
Kapoor 2007	0/15	0/15			Not estimable
Lobo 2000	3/19	6/18		3.04%	0.47[0.14,1.62]
Mayer 2010	2/30	2/30		1.28%	1[0.15,6.64]
Mckendry 2004	4/89	2/85		1.64%	1.91[0.36,10.16]
Mythen 1995	0/30	1/30		0.46%	0.33[0.01,7.87]
Noblett 2006	0/51	1/52		0.45%	0.34[0.01,8.15]
Pearse 2005	6/62	7/60		4.31%	0.83[0.3,2.33]
Pillai 2011	1/32	0/34		0.46%	3.18[0.13,75.38]
Pölönen 2000	2/196	6/197		1.82%	0.34[0.07,1.64]
Sandham 2003	78/997	77/997		50.12%	1.01[0.75,1.37]
Senagore 2009	1/42	0/22		0.46%	1.6[0.07,37.83]
Shoemaker 1988	1/28	18/60		1.19%	0.12[0.02,0.85]
Sinclair 1997	1/20	2/20		0.85%	0.5[0.05,5.08]
Ueno 1998	0/16	2/18		0.52%	0.22[0.01,4.34]
Valentine 1998	3/60	1/60		0.92%	3[0.32,28.03]
Van der Linden 2010	0/20	0/17			Not estimable
Venn 2002	3/30	8/60		2.92%	0.75[0.21,2.62]
Wakeling 2005	0/67	0/67			Not estimable
Wilson 1999	3/92	8/46		2.8%	0.19[0.05,0.67]
Ziegler 1997	3/32	2/40		1.53%	1.88[0.33,10.55]
Total (95% CI)	**2677**	**2615**		**100%**	**0.81[0.65,1]**
Total events: 146 (Protocol), 192 (Control)					
Heterogeneity: Tau^2=0; Chi^2=24.34, df=24(P=0.44); I^2=1.38%					
Test for overall effect: Z=1.92(P=0.06)					



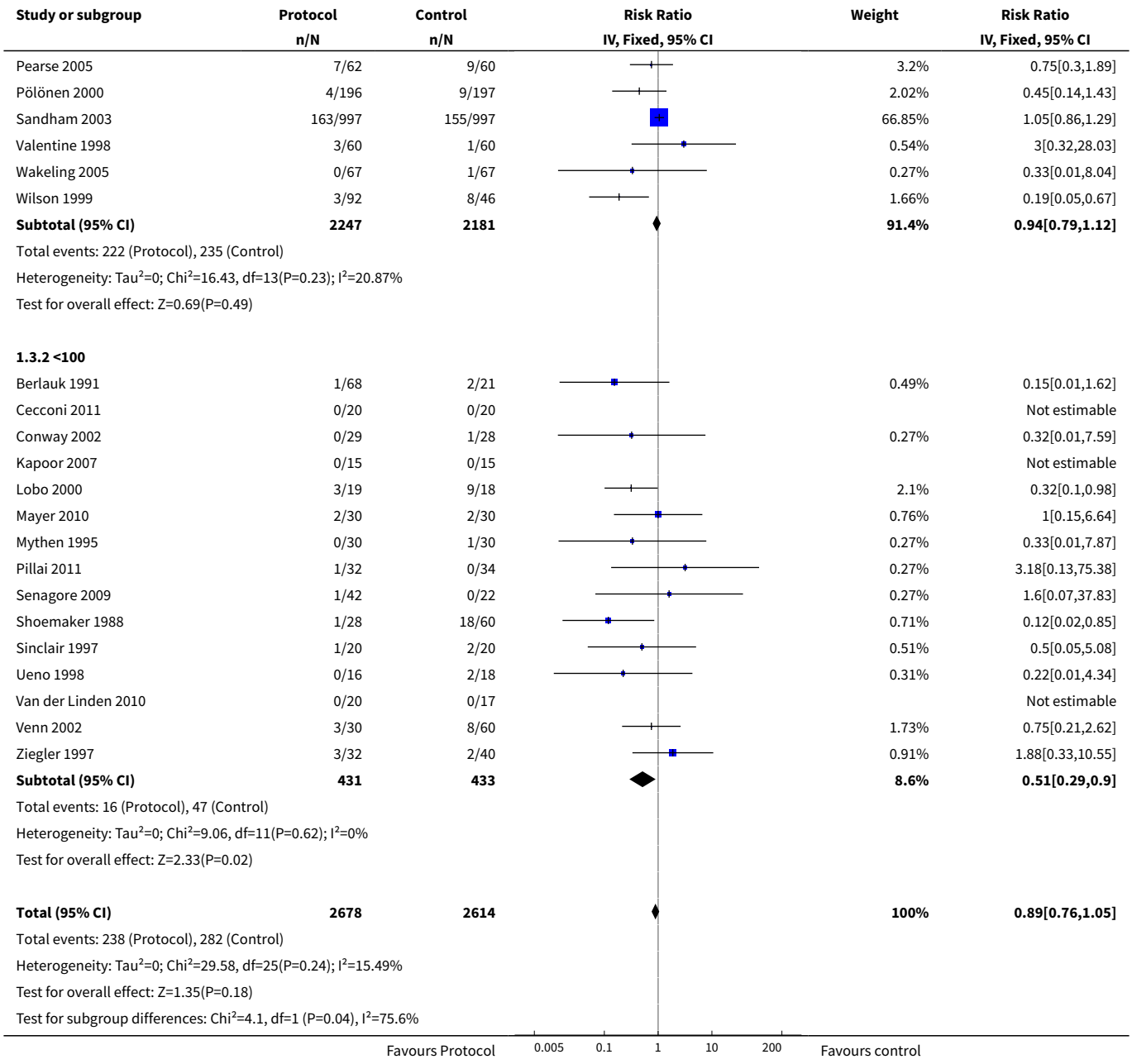
Favours Protocol — Favours control

Analysis 1.3. Comparison 1 Mortality, Outcome 3 Participant numbers.

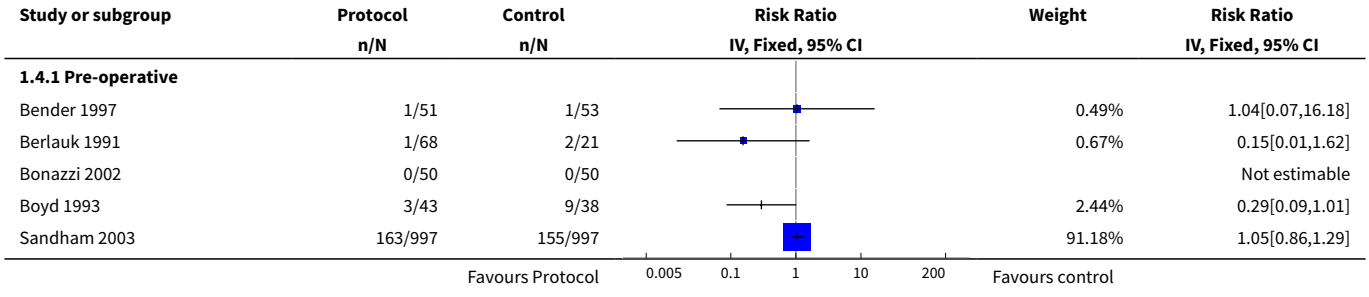
Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
1.3.1 >100					
Bender 1997	1/51	1/53		0.36%	1.04[0.07,16.18]
Bonazzi 2002	0/50	0/50			Not estimable
Boyd 1993	3/53	12/54		1.86%	0.25[0.08,0.85]
Challand 2012	7/89	7/90		2.69%	1.01[0.37,2.76]
Donati 2007	2/68	2/67		0.73%	0.99[0.14,6.79]
Gan 2002	0/50	0/50			Not estimable
Jerez 2001	16/181	21/209		7.09%	0.88[0.47,1.63]
Jhanji 2010	9/90	6/45		2.89%	0.75[0.28,1.98]
Mckendry 2004	4/89	2/85		0.97%	1.91[0.36,10.16]
Noblett 2006	0/52	1/51		0.27%	0.33[0.01,7.85]

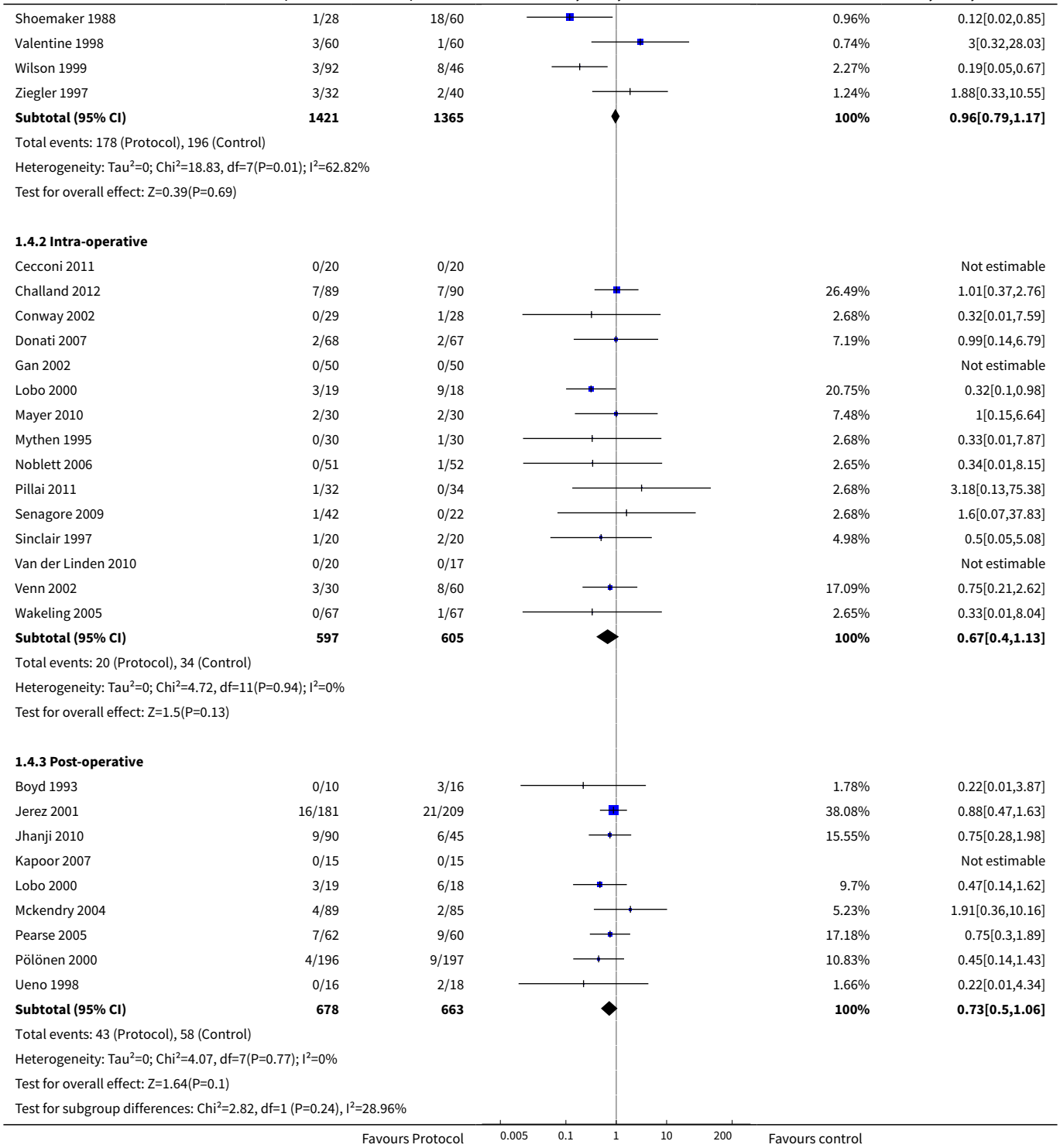


Favours Protocol — Favours control



Analysis 1.4. Comparison 1 Mortality, Outcome 4 Time intervention started.





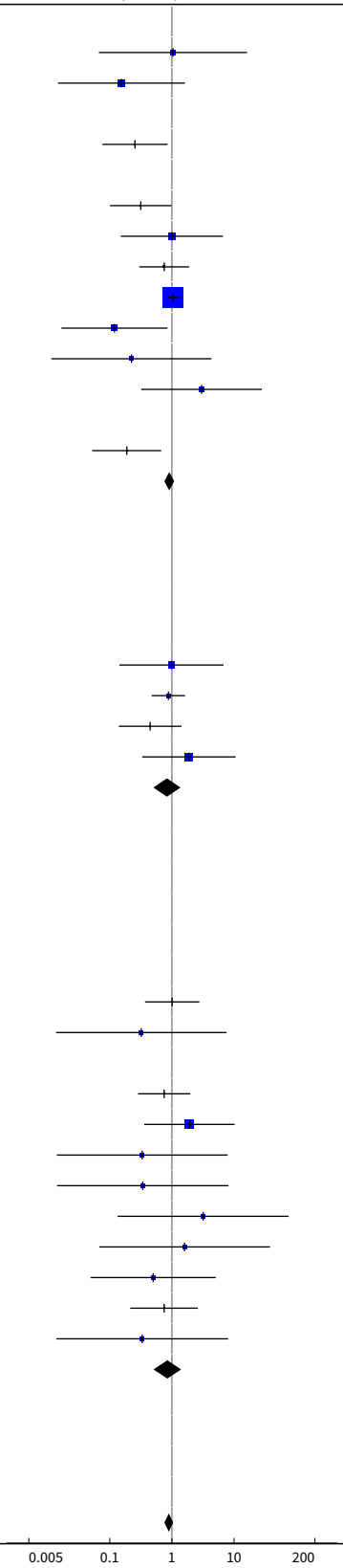
Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Shoemaker 1988	1/28	18/60		0.96%	0.12[0.02,0.85]
Valentine 1998	3/60	1/60		0.74%	3[0.32,28.03]
Wilson 1999	3/92	8/46		2.27%	0.19[0.05,0.67]
Ziegler 1997	3/32	2/40		1.24%	1.88[0.33,10.55]
Subtotal (95% CI)	**1421**	**1365**		**100%**	**0.96[0.79,1.17]**
Total events: 178 (Protocol), 196 (Control)					
Heterogeneity: Tau²=0; Chi²=18.83, df=7(P=0.01); I²=62.82%					
Test for overall effect: Z=0.39(P=0.69)					
1.4.2 Intra-operative					
Cecconi 2011	0/20	0/20			Not estimable
Challand 2012	7/89	7/90		26.49%	1.01[0.37,2.76]
Conway 2002	0/29	1/28		2.68%	0.32[0.01,7.59]
Donati 2007	2/68	2/67		7.19%	0.99[0.14,6.79]
Gan 2002	0/50	0/50			Not estimable
Lobo 2000	3/19	9/18		20.75%	0.32[0.1,0.98]
Mayer 2010	2/30	2/30		7.48%	1[0.15,6.64]
Mythen 1995	0/30	1/30		2.68%	0.33[0.01,7.87]
Noblett 2006	0/51	1/52		2.65%	0.34[0.01,8.15]
Pillai 2011	1/32	0/34		2.68%	3.18[0.13,75.38]
Senagore 2009	1/42	0/22		2.68%	1.6[0.07,37.83]
Sinclair 1997	1/20	2/20		4.98%	0.5[0.05,5.08]
Van der Linden 2010	0/20	0/17			Not estimable
Venn 2002	3/30	8/60		17.09%	0.75[0.21,2.62]
Wakeling 2005	0/67	1/67		2.65%	0.33[0.01,8.04]
Subtotal (95% CI)	**597**	**605**		**100%**	**0.67[0.4,1.13]**
Total events: 20 (Protocol), 34 (Control)					
Heterogeneity: Tau²=0; Chi²=4.72, df=11(P=0.94); I²=0%					
Test for overall effect: Z=1.5(P=0.13)					
1.4.3 Post-operative					
Boyd 1993	0/10	3/16		1.78%	0.22[0.01,3.87]
Jerez 2001	16/181	21/209		38.08%	0.88[0.47,1.63]
Jhanji 2010	9/90	6/45		15.55%	0.75[0.28,1.98]
Kapoor 2007	0/15	0/15			Not estimable
Lobo 2000	3/19	6/18		9.7%	0.47[0.14,1.62]
Mckendry 2004	4/89	2/85		5.23%	1.91[0.36,10.16]
Pearse 2005	7/62	9/60		17.18%	0.75[0.3,1.89]
Pölönen 2000	4/196	9/197		10.83%	0.45[0.14,1.43]
Ueno 1998	0/16	2/18		1.66%	0.22[0.01,4.34]
Subtotal (95% CI)	**678**	**663**		**100%**	**0.73[0.5,1.06]**
Total events: 43 (Protocol), 58 (Control)					
Heterogeneity: Tau²=0; Chi²=4.07, df=7(P=0.77); I²=0%					
Test for overall effect: Z=1.64(P=0.1)					
Test for subgroup differences: Chi²=2.82, df=1 (P=0.24), I²=28.96%					

Analysis 1.5. Comparison 1 Mortality, Outcome 5 Type of intervention.

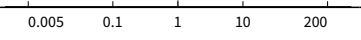
Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
1.5.1 Fluids and Inotropes					
Bender 1997	1/51	1/53		0.39%	1.04[0.07,16.18]
Berlauk 1991	1/68	2/21		0.53%	0.15[0.01,1.62]
Bonazzi 2002	0/50	0/50			Not estimable
Boyd 1993	3/53	12/54		2.02%	0.25[0.08,0.85]
Cecconi 2011	0/20	0/20			Not estimable
Donati 2007	2/68	2/67		0.79%	0.99[0.14,6.79]
Jerez 2001	16/181	21/209		7.66%	0.88[0.47,1.63]
Jhanji 2010	4/45	6/45		2.06%	0.67[0.2,2.2]
Kapoor 2007	0/15	0/15			Not estimable
Lobo 2000	3/19	9/18		2.27%	0.32[0.1,0.98]
Mayer 2010	2/30	2/30		0.82%	1[0.15,6.64]
Mckendry 2004	4/89	2/85		1.05%	1.91[0.36,10.16]
Pearse 2005	7/62	9/60		3.46%	0.75[0.3,1.89]
Pölönen 2000	4/196	9/197		2.18%	0.45[0.14,1.43]
Sandham 2003	163/997	155/997		72.3%	1.05[0.86,1.29]
Shoemaker 1988	1/28	18/60		0.76%	0.12[0.02,0.85]
Ueno 1998	0/16	2/18		0.33%	0.22[0.01,4.34]
Valentine 1998	3/60	1/60		0.59%	3[0.32,28.03]
Van der Linden 2010	0/20	0/17			Not estimable
Wilson 1999	3/92	8/46		1.8%	0.19[0.05,0.67]
Ziegler 1997	3/32	2/40		0.98%	1.88[0.33,10.55]
Subtotal (95% CI)	**2192**	**2162**		**100%**	**0.9[0.76,1.07]**
Total events: 220 (Protocol), 261 (Control)					
Heterogeneity: Tau^2=0; Chi^2=27.03, df=16(P=0.04); I^2=40.8%					
Test for overall effect: Z=1.2(P=0.23)					
1.5.2 Fluids					
Challand 2012	7/89	7/90		30.72%	1.01[0.37,2.76]
Conway 2002	0/29	1/28		3.11%	0.32[0.01,7.59]
Gan 2002	0/50	0/50			Not estimable
Jhanji 2010	5/45	6/45		25.11%	0.83[0.27,2.54]
Mythen 1995	0/30	1/30		3.11%	0.33[0.01,7.87]
Noblett 2006	0/51	1/52		3.08%	0.34[0.01,8.15]
Pillai 2011	1/32	0/34		3.1%	3.18[0.13,75.38]
Senagore 2009	1/42	0/22		3.11%	1.6[0.07,37.83]
Sinclair 1997	1/20	2/20		5.78%	0.5[0.05,5.08]
Venn 2002	3/30	8/60		19.81%	0.75[0.21,2.62]
Wakeling 2005	0/67	1/67		3.07%	0.33[0.01,8.04]
Subtotal (95% CI)	**485**	**498**		**100%**	**0.8[0.46,1.39]**
Total events: 18 (Protocol), 27 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.48, df=9(P=0.98); I^2=0%					
Test for overall effect: Z=0.79(P=0.43)					
Test for subgroup differences: Chi^2=0.16, df=1 (P=0.69), I^2=0%					

Analysis 1.6. Comparison 1 Mortality, Outcome 6 Goals of intervention.

Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
1.6.1 CO, DO2					
Bender 1997	1/51	1/53		0.36%	1.04[0.07,16.18]
Berlauk 1991	1/68	2/21		0.49%	0.15[0.01,1.62]
Bonazzi 2002	0/50	0/50			Not estimable
Boyd 1993	3/53	12/54		1.86%	0.25[0.08,0.85]
Kapoor 2007	0/15	0/15			Not estimable
Lobo 2000	3/19	9/18		2.1%	0.32[0.1,0.98]
Mayer 2010	2/30	2/30		0.76%	1[0.15,6.64]
Pearse 2005	7/62	9/60		3.2%	0.75[0.3,1.89]
Sandham 2003	163/997	155/997		66.85%	1.05[0.86,1.29]
Shoemaker 1988	1/28	18/60		0.71%	0.12[0.02,0.85]
Ueno 1998	0/16	2/18		0.31%	0.22[0.01,4.34]
Valentine 1998	3/60	1/60		0.54%	3[0.32,28.03]
Van der Linden 2010	0/20	0/17			Not estimable
Wilson 1999	3/92	8/46		1.66%	0.19[0.05,0.67]
Subtotal (95% CI)	**1561**	**1499**		**78.85%**	**0.91[0.75,1.09]**
Total events: 187 (Protocol), 219 (Control)					
Heterogeneity: Tau^2=0; Chi^2=23.89, df=10(P=0.01); I^2=58.15%					
Test for overall effect: Z=1.01(P=0.31)					
1.6.2 Lactate, SVO2, O2ER					
Donati 2007	2/68	2/67		0.73%	0.99[0.14,6.79]
Jerez 2001	16/181	21/209		7.09%	0.88[0.47,1.63]
Pölönen 2000	4/196	9/197		2.02%	0.45[0.14,1.43]
Ziegler 1997	3/32	2/40		0.91%	1.88[0.33,10.55]
Subtotal (95% CI)	**477**	**513**		**10.74%**	**0.83[0.5,1.38]**
Total events: 25 (Protocol), 34 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.01, df=3(P=0.57); I^2=0%					
Test for overall effect: Z=0.71(P=0.47)					
1.6.3 SV					
Cecconi 2011	0/20	0/20			Not estimable
Challand 2012	7/89	7/90		2.69%	1.01[0.37,2.76]
Conway 2002	0/29	1/28		0.27%	0.32[0.01,7.59]
Gan 2002	0/50	0/50			Not estimable
Jhanji 2010	9/90	6/45		2.89%	0.75[0.28,1.98]
Mckendry 2004	4/89	2/85		0.97%	1.91[0.36,10.16]
Mythen 1995	0/30	1/30		0.27%	0.33[0.01,7.87]
Noblett 2006	0/51	1/52		0.27%	0.34[0.01,8.15]
Pillai 2011	1/32	0/34		0.27%	3.18[0.13,75.38]
Senagore 2009	1/42	0/22		0.27%	1.6[0.07,37.83]
Sinclair 1997	1/20	2/20		0.51%	0.5[0.05,5.08]
Venn 2002	3/30	8/60		1.73%	0.75[0.21,2.62]
Wakeling 2005	0/67	1/67		0.27%	0.33[0.01,8.04]
Subtotal (95% CI)	**639**	**603**		**10.41%**	**0.84[0.51,1.41]**
Total events: 26 (Protocol), 29 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.49, df=10(P=0.97); I^2=0%					
Test for overall effect: Z=0.65(P=0.51)					
Total (95% CI)	**2677**	**2615**		**100%**	**0.89[0.76,1.05]**

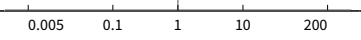


Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Total events: 238 (Protocol), 282 (Control)					
Heterogeneity: Tau²=0; Chi²=29.55, df=25(P=0.24); I²=15.41%					
Test for overall effect: Z=1.35(P=0.18)					
Test for subgroup differences: Chi²=0.16, df=1 (P=0.93), I²=0%					

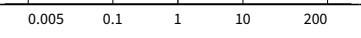


Analysis 1.7. Comparison 1 Mortality, Outcome 7 Mode of surgery.

Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
1.7.1 Elective					
Bender 1997	1/51	1/53		0.36%	1.04[0.07,16.18]
Berlauk 1991	1/68	2/21		0.49%	0.15[0.01,1.62]
Bonazzi 2002	0/50	0/50			Not estimable
Cecconi 2011	0/20	0/20			Not estimable
Challand 2012	7/89	7/90		2.69%	1.01[0.37,2.76]
Conway 2002	0/29	1/28		0.27%	0.32[0.01,7.59]
Donati 2007	2/68	2/67		0.73%	0.99[0.14,6.79]
Gan 2002	0/50	0/50			Not estimable
Jerez 2001	16/181	21/209		7.09%	0.88[0.47,1.63]
Jhanji 2010	9/90	6/45		2.89%	0.75[0.28,1.98]
Kapoor 2007	0/15	0/15			Not estimable
Lobo 2000	3/19	9/18		2.1%	0.32[0.1,0.98]
Mayer 2010	2/30	2/30		0.76%	1[0.15,6.64]
Mythen 1995	0/30	1/30		0.27%	0.33[0.01,7.87]
Noblett 2006	0/51	1/52		0.27%	0.34[0.01,8.15]
Pillai 2011	1/32	0/34		0.27%	3.18[0.13,75.38]
Pölönen 2000	4/196	9/197		2.02%	0.45[0.14,1.43]
Senagore 2009	1/42	0/22		0.27%	1.6[0.07,37.83]
Ueno 1998	0/16	2/18		0.31%	0.22[0.01,4.34]
Valentine 1998	3/60	1/60		0.54%	3[0.32,28.03]
Van der Linden 2010	0/20	0/17			Not estimable
Wakeling 2005	0/67	1/67		0.27%	0.33[0.01,8.04]
Wilson 1999	3/92	8/46		1.66%	0.19[0.05,0.67]
Ziegler 1997	3/32	2/40		0.91%	1.88[0.33,10.55]
Subtotal (95% CI)	**1398**	**1279**		**24.17%**	**0.68[0.48,0.94]**
Total events: 56 (Protocol), 76 (Control)					
Heterogeneity: Tau²=0; Chi²=14.91, df=18(P=0.67); I²=0%					
Test for overall effect: Z=2.3(P=0.02)					
1.7.2 Emergency					
Sinclair 1997	1/20	2/20		0.51%	0.5[0.05,5.08]
Venn 2002	3/30	8/60		1.73%	0.75[0.21,2.62]
Subtotal (95% CI)	**50**	**80**		**2.24%**	**0.68[0.23,2.06]**
Total events: 4 (Protocol), 10 (Control)					
Heterogeneity: Tau²=0; Chi²=0.09, df=1(P=0.76); I²=0%					
Test for overall effect: Z=0.67(P=0.5)					
1.7.3 Elective and Emergency					

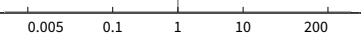


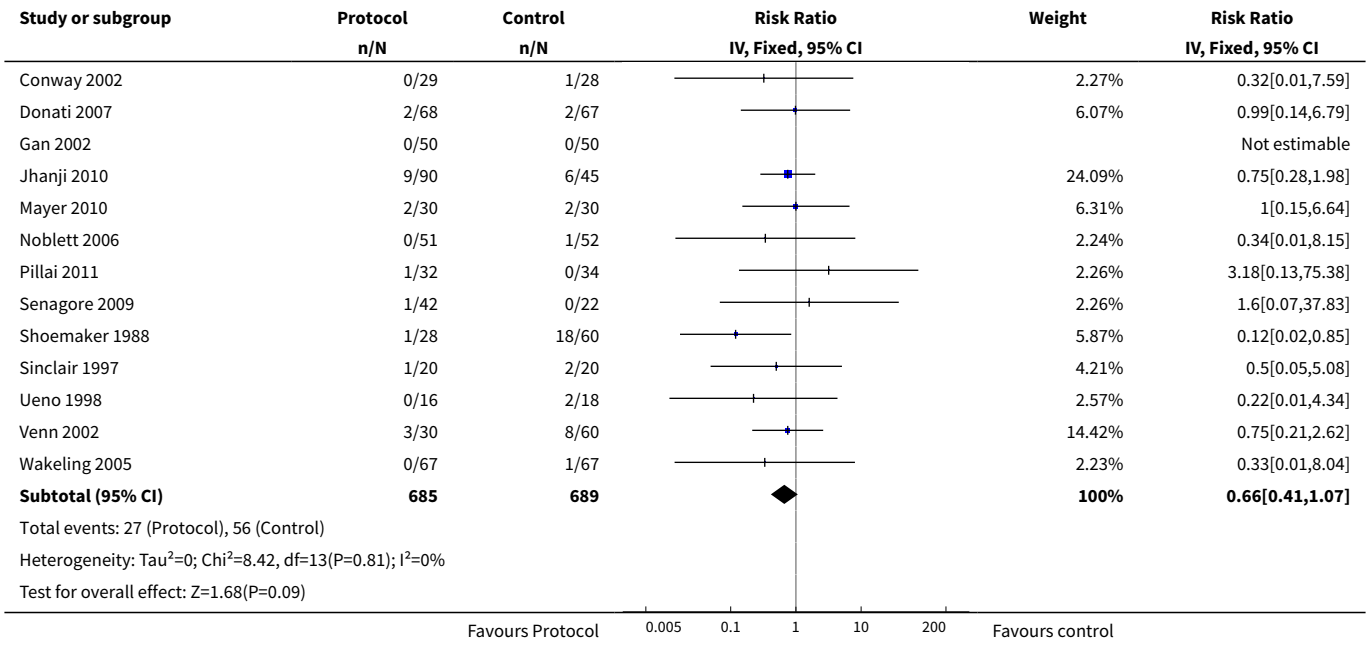
Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Boyd 1993	3/53	12/54		1.86%	0.25[0.08,0.85]
Mckendry 2004	4/89	2/85		0.97%	1.91[0.36,10.16]
Pearse 2005	7/62	9/60		3.2%	0.75[0.3,1.89]
Sandham 2003	163/997	155/997		66.85%	1.05[0.86,1.29]
Shoemaker 1988	1/28	18/60		0.71%	0.12[0.02,0.85]
Subtotal (95% CI)	**1229**	**1256**		**73.59%**	**0.99[0.81,1.2]**
Total events: 178 (Protocol), 196 (Control)					
Heterogeneity: Tau²=0; Chi²=10.61, df=4(P=0.03); I²=62.3%					
Test for overall effect: Z=0.13(P=0.89)					
Total (95% CI)	**2677**	**2615**		**100%**	**0.89[0.76,1.05]**
Total events: 238 (Protocol), 282 (Control)					
Heterogeneity: Tau²=0; Chi²=29.55, df=25(P=0.24); I²=15.41%					
Test for overall effect: Z=1.35(P=0.18)					
Test for subgroup differences: Chi²=3.94, df=1 (P=0.14), I²=49.24%					



Analysis 1.8. Comparison 1 Mortality, Outcome 8 Type of surgery.

Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
1.8.1 Vascular					
Bender 1997	1/51	1/53		9.13%	1.04[0.07,16.18]
Berlauk 1991	1/68	2/21		12.46%	0.15[0.01,1.62]
Bonazzi 2002	0/50	0/50			Not estimable
Boyd 1993	3/30	6/28		41.57%	0.47[0.13,1.69]
Valentine 1998	3/60	1/60		13.78%	3[0.32,28.03]
Van der Linden 2010	0/20	0/17			Not estimable
Ziegler 1997	3/32	2/40		23.05%	1.88[0.33,10.55]
Subtotal (95% CI)	**311**	**269**		**100%**	**0.78[0.34,1.79]**
Total events: 11 (Protocol), 12 (Control)					
Heterogeneity: Tau²=0; Chi²=4.86, df=4(P=0.3); I²=17.78%					
Test for overall effect: Z=0.59(P=0.56)					
1.8.2 Cardiac					
Jerez 2001	16/181	21/209		68.49%	0.88[0.47,1.63]
Kapoor 2007	0/15	0/15			Not estimable
Mckendry 2004	4/89	2/85		9.4%	1.91[0.36,10.16]
Mythen 1995	0/30	1/30		2.63%	0.33[0.01,7.87]
Pölönen 2000	4/196	9/197		19.48%	0.45[0.14,1.43]
Subtotal (95% CI)	**511**	**536**		**100%**	**0.81[0.48,1.35]**
Total events: 24 (Protocol), 33 (Control)					
Heterogeneity: Tau²=0; Chi²=2.39, df=3(P=0.49); I²=0%					
Test for overall effect: Z=0.81(P=0.42)					
1.8.3 General					
Boyd 1993	0/23	6/26		2.84%	0.09[0.01,1.46]
Cecconi 2011	0/20	0/20			Not estimable
Challand 2012	7/89	7/90		22.36%	1.01[0.37,2.76]





Comparison 2. Complications

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Renal impairment	21	4307	Risk Ratio (IV, Fixed, 95% CI)	0.71 [0.57, 0.90]
2 Arrhythmia	12	2921	Risk Ratio (IV, Fixed, 95% CI)	0.84 [0.67, 1.06]
3 Infection: numbers	9	733	Risk Ratio (IV, Fixed, 95% CI)	0.88 [0.69, 1.12]
4 Infections: types	16		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
4.1 Chest Infections/ Pneumonia	13	2945	Risk Ratio (IV, Fixed, 95% CI)	0.78 [0.61, 1.00]
4.2 Sepsis	5	474	Risk Ratio (IV, Fixed, 95% CI)	0.68 [0.26, 1.77]
4.3 Abdominal Infections	6	555	Risk Ratio (IV, Fixed, 95% CI)	0.53 [0.23, 1.22]
4.4 Wound Infections	10	2802	Risk Ratio (IV, Fixed, 95% CI)	0.65 [0.50, 0.84]
4.5 Urinary Tract Infections	8	612	Risk Ratio (IV, Fixed, 95% CI)	0.54 [0.26, 1.15]
5 Respiratory failure / ARDS	9	844	Risk Ratio (IV, Fixed, 95% CI)	0.51 [0.28, 0.93]
6 Myocardial infarction	15	3328	Risk Ratio (IV, Fixed, 95% CI)	1.01 [0.71, 1.45]
7 Congestive heart failure / pulmonary oedema	14	3223	Risk Ratio (IV, Fixed, 95% CI)	1.00 [0.81, 1.24]
8 Venous thrombosis	10	2740	Risk Ratio (IV, Fixed, 95% CI)	1.04 [0.39, 2.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Number of participants with complications	17	1841	Risk Ratio (IV, Random, 95% CI)	0.68 [0.58, 0.80]

Analysis 2.1. Comparison 2 Complications, Outcome 1 Renal impairment.

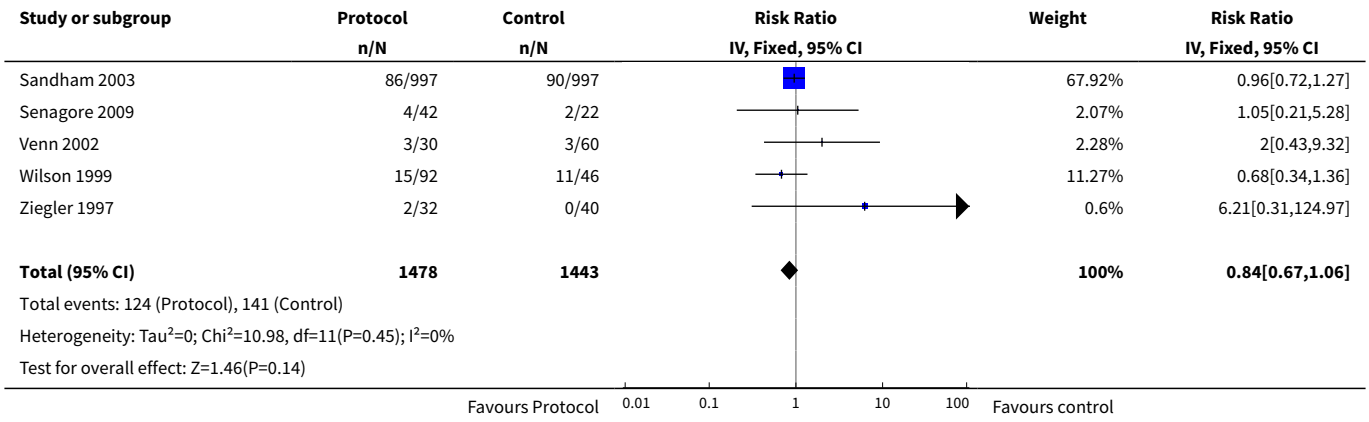
Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Bender 1997	0/51	0/53			Not estimable
Berlauk 1991	1/68	1/21		0.71%	0.31[0.02,4.73]
Bonazzi 2002	0/50	0/50			Not estimable
Boyd 1993	3/53	7/54		3.15%	0.44[0.12,1.6]
Cecconi 2011	0/20	0/20			Not estimable
Challand 2012	20/89	13/90		13.22%	1.56[0.83,2.93]
Donati 2007	2/68	7/67		2.25%	0.28[0.06,1.31]
Gan 2002	2/50	4/50		1.95%	0.5[0.1,2.61]
Jhanji 2010	7/90	10/45		6.6%	0.35[0.14,0.86]
Kapoor 2007	1/15	1/15		0.74%	1[0.07,14.55]
Lobo 2000	2/19	1/18		0.99%	1.89[0.19,19.13]
Mayer 2010	1/30	5/30		1.22%	0.2[0.02,1.61]
Mckendry 2004	1/89	3/85		1.06%	0.32[0.03,3]
Mythen 1995	0/30	2/30		0.59%	0.2[0.01,4]
Pölönen 2000	1/196	3/197		1.04%	0.34[0.04,3.19]
Sandham 2003	70/997	95/997		60.62%	0.74[0.55,0.99]
Shoemaker 1988	0/28	14/60		0.69%	0.07[0,1.17]
Valentine 1998	4/60	1/60		1.14%	4[0.46,34.75]
Venn 2002	0/30	2/60		0.59%	0.39[0.02,7.95]
Wakeling 2005	3/67	2/67		1.72%	1.5[0.26,8.69]
Wilson 1999	2/92	3/46		1.73%	0.33[0.06,1.93]
Total (95% CI)	**2192**	**2115**		**100%**	**0.71[0.57,0.9]**
Total events: 120 (Protocol), 174 (Control)					
Heterogeneity: Tau^2=0; Chi^2=21.17, df=17(P=0.22); I^2=19.68%					
Test for overall effect: Z=2.88(P=0)					

Favours protocol — Favours control

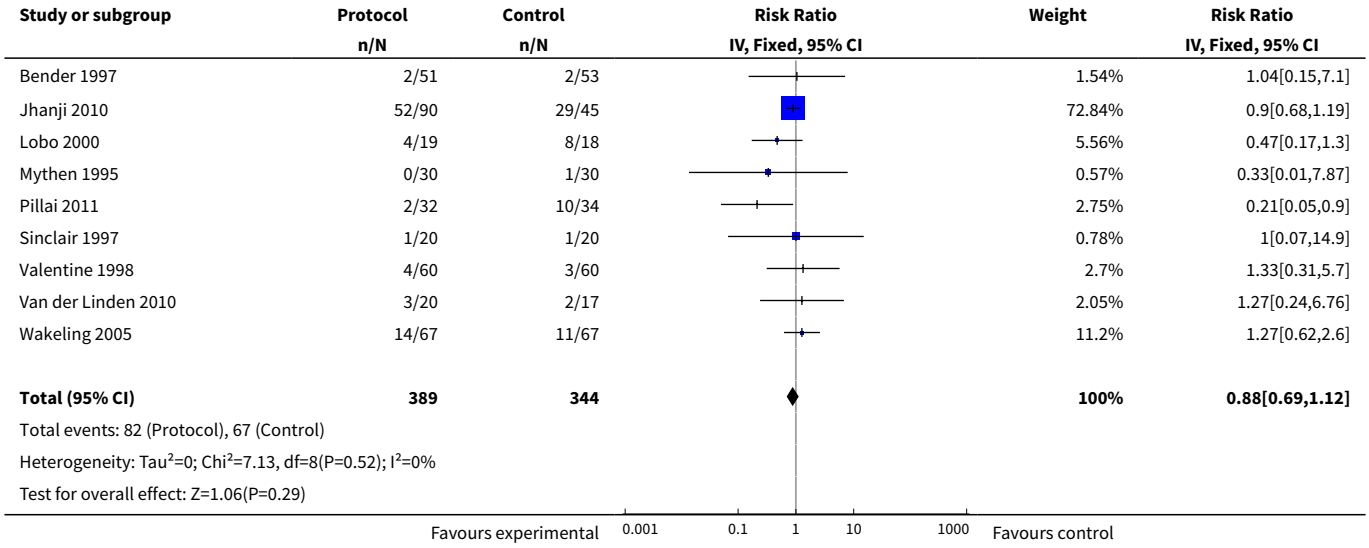
Analysis 2.2. Comparison 2 Complications, Outcome 2 Arrhythmia.

Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Bonazzi 2002	2/50	3/50		1.78%	0.67[0.12,3.82]
Cecconi 2011	0/20	4/20		0.66%	0.11[0.01,1.94]
Kapoor 2007	0/15	2/15		0.62%	0.2[0.01,3.85]
Lobo 2000	0/19	3/18		0.65%	0.14[0.01,2.46]
Mayer 2010	2/30	3/30		1.84%	0.67[0.12,3.71]
Mckendry 2004	5/89	11/85		5.26%	0.43[0.16,1.2]
Pearse 2005	5/62	9/60		5.06%	0.54[0.19,1.51]

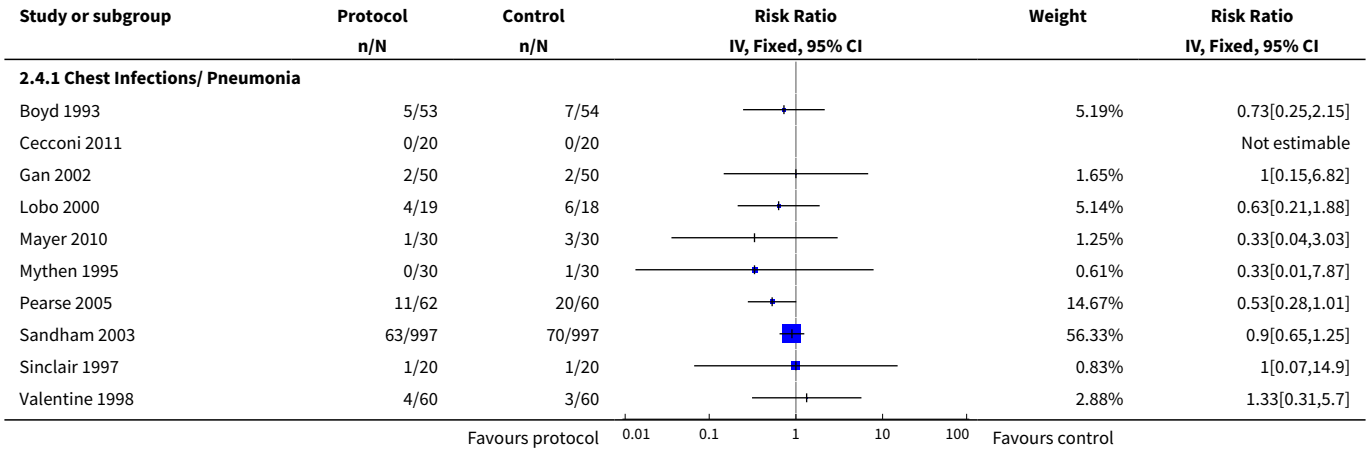
Favours Protocol — Favours control



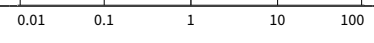
Analysis 2.3. Comparison 2 Complications, Outcome 3 Infection: numbers.



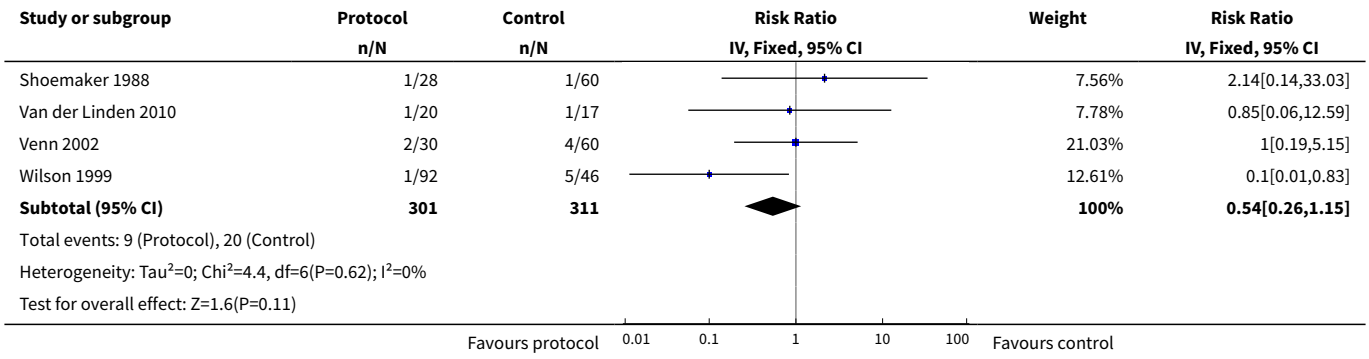
Analysis 2.4. Comparison 2 Complications, Outcome 4 Infections: types.



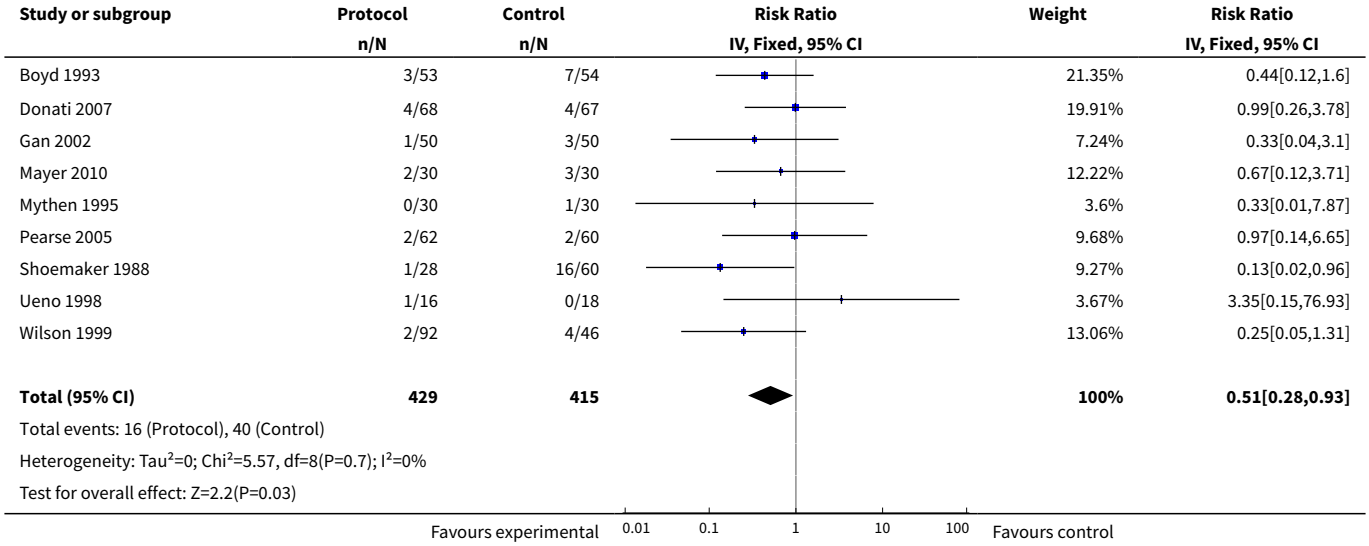
Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Van der Linden 2010	2/20	1/17		1.14%	1.7[0.17,17.16]
Venn 2002	2/30	8/60		2.76%	0.5[0.11,2.21]
Wilson 1999	10/92	7/46		7.54%	0.71[0.29,1.75]
Subtotal (95% CI)	**1483**	**1462**		**100%**	**0.78[0.61,1]**
Total events: 105 (Protocol), 129 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.52, df=11(P=0.95); I^2=0%					
Test for overall effect: Z=1.93(P=0.05)					
2.4.2 Sepsis					
Bender 1997	2/51	2/53		24.47%	1.04[0.15,7.1]
Boyd 1993	1/53	3/54		18.15%	0.34[0.04,3.16]
Lobo 2000	2/19	2/18		26.38%	0.95[0.15,6.03]
Shoemaker 1988	0/28	15/60		11.68%	0.07[0,1.1]
Wilson 1999	4/92	1/46		19.32%	2[0.23,17.39]
Subtotal (95% CI)	**243**	**231**		**100%**	**0.68[0.26,1.77]**
Total events: 9 (Protocol), 23 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.28, df=4(P=0.37); I^2=6.46%					
Test for overall effect: Z=0.79(P=0.43)					
2.4.3 Abdominal Infections					
Boyd 1993	0/53	1/54		7.01%	0.34[0.01,8.15]
Cecconi 2011	0/20	1/20		7.17%	0.33[0.01,7.72]
Mayer 2010	1/30	4/30		15.57%	0.25[0.03,2.11]
Pearse 2005	4/62	5/60		44.17%	0.77[0.22,2.75]
Shoemaker 1988	0/28	1/60		7.04%	0.7[0.03,16.69]
Wilson 1999	2/92	2/46		19.05%	0.5[0.07,3.44]
Subtotal (95% CI)	**285**	**270**		**100%**	**0.53[0.23,1.22]**
Total events: 7 (Protocol), 14 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.01, df=5(P=0.96); I^2=0%					
Test for overall effect: Z=1.49(P=0.14)					
2.4.4 Wound Infections					
Boyd 1993	3/53	3/54		2.88%	1.02[0.22,4.82]
Gan 2002	4/50	5/50		4.42%	0.8[0.23,2.81]
Lobo 2000	0/19	2/18		0.79%	0.19[0.01,3.71]
Mayer 2010	3/30	8/30		4.63%	0.38[0.11,1.28]
Pearse 2005	4/62	20/60		6.79%	0.19[0.07,0.53]
Pillai 2011	2/32	10/34		3.36%	0.21[0.05,0.9]
Sandham 2003	66/997	83/997		71.98%	0.8[0.58,1.09]
Shoemaker 1988	1/28	4/60		1.51%	0.54[0.06,4.58]
Venn 2002	0/30	2/60		0.77%	0.39[0.02,7.95]
Wilson 1999	3/92	3/46		2.86%	0.5[0.1,2.38]
Subtotal (95% CI)	**1393**	**1409**		**100%**	**0.65[0.5,0.84]**
Total events: 86 (Protocol), 140 (Control)					
Heterogeneity: Tau^2=0; Chi^2=11.53, df=9(P=0.24); I^2=21.92%					
Test for overall effect: Z=3.21(P=0)					
2.4.5 Urinary Tract Infections					
Cecconi 2011	3/20	5/20		33.97%	0.6[0.17,2.18]
Lobo 2000	0/19	1/18		5.74%	0.32[0.01,7.3]
Mayer 2010	0/30	0/30			Not estimable
Pearse 2005	1/62	3/60		11.32%	0.32[0.03,3.02]



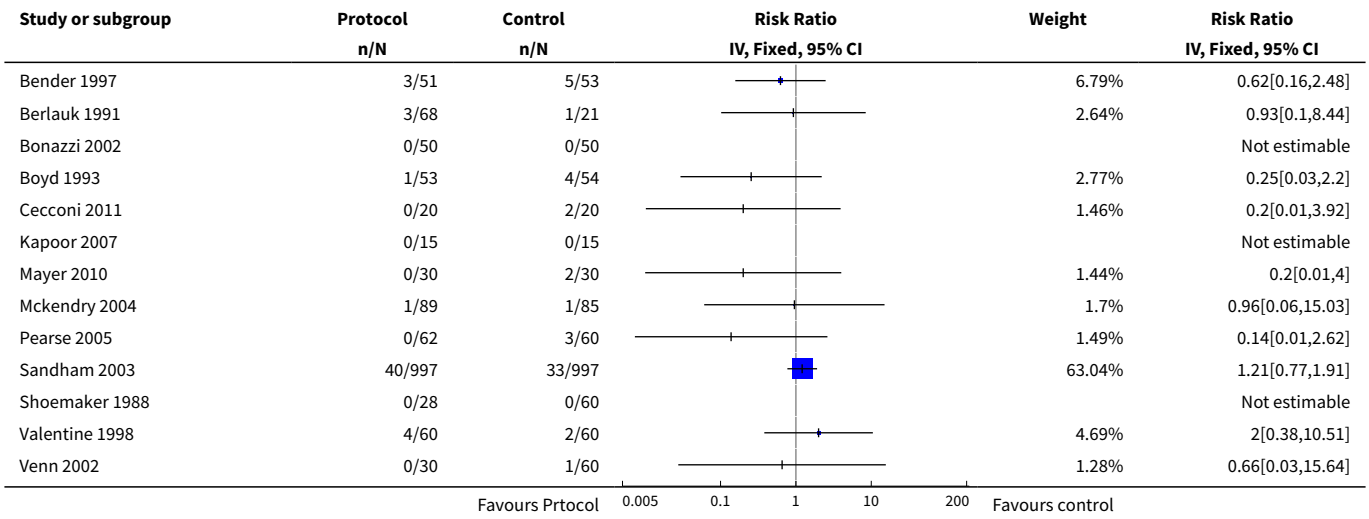
Favours protocol — Favours control

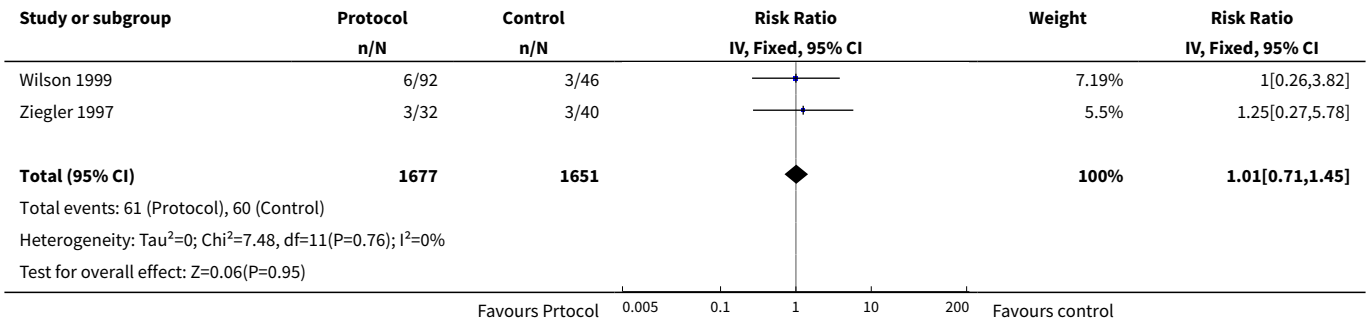


Analysis 2.5. Comparison 2 Complications, Outcome 5 Respiratory failure / ARDS.

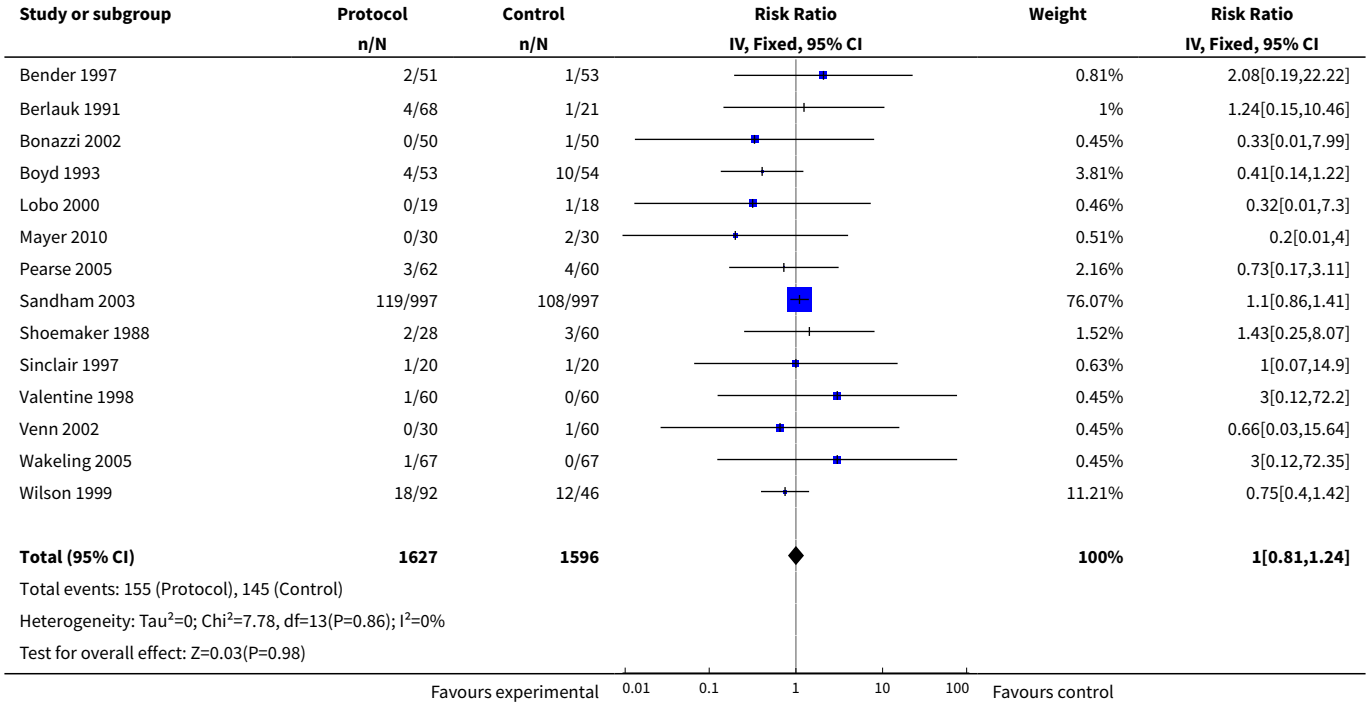


Analysis 2.6. Comparison 2 Complications, Outcome 6 Myocardial infarction.

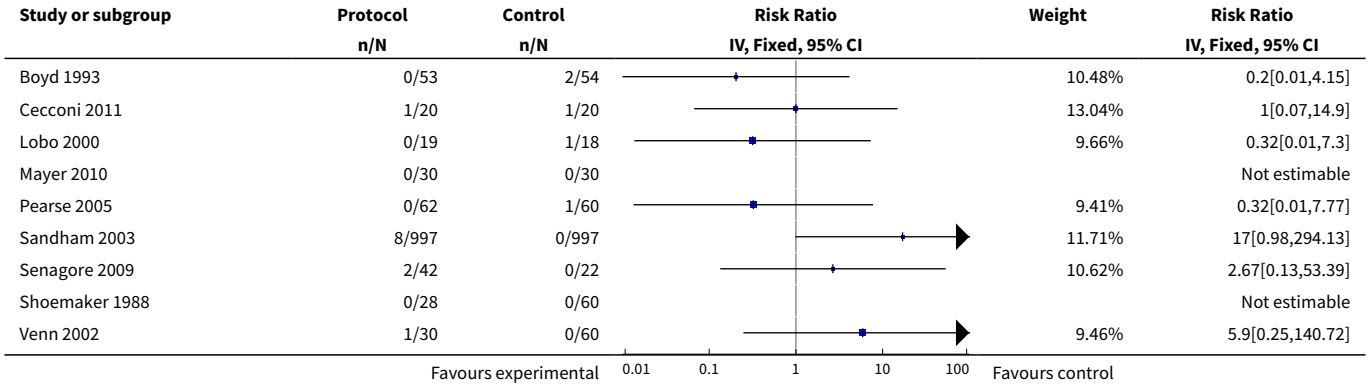


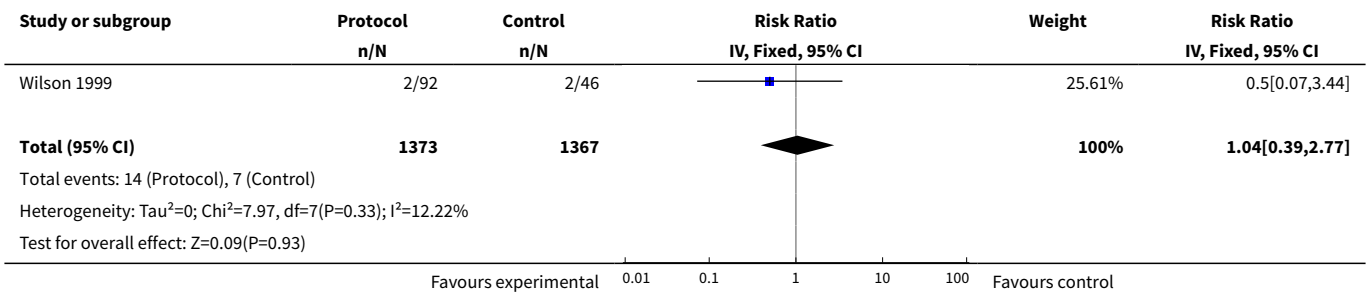


Analysis 2.7. Comparison 2 Complications, Outcome 7 Congestive heart failure / pulmonary oedema.

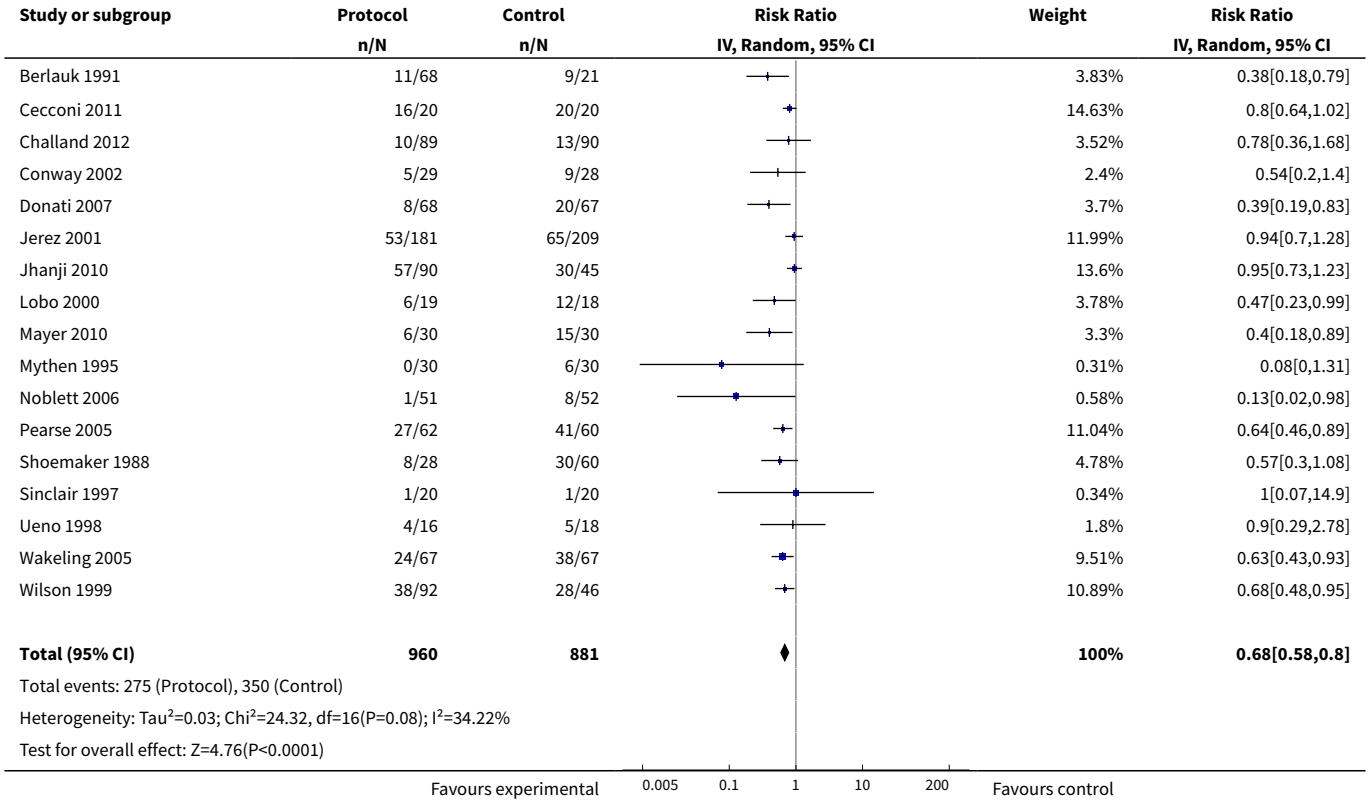


Analysis 2.8. Comparison 2 Complications, Outcome 8 Venous thrombosis.





Analysis 2.9. Comparison 2 Complications, Outcome 9 Number of participants with complications.



Comparison 3. Resource utilization

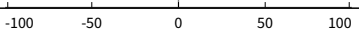
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Length of hospital stay	27	4729	Mean Difference (IV, Random, 95% CI)	-1.16 [-1.89, -0.43]
2 Length of critical care stay	14	1873	Mean Difference (IV, Random, 95% CI)	-0.45 [-0.94, 0.03]

Analysis 3.1. Comparison 3 Resource utilization, Outcome 1 Length of hospital stay.

Study or subgroup	Protocol N	Protocol Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Bender 1997	51	12.5 (10)	53	12 (9.5)		2.44%	0.5[-3.25,4.25]
Berlauk 1991	68	18.9 (11.7)	21	15.4 (7.5)		2.07%	3.5[-0.75,7.75]
Bonazzi 2002	50	12 (2)	50	11 (1.8)		6.36%	1[0.26,1.74]
Boyd 1993	53	16 (19)	54	12.5 (8.3)		1.38%	3.5[-2.07,9.07]
Cecconi 2011	20	10 (0.7)	20	10 (1.5)		6.38%	0[-0.73,0.73]
Challand 2012	89	8.8 (4.4)	90	6.7 (6.3)		5.16%	2.1[0.51,3.69]
Conway 2002	26	12 (24)	28	11 (5.8)		0.55%	1[-8.47,10.47]
Donati 2007	68	11.3 (3.8)	67	13.4 (6.1)		4.95%	-2.1[-3.82,-0.38]
Gan 2002	50	5 (3)	50	7 (3)		5.79%	-2[-3.18,-0.82]
Jhanji 2010	90	20.8 (13.3)	45	18.5 (11.5)		2.01%	2.3[-2.04,6.64]
Kapoor 2007	15	5.8 (1.2)	15	8.8 (2.1)		5.72%	-3[-4.22,-1.78]
Lobo 2000	19	16 (8)	18	13.8 (8.8)		1.44%	2.25[-3.16,7.66]
Mayer 2010	30	15 (4.3)	30	19 (7)		3.24%	-4[-6.94,-1.06]
Mckendry 2004	89	7 (2.2)	85	9 (3.7)		6.15%	-2[-2.91,-1.09]
Mythen 1995	30	6.4 (1.1)	30	10.1 (9.4)		2.77%	-3.7[-7.09,-0.31]
Noblett 2006	51	8 (5)	52	12.4 (9.4)		3.3%	-4.4[-7.3,-1.5]
Pearse 2005	62	17.5 (20.8)	60	29.5 (34.8)		0.48%	-12[-22.21,-1.79]
Pillai 2011	32	18 (10.7)	34	22 (10.7)		1.55%	-4[-9.17,1.17]
Pölönen 2000	196	6 (1.5)	197	7 (0.7)		6.75%	-1[-1.23,-0.77]
Sandham 2003	997	10 (5.9)	997	10 (5.9)		6.58%	0[-0.52,0.52]
Shoemaker 1988	28	19.3 (2.4)	60	23.7 (3.4)		5.69%	-4.4[-5.64,-3.16]
Sinclair 1997	20	11.3 (1.3)	20	27.8 (12.8)		1.36%	-16.5[-22.11,-10.89]
Valentine 1998	60	13 (2)	60	13 (2)		6.39%	0[-0.72,0.72]
Van der Linden 2010	20	18.5 (1.5)	17	15 (3.5)		4.84%	3.5[1.71,5.29]
Venn 2002	30	13.5 (9.2)	60	15.3 (13.2)		1.8%	-1.8[-6.49,2.89]
Wakeling 2005	67	11 (6)	67	13.1 (7.4)		4.1%	-2.15[-4.43,0.13]
Wilson 1999	92	16 (12)	46	21.9 (25.9)		0.77%	-5.9[-13.78,1.98]
Total ***	**2403**		**2326**			**100%**	**-1.16[-1.89,-0.43]**

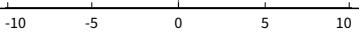
Heterogeneity: Tau^2=2.05; Chi^2=199.57, df=26(P<0.0001); I^2=86.97%

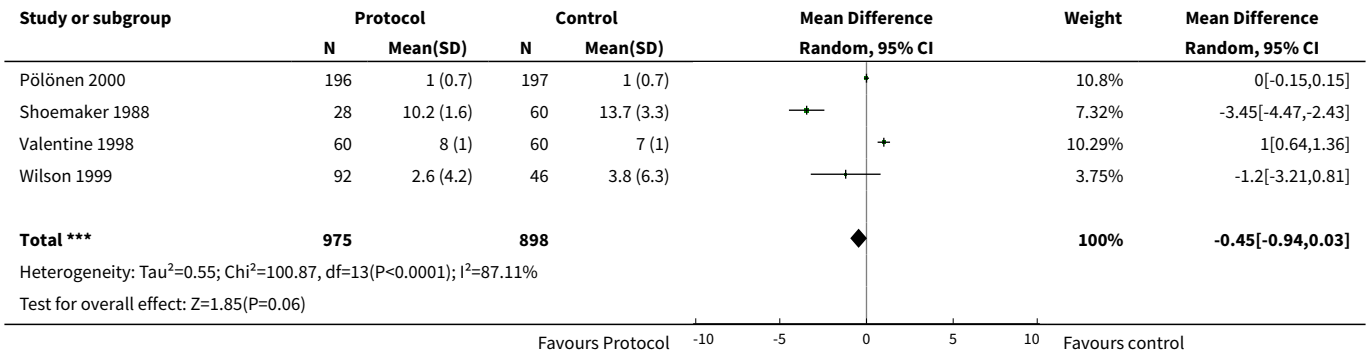
Test for overall effect: Z=3.11(P=0)



Analysis 3.2. Comparison 3 Resource utilization, Outcome 2 Length of critical care stay.

Study or subgroup	Protocol N	Protocol Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Bender 1997	51	2.7 (1.4)	53	2.6 (3.6)		7.16%	0.1[-0.96,1.16]
Berlauk 1991	68	3.2 (1.8)	21	2.6 (2.1)		7.44%	0.6[-0.39,1.59]
Boyd 1993	53	1.7 (0.9)	54	1.7 (0.8)		10.4%	0[-0.32,0.32]
Jerez 2001	181	4.8 (7)	209	5.7 (9)		4.98%	-0.9[-2.49,0.69]
Jhanji 2010	90	5.5 (6)	45	5.8 (6.5)		3.19%	-0.35[-2.62,1.92]
Kapoor 2007	15	2.6 (0.9)	15	4.9 (1.8)		7.33%	-2.3[-3.32,-1.28]
Lobo 2000	19	6.8 (3.3)	18	7.3 (4.8)		2.55%	-0.5[-3.14,2.14]
Mayer 2010	30	1.7 (1.6)	30	1.7 (1.8)		8%	-0.09[-0.97,0.79]
Mythen 1995	30	1 (1)	30	1.7 (1.9)		8.54%	-0.7[-1.47,0.07]
Pearse 2005	62	1.8 (2.4)	60	1.9 (2.3)		8.23%	-0.08[-0.92,0.75]



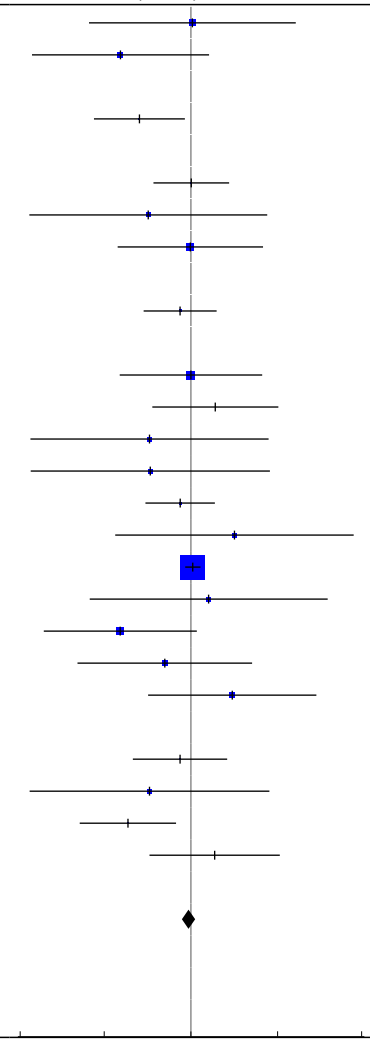


Comparison 4. Sensitivity analysis: excluding studies with active controls

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality (Longest follow-up)	27	4408	Risk Ratio (IV, Fixed, 95% CI)	0.94 [0.79, 1.12]
2 Mortality (Hospital or 28 days)	27	4408	Risk Ratio (IV, Fixed, 95% CI)	0.84 [0.67, 1.07]
3 Renal Impairment	19	3847	Risk Ratio (IV, Fixed, 95% CI)	0.71 [0.56, 0.90]
4 Arrhythmia	11	2884	Risk Ratio (IV, Fixed, 95% CI)	0.85 [0.67, 1.07]
5 Infection (Number of patients with infections)	8	696	Risk Ratio (IV, Fixed, 95% CI)	0.91 [0.71, 1.16]
6 Respiratory Failure/ ARDS	8	780	Risk Ratio (IV, Fixed, 95% CI)	0.48 [0.26, 0.89]
7 Myocardial Infarction	15	3298	Risk Ratio (IV, Fixed, 95% CI)	1.01 [0.71, 1.45]
8 Congestive Heart Failure/ Pulmonary oedema	13	3156	Risk Ratio (IV, Fixed, 95% CI)	1.01 [0.82, 1.26]
9 Venous Thrombosis	9	2673	Risk Ratio (IV, Fixed, 95% CI)	1.19 [0.42, 3.31]
10 Number of patients with complications	14	1350	Risk Ratio (IV, Fixed, 95% CI)	0.71 [0.63, 0.80]
11 Length of Hospital Stay [Days]	25	4269	Mean Difference (IV, Random, 95% CI)	-1.21 [-2.08, -0.33]
12 Length of Critical Care Stay [Days]	11	1023	Mean Difference (IV, Random, 95% CI)	-0.32 [-0.89, 0.26]

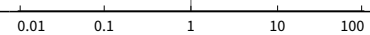
Analysis 4.1. Comparison 4 Sensitivity analysis: excluding studies with active controls, Outcome 1 Mortality (Longest follow-up).

Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Bender 1997	1/51	1/53		0.41%	1.04[0.07,16.18]
Berlauk 1991	1/68	2/21		0.56%	0.15[0.01,1.62]
Bonazzi 2002	0/50	0/50			Not estimable
Boyd 1993	3/53	12/54		2.11%	0.25[0.08,0.85]
Cecconi 2011	0/20	0/20			Not estimable
Challand 2012	7/89	7/90		3.04%	1.01[0.37,2.76]
Conway 2002	0/29	1/28		0.31%	0.32[0.01,7.59]
Donati 2007	2/68	2/67		0.82%	0.99[0.14,6.79]
Gan 2002	0/50	0/50			Not estimable
Jhanji 2010	9/90	6/45		3.27%	0.75[0.28,1.98]
Kapoor 2007	0/15	0/15			Not estimable
Mayer 2010	2/30	2/30		0.86%	1[0.15,6.64]
Mckendry 2004	4/89	2/85		1.1%	1.91[0.36,10.16]
Mythen 1995	0/30	1/30		0.31%	0.33[0.01,7.87]
Noblett 2006	0/51	1/52		0.3%	0.34[0.01,8.15]
Pearse 2005	7/62	9/60		3.62%	0.75[0.3,1.89]
Pillai 2011	1/32	0/34		0.31%	3.18[0.13,75.38]
Sandham 2003	163/997	155/997		75.59%	1.05[0.86,1.29]
Senagore 2009	1/42	0/22		0.31%	1.6[0.07,37.83]
Shoemaker 1988	1/28	7/30		0.74%	0.15[0.02,1.17]
Sinclair 1997	1/20	2/20		0.57%	0.5[0.05,5.08]
Valentine 1998	3/60	1/60		0.62%	3[0.32,28.03]
Van der Linden 2010	0/20	0/17			Not estimable
Venn 2002	3/30	8/60		1.96%	0.75[0.21,2.62]
Wakeling 2005	0/67	1/67		0.3%	0.33[0.01,8.04]
Wilson 1999	3/92	8/46		1.88%	0.19[0.05,0.67]
Ziegler 1997	3/32	2/40		1.03%	1.88[0.33,10.55]
Total (95% CI)	**2265**	**2143**		**100%**	**0.94[0.79,1.12]**
Total events: 215 (Protocol), 230 (Control)					
Heterogeneity: Tau^2=0; Chi^2=22.68, df=21(P=0.36); I^2=7.39%					
Test for overall effect: Z=0.71(P=0.48)					

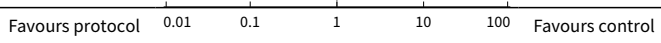


Analysis 4.2. Comparison 4 Sensitivity analysis: excluding studies with active controls, Outcome 2 Mortality (Hospital or 28 days).

Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Bender 1997	1/51	1/53		0.74%	1.04[0.07,16.18]
Berlauk 1991	1/68	2/21		1%	0.15[0.01,1.62]
Bonazzi 2002	0/50	0/50			Not estimable
Boyd 1993	3/53	12/54		3.81%	0.25[0.08,0.85]
Cecconi 2011	0/20	0/20			Not estimable
Challand 2012	3/89	4/90		2.57%	0.76[0.17,3.29]
Conway 2002	0/29	1/28		0.56%	0.32[0.01,7.59]
Donati 2007	2/68	2/67		1.49%	0.99[0.14,6.79]

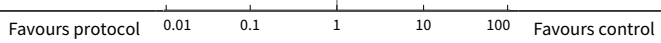


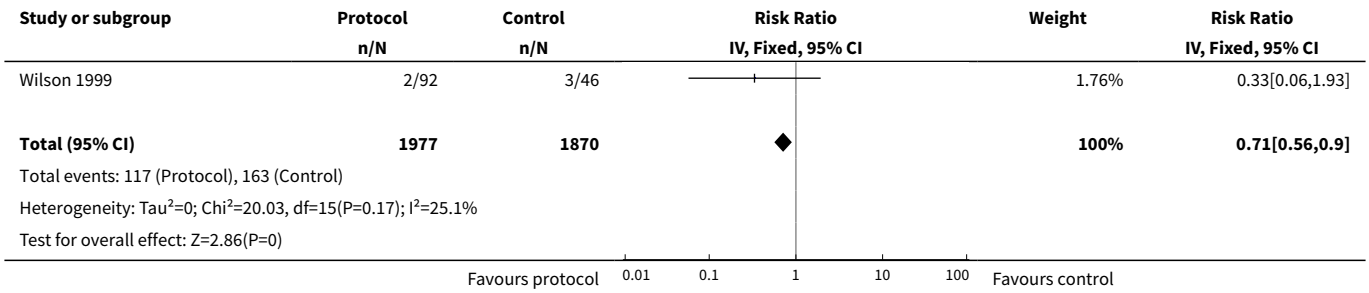
Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Gan 2002	0/50	0/50			Not estimable
Jhanji 2010	9/90	6/45		5.91%	0.75[0.28,1.98]
Kapoor 2007	0/15	0/15			Not estimable
Mayer 2010	2/30	2/30		1.55%	1[0.15,6.64]
Mckendry 2004	4/89	2/85		1.99%	1.91[0.36,10.16]
Mythen 1995	0/30	1/30		0.56%	0.33[0.01,7.87]
Noblett 2006	0/51	1/52		0.55%	0.34[0.01,8.15]
Pearse 2005	6/62	7/60		5.22%	0.83[0.3,2.33]
Pillai 2011	1/32	0/34		0.55%	3.18[0.13,75.38]
Sandham 2003	78/997	77/997		60.68%	1.01[0.75,1.37]
Senagore 2009	1/42	0/22		0.56%	1.6[0.07,37.83]
Shoemaker 1988	1/28	7/30		1.35%	0.15[0.02,1.17]
Sinclair 1997	1/20	2/20		1.03%	0.5[0.05,5.08]
Valentine 1998	3/60	1/60		1.11%	3[0.32,28.03]
Van der Linden 2010	0/20	0/17			Not estimable
Venn 2002	3/30	8/60		3.54%	0.75[0.21,2.62]
Wakeling 2005	0/67	0/67			Not estimable
Wilson 1999	3/92	8/46		3.39%	0.19[0.05,0.67]
Ziegler 1997	3/32	2/40		1.86%	1.88[0.33,10.55]
Total (95% CI)	**2265**	**2143**		**100%**	**0.84[0.67,1.07]**
Total events: 125 (Protocol), 146 (Control)					
Heterogeneity: $Tau^2=0$; $Chi^2=20.42$, df=20(P=0.43); $I^2=2.05\%$					
Test for overall effect: Z=1.4(P=0.16)					



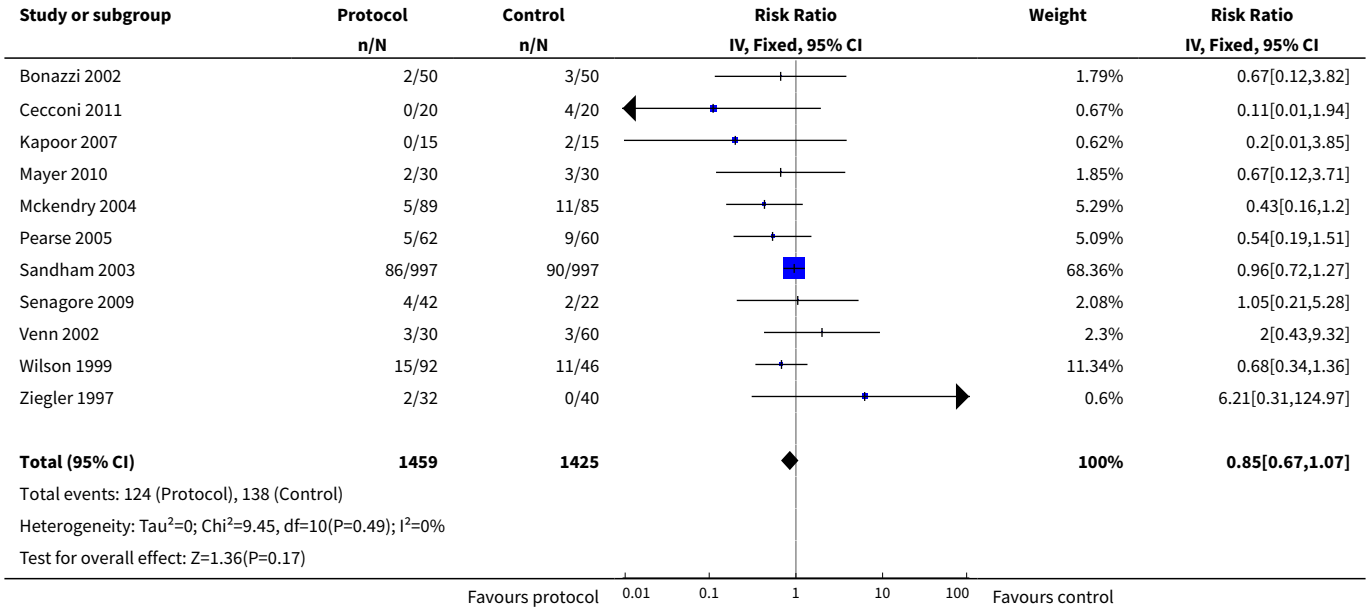
Analysis 4.3. Comparison 4 Sensitivity analysis: excluding studies with active controls, Outcome 3 Renal Impairment.

Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Bender 1997	0/51	0/53			Not estimable
Berlauk 1991	1/68	1/21		0.73%	0.31[0.02,4.73]
Bonazzi 2002	0/50	0/50			Not estimable
Boyd 1993	3/53	7/54		3.22%	0.44[0.12,1.6]
Cecconi 2011	0/20	0/20			Not estimable
Challand 2012	20/89	13/90		13.5%	1.56[0.83,2.93]
Donati 2007	2/68	7/67		2.3%	0.28[0.06,1.31]
Gan 2002	2/50	4/50		1.99%	0.5[0.1,2.61]
Jhanji 2010	7/90	10/45		6.74%	0.35[0.14,0.86]
Kapoor 2007	1/15	1/15		0.76%	1[0.07,14.55]
Mayer 2010	1/30	5/30		1.25%	0.2[0.02,1.61]
Mckendry 2004	1/89	3/85		1.08%	0.32[0.03,3]
Mythen 1995	0/30	2/30		0.6%	0.2[0.01,4]
Sandham 2003	70/997	95/997		61.89%	0.74[0.55,0.99]
Shoemaker 1988	0/28	7/30		0.68%	0.07[0,1.19]
Valentine 1998	4/60	1/60		1.16%	4[0.46,34.75]
Venn 2002	0/30	2/60		0.6%	0.39[0.02,7.95]
Wakeling 2005	3/67	2/67		1.76%	1.5[0.26,8.69]

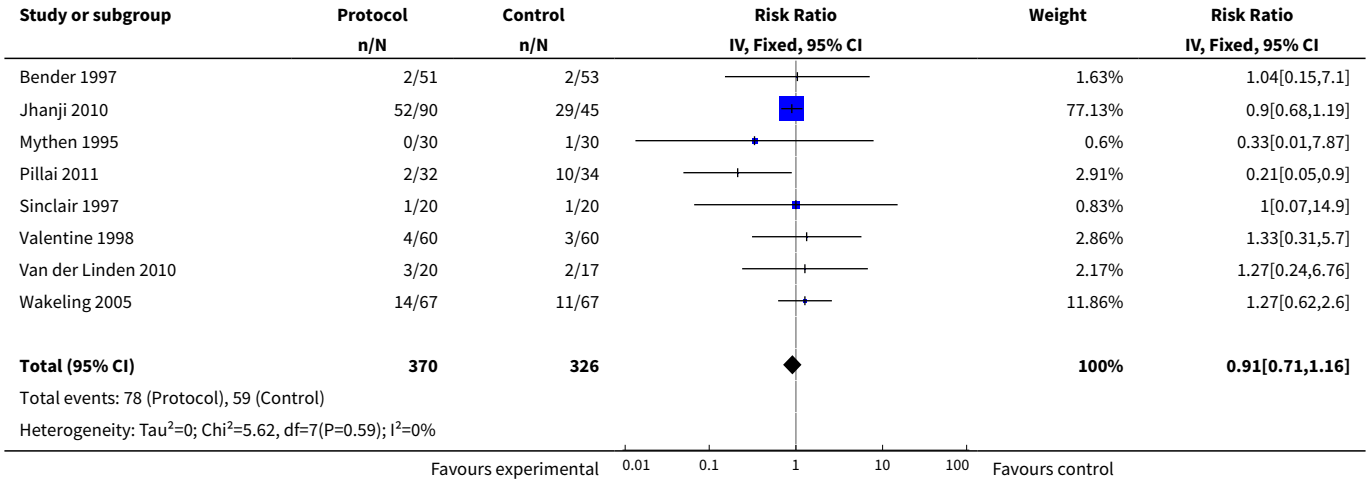




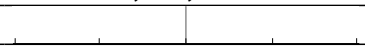
Analysis 4.4. Comparison 4 Sensitivity analysis: excluding studies with active controls, Outcome 4 Arrhythmia.



Analysis 4.5. Comparison 4 Sensitivity analysis: excluding studies with active controls, Outcome 5 Infection (Number of patients with infections).

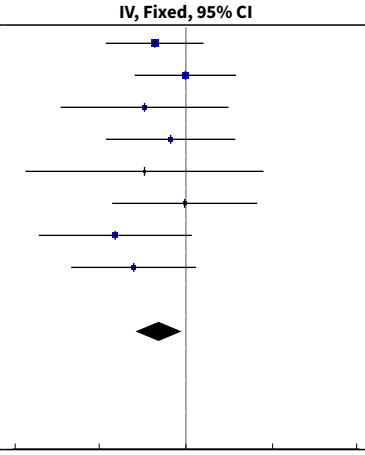


Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Test for overall effect: Z=0.74(P=0.46)					



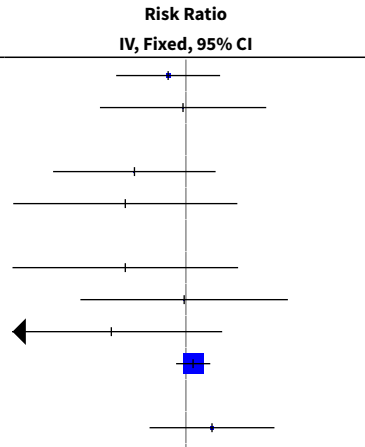
Analysis 4.6. Comparison 4 Sensitivity analysis: excluding studies with active controls, Outcome 6 Respiratory Failure/ ARDS.

Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Boyd 1993	3/53	7/54		22.29%	0.44[0.12,1.6]
Donati 2007	4/68	4/67		20.79%	0.99[0.26,3.78]
Gan 2002	1/50	3/50		7.56%	0.33[0.04,3.1]
Mayer 2010	2/30	3/30		12.76%	0.67[0.12,3.71]
Mythen 1995	0/30	1/30		3.76%	0.33[0.01,7.87]
Pearse 2005	2/62	2/60		10.11%	0.97[0.14,6.65]
Shoemaker 1988	1/28	7/30		9.11%	0.15[0.02,1.17]
Wilson 1999	2/92	4/46		13.63%	0.25[0.05,1.31]
Total (95% CI)	**413**	**367**		**100%**	**0.48[0.26,0.89]**
Total events: 15 (Protocol), 31 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.73, df=7(P=0.81); I^2=0%					
Test for overall effect: Z=2.32(P=0.02)					

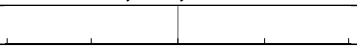


Analysis 4.7. Comparison 4 Sensitivity analysis: excluding studies with active controls, Outcome 7 Myocardial Infarction.

Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Bender 1997	3/51	5/53		6.79%	0.62[0.16,2.48]
Berlauk 1991	3/68	1/21		2.64%	0.93[0.1,8.44]
Bonazzi 2002	0/50	0/50			Not estimable
Boyd 1993	1/53	4/54		2.77%	0.25[0.03,2.2]
Cecconi 2011	0/20	2/20		1.46%	0.2[0.01,3.92]
Kapoor 2007	0/15	0/15			Not estimable
Mayer 2010	0/30	2/30		1.44%	0.2[0.01,4]
Mckendry 2004	1/89	1/85		1.7%	0.96[0.06,15.03]
Pearse 2005	0/62	3/60		1.49%	0.14[0.01,2.62]
Sandham 2003	40/997	33/997		63.04%	1.21[0.77,1.91]
Shoemaker 1988	0/28	0/30			Not estimable
Valentine 1998	4/60	2/60		4.69%	2[0.38,10.51]
Venn 2002	0/30	1/60		1.28%	0.66[0.03,15.64]
Wilson 1999	6/92	3/46		7.19%	1[0.26,3.82]
Ziegler 1997	3/32	3/40		5.5%	1.25[0.27,5.78]
Total (95% CI)	**1677**	**1621**		**100%**	**1.01[0.71,1.45]**
Total events: 61 (Protocol), 60 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.48, df=11(P=0.76); I^2=0%					



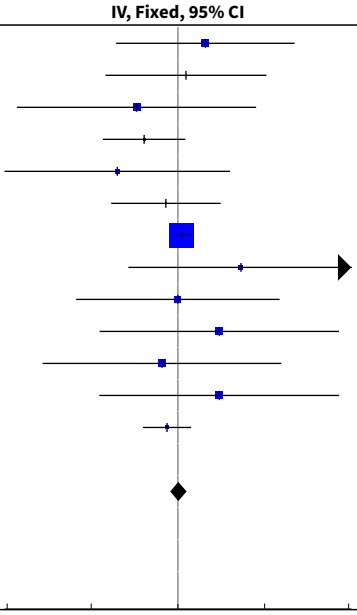
Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Test for overall effect: Z=0.06(P=0.95)					



Favours protocol Favours control

Analysis 4.8. Comparison 4 Sensitivity analysis: excluding studies with active controls, Outcome 8 Congestive Heart Failure/ Pulmonary oedema.

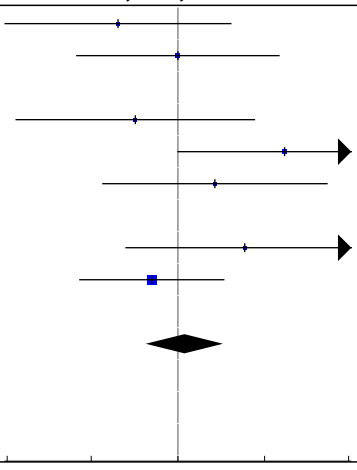
Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Bender 1997	2/51	1/53		0.83%	2.08[0.19,22.22]
Berlauk 1991	4/68	1/21		1.02%	1.24[0.15,10.46]
Bonazzi 2002	0/50	1/50		0.46%	0.33[0.01,7.99]
Boyd 1993	4/53	10/54		3.87%	0.41[0.14,1.22]
Mayer 2010	0/30	2/30		0.52%	0.2[0.01,4]
Pearse 2005	3/62	4/60		2.2%	0.73[0.17,3.11]
Sandham 2003	119/997	108/997		77.21%	1.1[0.86,1.41]
Shoemaker 1988	2/28	0/30		0.52%	5.34[0.27,106.7]
Sinclair 1997	1/20	1/20		0.64%	1[0.07,14.9]
Valentine 1998	1/60	0/60		0.46%	3[0.12,72.2]
Venn 2002	0/30	1/60		0.46%	0.66[0.03,15.64]
Wakeling 2005	1/67	0/67		0.46%	3[0.12,72.35]
Wilson 1999	18/92	12/46		11.37%	0.75[0.4,1.42]
Total (95% CI)	**1608**	**1548**		**100%**	**1.01[0.82,1.26]**
Total events: 155 (Protocol), 141 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.29, df=12(P=0.76); I^2=0%					
Test for overall effect: Z=0.11(P=0.91)					



Favours protocol Favours control

Analysis 4.9. Comparison 4 Sensitivity analysis: excluding studies with active controls, Outcome 9 Venous Thrombosis.

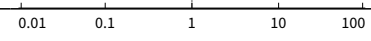
Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Boyd 1993	0/53	2/54		11.61%	0.2[0.01,4.15]
Cecconi 2011	1/20	1/20		14.44%	1[0.07,14.9]
Mayer 2010	0/30	0/30			Not estimable
Pearse 2005	0/62	1/60		10.41%	0.32[0.01,7.77]
Sandham 2003	8/997	0/997		12.96%	17[0.98,294.13]
Senagore 2009	2/42	0/22		11.75%	2.67[0.13,53.39]
Shoemaker 1988	0/28	0/30			Not estimable
Venn 2002	1/30	0/60		10.48%	5.9[0.25,140.72]
Wilson 1999	2/92	2/46		28.35%	0.5[0.07,3.44]
Total (95% CI)	**1354**	**1319**		**100%**	**1.19[0.42,3.31]**
Total events: 14 (Protocol), 6 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.36, df=6(P=0.29); I^2=18.49%					
Test for overall effect: Z=0.32(P=0.75)					



Favours protocol Favours control

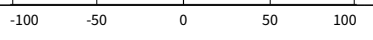
Analysis 4.10. Comparison 4 Sensitivity analysis: excluding studies with active controls, Outcome 10 Number of patients with complications.

Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Berlauk 1991	11/68	9/21		2.72%	0.38[0.18,0.79]
Cecconi 2011	16/20	20/20		26.82%	0.8[0.64,1.02]
Challand 2012	10/89	13/90		2.45%	0.78[0.36,1.68]
Conway 2002	5/29	9/28		1.57%	0.54[0.2,1.4]
Donati 2007	8/68	20/67		2.61%	0.39[0.19,0.83]
Jhanji 2010	57/90	30/45		21.63%	0.95[0.73,1.23]
Mayer 2010	6/30	15/30		2.28%	0.4[0.18,0.89]
Mythen 1995	0/30	6/30		0.18%	0.08[0,1.31]
Noblett 2006	1/51	8/52		0.35%	0.13[0.02,0.98]
Pearse 2005	27/62	41/60		13.25%	0.64[0.46,0.89]
Shoemaker 1988	8/28	15/30		3.09%	0.57[0.29,1.14]
Sinclair 1997	1/20	1/20		0.2%	1[0.07,14.9]
Wakeling 2005	24/67	38/67		9.95%	0.63[0.43,0.93]
Wilson 1999	38/92	28/46		12.9%	0.68[0.48,0.95]
Total (95% CI)	**744**	**606**		**100%**	**0.71[0.63,0.8]**
Total events: 212 (Protocol), 253 (Control)					
Heterogeneity: Tau^2=0; Chi^2=19.9, df=13(P=0.1); I^2=34.69%					
Test for overall effect: Z=5.54(P<0.0001)					

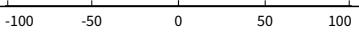


Analysis 4.11. Comparison 4 Sensitivity analysis: excluding studies with active controls, Outcome 11 Length of Hospital Stay [Days].

Study or subgroup	Protocol N	Protocol Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Bender 1997	51	12.5 (10)	53	12 (9.5)		3%	0.5[-3.25,4.25]
Berlauk 1991	68	18.9 (11.7)	21	15.4 (7.5)		2.59%	3.5[-0.75,7.75]
Bonazzi 2002	50	12 (2)	50	11 (1.8)		6.42%	1[0.26,1.74]
Boyd 1993	53	16 (19)	54	12.5 (8.3)		1.8%	3.5[-2.07,9.07]
Cecconi 2011	20	10 (0.7)	20	10 (1.5)		6.43%	0[-0.73,0.73]
Challand 2012	89	8.8 (4.4)	90	6.7 (6.3)		5.5%	2.1[0.51,3.69]
Conway 2002	26	12 (24)	28	11 (5.8)		0.75%	1[-8.47,10.47]
Donati 2007	68	11.3 (3.8)	67	13.4 (6.1)		5.34%	-2.1[-3.82,-0.38]
Gan 2002	50	5 (3)	50	7 (3)		6%	-2[-3.18,-0.82]
Jhanji 2010	90	20.8 (13.3)	45	18.5 (11.5)		2.52%	2.3[-2.04,6.64]
Kapoor 2007	15	5.8 (1.2)	15	8.8 (2.1)		5.94%	-3[-4.22,-1.78]
Mayer 2010	30	15 (4.3)	30	19 (7)		3.81%	-4[-6.94,-1.06]
Mckendry 2004	89	7 (2.2)	85	9 (3.7)		6.27%	-2[-2.91,-1.09]
Mythen 1995	30	6.4 (1.1)	30	10.1 (9.4)		3.34%	-3.7[-7.09,-0.31]
Noblett 2006	51	8 (5)	52	12.4 (9.4)		3.86%	-4.4[-7.3,-1.5]
Pearse 2005	62	17.5 (20.8)	60	29.5 (34.8)		0.66%	-12[-22.21,-1.79]
Pillai 2011	32	18 (10.7)	34	22 (10.7)		2%	-4[-9.17,1.17]
Sandham 2003	997	10 (5.9)	997	10 (5.9)		6.57%	0[-0.52,0.52]
Shoemaker 1988	28	19.3 (2.4)	30	22.2 (2.8)		5.81%	-2.9[-4.24,-1.56]



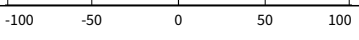
Study or subgroup	Protocol N	Protocol Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Sinclair 1997	20	11.3 (1.3)	20	27.8 (12.8)		1.78%	-16.5[-22.11,-10.89]
Valentine 1998	60	13 (2)	60	13 (2)		6.44%	0[-0.72,0.72]
Van der Linden 2010	20	18.5 (1.5)	17	15 (3.5)		5.24%	3.5[1.71,5.29]
Venn 2002	30	13.5 (9.2)	60	15.3 (13.2)		2.28%	-1.8[-6.49,2.89]
Wakeling 2005	67	11 (6)	67	13.1 (7.4)		4.61%	-2.15[-4.43,0.13]
Wilson 1999	92	16 (12)	46	21.9 (25.9)		1.04%	-5.9[-13.78,1.98]
Total * **	**2188**		**2081**			**100%**	**-1.21[-2.08,-0.33]**
Heterogeneity: Tau²=2.94; Chi²=166.13, df=24(P<0.0001); I²=85.55%							
Test for overall effect: Z=2.71(P=0.01)							



Favours experimental | Favours control

Analysis 4.12. Comparison 4 Sensitivity analysis: excluding studies with active controls, Outcome 12 Length of Critical Care Stay [Days].

Study or subgroup	Protocol N	Protocol Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Bender 1997	51	2.7 (1.4)	53	2.6 (3.6)		8.79%	0.1[-0.96,1.16]
Berlauk 1991	68	3.2 (1.8)	21	2.6 (2.1)		9.09%	0.6[-0.39,1.59]
Boyd 1993	53	1.7 (0.9)	54	1.7 (0.8)		12.03%	0[-0.32,0.32]
Jhanji 2010	90	5.5 (6)	45	5.8 (5.8)		4.68%	-0.35[-2.45,1.75]
Kapoor 2007	15	2.6 (0.9)	15	4.9 (1.8)		8.97%	-2.3[-3.32,-1.28]
Mayer 2010	30	1.7 (1.6)	30	1.7 (1.8)		9.67%	-0.09[-0.97,0.79]
Mythen 1995	30	1 (1)	30	1.7 (1.9)		10.21%	-0.7[-1.47,0.07]
Pearse 2005	62	1.8 (2.4)	60	1.9 (2.3)		9.9%	-0.08[-0.92,0.75]
Shoemaker 1988	28	10.2 (1.6)	30	11.5 (1.7)		9.82%	-1.3[-2.15,-0.45]
Valentine 1998	60	8 (1)	60	7 (1)		11.92%	1[0.64,1.36]
Wilson 1999	92	2.6 (4.2)	46	3.8 (6.3)		4.93%	-1.2[-3.21,0.81]
Total * **	**579**		**444**			**100%**	**-0.32[-0.89,0.26]**
Heterogeneity: Tau²=0.69; Chi²=63.72, df=10(P<0.0001); I²=84.31%							
Test for overall effect: Z=1.08(P=0.28)							



Favours experimental | Favours control

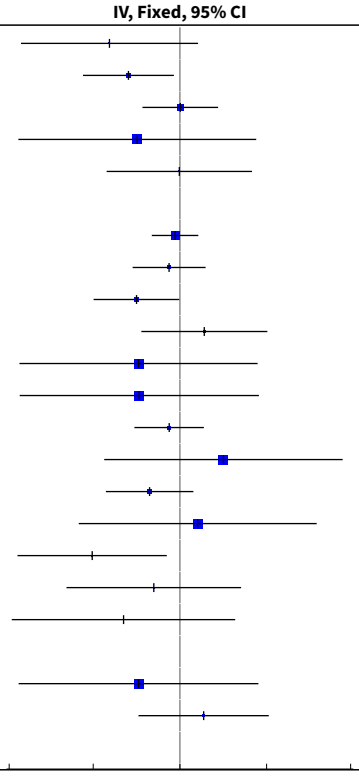
Comparison 5. Sensitivity analysis: excluding poorly-controlled studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality (Longest follow-up)	22	2586	Risk Ratio (IV, Fixed, 95% CI)	0.65 [0.48, 0.89]
2 Mortality (Hospital or 28 day)	22	2586	Risk Ratio (IV, Fixed, 95% CI)	0.66 [0.47, 0.92]
3 Renal Impairment	12	1601	Risk Ratio (IV, Fixed, 95% CI)	0.69 [0.47, 1.03]
4 Arrhythmia	5	469	Risk Ratio (IV, Fixed, 95% CI)	0.57 [0.30, 1.07]

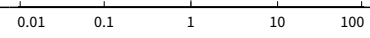
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Infection (Number of patients with infections)	7	509	Risk Ratio (IV, Fixed, 95% CI)	0.87 [0.68, 1.11]
6 Respiratory Failure/ ARDS	7	616	Risk Ratio (IV, Fixed, 95% CI)	0.55 [0.27, 1.10]
7 Myocardial Infarction	6	622	Risk Ratio (IV, Fixed, 95% CI)	0.66 [0.25, 1.73]
8 Congestive Heart Failure/ Pulmonary oedema	7	587	Risk Ratio (IV, Fixed, 95% CI)	0.64 [0.33, 1.26]
9 Venous Thrombosis	5	388	Risk Ratio (IV, Fixed, 95% CI)	0.50 [0.11, 2.32]
10 Number of patients with complications	14	1573	Risk Ratio (IV, Random, 95% CI)	0.66 [0.53, 0.81]
11 Length of Hospital Stay [Days]	18	2023	Mean Difference (IV, Random, 95% CI)	-1.61 [-2.85, -0.37]
12 Length of Critical Care Stay [Days]	9	1391	Mean Difference (IV, Random, 95% CI)	-0.74 [-1.43, -0.06]

Analysis 5.1. Comparison 5 Sensitivity analysis: excluding poorly-controlled studies, Outcome 1 Mortality (Longest follow-up).

Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Berlauk 1991	1/68	2/21		1.75%	0.15[0.01,1.62]
Boyd 1993	3/53	12/54		6.64%	0.25[0.08,0.85]
Challand 2012	7/89	7/90		9.56%	1.01[0.37,2.76]
Conway 2002	0/29	1/28		0.97%	0.32[0.01,7.59]
Donati 2007	2/68	2/67		2.6%	0.99[0.14,6.79]
Gan 2002	0/50	0/50			Not estimable
Jerez 2001	16/181	21/209		25.23%	0.88[0.47,1.63]
Jhanji 2010	9/90	6/45		10.3%	0.75[0.28,1.98]
Lobo 2000	3/19	9/18		7.49%	0.32[0.1,0.98]
Mckendry 2004	4/89	2/85		3.46%	1.91[0.36,10.16]
Mythen 1995	0/30	1/30		0.97%	0.33[0.01,7.87]
Noblett 2006	0/51	1/52		0.96%	0.34[0.01,8.15]
Pearse 2005	7/62	9/60		11.39%	0.75[0.3,1.89]
Pillai 2011	1/32	0/34		0.97%	3.18[0.13,75.38]
Pölönen 2000	4/196	9/197		7.18%	0.45[0.14,1.43]
Senagore 2009	1/42	0/22		0.97%	1.6[0.07,37.83]
Shoemaker 1988	1/28	11/30		2.46%	0.1[0.01,0.71]
Sinclair 1997	1/20	2/20		1.8%	0.5[0.05,5.08]
Ueno 1998	0/16	2/18		1.1%	0.22[0.01,4.34]
Van der Linden 2010	0/20	0/17			Not estimable
Wakeling 2005	0/67	1/67		0.96%	0.33[0.01,8.04]
Ziegler 1997	3/32	2/40		3.24%	1.88[0.33,10.55]



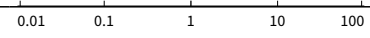
Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Total (95% CI)	**1332**	**1254**		**100%**	**0.65[0.48,0.89]**
Total events: 63 (Protocol), 100 (Control)					
Heterogeneity: Tau^2=0; Chi^2=16.81, df=19(P=0.6); I^2=0%					
Test for overall effect: Z=2.72(P=0.01)					



Favours protocol — Favours control

Analysis 5.2. Comparison 5 Sensitivity analysis: excluding poorly-controlled studies, Outcome 2 Mortality (Hospital or 28 day).

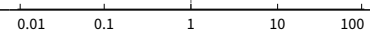
Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Berlauk 1991	1/68	2/21		2.01%	0.15[0.01,1.62]
Boyd 1993	3/53	12/54		7.61%	0.25[0.08,0.85]
Challand 2012	3/89	4/90		5.15%	0.76[0.17,3.29]
Conway 2002	0/29	1/28		1.11%	0.32[0.01,7.59]
Donati 2007	2/68	2/67		2.97%	0.99[0.14,6.79]
Gan 2002	0/50	0/50			Not estimable
Jerez 2001	16/181	21/209		28.92%	0.88[0.47,1.63]
Jhanji 2010	9/90	6/45		11.81%	0.75[0.28,1.98]
Lobo 2000	3/19	6/18		7.37%	0.47[0.14,1.62]
Mckendry 2004	4/89	2/85		3.97%	1.91[0.36,10.16]
Mythen 1995	0/30	1/30		1.11%	0.33[0.01,7.87]
Noblett 2006	0/51	1/52		1.1%	0.34[0.01,8.15]
Pearse 2005	6/62	7/60		10.43%	0.83[0.3,2.33]
Pillai 2011	1/32	0/34		1.11%	3.18[0.13,75.38]
Pölönen 2000	2/196	6/197		4.4%	0.34[0.07,1.64]
Senagore 2009	1/42	0/22		1.11%	1.6[0.07,37.83]
Shoemaker 1988	1/28	10/30		2.8%	0.11[0.01,0.78]
Sinclair 1997	1/20	2/20		2.06%	0.5[0.05,5.08]
Ueno 1998	0/16	2/18		1.26%	0.22[0.01,4.34]
Van der Linden 2010	0/20	0/17			Not estimable
Wakeling 2005	0/67	0/67			Not estimable
Ziegler 1997	3/32	2/40		3.71%	1.88[0.33,10.55]
Total (95% CI)	**1332**	**1254**		**100%**	**0.66[0.47,0.92]**
Total events: 56 (Protocol), 87 (Control)					
Heterogeneity: Tau^2=0; Chi^2=14.65, df=18(P=0.69); I^2=0%					
Test for overall effect: Z=2.44(P=0.01)					



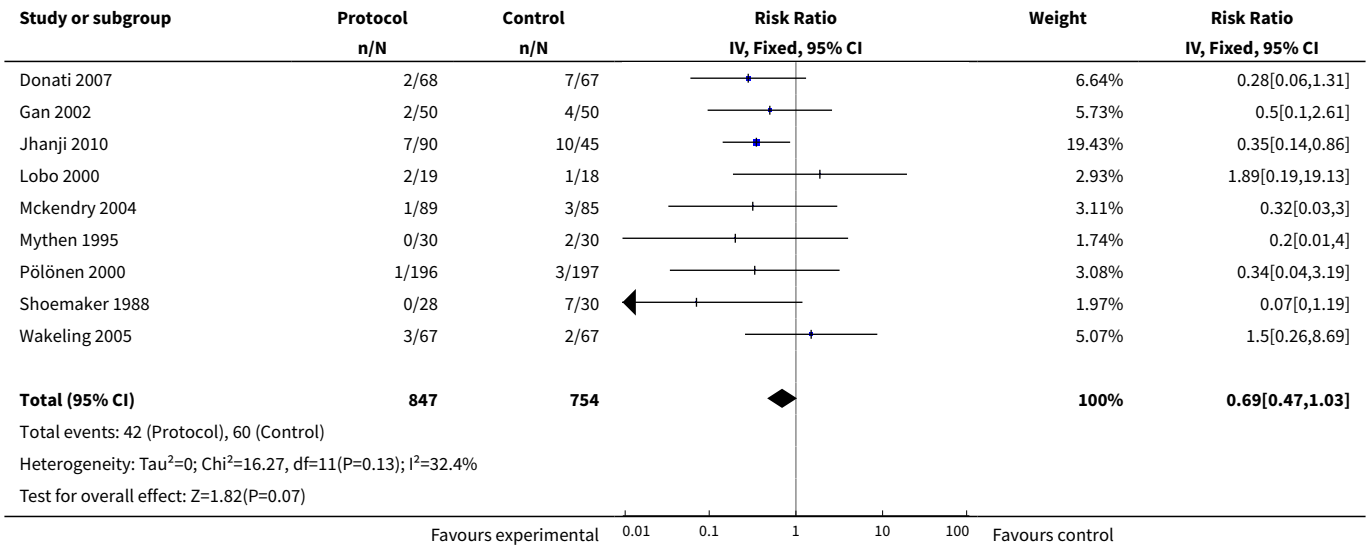
Favours experimental — Favours control

Analysis 5.3. Comparison 5 Sensitivity analysis: excluding poorly-controlled studies, Outcome 3 Renal Impairment.

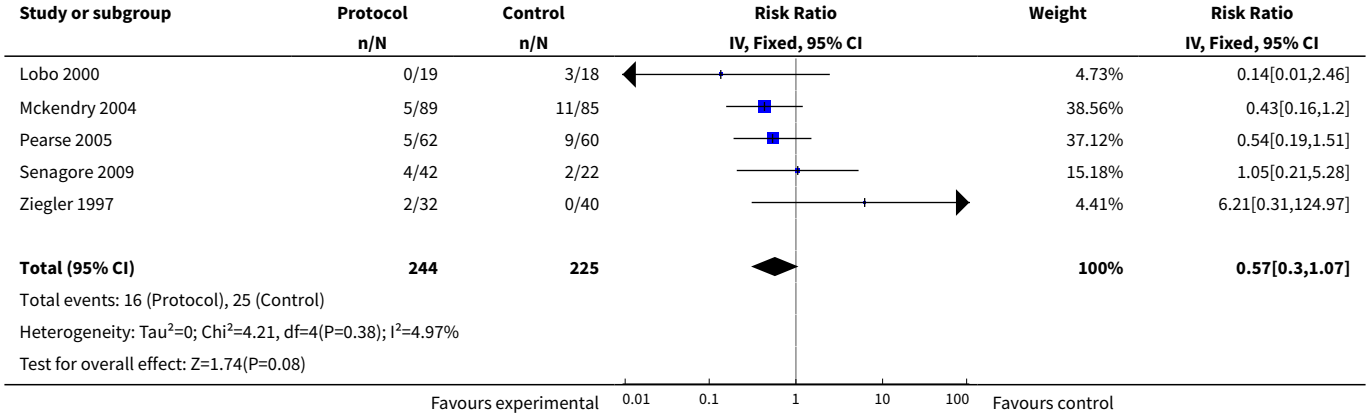
Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Berlauk 1991	1/68	1/21		2.1%	0.31[0.02,4.73]
Boyd 1993	3/53	7/54		9.28%	0.44[0.12,1.6]
Challand 2012	20/89	13/90		38.93%	1.56[0.83,2.93]



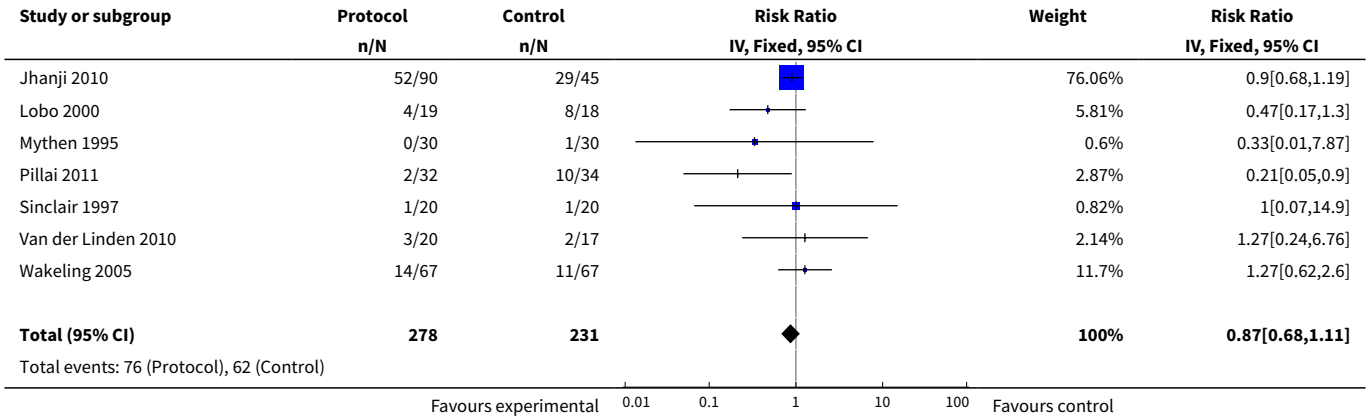
Favours experimental — Favours control



Analysis 5.4. Comparison 5 Sensitivity analysis: excluding poorly-controlled studies, Outcome 4 Arrhythmia.



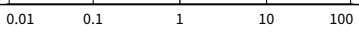
Analysis 5.5. Comparison 5 Sensitivity analysis: excluding poorly-controlled studies, Outcome 5 Infection (Number of patients with infections).



Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=6.77, df=6(P=0.34); I²=11.37%					
Test for overall effect: Z=1.16(P=0.25)					

Analysis 5.6. Comparison 5 Sensitivity analysis: excluding poorly-controlled studies, Outcome 6 Respiratory Failure/ ARDS.

Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Boyd 1993	3/53	7/54		28.68%	0.44[0.12,1.6]
Donati 2007	4/68	4/67		26.75%	0.99[0.26,3.78]
Gan 2002	1/50	3/50		9.73%	0.33[0.04,3.1]
Mythen 1995	0/30	1/30		4.84%	0.33[0.01,7.87]
Pearse 2005	2/62	2/60		13.01%	0.97[0.14,6.65]
Shoemaker 1988	1/28	9/30		12.07%	0.12[0.02,0.88]
Ueno 1998	1/16	0/18		4.92%	3.35[0.15,76.93]
Total (95% CI)	**307**	**309**		**100%**	**0.55[0.27,1.1]**
Total events: 12 (Protocol), 26 (Control)					
Heterogeneity: Tau²=0; Chi²=4.99, df=6(P=0.55); I²=0%					
Test for overall effect: Z=1.7(P=0.09)					



Analysis 5.7. Comparison 5 Sensitivity analysis: excluding poorly-controlled studies, Outcome 7 Myocardial Infarction.

Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Berlauk 1991	3/68	1/21		18.74%	0.93[0.1,8.44]
Boyd 1993	1/53	4/54		19.64%	0.25[0.03,2.2]
Mckendry 2004	1/89	1/85		12.05%	0.96[0.06,15.03]
Pearse 2005	0/62	3/60		10.57%	0.14[0.01,2.62]
Shoemaker 1988	0/28	0/30			Not estimable
Ziegler 1997	3/32	3/40		39.01%	1.25[0.27,5.78]
Total (95% CI)	**332**	**290**		**100%**	**0.66[0.25,1.73]**
Total events: 8 (Protocol), 12 (Control)					
Heterogeneity: Tau²=0; Chi²=2.66, df=4(P=0.62); I²=0%					
Test for overall effect: Z=0.84(P=0.4)					

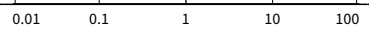
Analysis 5.8. Comparison 5 Sensitivity analysis: excluding poorly-controlled studies, Outcome 8 Congestive Heart Failure/ Pulmonary oedema.

Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Berlauk 1991	4/68	1/21		9.95%	1.24[0.15,10.46]
Boyd 1993	4/53	10/54		37.81%	0.41[0.14,1.22]
Lobo 2000	0/19	1/18		4.61%	0.32[0.01,7.3]
Pearse 2005	3/62	4/60		21.47%	0.73[0.17,3.11]
Shoemaker 1988	2/28	3/30		15.46%	0.71[0.13,3.96]
Sinclair 1997	1/20	1/20		6.22%	1[0.07,14.9]
Wakeling 2005	1/67	0/67		4.48%	3[0.12,72.35]
Total (95% CI)	**317**	**270**		**100%**	**0.64[0.33,1.26]**
Total events: 15 (Protocol), 20 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.26, df=6(P=0.89); I^2=0%					
Test for overall effect: Z=1.29(P=0.2)					

Favours experimental — Favours control

Analysis 5.9. Comparison 5 Sensitivity analysis: excluding poorly-controlled studies, Outcome 9 Venous Thrombosis.

Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Boyd 1993	0/53	2/54		26.1%	0.2[0.01,4.15]
Lobo 2000	0/19	1/18		24.06%	0.32[0.01,7.3]
Pearse 2005	0/62	1/60		23.41%	0.32[0.01,7.77]
Senagore 2009	2/42	0/22		26.43%	2.67[0.13,53.39]
Shoemaker 1988	0/28	0/30			Not estimable
Total (95% CI)	**204**	**184**		**100%**	**0.5[0.11,2.32]**
Total events: 2 (Protocol), 4 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.7, df=3(P=0.64); I^2=0%					
Test for overall effect: Z=0.89(P=0.38)					



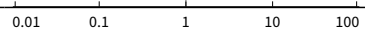
Favours experimental — Favours control

Analysis 5.10. Comparison 5 Sensitivity analysis: excluding poorly-controlled studies, Outcome 10 Number of patients with complications.

Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Berlauk 1991	11/68	9/21		6.04%	0.38[0.18,0.79]
Challand 2012	10/89	13/90		5.6%	0.78[0.36,1.68]
Conway 2002	5/29	9/28		3.93%	0.54[0.2,1.4]
Donati 2007	8/68	20/67		5.87%	0.39[0.19,0.83]
Jerez 2001	53/181	65/209		15.71%	0.94[0.7,1.28]
Jhanji 2010	57/90	30/45		17.23%	0.95[0.73,1.23]
Lobo 2000	6/19	12/18		5.98%	0.47[0.23,0.99]
Mythen 1995	0/30	6/30		0.53%	0.08[0,1.31]

Favours experimental — Favours control

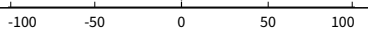
Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Noblett 2006	1/51	8/52		1%	0.13[0.02,0.98]
Pearse 2005	27/62	41/60		14.75%	0.64[0.46,0.89]
Shoemaker 1988	8/28	15/30		6.65%	0.57[0.29,1.14]
Sinclair 1997	1/20	1/20		0.58%	1[0.07,14.9]
Ueno 1998	4/16	5/18		2.99%	0.9[0.29,2.78]
Wakeling 2005	24/67	38/67		13.13%	0.63[0.43,0.93]
Total (95% CI)	**818**	**755**		**100%**	**0.66[0.53,0.81]**
Total events: 215 (Protocol), 272 (Control)					
Heterogeneity: Tau^2=0.05; Chi^2=21.22, df=13(P=0.07); I^2=38.74%					
Test for overall effect: Z=3.91(P<0.0001)					



Favours experimental — Favours control

Analysis 5.11. Comparison 5 Sensitivity analysis: excluding poorly-controlled studies, Outcome 11 Length of Hospital Stay [Days].

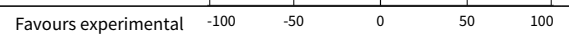
Study or subgroup	Protocol N	Protocol Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Berlauk 1991	68	18.9 (11.7)	21	15.4 (7.5)		4.39%	3.5[-0.75,7.75]
Boyd 1993	53	16 (19)	54	12.5 (8.3)		3.2%	3.5[-2.07,9.07]
Challand 2012	89	8.8 (4.4)	90	6.7 (6.3)		7.86%	2.1[0.51,3.69]
Conway 2002	26	12 (24)	28	11 (5.8)		1.44%	1[-8.47,10.47]
Donati 2007	68	11.3 (3.8)	67	13.4 (6.1)		7.69%	-2.1[-3.82,-0.38]
Gan 2002	50	5 (3)	50	7 (3)		8.35%	-2[-3.18,-0.82]
Jhanji 2010	90	20.8 (13.3)	45	18.5 (11.5)		4.29%	2.3[-2.04,6.64]
Lobo 2000	19	16 (8)	18	13.8 (8.8)		3.32%	2.25[-3.16,7.66]
Mckendry 2004	89	7 (2.2)	85	9 (3.7)		8.61%	-2[-2.91,-1.09]
Mythen 1995	30	6.4 (1.1)	30	10.1 (9.4)		5.39%	-3.7[-7.09,-0.31]
Noblett 2006	51	8 (5)	52	12.4 (9.4)		6.05%	-4.4[-7.3,-1.5]
Pearse 2005	62	17.5 (20.8)	60	29.5 (34.8)		1.27%	-12[-22.21,-1.79]
Pillai 2011	32	18 (10.7)	34	22 (10.7)		3.51%	-4[-9.17,1.17]
Pölönen 2000	196	6 (1.5)	197	7 (0.7)		9%	-1[-1.23,-0.77]
Shoemaker 1988	28	19.3 (2.4)	30	25.2 (3.4)		7.96%	-5.9[-7.41,-4.39]
Sinclair 1997	20	11.3 (1.3)	20	27.8 (12.8)		3.17%	-16.5[-22.11,-10.89]
Van der Linden 2010	20	18.5 (1.5)	17	15 (3.5)		7.6%	3.5[1.71,5.29]
Wakeling 2005	67	11 (6)	67	13.1 (7.4)		6.91%	-2.15[-4.43,0.13]
Total * **	**1058**		**965**			**100%**	**-1.61[-2.85,-0.37]**
Heterogeneity: Tau^2=4.44; Chi^2=141.69, df=17(P<0.0001); I^2=88%							
Test for overall effect: Z=2.54(P=0.01)							



Favours experimental — Favours control

Analysis 5.12. Comparison 5 Sensitivity analysis: excluding poorly-controlled studies, Outcome 12 Length of Critical Care Stay [Days].

Study or subgroup	Protocol N	Protocol Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Berlauk 1991	68	3.2 (1.8)	21	2.6 (2.1)		12.07%	0.6[-0.39,1.59]
Boyd 1993	53	1.7 (0.9)	54	1.7 (0.8)		15.6%	0[-0.32,0.32]
Jerez 2001	181	4.8 (7)	209	5.7 (9)		8.66%	-0.9[-2.49,0.69]
Jhanji 2010	90	5.5 (6)	45	5.8 (6.5)		5.85%	-0.35[-2.62,1.92]
Lobo 2000	19	6.8 (3.3)	18	7.3 (4.8)		4.78%	-0.5[-3.14,2.14]
Mythen 1995	30	1 (1)	30	1.7 (1.9)		13.44%	-0.7[-1.47,0.07]
Pearse 2005	62	1.8 (2.4)	60	1.9 (2.3)		13.06%	-0.08[-0.92,0.75]
Pölönen 2000	196	1 (0.7)	197	1 (0.7)		16.04%	0[-0.15,0.15]
Shoemaker 1988	28	10.2 (1.6)	30	15.8 (3.1)		10.48%	-5.6[-6.86,-4.34]
Total ***	**727**		**664**			**100%**	**-0.74[-1.43,-0.06]**
Heterogeneity: Tau²=0.76; Chi²=80.85, df=8(P<0.0001); I²=90.11%							
Test for overall effect: Z=2.12(P=0.03)							

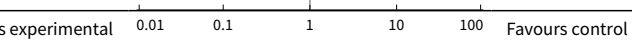


Comparison 6. Sensitivity analysis: Sandham 2003

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality (Longest Follow-up)- excluding patients lost follow-up	31	5139	Risk Ratio (IV, Fixed, 95% CI)	0.91 [0.78, 1.08]
2 Mortality (Longest Follow-up)- if all patients lost follow-up have died	31	5292	Risk Ratio (IV, Fixed, 95% CI)	1.02 [0.89, 1.18]

Analysis 6.1. Comparison 6 Sensitivity analysis: Sandham 2003, Outcome 1 Mortality (Longest Follow-up)- excluding patients lost follow-up.

Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Bender 1997	1/51	1/53		0.36%	1.04[0.07,16.18]
Berlauk 1991	1/68	2/21		0.49%	0.15[0.01,1.62]
Bonazzi 2002	0/50	0/50			Not estimable
Boyd 1993	3/53	12/54		1.85%	0.25[0.08,0.85]
Cecconi 2011	0/20	0/20			Not estimable
Challand 2012	7/89	7/90		2.66%	1.01[0.37,2.76]
Conway 2002	0/29	1/28		0.27%	0.32[0.01,7.59]
Donati 2007	2/68	2/67		0.72%	0.99[0.14,6.79]
Gan 2002	0/50	0/50			Not estimable
Jerez 2001	16/181	21/209		7.02%	0.88[0.47,1.63]
Jhanji 2010	9/90	6/45		2.86%	0.75[0.28,1.98]
Kapoor 2007	0/15	0/15			Not estimable
Lobo 2000	3/19	9/18		2.08%	0.32[0.1,0.98]
Mayer 2010	2/30	2/30		0.75%	1[0.15,6.64]



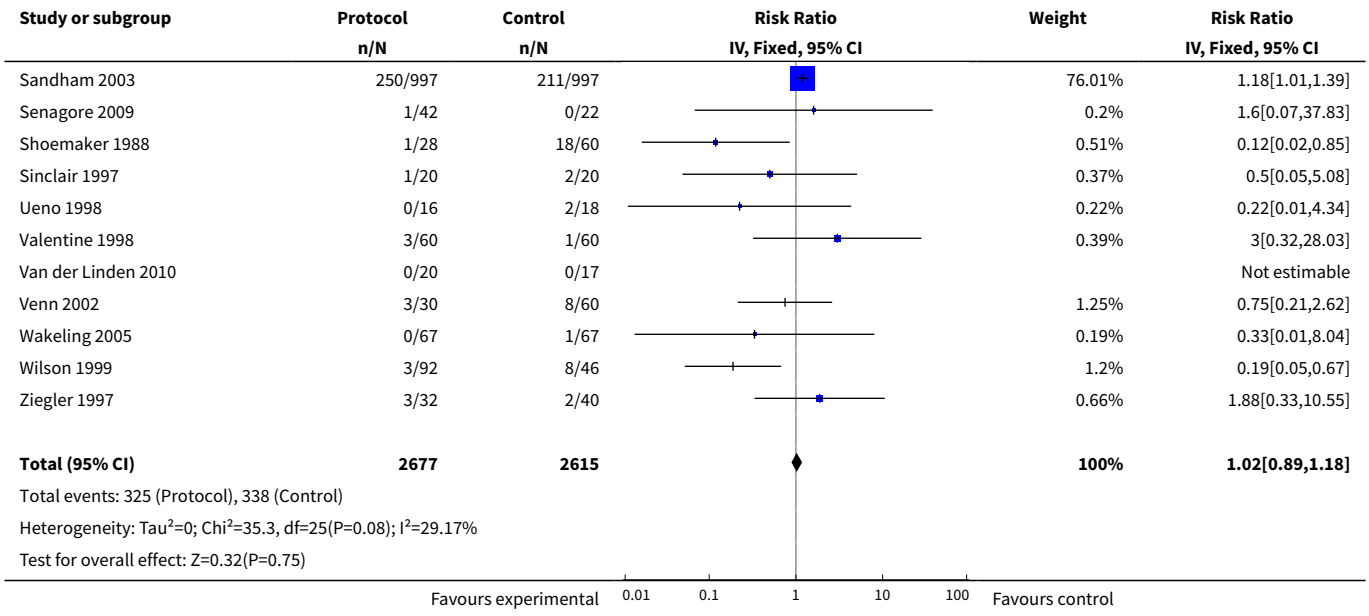
Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Mckendry 2004	4/89	2/85		0.96%	1.91[0.36,10.16]
Mythen 1995	0/30	1/30		0.27%	0.33[0.01,7.87]
Noblett 2006	0/51	1/52		0.27%	0.34[0.01,8.15]
Pearse 2005	7/62	9/60		3.17%	0.75[0.3,1.89]
Pillai 2011	1/32	0/34		0.27%	3.18[0.13,75.38]
Pölönen 2000	4/196	9/187		2%	0.42[0.13,1.35]
Sandham 2003	163/910	155/941		67.18%	1.09[0.89,1.33]
Senagore 2009	1/42	0/22		0.27%	1.6[0.07,37.83]
Shoemaker 1988	1/28	18/60		0.7%	0.12[0.02,0.85]
Sinclair 1997	1/20	2/20		0.5%	0.5[0.05,5.08]
Ueno 1998	0/16	2/18		0.31%	0.22[0.01,4.34]
Valentine 1998	3/60	1/60		0.54%	3[0.32,28.03]
Van der Linden 2010	0/20	0/17			Not estimable
Venn 2002	3/30	8/60		1.72%	0.75[0.21,2.62]
Wakeling 2005	0/67	1/67		0.27%	0.33[0.01,8.04]
Wilson 1999	3/92	8/46		1.64%	0.19[0.05,0.67]
Ziegler 1997	3/32	2/40		0.9%	1.88[0.33,10.55]
Total (95% CI)	**2590**	**2549**		**100%**	**0.91[0.78,1.08]**
Total events: 238 (Protocol), 282 (Control)					
Heterogeneity: Tau²=0; Chi²=30.89, df=25(P=0.19); I²=19.07%					
Test for overall effect: Z=1.08(P=0.28)					

Favours experimental — Favours control

Analysis 6.2. Comparison 6 Sensitivity analysis: Sandham 2003, Outcome 2 Mortality (Longest Follow-up)- if all patients lost follow-up have died.

Study or subgroup	Protocol n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Bender 1997	1/51	1/53		0.26%	1.04[0.07,16.18]
Berlauk 1991	1/68	2/21		0.36%	0.15[0.01,1.62]
Bonazzi 2002	0/50	0/50			Not estimable
Boyd 1993	3/53	12/54		1.35%	0.25[0.08,0.85]
Cecconi 2011	0/20	0/20			Not estimable
Challand 2012	7/89	7/90		1.94%	1.01[0.37,2.76]
Conway 2002	0/29	1/28		0.2%	0.32[0.01,7.59]
Donati 2007	2/68	2/67		0.53%	0.99[0.14,6.79]
Gan 2002	0/50	0/50			Not estimable
Jerez 2001	16/181	21/209		5.13%	0.88[0.47,1.63]
Jhanji 2010	9/90	6/45		2.09%	0.75[0.28,1.98]
Kapoor 2007	0/15	0/15			Not estimable
Lobo 2000	3/19	9/18		1.52%	0.32[0.1,0.98]
Mayer 2010	2/30	2/30		0.55%	1[0.15,6.64]
Mckendry 2004	4/89	2/85		0.7%	1.91[0.36,10.16]
Mythen 1995	0/30	1/30		0.2%	0.33[0.01,7.87]
Noblett 2006	0/51	1/52		0.19%	0.34[0.01,8.15]
Pearse 2005	7/62	9/60		2.31%	0.75[0.3,1.89]
Pillai 2011	1/32	0/34		0.2%	3.18[0.13,75.38]
Pölönen 2000	4/196	9/197		1.46%	0.45[0.14,1.43]

Favours experimental — Favours control



ADDITIONAL TABLES

Table 1. Study outcomes

Study	Mortality	Morbidity	Resource use	Cost
Bender 1997	Hospital	Pulmonary oedema, acute myocardial infarction, arrhythmia, acute renal failure, wound infection, haemorrhage, sepsis, graft thrombosis or infection, groin haematoma.	HLOS, ICULOS	Cost
Berlauk 1991	Hospital	Acute renal failure, congestive cardiac failure, graft thrombosis, acute myocardial infarction, arrhythmia,	HLOS, ICULOS	Cost
Bonazzi 2002	Hospital	Arrhythmias, myocardial infarction, congestive heart failure, renal failure	HLOS	None
Boyd 1993	28 day	Respiratory failure, acute renal failure, sepsis, cardiorespiratory arrest, pulmonary oedema, pleural fluid, wound infection, disseminated intravascular coagulation, acute myocardial infarction, abdominal abscess, haemorrhage, gastric outlet obstruction, cerebrovascular accident, pulmonary embolism, chest infection, psychosis, distal ischaemia	HLOS, ICULOS	Reported separately
Cecconi 2011	28 day	Infections, hypotension, anaemia, pneumonia, pulmonary embolism, tachyarrhythmias, acute coronary syndrome, acute renal failure	HLOS	None
Challand 2012	30 days 90 days	Serious postoperative complications, renal complications, creatinine increase, critical care admission	HLOS	None

Table 1. Study outcomes *(Continued)*

Conway 2002	Hospital	Tolerating oral diet	HLOS, ICULOS	None
Donati 2007	Hospital	Organ failures	HLOS	None
Gan 2002	Hospital	Acute renal dysfunction (urine output <500mls), respiratory support for > 24 hours, cardiovascular (hypotension, pulmonary oedema, arrhythmia), chest infection (clinical diagnosis), severe post-operative nausea and vomiting requiring rescue antiemetic, coagulopathy, wound infection, toleration of oral solid diet.	HLOS	None
Jerez 2001	Hospital	Organ failures	ICULOS	None
Jhanji 2010	Hospital	Cardiac complications, infections, acute kidney injury	HLOS, ICULOS	None
Kapoor 2007	Hospital	arrhythmia, renal dysfunction, low cardiac output	HLOS, ICULOS	None
Lobo 2000	28 day, 60 day	Sepsis, shock, septic shock, cardiogenic shock, nosocomial infection, acute pancreatitis, postoperative fistula, arrhythmia, cerebrovascular accident, deep vein thrombosis, gastrointestinal bleeding, hypothermia, sepsis related organ failure assessment (SOFA) score, bronchopneumonia, urinary tract infection, wound infection. ventilator days, organ dysfunction	HLOS, ICULOS	None
Mayer 2010	Hospital	Infection (pneumonia, abdominal, urinary tract, wound), respiratory (PE, respiratory support), cardiovascular (pulmonary oedema, arrhythmia, hypotension, acute myocardial infarction, stroke), abdominal (bowel obstruction, gastrointestinal bleeding, anastomotic leak), renal (urine output ,500ml/day or required dialysis for acute renal failure), post operative haemorrhage	HLOS, ICULOS	None
Mckendry 2004	Hospital mortality	Atrial fibrillation requiring treatment, pneumothorax, cerebrovascular accident, chest infection or sternal wound infection, GI bleed, acute renal failure, pleural effusion, infected leg wound, aortic regurgitation	HLOS, ICULOS	None
Mythen 1995	Hospital	Knaus organ failure criteria, chest infection, pleural effusion, disorientation, respiratory failure, nausea and vomiting, cerebrovascular accident, paralytic ileus, pericardial effusion.	HLOS, ICULOS	Reported separately
Noblett 2006	Hospital	surgical fitness for discharge, return of gastrointestinal function, flatus, bowel movement, food tolerance, readmission rate, cytokine markers of the systemic inflammatory response	HLOS, ICULOS	None
Pearse 2005	Hospital, 28 and 60 day mortality	Number of patients with complications, infection (pneumonia, abdominal, urinary tract, CVC, wound), respiratory (pleural effusion, pneumotho-	HLOS, ICUOS	None

Table 1. Study outcomes *(Continued)*

		rax, pulmonary embolism, ARDS), cardiovascular (arrhythmia, pulmonary oedema, MI, stroke), abdominal (*C. Diff*, diarrhoea, acute bowel obstruction, upper GI bleed, paralytic ileus, anastomotic leak, intra-abdominal hypertension), postoperative massive haemorrhage.		
Pillai 2011	None	Nausea and vomiting, wound dehiscence, wound infection, ileus	HLOS	None
Pölönen 2000	28 day, 6 month, 12 month	Organ dysfunctions: central nervous system (hemiplegia, stroke, Glasgow coma scale (GCS <10), circulatory (vasoactive medication or intraaortic counterpulsation to treat hypotension or low cardiac output), respiratory (need for mechanical or assisted ventilation), renal (low urine output or increased creatinine), hepatic (increased liver enzymes or bilirubin), gastrointestinal (macroscopic bleeding or paralytic ileus), haematological (low white cell or platelet count), ICU readmission.	HLOS, ICULOS	None
Sandham 2003	Hospital, 6 month, 12 month	Myocardial infarction, congestive heart failure, supraventricular tachycardia, pulmonary embolism, renal insufficiency, hepatic insufficiency, sepsis from central venous catheter (CVC) or pulmonary artery catheter (PAC), wound infection, pneumonia, adverse events related to PAC or CVC: pulmonary infarction, haemothorax, pulmonary haemorrhage, pneumothorax, arterial puncture.	HLOS	None
Senagore 2009	Hospital	Complications: Gastrointestinal failure, blood pressure lability, arrhythmia, dehydration, electrolyte imbalance, hyperglycaemia, wound/infectious complications, sepsis, DVT/PE, intraoperative hypothermia, urinary dysfunction,respiratory dysfunction, abdominal pain, chest pain, bleeding, anaemia, altered mental status.	HLOS	None
Shoemaker 1988	Hospital	Respiratory failure, renal failure, sepsis and septic shock, hepatic failure, cardiac arrest, pulmonary edema, pleural effusion, wound infection, disseminated intravascular coagulation (DIC), acute myocardial infarction, evisceration, abdominal abscess, haemorrhage, pancreatitis, gastric outlet obstruction, urinary tract infection, cerebral infarct, pulmonary embolism, ventilator days	HLOS, ICULOS	Cost
Sinclair 1997	Hospital	None, "time declared fit for medical discharge"	HLOS	None
Ueno 1998	Hospital	Bleeding, peritoneal infection, adult respiratory distress syndrome, hyperbilirubinaemia, liver failure	None	None
Valentine 1998	Hospital	Myocardial infarction, arrhythmia, congestive heart failure, pneumonia, non-cardiogenic pulmonary insufficiency, acute renal insufficiency, catheter sepsis. ventilator days	HLOS, ICULOS	None

Table 1. Study outcomes *(Continued)*

Van der Linden 2010	Hospital	Blood loss, infection	HLOS	None
Venn 2002	Hospital	"Time to medical fitness for discharge", deep haemorrhage requiring >2 unit blood transfusion, haematemesis, chest infection, wound infection, cellulitis, pancreatitis, pulmonary embolus, cerebrovascular accident, myocardial infarction, cardiac failure, rapid atrial fibrillation, hypotension, impaired renal function, pseudo-obstruction.	HLOS	None
Wakeling 2005	hospital and 6 month mortality	Time until fit for discharge, bowel recovery (flatus, bowels opening, full diet), quality of recovery score, postoperative morbidity survey (POMS), quality of life questionnaires (European Organisation for the Research and Treatment of Cancer (EORTC) - QLQ-C30 and QLQ-CR38)	HLOS	None
Wilson 1999	Hospital	Respiratory (prolonged weaning, adult respiratory distress syndrome (ARDS), pleural effusion, secondary ventilation, sputum retention), cardiovascular (myocardial infarction, arrhythmia, cardiac arrest, pulmonary embolus, cerebrovascular accident, transient ischaemic attack, cardiac failure), gastrointestinal (infarction, haemorrhage), acute renal failure, coagulopathy, infection (bacteraemia, sepsis syndrome, septic shock, respiratory sepsis, urinary sepsis, abdominal sepsis, wound sepsis, line sepsis, other sepsis), surgical (anastomotic breakdown, deep haemorrhage, wound haemorrhage)	HLOS, ICULOS	Reported separately
Ziegler 1997	Hospital	Hypotension, congestive heart failure, myocardial infarction, arrhythmia, oliguria, graft thrombosis, cerebrovascular accident	ICULOS	None

APPENDICES

Appendix 1. Search strategy for CENTRAL , The Cochrane Library

#1 (Vasoactive or Fluid* or Drug Administration or fluid therapy or starch or gelatin* or crystalloid* or colloid* or splanchnic* or pulmonary artery flotation or catheter* or PAFC or Swan Ganz or Doppler):ti,ab
#2 ((fluid* near (load* or administrat*)) or (perfusion near (renal or tissue)))
#3 base near (acid or excess or deficit)
#4 Venous near (Oxygen Saturation)
#5 ((Stroke Volume Index) or (Oxygen Consumption Index)):ti,ab
#6 (oxygen near (delivery or consumption or saturation)):ti,ab
#7 (cardiac near (output or index)):ti,ab
#8 (lactat* or CVP or pHi or PCO2 or SvO2 or VO2 or DO2 or Tonometry):ti,ab
#9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10 ((surg* or operat*) near (general or high?risk or vascular or cardiac or cancer or trauma* or emergency or orthopaed*)):ti,ab
#11 (peri?operativ* or post?operativ* or intra?operativ* or optimi?ation or goal?directed or supra?normal or aneurysm):ti,ab
#12 (#10 OR #11)
#13 (#9 AND #12)

Appendix 2. Search strategy for MEDLINE (OvidSP)

1. Fluid-Therapy/ or Body-Fluids/ or Catheterization-Swan-Ganz/ or Catheterization/ or Heart-Catheterization/
2. (Vasoactive or Fluid* or Drug Administration or fluid therapy or starch or gelatin* or crystalloid* or colloid* or splanchnic* or pulmonary artery flotation or catheter* or PAFC or Swan Ganz or Doppler).ti,ab.
3. ((fluid* adj3 (load* or administrat*)) or (perfusion adj3 (renal or tissue))).mp.
4. Blood-Volume/ or Oxygen-Consumption/ or Central-Venous-Pressure/ or Stroke-Volume/ or Cardiac-Output/ or Echocardiography/ or Echocardiography-Doppler/
5. ((base adj3 (acid or excess or deficit)) or ((Venous adj3 Oxygen Saturation) or Stroke Volume Index or Oxygen Consumption Index)).mp. or ((oxygen adj3 (delivery or consumption or saturation)) or (cardiac adj3 (output or index)) or lactat* or CVP or pHi or PCO2 or SvO2 or VO2 or DO2 or Tonometry).ti,ab.
6. 1 or 2 or 3 or 4 or 5
7. Perioperative-Care/ or Intraoperative-Period/ or Postoperative-Period/ or Aneurysm/ or Vascular-Surgical-Procedures/ or Thoracic-Surgery/ or Emergency-Treatment/ or Specialties-Surgical/ or Orthopedics/ or Surgical-Procedures-Operative/
8. ((surg* or operat*) adj3 (general or high?risk or vascular or cardiac or cancer or trauma* or emergency or orthopaed*)).ti,ab.
9. (peri?operativ* or post?operativ* or intra?operativ* or optimi?ation or goal?directed or supra?normal or aneurysm).ti,ab.
10. 8 or 7 or 9
11. 6 and 10
12. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.
13. 11 and 12

Appendix 3. Search strategy for EMBASE (OvidSP)

1. fluid therapy/ or body fluid/ or Swan Ganz catheter/ or heart catheterization/ or blood volume/ or oxygen consumption/ or central venous pressure/ or heart stroke volume/ or heart output/ or Doppler echocardiography/ or echocardiography/
2. (Vasoactive or Fluid* or Drug Administration or fluid therapy or starch or gelatin* or crystalloid* or colloid* or splanchnic* or pulmonary artery flotation or catheter* or PAFC or Swan Ganz or Doppler).ti,ab. or ((fluid* adj3 (load* or administrat*)) or (perfusion adj3 (renal or tissue))).mp.
3. ((base adj3 (acid or excess or deficit)) or ((Venous adj3 Oxygen Saturation) or Stroke Volume Index or Oxygen Consumption Index)).mp. or ((oxygen adj3 (delivery or consumption or saturation)) or (cardiac adj3 (output or index)) or lactate* or CVP or pHi or PCO2 or SvO2 or VO2 or DO2 or Tonometry).ti,ab.
4. 1 or 2 or 3
5. perioperative period/ or postoperative period/ or aneurysm/ or vascular surgery/ or thorax surgery/ or emergency treatment/ or orthopedics/ or surgery/
6. ((surg* or operat*) adj3 (general or high?risk or vascular or cardiac or cancer or trauma* or emergency or orthopaed*)).ti,ab.
7. (peri?operativ* or post?operativ* or intra?operativ* or optimi?ation or goal?directed or supra?normal or aneurysm).ti,ab.
8. 6 or 7 or 5
9. 8 and 4
10. (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab.) not (animals not (humans and animals)).sh.
11. 10 and 9

Appendix 4. Keywords used in search strategy

We used the following topic specific key words :

Population:high-risk surgery, peri-operative, pre-operative, post-operative, intra-operative,aneurysm, vascular surgery, cardiac surgery, cancer surgery, trauma surgery, emergency surgery, orthopaedic surgery

Intervention: Optimisation, optimization, goal-directed, supra-normal, Vasoactive, fluids,starch, gelatin, blood product, crystalloid, colloid, fluid therapy,fluid loading, fluid administration, body fluid

Comparison: Oxygen delivery, lactate, acid base, oxygen consumption, base excess, base deficit, blood volume,central venous pressure, CVP, cardiac output, cardiac index, pulmonary artery flotation catheter, PAFC, right-heart catheter, Swan Ganz, Doppler, pHi, tonometry, PCO_2 gap, echocardiography, stroke volume, SvO_2, mixed venous oxygen saturation.

Outcomes: Splanchnic, renal perfusion, tissue perfusion, blood flow.

Appendix 5. Included studies

Study and Year of Publication	Country	Journal

(Continued)

Bender 1997	USA	*Annals of Surgery*
Berlauk 1991	USA	*Annals of Surgery*
Bonazzi 2002	Italy	*Eurpoean Journal of Vascular Surgery*
Boyd 1993	UK	*JAMA*
Cecconi 2011	Italy	*Critical Care*
Challand 2012	UK	*British Journal of Anaesthesia*
Conway 2002	UK	*Anaesthesia*
Donati 2007	Italy	*Chest*
Gan 2002	USA	*Anesthesiology*
Jerez 2001	Spain	*Medicina Intensiva*
Jhanji 2010	UK	*Critical Care*
Kapoor 2007	India	*Annals of Cardiac Anaesthesia*
Lobo 2000	Brazil	*Critical Care Medicine*
Mayer 2010	Germany	*Critical Care*
Mckendry 2004	UK	*BMJ*
Mythen 1995	UK	*Archives of Surgery*
Noblett 2006	UK	*The British Journal of Surgery*
Pearse 2005	UK	*Critical Care*
Pillai 2011	UK	*The Journal of Urology*
Pölönen 2000	Finland	*Anesthesia and Analgesia*
Sandham 2003	Canada	*New England Journal of Medicine*
Senagore 2009	USA	*Diseases of Colon and Rectum*
Shoemaker 1988	USA	*Chest*
Sinclair 1997	UK	*BMJ*
Ueno 1998	Japan	*Surgery*
Valentine 1998	USA	*Journal of Vascular Surgery*
Van der Linden 2010	Belgium	*European Journal of Anaesthesiology*
Venn 2002	UK	*British Journal of Anaesthesia*

(Continued)

Wakeling 2005	UK	*British Journal of Anaesthesia*
Wilson 1999	UK	*BMJ*
Ziegler 1997	USA	*Surgery*

Footnotes

Appendix 6. Characteristics of eligible studies

Study	Design	Study Population		Intervention		
	Patients	Modee of surgery	Type of surgery	Timing	Fluids +/- Inotropes	Goals
Bender 1997	104	elective	vascular	pre	fluids and inotropes	CI
Berlauk 1991	89	elective	vascular	pre	fluids and inotropes	CI
Bonazzi 2002	100	elective	vascular	pre	fluids and inotropes	CI, DO_2I
Boyd 1993	107	elective, emergency	general, vascular	pre, post	fluids and inotropes	DO_2I
Cecconi 2011	40	elective	orthopaedic	intra	fluids and inotropes	SV
Challand 2012	179	elective	gastrointestinal	intra	fluids	SV
Conway 2002	57	elective	general	intra	fluids	SV,FTc
Donati 2007	135	elective	major abdominal surgery	intra	fluids and inotropes	0_2ER
Gan 2002	100	elective	general	intra	fluids	SV, FTc
Jerez 2001	390	elective	cardiac	post	fluids and inotropes	SVO_2, CI
Jhanji 2010	135	elective	gastrointestinal surgery	post	fluids and inotropes	SV
Kapoor 2007	30	elective	cardiac	post	fluids and inotropes	CI, SVV
Lobo 2000	37	elective	general, vascular	pre	fluids and inotropes	DO_2I
Mayer 2010	60	elective	major abdominal surgery	intra	fluids and inotropes	CI, SV
Mckendry 2004	174	elective, emergency	cardiac	post	fluids and inotropes	SVI
Mythen 1995	60	elective	cardiac	intra	fluids	SV
Noblett 2006	103	elective	general	intra	fluids	SV, FTc

(Continued)

Pearse 2005	122	elective, emergency	vascular, general, urology	post	fluids and inotropes	DO_2I
Pillai 2011	66	elective	urology	intra	fluids	SV, FTc
Pölönen 2000	393	elective	cardiac	post	fluids and inotropes	SvO_2, lactate
Sandham 2003	1994	elective, emergency	general, vascular, thoracic, hip fracture	pre	fluids and inotropes	DO_2I, CI
Senagore 2009	64	elective	Laparoscopic colectomy	intra	fluids	SV
Shoemaker 1988	58	elective, emergency	general, vascular	pre	fluids and inotropes	CI, DO_2I, VO_2I
Sinclair 1997	40	emergency	hip fracture	intra	fluids	SV, FTc
Ueno 1998	34	elective	liver	post	fluids and inotropes	CI, DO_2I, VO_2I
Valentine 1998	120	elective	vascular	pre	fluids and inotropes	CI
Van der Linden 2010	57	elective	vascular	intra	fluids and inotropes	CI
Venn 2002	59	emergency	hip fracture	intra	fluids	SV, FTc
Wakeling 2005	134	elective	general	intra	fluids	SV
Wilson 1999	138	elective	general, vascular	pre	fluids and inotropes	DO_2I
Ziegler 1997	72	elective	vascular	pre	fluids and inotropes	SvO_2

Footnotes

Appendix 7. Sensitivity analysis using analytical methods for the primary outcome (mortality for the longest follow-up)

Analytical method	Results
Inverse variance Relative Risk Fixed-effect model	0.89 (95% CI 0.76 to 1.05), P = 0.18, I^2 = 15%
Inverse variance Relative Risk Random-effects model	0.72 (95% CI 0.55 to 0.95), P = 0.02, I^2 = 15%
Inverse variance Odds Ratio Fixed-effects model	0.87 (95% CI 0.72 to 1.05), P = 0.14, I^2 = 20%
Inverse variance Odd's Ratio Random-effects model	0.67 (95% CI 0.49 to 0.92), P = 0.01, I^2 = 20%
Peto Odd's Ratio	0.83 (95% CI 0.69 to 1.00), P = 0.05, I^2 = 37%

(Continued)

MH Odd's ratio Fixed-effect model	0.83 (95% CI 0.69 to 1.00), P = 0.05, I^2 = 21%
MH Odd's ratio Random-effects model	0.67 (95% CI 0.49 to 0.92), P = 0.01, I^2 = 21%
MH Relative Risk Fixed-effect model	0.85 (95% CI 0.73 to 1.00), P = 0.05, I^2 = 16%
MH Relative Risk Random-effects model	0.72 (95% CI 0.55 to 0.95), P = 0.02, I^2 = 16%

Appendix 8. Sensitivity analysis using analytical methods for hospital or 28 day mortality

Analytical method	Results
Inverse variance Relative Risk Fixed-effect model	0.81 (95% CI 0.65 to 1.00), P = 0.06, I^2 = 1%
Inverse variance Relative Risk Random-effects model	0.79 (95% CI 0.63 to 0.99), P = 0.04, I^2 = 1%
Inverse variance Odds Ratio Fixed-effect model	0.79 (95% CI 0.63 to 1.00), P = 0.05, I^2 = 7%
Inverse variance Odd's Ratio Random-effects model	0.72 (95% CI 0.54 to 0.96), P = 0.02, I^2 = 7%
Peto Odd's Ratio	0.75 (95% CI 0.60 to 0.94), P = 0.01, I^2 = 26%
MH Odd's ratio Fixed-effect model	0.76 (95% CI 0.60 to 0.95), P = 0.01, I^2 = 8%
MH Odd's ratio Random-effects model	0.72 (95% CI 0.54 to 0.96), P = 0.02, I^2 = 8%
MH Relative Risk Fixed-effect model	0.77 (95% CI 0.63 to 0.95), P = 0.01, I^2 = 2%
MH Relative Risk Random-effects model	0.78 (95% CI 0.62 to 0.99), P = 0.04, I^2 = 2%

WHAT'S NEW

Date	Event	Description
7 October 2016	Amended	New entry created in Published notes regarding status of Mayer 2010 study

HISTORY

Protocol first published: Issue 1, 2003
Review first published: Issue 11, 2012

Date	Event	Description
1 July 2013	Amended	Journal version of review (Grocott 2013) cited in 'Other published versions of this review'.

Date	Event	Description
25 October 2012	Amended	Amendment to acknowledgment section: acknowledging University Hospital Southampton NHS Foundation Trust-University of Southampton Respiratory Biomedical Research Unit and University College London Hospital–University College London Comprehensive Biomedical Research Centre.
1 February 2006	Amended	February 2006: The authors appealed against the original decision of the Cochrane Funders Arbiter. Their appeal was recently upheld by the Co-chairs of the Steering Group and the decision of the funding arbiter over turned. The “Perioperative increase in global blood flow to explicit defined goals and outcomes following surgery" will be republished in The Cochrane Library in issue 2, 2006. The authors are working on the draft review.
1 February 2005	Amended	February 2005: "Perioperative increase in global blood flow to explicit defined goals and outcomes following surgery" was withdrawn from The Cochrane Library in issue 2, 2005 on the advice of the Cochrane Funders Arbiter. This was because the authors received funding from a commercial source (Elan Pharma) for the preparation of this review. This contravenes the current Cochrane policy on sponsorship.

CONTRIBUTIONS OF AUTHORS

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Providing additional data about papers: authors of papers.

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Guarantor for the review (one author): MG

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The Optimisation Systematic Review Steering Group are, in alphabetical order: Beale R, Boyd O, Emberton M, Langham J, Roberts I, Thompson J.

DECLARATIONS OF INTEREST

Dr Boyd and Professor Mythen are authors of included studies.

None known: Beale R, Emberton M, Langham J, Roberts I, Thompson J, Dushianthan A.

Received funding from industry for studies and lecturing in the area: Boyd O, Mythen M, Grocott M, Hamilton MA.

Pre-existing views

None: Emberton M, Langham J, Rowan K, Dushianthan A

Against: no-one.

Uncertain: Beale R, Roberts I, Thompson J.

In favour: Boyd O, Mythen M, Grocott M, Hamilton MA.

Professor Mike Grocott has received unrestricted grant funding (paid to his institution) not related to this review from John Caudwell, British Oxygen Company (Linde Gas Therapeutics), Smiths Medical Ltd., Ely-Lilly Critical Care Ltd., Deltex Medical Ltd., The London Clinic, UCL Business, Rolex Ltd., Association of Anaesthetists of Great Britain and Ireland, The Intensive Care Foundation, National Institute of Health Research, National Institute of Academic Anaesthesia, The Sir Halley-Stuart Trust, The Frances and Augustus Newman Trust and The Down Syndrome Trust. Mike Grocott has also received fees for lecturing, unrelated to this review, from Fresenius Kabi, Edwards Lifesciences and Cortex GmBH.

Professor Mythen has received honoraria for speaking/consultation and/or travel expenses from Baxter, BBraun, Covidien, Fresenius-Kabi, Hospira, LidCo and as a consultant to AQIX (start up company with a novel crystalloid solution – pre-clinical). He is a director of Medical Defence Technologies LLC ("Gastrostim" patented) and a co-Inventor of "QUENCH" IP being exploited by UCL Business. Professor Mythen's chair at UCL is endowed by Smiths Medical Ltd and this company provide charitable donations to the department on an annual basis. Deltex Medical also provide unrestricted grant funds to Prof Mythen's Department. Professor Mythen is a member of the IV Fluids Guideline Development Group for the National Institute of Clinical Excellence (NICE) and he is a co-Author of the GIFTASUP fluid guidelines.

Mark Hamiltion has received lecture fees from Edwards Life Sciences for two lectures related to optimization.

Professor Kathy Rowan is ICNARC CTU Director and the ICNARC CTU is managing a trial (evaluating the effectiveness of perioperative goal directed
haemodynamic therapy in high-risk patients undergoing major abdominal surgery involving the gastrointestinal tract) part-funded via a National Institute for Health Research (NIHR) Clinician Scientist Award given to Dr Rupert Pearse.

All other authors': none known.

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- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The search strategy was changed after December 2000, after consultation with Cochrane search editors.

NOTES

October 2016

This review includes the following study Mayer 2010.

Joachim Boldt is a co-author of this study. Many publications by Joachim Boldt have been retracted or are being investigated; Mayer 2010 has not been retracted and future publication status is unknown. If the Mayer study is retracted in the future, then the study will be excluded in the updated version of this review.

INDEX TERMS

Medical Subject Headings (MeSH)

Arrhythmias, Cardiac [etiology]; Blood Circulation [*physiology]; Cardiovascular Agents [administration & dosage]; Length of Stay; Oxygen Consumption [*physiology]; Plasma Substitutes [administration & dosage]; Postoperative Complications [*mortality] [prevention & control]; Randomized Controlled Trials as Topic; Renal Insufficiency [prevention & control]; Respiratory Insufficiency [prevention & control]; Surgical Procedures, Operative [adverse effects] [*mortality]; Surgical Wound Infection [prevention & control]

MeSH check words

Adult; Humans