Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review.

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Effect of a peri-operative, cardiac output-guided, hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: A multi-center randomized controlled trial

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Keywords: surgery, complications; peri-operative care; fluid therapy; randomized trial
Revised: 21st March 2014 **Word count:** 3825

Summary

Importance

Annually, over 230 million patients undergo surgery worldwide. Complications and death are frequent among high-risk patients undergoing major gastrointestinal surgery. Pooled small trials suggest outcomes may be improved by peri-operative, cardiac output-guided, hemodynamic therapy.

Objective

To evaluate the clinical effectiveness of a peri-operative, cardiac output-guided, hemodynamic therapy algorithm.

Design

Pragmatic, multi-center, randomized trial and updated systematic review.

Setting

17 acute hospitals in the UK.

Participants

734 high-risk patients; aged over 50 years undergoing major gastrointestinal surgery.

Interventions

Delivery of a peri-operative, cardiac output-guided, hemodynamic therapy algorithm for intra-venous fluid and inotrope (dopexamine) infusion during and for six hours following surgery, compared with usual peri-operative care.

Main outcome measures

The primary outcome was a composite of pre-defined moderate or major post-operative complications and mortality at 30 days following surgery. Secondary outcomes were morbidity on day 7, infectious complications, critical care free days and all cause mortality at 30 days following surgery, all cause mortality at 180 days following surgery and acute hospital length of stay.

Results

Baseline patient characteristics, clinical care and volumes of intra-venous fluid were similar between groups. Allocated care was non-compliant for fewer than 10% of patients in each group. The primary outcome was 36.6% for the intervention and 43.4% for usual care (RR 0.84 [0.71-1.01], ARR 6.8% [−0.3% to 13.9%]; p=0.07). There was no significant difference for any of the secondary outcomes. Five intervention patients (1·4%) experienced cardiovascular serious adverse events within 24 hours compared with none in the usual care group. In pre-specified analyses, the primary outcome treatment effect was strengthened after adjustment for protocol compliance (RR 0.80 [0.61-0.99]) and exclusion of the first ten patients recruited at each site (RR 0.59 [0.41-0.84]). The findings of the updated systematic review suggest that patients receiving the intervention are less likely to develop complications (Intervention 488/1548 [31.5%] vs Controls 614/1476 [41.6%]; RR 0·77 [0·71-0·83]).

Conclusions

Whilst the cardiac output-guided, hemodynamic therapy algorithm was not associated with a significant reduction in post-operative complications in this trial, the findings of the updated systematic review suggest this intervention is associated with clinically important reductions in complications rates.

Trial registration: http://www.controlled-trials.com/ISRCTN04386758

Short summary

Findings from small trials suggest post-operative outcomes may be improved by cardiac output-guided, hemodynamic therapy but this remains unconfirmed. In a multi-center randomized trial, we allocated 734 high-risk patients undergoing major gastrointestinal surgery to a hemodynamic therapy algorithm for intra-venous fluid and inotrope (dopexamine) infusion during and six hours following surgery, or usual care. The primary outcome of pre-defined moderate or major post-operative complications was met by 36.6% of intervention patients and 43.4% of usual care patients (RR 0.84 [0.71-1.01]; p=0.07). Whilst not statistically significant, these findings were consistent with those of a recent Cochrane systematic review. When the systematic review was updated to include our results, significantly fewer patients developed complications having received this intervention (RR 0·70 [0·62-0·80]; p=0.01). The combined findings of the randomized trial and systematic review suggest cardiac output-guided hemodynamic therapy may be associated with a clinically important reduction in complications after surgery.

Introduction

Estimates suggest that over 230 million patients undergo surgery worldwide each year with mortality reported between 1 and 4%.[1,2] Complications and deaths are most frequent among high-risk patients, those who are older or have co-morbid disease and undergo major gastrointestinal or vascular surgery. Patients who develop complications, but survive to leave hospital, suffer reduced functional independence and longer-term survival.[3-5] Variation in mortality indicates both the potential and the need to improve survival after major surgery.[2,6] Given the high volumes or surgery, even a low rate of avoidable harm will be associated with a large number of preventable deaths.

It is generally accepted that intra-venous fluid and inotropic drugs have an important effect on patient outcome, in particular following major gastrointestinal surgery. Yet, they are commonly prescribed on subjective criteria leading to wide variation in clinical practice.[7] One possible solution is the use of cardiac output monitoring to guide intra-venous fluid and inotropic drug therapy as part of a hemodynamic therapy algorithm. This approach has been shown to modify inflammatory pathways, improve tissue perfusion and oxygenation,[8,9] and possibly improve clinical outcomes.[10-16] The current evidence base consists of a number of small trials insufficient to resolve controversies regarding potential harm associated with fluid excess, myocardial injury and invasive forms of monitoring. As a result, this approach has not been widely adopted into clinical practice. More recently, hemodynamic therapy algorithms have been adapted to utilize less invasive forms of cardiac output monitoring and lower doses of inotropic therapy for shorter periods.[12] These refinements have improved the feasibility, safety and costs but clinical effectiveness remains unconfirmed. Despite this, use of hemodynamic therapy algorithms has been recommended in a report commissioned by the Centers for Medicare and Medicaid Services in the USA,[17] and by the National Institute for Health and Care Excellence (NICE) in the UK,[18]

based on the findings of a number of small trials which suggest improved clinical outcomes. A recent Cochrane review, however, has suggested that the treatment benefit may be more marginal than previously believed.[15] The mortality benefit has become less apparent in more recent trials with lower control group mortality.[14]

In this context, we developed a peri-operative, cardiac output-guided, hemodynamic therapy algorithm for the administration of intra-venous fluid and inotropic therapy, supported by solid clinical and mechanistic evidence. Our objective was to evaluate the clinical effectiveness of this algorithm in a large, pragmatic, multi-center randomized controlled trial in high-risk patients undergoing major gastrointestinal surgery. We then conducted an updated systematic review incorporating the findings of this trial.

Methods

Trial design

OPTIMISE was a multi-center, randomized controlled trial conducted in seventeen acute hospitals in the National Health Service in the United Kingdom. Adult patients, aged 50 years or over undergoing major abdominal surgery involving the gastrointestinal tract of expected duration greater than 90 minutes, were eligible for recruitment provided they satisfied one of the following high-risk criteria: aged 65 years or over; presence of a defined risk factor for cardiac or respiratory disease; renal impairment (serum creatinine ≥1.5 mg dl^{-1}); diabetes mellitus; or emergency surgery. Exclusion criteria included refusal of consent, pregnancy, acute pulmonary edema (within prior seven days), acute myocardial ischemia (within prior 30 days) and patients undergoing surgery for palliative treatment only. Investigators were asked not to randomize patients where the clinician intended to use cardiac output monitoring for clinical reasons. OPTIMISE was approved by the East London & City Research Ethics Committee (09/H0703/23) and the Medical and Healthcare products Regulatory Agency and registered with Controlled Trials (ISRCTN04386758). Written informed consent was obtained from all patients prior to surgery. Site visits were performed by RP and AA for training and for source data verification. The trial protocol was lodged and is available online at www.perioperativemedicine.net/OPTIMISE.

Randomization and procedures to minimize bias

Randomization was performed through a dedicated, secure, web-based system. Participants were allocated to treatment groups using a computer-generated, dynamic procedure (minimization) with a random component. Participants were allocated, with an 80% probability, to the group that minimized between group differences in trial site, urgency of surgery and surgical procedure category among all participants recruited to date. This was a pragmatic effectiveness trial and it was not possible to blind all investigators to study group allocation. To minimize bias, investigators

were instructed not to reveal study group allocation unnecessarily. Patients were followed up by another investigator who, wherever possible, was unaware of allocation. Investigators performing follow-up self-assessed the extent to which they remained blinded. Outcomes were verified according to pre-defined criteria by the principal investigator or designee at each site, who was always blinded to allocation. The decision to admit a trial patient to critical care was made by clinical staff and recorded prior to randomization and surgery, allowing comparison with actual location of post-operative care.

Clinical management

The intervention period commenced with induction of anesthesia and continued until six hours following completion of surgery.

All patients

Peri-operative care for all patients was loosely defined to avoid extremes of clinical practice and practice misalignment.[19] All patients received standard measures to maintain oxygenation (SpO_2 ≥94%), hemoglobin (>80 gl^{-1}), core temperature (37 °C) and heart rate (<100 beats min^{-1}). 5% dextrose was administered at 1 ml kg^{-1} hr^{-1} to satisfy maintenance fluid requirements. Additional fluid was administered at the discretion of the treating clinician guided by pulse rate, arterial pressure, urine output, core-peripheral temperature gradient, serum lactate and base excess. Mean arterial pressure was maintained between 60 and 100 mmHg using an alpha adrenoceptor agonist or vasodilator, as required. Post-operative analgesia was provided by epidural infusion (bupivacaine and fentanyl) or intra-venous infusion (morphine or fentanyl). With the exception of the interventions below, all other treatment decisions were at the discretion of, and taken by, senior clinicians.

Hemodynamic therapy algorithm group patients

Intervention group patients received intra-venous fluid and inotropes according to a cardiac output-guided, hemodynamic therapy algorithm (supplementary file). The algorithm was developed for OPTIMISE by an expert group. It was designed to be delivered in the operating room/post-anesthetic care unit by both medical and nursing staff, ensuring that admission for critical care was not necessary for compliance. A cardiac output monitor was chosen which could be used in conscious (extubated) patients (LiDCOrapid, LiDCO Ltd, UK). This technology has been extensively evaluated and in clinical use for more than ten years.[20] The hemodynamic therapy algorithm was supported by solid clinical and mechanistic evidence and had a good cardiovascular safety profile.[8-16,21-23] Intra-venous colloid solution was administered in 250ml boluses in order to achieve and maintain a maximal value of stroke volume; no attempt was made to standardize choice of colloid. Dopexamine was administered at a fixed, low dose of 0.5 $\mu g\ kg^{-1}\ min^{-1}$ either through a peripheral or a central venous catheter (Cephalon Ltd, Welwyn Garden City, UK). The choice and dose of inotrope was based on the findings of a previous meta-regression analysis.[13] The dose of dopexamine was reduced if the heart rate increased to 120% of baseline or 100 beats min^{-1} (whichever was greater) for more than 30 minutes despite adequate anesthesia and analgesia. If the heart rate did not decrease despite dose reduction, then the infusion was discontinued.

Usual care group patients

These patients received usual peri-operative care although the use of a dynamic central venous pressure target was recommended. Cardiac output monitoring was not used in the usual care group unless specifically requested by clinical staff because of patient deterioration.

Trial endpoints

The primary effect estimate was the relative risk of a composite of pre-defined moderate or major post-operative complications and mortality at 30 days following surgery (supplementary file).

Secondary outcomes were: Post-Operative Morbidity Survey (POMS) defined morbidity on day 7;[24] infectious complications, critical care free days (number of days alive and not in critical care) and all cause mortality at 30 days following surgery; all cause mortality at 180 days following surgery; and acute hospital length of stay. Level of post-operative critical care was categorized according to standard criteria.[25] Patients were followed for 30 days by visit and through local computerized records while in hospital. All patients were contacted at 30 days either by telephone for those who had left hospital or by visit for those who had not. Where necessary, investigators contacted community physicians or other hospitals, by telephone and in writing, for outstanding information describing the primary outcome. All cause mortality at 180 days was assessed through the Office for National Statistics. Data entry was performed through a dedicated, secure, web-based system. Automated validation checks included plausibility ranges and cross checks between data fields. Further data checks were performed centrally and through source data verification.

Statistical analysis

Assuming a type I error rate of 5%, 345 patients per group (690 total) were required to detect, with 90% power, a reduction in the composite of pre-defined moderate or major post-operative complications and mortality at 30 days following surgery from 50% in the usual care group to 37.5% in the hemodynamic therapy algorithm group (absolute risk reduction 12.5%; relative risk reduction 25%).[12] Allowing for a 3% one-way, cross-over rate due to use of cardiac output monitoring in the usual care group, this was increased to 367 per group (734 total). A planned interim analysis was performed at halfway. Pre-defined stopping guidelines permitted early termination of the trial for harm but not effectiveness.

Analyses were performed according to an a priori statistical analysis plan including all patients on an intention to treat basis (supplementary file). Categorical data were compared using Fisher's

exact test. Differences in critical care free days and acute hospital length of stay were tested using the Wilcoxon rank-sum test. Kaplan-Meier curves were plotted for all cause mortality up to 180 days following surgery. Adjustment for baseline data was made using a logistic regression model including age, gender, urgency of surgery, surgical procedure category, ASA grade, planned location following surgery, renal impairment, diabetes mellitus, risk factors for cardiac or respiratory disease and random effect of site. Baseline variables were selected for inclusion in the adjusted analysis according to anticipated relationship with outcome, including all variables used in the minimization algorithm. Results for primary and secondary outcomes are reported as relative risks (RR) with 95% confidence intervals (CI). Results for the primary outcome are additionally reported as absolute risk reduction (ARR) with 95% CI. Results of the logistic regression model are reported as adjusted odds ratios (OR) with 95% CI, with unadjusted OR for comparison.

Pre-specified secondary analyses were: a modified intention to treat analysis excluding patients who did not undergo surgery; a compliance-adjusted analysis in which patients whose treatment did not comply with allocation were assumed to have the same outcome as if they had been assigned to the alternative treatment group;[26] and scenario-based sensitivity analyses for missing primary outcomes (a best cases analysis assuming all missing outcomes in the intervention group were favorable and all missing outcomes in the usual care group were unfavorable and a worst case analysis assuming the reverse). Pre-specified sub-group analyses were performed: by urgency of surgery; by surgical procedure category; and by timing of recruitment (comparing the first ten patients recruited at each site with those recruited subsequently (sites recruiting fewer than ten patients were excluded). Continuous variables are presented as mean (SD) where normally distributed or median (quartiles) where not. Categorical variables are presented as n (%). Analyses were performed using Stata SE version 10.1. Significance was set at $p<0.05$ (two-tailed).

Systematic review

Using identical methods, we updated the previous Cochrane systematic review (SR) of published randomized trials of 'Peri-operative increase in global blood flow to explicit defined goals and outcomes following surgery' with the findings of the OPTIMISE Trial and other published trials identified by an updated search.[15] CENTRAL (Cochrane Library 2014), MEDLINE (1966 to February 2014) and EMBASE (1982 to February 2014) were searched for randomized trials involving adult patients (≥ 16 years) undergoing surgery in an operating room where the intervention met the following criteria: Peri-operative administration of fluids, with or without inotropes/vasoactive drugs, targeted to increase blood flow (relative to control) against explicit measured goals. 'Peri-operative' was defined as: initiated within 24 hours before surgery and lasting up to 6 after surgery. 'Explicit measured goals' were defined as: cardiac index, oxygen delivery, oxygen consumption, stroke volume, mixed venous oxygen saturation, oxygen extraction ratio or lactate. We selected the following key outcomes: number of patients with complications (primary outcome variable for the OPTIMISE trial), number of infections, length of postoperative hospital stay, mortality at longest follow-up (primary outcome variable of Cochrane SR) and 28 day/30 day/hospital mortality. Treatment effects were reported as relative risks (RR) with 95% CI for clinical variables or weighted mean differences (SD) for length of hospital stay. Analyses were performed using Review Manager (RevMan 5.2.8) using fixed effects models.

Results

A total of 734 patients were enrolled between June 2010 and November 2012; 368 patients were allocated to the cardiac output-guided, hemodynamic therapy algorithm, and 366 to usual care. In the usual care group, one patient was randomized in error and excluded from the study (eFigure 1). Baseline patient characteristics were similar between the groups (Table 1). Most patient types were well represented with the exception of those having emergency surgery (25 patients) and those having urological or gynecological surgery involving the gut (nine patients). Clinical care outside the trial intervention was also similar (Table 2), including admission for critical care. Overall volumes of intra-venous fluid (colloid and crystalloid combined) administered during the intervention period were similar (intervention 4190 ml versus usual care 4024 ml). For usual care group patients, more intra-venous fluid was administered during than after surgery, while for intervention group patients similar volumes were administered during surgery and during the six hours following surgery. Intervention group patients received more colloid and less crystalloid than usual care group patients. With the exception of dopexamine, use of vasopressor and inotropic agents was similar between the groups. Fewer than 10% of patients in each group were non-compliant with their allocated treatment (eTable 1). This was achieved through the presence of trained investigators, where necessary, to observe, advise or deliver the intervention (eTable 2). Investigator self-assessment of blinding for determination of outcomes also indicated a high rate of compliance with trial procedures (Table 3).

The primary outcome, a composite of pre-defined moderate or major post-operative complications and mortality at 30 days following surgery, was met by 36.6% (134 of 366) of patients in the intervention group and by 43.4% (158 of 364) of patients in the usual care group (RR 0.84 [0.71-1.01], ARR 6.8% [−0.3% to 13.9%]; p=0.07) (Table 3). Following adjustment for baseline risk factors, the observed treatment effect remained non-significant with an adjusted OR of 0.73 [0.53-1.00];

p=0.05 (unadjusted OR 0.75 [0.56-1.01]; p=0.07). The pre-specified, modified, intention to treat analysis, in which three patients (all in the usual care group) who did not undergo surgery were excluded, had little effect on the primary outcome (RR 0.84 [0.70-1.00]; p=0.06). In the pre-specified, compliance-adjusted analysis conducted using established methodology,[26] the observed treatment effect was strengthened when the 65 patients whose care was non-compliant (eTable 1) were assumed to experience the same outcome as if they had been allocated to the alternative group (RR 0.80 [0.61-0.99]; p=0.037). Scenario-based sensitivity analyses demonstrated that the very small number of patients with missing primary outcome data had minimal influence on treatment effect (RR 0.84 [0.70-1.00] to 0.85 [0.71-1.02]).

Five patients in the intervention group experienced serious adverse cardiac events within 24 hours of the end of the intervention period (two tachycardia, two myocardial infarction and one arrhythmia) compared with none in the usual care group (p=0.062). At 30 days following surgery, however, the incidence of cardiovascular events was similar between the groups (Table 3). There were no significant differences for any of the secondary outcomes: POMS defined morbidity on day 7; infectious complications, critical care free days and all cause mortality at 30 days following surgery; all cause mortality at 180 days following surgery; and duration of acute hospital length of stay (Table 4, Figure 1). No interaction was found for urgency of surgery, the intervention was associated with a slight reduction in the primary outcome for the elective surgery sub-group. No interaction was found for surgical procedure category, the intervention was associated with a slight reduction in the primary outcome for patients undergoing small bowel +/- pancreas surgery. A significant interaction (p=0.019) was found for timing of recruitment, the intervention was associated with a reduction in the primary outcome for patients recruited later (RR 0.59 [0.41-0.84] compared with earlier at each site (RR 1.51 [0.75-3.01] (Table 5).

Systematic review

The updated literature search identified seven additional trials including OPTIMISE, to provide a total of 38 trials that included 6595 participants with 23 trials including 3024 participants providing data describing our primary outcome. Fewer patients receiving the intervention developed complications (Intervention 488/1548 [31.5%] vs Controls 614/1476 [41.6%]; RR 0·77 [0·71-0·83]) (Figure 2). The intervention was associated with a reduced incidence of post-operative infection (Intervention 182/836 patients [21·8%] vs Controls 201/790 patients [25.4%]; RR 0·81 [0·69-0.95]) and a reduced duration of hospital stay (mean reduction 0.80 days (0·97-0.62) (eFigures 2 and 3). There was no significant reduction in hospital / 28 day / 30 day mortality (Intervention 159/3215 deaths [4.9%] vs Controls 206/3160 deaths [6·5%]; RR 0·82 [0·67-1·01]) and borderline evidence of a reduction in mortality at longest follow-up (Intervention 267/3215 deaths [8.3%] vs Controls 327/3160 deaths [10.3%]; RR 0·86 [0·74-1·00]) (eFigures 4 and 5).

Discussion

The findings of the OPTIMISE trial were that in high-risk patients undergoing major abdominal surgery involving the gastrointestinal tract, when compared with usual care, use of this peri-operative, cardiac output-guided, hemodynamic therapy algorithm was not associated with a significant reduction in the composite primary outcome of pre-defined moderate or major post-operative complications and mortality at 30 days following surgery. However, after incorporating the results of this large clinical trial into an updated systematic review of published trials, there was evidence that cardiac output-guided, hemodynamic therapy is associated with a clinically important reduction in the number of patients who develop complications after surgery.[15] In the OPTIMISE trial, there was no difference in the secondary outcomes of POMS defined morbidity at day 7; infectious complications, critical care-free days or all cause mortality at 30 days; all cause mortality at 180 days; or acute hospital length of stay. However, the findings of the updated systematic review suggest this treatment approach is associated with a significant reduction in the number of patients who develop post-operative infection as well as in duration of hospital stay. The findings of the mortality analyses provide borderline evidence but remain consistent with benefit.

This is the largest trial of a peri-operative, cardiac output-guided, hemodynamic therapy algorithm, to date. OPTIMISE was designed to address several limitations in the previous evidence base.[27] The large sample size allowed for comparison of the cardiac output-guided hemodynamic therapy algorithm with usual peri-operative care, avoiding problems associated with alternative 'control' treatment algorithms which do not reflect typical practice.[19] A large number of algorithms for cardiac output guided hemodynamic therapy have been published describing a variety of options in terms of hemodynamic end-points, use of inotropic agents and cardiac output monitoring. We used an algorithm suited to the care of patients during and after major gastrointestinal surgery, that was

supported by solid clinical and mechanistic evidence and a good cardiovascular safety profile.[8,9,10-15,24-26] The β_2-agonist dopexamine has mild inotropic and vasodilator effects and is the most widely studied agent in this context. The findings of a meta-regression analysis suggested that dopexamine infusion at low dose is associated with improved outcomes following major surgery.[15] Further modifications were made by an expert group to allow delivery in the operating room and post-anesthetic care unit by both medical and nursing staff and in particular to ensure admission to critical care was not necessary for compliance with the intervention. Importantly, the high rate of compliance with the hemodynamic therapy algorithm used in this trial suggests this treatment approach is feasible for use in routine clinical practice. A widely used cardiac output monitoring technology was employed (although our findings are not specific to this device). In keeping with the pragmatic nature of the trial, no attempt was made to standardize the choice of colloid in either group. Recent evidence has suggested an increased incidence of acute kidney injury in critically ill patients receiving starch-based, colloid solutions.[28,29] While we do not have individual patient data describing the use of starch, a post-hoc survey of investigators suggested few patients received this. A recent systematic review identified no evidence of acute kidney injury associated with the use of starch solutions in surgical patients.[30]

A potential weakness of OPTIMISE may be the use of a primary outcome that was a composite of moderate or major post-operative complications and mortality. The components of this outcome measure may reflect benefit, no effect or harm associated with the intervention. We controlled for bias by assessing and grading this outcome according to pre-defined criteria and, although it is not possible to blind all clinical staff administering complex interventions, our data suggest excellent compliance with blinding for patient outcome assessment. Finally, the event rate in the usual care arm was slightly lower than expected and cross-over in terms of cardiac output monitoring in the usual care group was more frequent than predicted. These factors reduced the power of the trial, perhaps resulting in failure to achieve statistical significance for the primary outcome. Although

emergency surgery was one of our inclusion criteria, we were only able to recruit a small number of these patients. The approach to recruiting elective and emergency patients is quite different and the design of future trials should take this into account. Whilst additional research staff were often present during the trial, anesthesia and critical care staff would be able to deliver such algorithms of care with minimal training. Myocardial injury is the most important adverse effect of hemodynamic therapy algorithms; there was a low rate of cardiovascular serious adverse events within 24 hours of the intervention and the incidence of cardiovascular events was similar between the groups at 30 days following surgery. The trial findings also suggests that cardiac output-guided fluid therapy need not result in excessive fluid administration but may lead to a more individualized approach to achieving the correct dose of fluid, as and when required. Finally, a pre-specified analysis of timing of recruitment suggested that a learning curve may have existed, consistent both with an expectation for trials of complex interventions and from previous experience from implementation in this field, and this warrants consideration in future research in this area.[31]

Conclusion

In this large multi-center trial, the use of a peri-operative, cardiac output-guided, hemodynamic therapy algorithm for the administration of intra-venous fluid and a low-dose inotrope (dopexamine) was not associated with a significant reduction in a composite primary outcome of pre-defined moderate or major post-operative complications and mortality at 30 days following surgery. However, when incorporated into an updated systematic review, these findings contributed to a clinically important reduction in the number of patients who developed complications.

Author contributions

Prof Pearse had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest disclosures

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. RP has received equipment loans from LiDCO Ltd, a research grant from Circassia Holdings Ltd. and has performed consultancy work for Edwards Lifesciences, Covidien and Massimo Inc. CH and RP are named inventors on a lapsed patent application relating to the peri-operative use of dopexamine. MG has received an honorarium from LiDCO Ltd for organizing a teaching workshop. All other authors declare they have no conflicts of interest. MPWG has received unrestricted grant funding from Deltex Medical Ltd, and fees for lecturing from Fresenius Kabi and Edwards Lifesciences.

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Funding / support

The trial was funded through a National Institute for Health Research (UK) Clinician Scientist Award held by RP. Cardiac output monitoring equipment was provided on loan without charge by LiDCO Ltd. Dopexamine was supplied at a small discount by Cephalon Inc. and through additional, non-grant funded provision of staff time and resources from the Intensive Care National Audit & Research Centre.

Role of the funder

The funding bodies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data, preparation, review, or approval of the manuscript and decision to submit the manuscript for publication.

References

1. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet.* 2008;372(9633):139-144.

2. Pearse RM, Moreno RP, Bauer P, et al. Mortality after surgery in Europe: a 7 day cohort study. *Lancet.* 2012;380(9847):1059-1065.

3. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg.* 2005;242(3):326-341.

4. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med.* 2009;360(14):1418-1428.

5. Head J, Ferrie JE, Alexanderson K, Westerlund H, Vahtera J, Kivimaki M. Diagnosis-specific sickness absence as a predictor of mortality: the Whitehall II prospective cohort study. *BMJ.* 2008;337:a1469.

6. Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. *N Engl J Med.* 2009;361(14):1368-1375.

7. Cannesson M, Pestel G, Ricks C, Hoeft A, Perel A. Hemodynamic monitoring and management in patients undergoing high risk surgery: a survey among North American and European anesthesiologists. *Critical Care.* 2011;15(4):R197.

8. Jhanji S, Vivian-Smith A, Lucena-Amaro S, Watson D, Hinds CJ, Pearse RM. Haemodynamic optimisation improves tissue microvascular flow and oxygenation after major surgery: a randomised controlled trial. *Crit Care.* 2010;14(4):R151.

9. Bangash MN, Patel NS, Benetti E, et al. Dopexamine can attenuate the inflammatory response and protect against organ injury in the absence of significant effects on haemodynamics or regional microvascular flow. *Critical Care.* 2013;17(2):R57.

10. Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. *JAMA.* 1993;270(22):2699-2707.

11. Wilson J, Woods I, Fawcett J, et al. Reducing the risk of major elective surgery: randomised controlled trial of preoperative optimisation of oxygen delivery. *BMJ.* 1999;318(7191):1099-1103.

12. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED. Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. *Crit Care.* 2005;9(6):R687-693.

13. Pearse RM, Belsey JD, Cole JN, Bennett ED. Effect of dopexamine infusion on mortality following major surgery: individual patient data meta-regression analysis of published clinical trials. *Crit Care Med.* 2008;36(4):1323-1329.

14. Hamilton MA, Cecconi M, Rhodes A. A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. *Anesth Analg.* 2011;112(6):1392-1402.

15. Grocott MP, Dushianthan A, Hamilton MA, Mythen MG, Harrison D, Rowan K. Perioperative increase in global blood flow to explicit defined goals and outcomes following surgery. *Cochrane Database of Systematic Reviews.* 2012;11:CD004082.

16. Gan TJ, Soppitt A, Maroof M, et al. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. *Anesthesiology.* 2002;97(4):820-826.

17. Esophageal Doppler ultrasound based cardiac output monitoring for real time therapeutic management of hospitalized patients. 2007; http://www.cms.gov/determinationprocess/downloads/id45TA.pdf.

18. CardioQ-ODM oesophageal doppler monitor. 2011; http://www.nice.org.uk/nicemedia/live/13312/52624/52624.pdf.

19. Deans KJ, Minneci PC, Suffredini AF, et al. Randomization in clinical trials of titrated therapies: unintended consequences of using fixed treatment protocols. *Critical care medicine.* 2007;35(6):1509-1516.

20. Marquez J, McCurry K, Severyn DA, Pinsky MR. Ability of pulse power, esophageal Doppler, and arterial pulse pressure to estimate rapid changes in stroke volume in humans. *Crit Care Med.* 2008;36(11):3001-3007.

21. Pearse RM, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett D. The incidence of myocardial injury following post-operative Goal Directed Therapy. *BMC Cardiovasc Disord.* 2007;7:10.

22. Takala J, Meier-Hellmann A, Eddleston J, Hulstaert P, Sramek V. Effect of dopexamine on outcome after major abdominal surgery: a prospective, randomized, controlled multicenter study. European Multicenter Study Group on Dopexamine in Major Abdominal Surgery. *Crit Care Med.* 2000;28(10):3417-3423.

23. Stone MD, Wilson RJ, Cross J, Williams BT. Effect of adding dopexamine to intraoperative volume expansion in patients undergoing major elective abdominal surgery. *Br J Anaesth.* 2003;91(5):619-624.

24. Grocott MP, Browne JP, Van der Meulen J, et al. The Postoperative Morbidity Survey was validated and used to describe morbidity after major surgery. *J Clin Epidemiol.* 2007;60(9):919-928.

25. Eddleston J, Goldhill D, Morris J. *Levels of Critical Care for Adult Patients.* London: Intensive Care Society;2009.

26. Cuzick J, Edwards R, Segnan N. Adjusting for non-compliance and contamination in randomized clinical trials. *Statistics in medicine.* 1997;16(9):1017-1029.

27. MacDonald N, Pearse RM. Peri-operative hemodynamic therapy: only large clinical trials can resolve our uncertainty. *Critical Care.* 2011;15(3):122.

28. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *The New England Journal of Medicine.* 2012;367(2):124-134.

29. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *The New England Journal of Medicine.* 2012;367(20):1901-1911.

30. Gillies MA, Habicher M, Jhanji S, et al. Incidence of postoperative death and acute kidney injury associated with i.v. 6% hydroxyethyl starch use: systematic review and meta-analysis. *Br J Anaesth.* 2013.

31. Kuper M, Gold SJ, Callow C, et al. Intraoperative fluid management guided by oesophageal Doppler monitoring. *BMJ.* 2011;342:d3016.

Figure legends

Figure 1. Kaplan-Meier cumulative incidence plots for mortality by treatment allocation to 180 days from start of surgery

Log rank test p-value: 0.093.

Figure 2. Forest plot of meta-analysis for number of patients developing complications after surgery.

637 **Table 1: Baseline patient characteristics**

638 **All data presented as n (%)**
639 *** Eligibility criterion**
640 **† Minimization criterion**
641 **‡ Patients may have more than one risk factor**
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	Cardiac output-guided hemodynamic therapy algorithm (n=368)	Usual care (n=365)
Age (years)	71.3 (8.4)	72.2 (8.6)
Age*		
50-64 years	68 (18.5)	57 (15.6)
≥ 65 years	300 (81.5)	308 (84.4)
Sex		
Male	237 (64.4)	229 (62.7)
Female	131 (35.6)	136 (37.3)
Urgency of surgery*†		
Elective	356 (96.7)	352 (96.4)
Emergency	12 (3.3)	13 (3.6)
Baseline risk factors*‡		
Renal impairment	26 (7.1)	12 (3.3)
Diabetes mellitus	57 (15.5)	65 (17.8)
Pre-defined risk factor for cardiac or respiratory disease	117 (31.8)	118 (32.3)
Planned surgical procedure category†		
Upper gastrointestinal	110 (29·9)	114 (31·2)
Lower gastrointestinal	167 (45·4)	163 (44·7)
Small bowel +/- pancreas	86 (23·4)	84 (23·0)
Urological or gynecological surgery involving gut	5 (1·4)	4 (1·1)
ASA grade		
1	21 (5.7)	24 (6.6)
2	200 (54.5)	174 (48.1)
3	143 (39.0)	155 (42.8)
4	3 (0.8)	9 (2.5)
Planned location following surgery		
Critical care unit (level 3)	275 (74.7)	276 (75.6)
Critical care unit (level 2)	33 (9.0)	33 (9.0)
Post-surgical recovery unit	4 (1.1)	7 (1.9)
Ward	56 (15.2)	49 (13.4)

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Table 2: Clinical management of patients during intervention period (during surgery and six hours following surgery)

Data presented as mean (SD) or n (%)

*** Two patients (one in each group) missing data on anesthetic technique**

† Two patients (both usual care) missing data on fluids both during surgery and during six hours following surgery; one patient (hemodynamic therapy algorithm) missing data on fluids during six hours following surgery; one patient (hemodynamic therapy algorithm) missing data on fluids during surgery; one patient (usual care) missing data on crystalloid during six hours following surgery; one patient (hemodynamic therapy algorithm) missing data on blood products during six hours following surgery

§Two patients (one in each group) missing data on vasopressor or inotrope agents both bolus and infusion; one patient (usual care) missing data on vasopressor or inotrope infusion

	Cardiac output-guided hemodynamic therapy algorithm (n=367)	**Usual care (n=362)**
Duration of surgery (minutes)	270 (200-350)	260 (195-360)
Anesthetic technique*		
General anesthetic only	107 (29.2)	105 (29.1)
General anesthetic plus epidural	259 (70.8)	256 (70.9)
Intravenous crystalloid (ml)†		
During surgery	1518 (1410)	2420 (1382)
During six hours following surgery	565 (254)	670 (367)
Intravenous colloid (ml)†		
During surgery	1465 (913)	708 (695)
During six hours following surgery	642 (498)	226 (361)
Blood products (ml)†		
During surgery	141 (723)	95 (542)
During six hours following surgery	80 (555)	10 (66)
Bolus vasopressor or inotrope agent used during intervention period§	301 (82.2)	270 (74.8)
Infusion of vasopressor or inotrope (other than dopexamine) used during intervention period§	103 (28.1)	108 (30.0)
Actual location of care following surgery		
Critical care unit (level 3)	258 (70.3)	246 (68.0)
Critical care unit (level 2)	42 (11.4)	40 (11.0)
Post-surgical recovery unit	10 (2.7)	9 (2.5)
Ward	57 (15.5)	67 (18.5)

Table 3: Results for primary outcome

All data presented as n (%)

***Six patients (three hemodynamic therapy algorithm, three usual care) missing data on self-assessment of blinding of outcome assessment**

†Includes three patients (two hemodynamic therapy algorithm, one usual care) who died within 30 days

	Cardiac output-guided hemodynamic therapy algorithm (n=366)	Usual care (n=364)	Relative risk (95% CI)	p-value
Composite				
Pre-defined moderate or major post-operative complications and mortality at 30 days following surgery	134 (36.6)	158 (43.4)	0.84 (0.71-1.01)	0.07
Individual elements				
Mortality	12 (3.3)	11 (3.0)		
Pulmonary embolism	4 (1.1)	1 (0.3)		
Myocardial ischemia or infarction	10 (2.7)	8 (2.2)		
Arrhythmia	39 (10.7)	40 (11.0)		
Cardiac or respiratory arrest	16 (4.4)	14 (3.8)		
Limb or digital ischemia	2 (0.5)	1 (0.3)		
Cardiogenic pulmonary edema	1 (0.3)	2 (0.5)		
Acute respiratory distress syndrome	3 (0.8)	4 (1.1)		
Gastrointestinal bleed	13 (3.6)	8 (2.2)		
Bowel infarction	2 (0.5)	5 (1.4)		
Anastomotic breakdown	12 (3.3)	16 (4.4)		
Paralytic ileus	20 (5.5)	27 (7.4)		
Acute psychosis	3 (0.8)	8 (2.2)		
Stroke	1 (0.3)	0 (0)		
Acute kidney injury	17 (4.6)	17 (4.7)		
Infection, source uncertain	11 (3.0)	9 (2.5)		
Urinary tract infection	9 (2.5)	9 (2.5)		
Surgical site infection	22 (6.0)	39 (10.7)		
Organ/space infection	20 (5.5)	36 (9.9)		
Bloodstream infection	6 (1.6)	15 (4.1)		
Nosocomial pneumonia	36 (9.8)	39 (10.7)		
Post-operative hemorrhage	6 (1.6)	4 (1.1)		
Self-assessment of blinding for outcome assessment*				
Assessor suitably blinded	342 (94.2)	349 (96.7)		
Assessor may have known allocation	9 (2.5)	6 (1.7)		
Assessor knew allocation†	12 (3.3)	6 (1.7)		

Table 4: Results for secondary outcomes

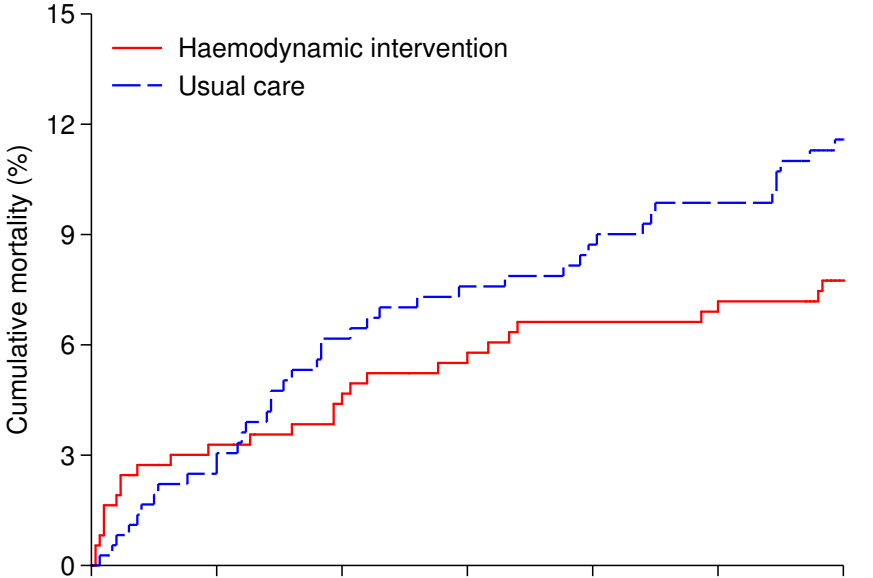
Odds ratios for all cause mortality at 30 days following surgery: unadjusted 1.09 (0.48-2.45); adjusted 1.20 (0.51-2.82); p=0.68

Odds ratios for all cause mortality at 180 days following surgery: unadjusted 0.63 (0.39-1.04); adjusted 0.61 (0.36-1.04); p=0.071

Data presented as median (quartiles) or n (%)

***For patients alive and in hospital on day 7 following start of surgery**

	Cardiac output-guided, hemodynamic therapy algorithm	Usual care	Relative risk (95% CI)	p-value
Post-Operative Morbidity Survey defined morbidity at 7 days following surgery*	182 (66.2) (n=275)	195 (67.9) (n=287)	0.97 (0.87-1.09)	0.72
Infectious complications at 30 days following surgery	87 (23.8) (n=366)	108 (29.7) (n=364)	0.80 (0.63-1.02)	0.08
Critical care free days at 30 days following surgery	27 (26-29) (n=366)	28 (25-29) (n=364)	--	0.98
All cause mortality at 30 days following surgery	12 (3.3) (n=366)	11 (3.0) (n=364)	1.08 (0.48-2.43)	1.00
All cause mortality at 180 days following surgery	28 (7.7) (n=363)	42 (11.6) (n=361)	0.66 (0.42-1.05)	0.08
Duration of post-operative hospital stay	10 (7-14) (n=359)	11 (7-17) (n=356)	--	0.05
Survivors	10 (7-14) (n=343)	11 (7-17) (n=343)		
Non-survivors	7 (3-33) (n=16)	16 (9-36) (n=13)		



Number at risk							
Intervention	368	350	344	339	334	333	306
Usual care	365	348	331	325	321	317	286

Study or Subgroup	Protocol Events	Protocol Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI	Year
Shoemaker 1988	8	28	30	60	1.7%	0.57 [0.30, 1.08]	1988
Berlauk 1991	11	68	9	21	1.3%	0.38 [0.18, 0.79]	1991
Mythen 1995	0	30	6	30	0.1%	0.08 [0.00, 1.31]	1995
Sinclair 1997	1	20	1	20	0.1%	1.00 [0.07, 14.90]	1997
Ueno 1998	4	16	5	18	0.5%	0.90 [0.29, 2.78]	1998
Wilson 1999	38	92	28	46	6.2%	0.68 [0.48, 0.95]	1999
Lobo 2000	6	19	12	18	1.3%	0.47 [0.23, 0.99]	2000
Conway 2002	5	29	9	28	0.8%	0.54 [0.20, 1.40]	2002
Pearse 2005	27	62	41	60	6.3%	0.64 [0.46, 0.89]	2005
Wakeling 2005	24	67	38	67	4.8%	0.63 [0.43, 0.93]	2005
Noblett 2006	1	51	8	52	0.2%	0.13 [0.02, 0.98]	2006
Jerez 2001	53	181	65	209	7.6%	0.94 [0.70, 1.28]	2006
Donati 2007	8	68	20	67	1.3%	0.39 [0.19, 0.83]	2007
*Smetkin 2009	1	20	4	20	0.2%	0.25 [0.03, 2.05]	2009
Mayer 2010	6	30	15	30	1.1%	0.40 [0.18, 0.89]	2010
Jhanji 2010	57	90	30	45	10.4%	0.95 [0.73, 1.23]	2010
Cecconi 2011	16	20	20	20	12.8%	0.80 [0.64, 1.02]	2011
*Brandstrup 2012	23	71	24	79	3.1%	1.07 [0.66, 1.71]	2012
Challand 2012	10	89	13	90	1.2%	0.78 [0.36, 1.68]	2012
*Goepfert 2013	34	50	42	50	13.7%	0.81 [0.65, 1.01]	2013
*Salzwedel 2013	21	79	36	81	3.6%	0.60 [0.39, 0.93]	2013
*Optimise 2014	134	368	158	365	21.8%	0.84 [0.70, 1.01]	2014
Total (95% CI)		**1548**		**1476**	**100.0%**	**0.77 [0.71, 0.83]**	
Total events	488		614				

Heterogeneity: $Chi^2 = 30.44$, df = 21 (P = 0.08); $I^2 = 31\%$

Test for overall effect: Z = 6.22 (P < 0.00001)

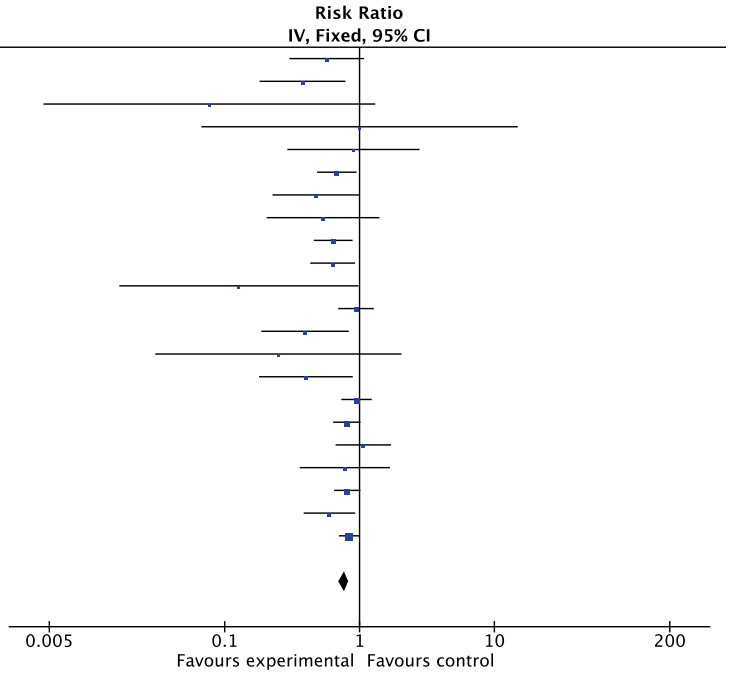
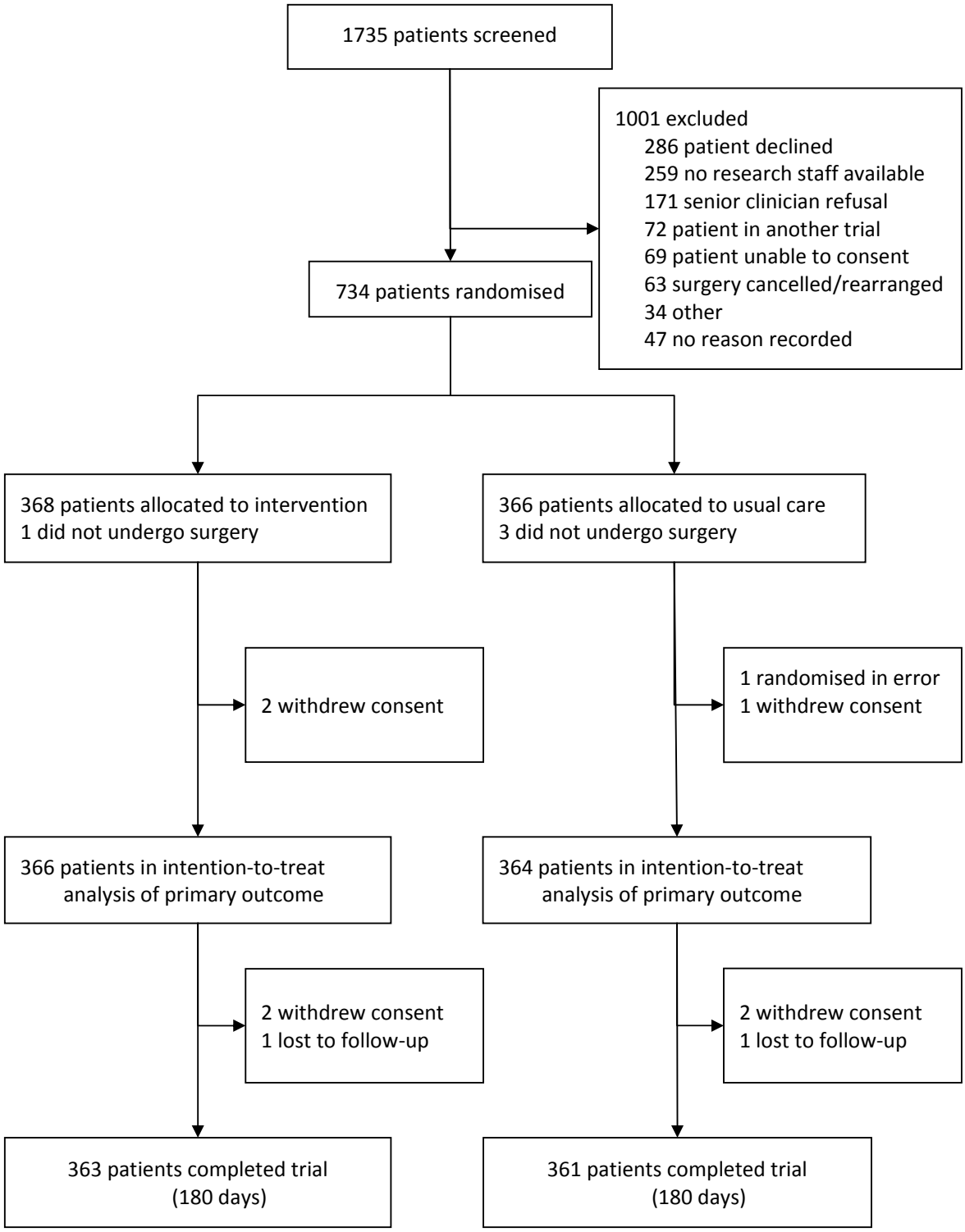


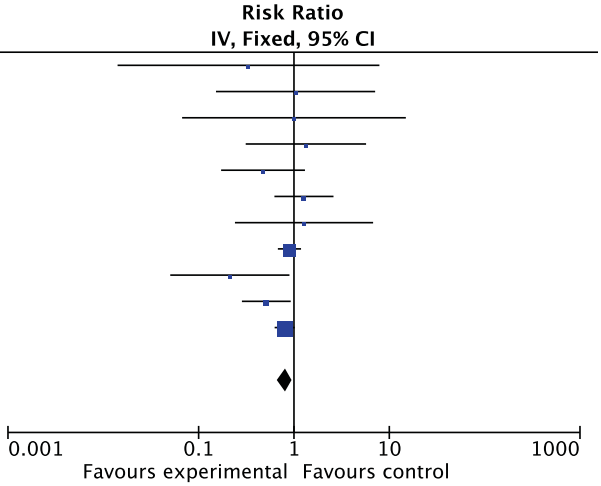
Figure 1. CONSORT flow diagram.

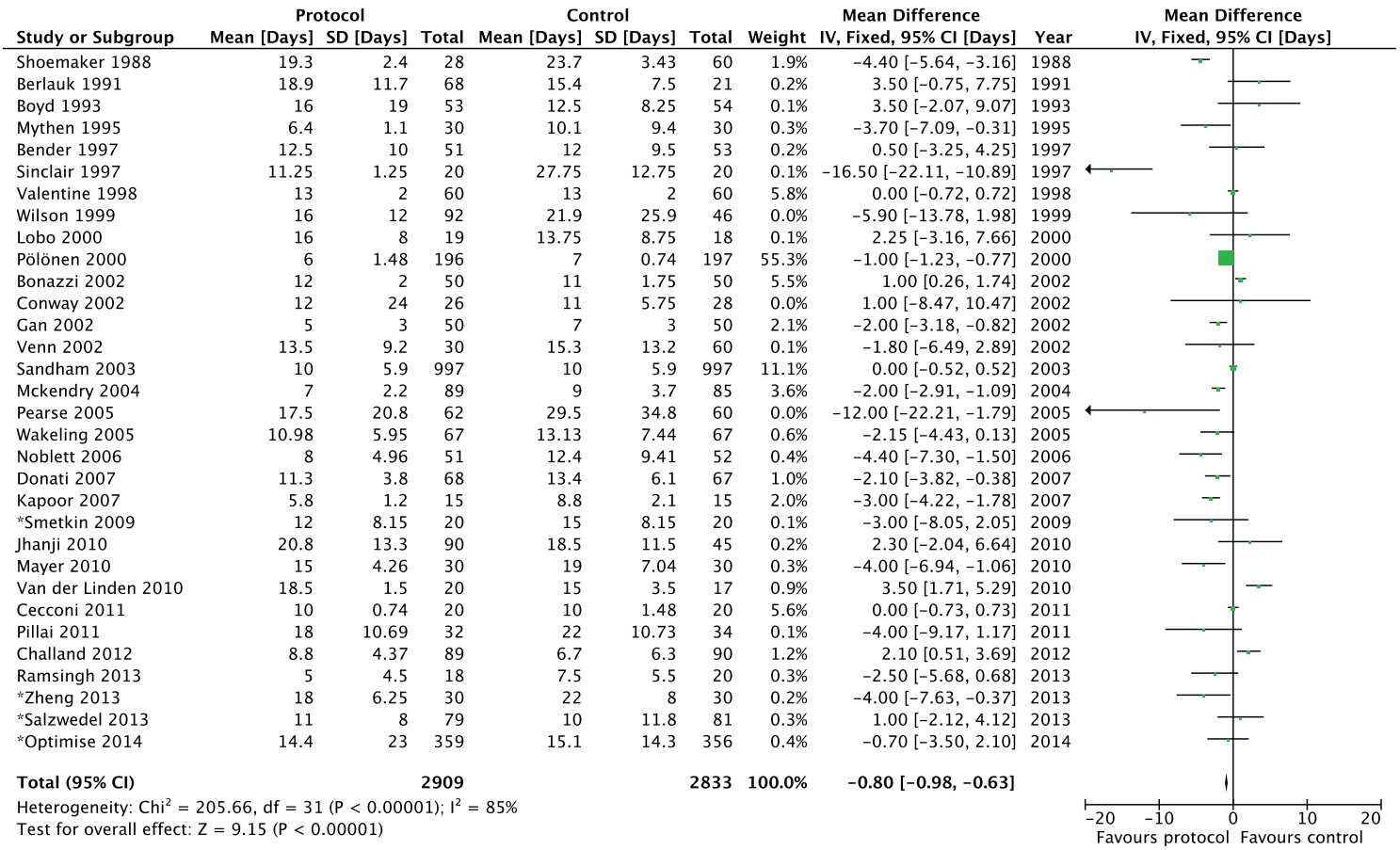


Study or Subgroup	Protocol Events	Protocol Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI	Year
Mythen 1995	0	30	1	30	0.3%	0.33 [0.01, 7.87]	1995
Bender 1997	2	51	2	53	0.7%	1.04 [0.15, 7.10]	1997
Sinclair 1997	1	20	1	20	0.4%	1.00 [0.07, 14.90]	1997
Valentine 1998	4	60	3	60	1.3%	1.33 [0.31, 5.70]	1998
Lobo 2000	4	19	8	18	2.6%	0.47 [0.17, 1.30]	2000
Wakeling 2005	14	67	11	67	5.2%	1.27 [0.62, 2.60]	2005
Van der Linden 2010	3	20	2	17	1.0%	1.27 [0.24, 6.76]	2010
Jhanji 2010	52	90	29	45	34.1%	0.90 [0.68, 1.19]	2010
Pillai 2011	2	32	10	34	1.3%	0.21 [0.05, 0.90]	2011
*Salzwedel 2013	13	79	26	81	7.7%	0.51 [0.28, 0.92]	2013
*Optimise 2014	87	368	108	365	45.5%	0.80 [0.63, 1.02]	2014
Total (95% CI)		**836**		**790**	**100.0%**	**0.81 [0.69, 0.95]**	
Total events	182		201				

Heterogeneity: $Chi^2 = 9.90$, df = 10 (P = 0.45); $I^2 = 0\%$

Test for overall effect: Z = 2.57 (P = 0.01)

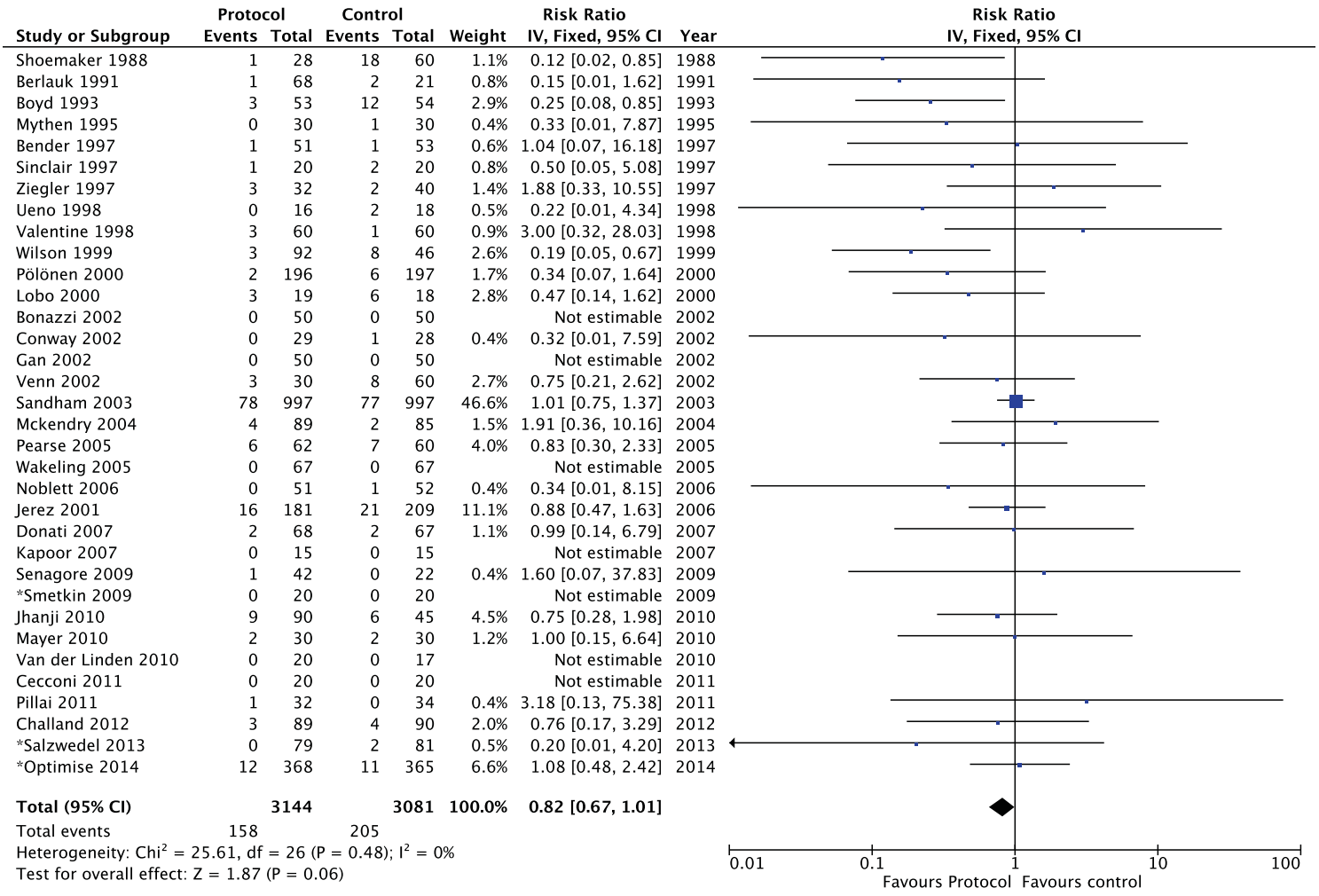




Study or Subgroup	Protocol Mean [Days]	Protocol SD [Days]	Protocol Total	Control Mean [Days]	Control SD [Days]	Control Total	Weight	Mean Difference IV, Fixed, 95% CI [Days]	Year
Shoemaker 1988	19.3	2.4	28	23.7	3.43	60	1.9%	−4.40 [−5.64, −3.16]	1988
Berlauk 1991	18.9	11.7	68	15.4	7.5	21	0.2%	3.50 [−0.75, 7.75]	1991
Boyd 1993	16	19	53	12.5	8.25	54	0.1%	3.50 [−2.07, 9.07]	1993
Mythen 1995	6.4	1.1	30	10.1	9.4	30	0.3%	−3.70 [−7.09, −0.31]	1995
Bender 1997	12.5	10	51	12	9.5	53	0.2%	0.50 [−3.25, 4.25]	1997
Sinclair 1997	11.25	1.25	20	27.75	12.75	20	0.1%	−16.50 [−22.11, −10.89]	1997
Valentine 1998	13	2	60	13	2	60	5.8%	0.00 [−0.72, 0.72]	1998
Wilson 1999	16	12	92	21.9	25.9	46	0.0%	−5.90 [−13.78, 1.98]	1999
Lobo 2000	16	8	19	13.75	8.75	18	0.1%	2.25 [−3.16, 7.66]	2000
Pölönen 2000	6	1.48	196	7	0.74	197	55.3%	−1.00 [−1.23, −0.77]	2000
Bonazzi 2002	12	2	50	11	1.75	50	5.5%	1.00 [0.26, 1.74]	2002
Conway 2002	12	24	26	11	5.75	28	0.0%	1.00 [−8.47, 10.47]	2002
Gan 2002	5	3	50	7	3	50	2.1%	−2.00 [−3.18, −0.82]	2002
Venn 2002	13.5	9.2	30	15.3	13.2	60	0.1%	−1.80 [−6.49, 2.89]	2002
Sandham 2003	10	5.9	997	10	5.9	997	11.1%	0.00 [−0.52, 0.52]	2003
Mckendry 2004	7	2.2	89	9	3.7	85	3.6%	−2.00 [−2.91, −1.09]	2004
Pearse 2005	17.5	20.8	62	29.5	34.8	60	0.0%	−12.00 [−22.21, −1.79]	2005
Wakeling 2005	10.98	5.95	67	13.13	7.44	67	0.6%	−2.15 [−4.43, 0.13]	2005
Noblett 2006	8	4.96	51	12.4	9.41	52	0.4%	−4.40 [−7.30, −1.50]	2006
Donati 2007	11.3	3.8	68	13.4	6.1	67	1.0%	−2.10 [−3.82, −0.38]	2007
Kapoor 2007	5.8	1.2	15	8.8	2.1	15	2.0%	−3.00 [−4.22, −1.78]	2007
*Smetkin 2009	12	8.15	20	15	8.15	20	0.1%	−3.00 [−8.05, 2.05]	2009
Jhanji 2010	20.8	13.3	90	18.5	11.5	45	0.2%	2.30 [−2.04, 6.64]	2010
Mayer 2010	15	4.26	30	19	7.04	30	0.3%	−4.00 [−6.94, −1.06]	2010
Van der Linden 2010	18.5	1.5	20	15	3.5	17	0.9%	3.50 [1.71, 5.29]	2010
Cecconi 2011	10	0.74	20	10	1.48	20	5.6%	0.00 [−0.73, 0.73]	2011
Pillai 2011	18	10.69	32	22	10.73	34	0.1%	−4.00 [−9.17, 1.17]	2011
Challand 2012	8.8	4.37	89	6.7	6.3	90	1.2%	2.10 [0.51, 3.69]	2012
Ramsingh 2013	5	4.5	18	7.5	5.5	20	0.3%	−2.50 [−5.68, 0.68]	2013
*Zheng 2013	18	6.25	30	22	8	30	0.2%	−4.00 [−7.63, −0.37]	2013
*Salzwedel 2013	11	8	79	10	11.8	81	0.3%	1.00 [−2.12, 4.12]	2013
*Optimise 2014	14.4	23	359	15.1	14.3	356	0.4%	−0.70 [−3.50, 2.10]	2014
Total (95% CI)			**2909**			**2833**	**100.0%**	**−0.80 [−0.98, −0.63]**	

Heterogeneity: $Chi^2 = 205.66$, df = 31 ($P < 0.00001$); $I^2 = 85\%$

Test for overall effect: $Z = 9.15$ ($P < 0.00001$)


Protocol
Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight IV, Fixed, 95% CI Year
IV, Fixed, 95% CI
Shoemaker 1988 1 28 18 60 1.1% 0.12 [0.02, 0.85] 1988
Berlauk 1991 1 68 2 21 0.8% 0.15 [0.01, 1.62] 1991
Boyd 1993 3 53 12 54 2.9% 0.25 [0.08, 0.85] 1993
Mythen 1995 0 30 1 30 0.4% 0.33 [0.01, 7.87] 1995
Bender 1997 1 51 1 53 0.6% 1.04 [0.07, 16.18] 1997
Sinclair 1997 1 20 2 20 0.8% 0.50 [0.05, 5.08] 1997
Ziegler 1997 3 32 2 40 1.4% 1.88 [0.33, 10.55] 1997
Ueno 1998 0 16 2 18 0.5% 0.22 [0.01, 4.34] 1998
Valentine 1998 3 60 1 60 0.9% 3.00 [0.32, 28.03] 1998
Wilson 1999 3 92 8 46 2.6% 0.19 [0.05, 0.67] 1999
Pölönen 2000 2 196 6 197 1.7% 0.34 [0.07, 1.64] 2000
Lobo 2000 3 19 6 18 2.8% 0.47 [0.14, 1.62] 2000
Bonazzi 2002 0 50 0 50 Not estimable 2002
Conway 2002 0 29 1 28 0.4% 0.32 [0.01, 7.59] 2002
Gan 2002 0 50 0 50 Not estimable 2002
Venn 2002 3 30 8 60 2.7% 0.75 [0.21, 2.62] 2002
Sandham 2003 78 997 77 997 46.6% 1.01 [0.75, 1.37] 2003
Mckendry 2004 4 89 2 85 1.5% 1.91 [0.36, 10.16] 2004
Pearse 2005 6 62 7 60 4.0% 0.83 [0.30, 2.33] 2005
Wakeling 2005 0 67 0 67 Not estimable 2005
Noblett 2006 0 51 1 52 0.4% 0.34 [0.01, 8.15] 2006
Jerez 2001 16 181 21 209 11.1% 0.88 [0.47, 1.63] 2006
Donati 2007 2 68 2 67 1.1% 0.99 [0.14, 6.79] 2007
Kapoor 2007 0 15 0 15 Not estimable 2007
Senagore 2009 1 42 0 22 0.4% 1.60 [0.07, 37.83] 2009
*Smetkin 2009 0 20 0 20 Not estimable 2009
Jhanji 2010 9 90 6 45 4.5% 0.75 [0.28, 1.98] 2010
Mayer 2010 2 30 2 30 1.2% 1.00 [0.15, 6.64] 2010
Van der Linden 2010 0 20 0 17 Not estimable 2010
Cecconi 2011 0 20 0 20 Not estimable 2011
Pillai 2011 1 32 0 34 0.4% 3.18 [0.13, 75.38] 2011
Challand 2012 3 89 4 90 2.0% 0.76 [0.17, 3.29] 2012
*Salzwedel 2013 0 79 2 81 0.5% 0.20 [0.01, 4.20] 2013
*Optimise 2014 12 368 11 365 6.6% 1.08 [0.48, 2.42] 2014
Total (95% CI) 3144 3081 100.0% 0.82 [0.67, 1.01]
Total events 158 205
Heterogeneity: Chi² = 25.61, df = 26 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.87 (P = 0.06)
0.01 0.1 1 10 100
Favours Protocol Favours control

Study or Subgroup	Protocol Events	Protocol Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI	Year
Shoemaker 1988	1	28	18	60	0.6%	0.12 [0.02, 0.85]	1988
Berlauk 1991	1	68	2	21	0.4%	0.15 [0.01, 1.62]	1991
Boyd 1993	3	53	12	54	1.6%	0.25 [0.08, 0.85]	1993
Mythen 1995	0	30	1	30	0.2%	0.33 [0.01, 7.87]	1995
Ziegler 1997	3	32	2	40	0.8%	1.88 [0.33, 10.55]	1997
Bender 1997	1	51	1	53	0.3%	1.04 [0.07, 16.18]	1997
Sinclair 1997	1	20	2	20	0.4%	0.50 [0.05, 5.08]	1997
Valentine 1998	3	60	1	60	0.5%	3.00 [0.32, 28.03]	1998
Ueno 1998	0	16	2	18	0.3%	0.22 [0.01, 4.34]	1998
Wilson 1999	3	92	8	46	1.5%	0.19 [0.05, 0.67]	1999
Pölönen 2000	4	196	9	197	1.8%	0.45 [0.14, 1.43]	2000
Lobo 2000	3	19	9	18	1.9%	0.32 [0.10, 0.98]	2000
Venn 2002	3	30	8	60	1.5%	0.75 [0.21, 2.62]	2002
Bonazzi 2002	0	50	0	50		Not estimable	2002
Conway 2002	0	29	1	28	0.2%	0.32 [0.01, 7.59]	2002
Gan 2002	0	50	0	50		Not estimable	2002
Sandham 2003	163	997	155	997	59.0%	1.05 [0.86, 1.29]	2003
Mckendry 2004	4	89	2	85	0.9%	1.91 [0.36, 10.16]	2004
Wakeling 2005	0	67	1	67	0.2%	0.33 [0.01, 8.04]	2005
Pearse 2005	7	62	9	60	2.8%	0.75 [0.30, 1.89]	2005
Jerez 2001	16	181	21	209	6.3%	0.88 [0.47, 1.63]	2006
Noblett 2006	0	51	1	52	0.2%	0.34 [0.01, 8.15]	2006
Donati 2007	2	68	2	67	0.6%	0.99 [0.14, 6.79]	2007
Kapoor 2007	0	15	0	15		Not estimable	2007
Senagore 2009	1	42	0	22	0.2%	1.60 [0.07, 37.83]	2009
*Smetkin 2009	0	20	0	20		Not estimable	2009
Van der Linden 2010	0	20	0	17		Not estimable	2010
Jhanji 2010	9	90	6	45	2.6%	0.75 [0.28, 1.98]	2010
Mayer 2010	2	30	2	30	0.7%	1.00 [0.15, 6.64]	2010
Cecconi 2011	0	20	0	20		Not estimable	2011
Pillai 2011	1	32	0	34	0.2%	3.18 [0.13, 75.38]	2011
Challand 2012	7	89	7	90	2.4%	1.01 [0.37, 2.76]	2012
*Salzwedel 2013	0	79	2	81	0.3%	0.20 [0.01, 4.20]	2013
*Optimise 2014	28	368	42	365	11.5%	0.66 [0.42, 1.04]	2014
Total (95% CI)		**3144**		**3081**	**100.0%**	**0.86 [0.74, 1.00]**	
Total events	266		326				

Heterogeneity: Chi^2 = 31.90, df = 27 (P = 0.24); I^2 = 15%

Test for overall effect: Z = 1.92 (P = 0.05)