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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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IMPORTANCE Small trials suggest that postoperative outcomes may be improved by the use of cardiac output monitoring to guide administration of intravenous fluid and inotropic drugs as part of a hemodynamic therapy algorithm.

OBJECTIVE To evaluate the clinical effectiveness of a perioperative, cardiac output–guided hemodynamic therapy algorithm.

DESIGN, SETTING, AND PARTICIPANTS OPTIMISE was a pragmatic, multicenter, randomized, observer-blinded trial of 734 high-risk patients aged 50 years or older undergoing major gastrointestinal surgery at 17 acute care hospitals in the United Kingdom. An updated systematic review and meta-analysis were also conducted including randomized trials published from 1966 to February 2014.

INTERVENTIONS Patients were randomly assigned to a cardiac output–guided hemodynamic therapy algorithm for intravenous fluid and inotrope (dopexamine) infusion during and 6 hours following surgery (n=368) or to usual care (n=366).

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of predefined 30-day moderate or major complications and mortality. Secondary outcomes were morbidity on day 7; infection, critical care–free days, and all-cause mortality at 30 days; all-cause mortality at 180 days; and length of hospital stay.

RESULTS Baseline patient characteristics, clinical care, and volumes of intravenous fluid were similar between groups. Care was nonadherent to the allocated treatment for less than 10% of patients in each group. The primary outcome occurred in 36.6% of intervention and 43.4% of usual care participants (relative risk [RR], 0.84 [95% CI, 0.71-1.01]; absolute risk reduction, 6.8% [95% CI, –0.3% to 13.9%]; $P = .07$). There was no significant difference between groups for any secondary outcomes. Five intervention patients (1.4%) experienced cardiovascular serious adverse events within 24 hours compared with none in the usual care group. Findings of the meta-analysis of 38 trials, including data from this study, suggest that the intervention is associated with fewer complications (intervention, 488/1548 [31.5%] vs control, 614/1476 [41.6%]; RR, 0.77 [95% CI, 0.71-0.83]) and a nonsignificant reduction in hospital, 28-day, or 30-day mortality (intervention, 159/3215 deaths [4.9%] vs control, 206/3160 deaths [6.5%]; RR, 0.82 [95% CI, 0.67-1.01]) and mortality at longest follow-up (intervention, 267/3215 deaths [8.3%] vs control, 327/3160 deaths [10.3%]; RR, 0.86 [95% CI, 0.74-1.00]).

CONCLUSIONS AND RELEVANCE In a randomized trial of high-risk patients undergoing major gastrointestinal surgery, use of a cardiac output–guided hemodynamic therapy algorithm compared with usual care did not reduce a composite outcome of complications and 30-day mortality. However, inclusion of these data in an updated meta-analysis indicates that the intervention was associated with a reduction in complication rates.

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Estimates suggest that more than 230 million patients undergo surgery worldwide each year, with reported mortality rates between 1% and 4%.^{1,2} Complications and deaths are most frequent among high-risk patients, those who are older or have comorbid disease, and those who undergo major gastrointestinal or vascular surgery. Importantly, patients who develop complications but survive to hospital discharge have reduced long-term survival.^{3,4}

It is accepted that intravenous fluid and inotropic drugs have an important effect on patient outcomes, in particular following major gastrointestinal surgery. Yet they are commonly prescribed to subjective criteria, leading to wide variation in clinical practice.⁵ One possible solution is the use of cardiac output monitoring to guide administration of intravenous fluid and inotropic drugs as part of a hemodynamic therapy algorithm. This approach has been shown to modify inflammatory pathways and improve tissue perfusion and oxygenation.^{6,7} Use of hemodynamic therapy algorithms has been recommended in a report commissioned by the US Centers for Medicare & Medicaid Services⁸ and by the UK National Institute for Health and Care Excellence (NICE).⁹ A recent Cochrane review, however, has suggested that the treatment benefit may be more marginal than previously believed.¹⁰ The current evidence consists primarily of small trials and is insufficient to resolve controversies regarding potential harm associated with fluid excess, myocardial injury, and invasive forms of monitoring. As a result, this treatment has not been widely adopted into clinical practice.

In this context, we evaluated the clinical effectiveness of cardiac output monitoring to guide administration of intravenous fluid and inotropic drugs as part of a hemodynamic therapy algorithm in a large, pragmatic, multicenter randomized 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

The OPTIMISE (Optimisation of Cardiovascular Management to Improve Surgical Outcome) trial was conducted in 17 acute care hospitals in the UK National Health Service. Adult patients aged 50 years or older undergoing major abdominal surgery involving the gastrointestinal tract with an expected duration greater than 90 minutes were eligible for recruitment provided they satisfied 1 of the following high-risk criteria: aged 65 years or older; presence of a defined risk factor for cardiac or respiratory disease (exercise tolerance equivalent to 6 metabolic equivalents or less as defined by the American College of Cardiology/American Heart Association guidelines¹¹); ischemic heart disease; ejection fraction less than 30% (echocardiography); moderate or severe valvular heart disease; heart failure; chronic obstructive pulmonary disease; poor lung function demonstrated by spirometry; radiographically confirmed chronic lung disease; anaerobic threshold of 14 mL/min/kg or less on submaximal exercise testing; heavy smoker; renal impairment (serum creatinine ≥ 1.5 mg/dL); diabetes melli-

tus; or emergency surgery. Exclusion criteria included refusal of consent, pregnancy, acute pulmonary edema (within prior 7 days), acute myocardial ischemia (within prior 30 days), and surgery for palliative treatment only. Investigators were asked not to randomize patients when the clinician intended to use cardiac output monitoring for clinical reasons. OPTIMISE was approved by the East London and City Research Ethics Committee and the Medical and Healthcare Products Regulatory Agency. Written informed consent was obtained from all patients prior to surgery. Site visits were performed by R.M.P. and A.A. for training and for source data verification.

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 (see study protocol in the Supplement). 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 predefined 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 postoperative care.

Clinical Management

The intervention period commenced with induction of anesthesia and continued until 6 hours following completion of surgery.

All Patients

Perioperative treatment goals were flexibly defined for all patients to avoid both extremes of clinical practice and practice misalignment.¹² All patients received standard measures to maintain oxygenation (oxygen saturation by pulse oximetry $\geq 94\%$), hemoglobin (>80 g/L), core temperature (37°C [99°F]) and heart rate (<100 /min). Five percent dextrose was administered at 1 mL/kg/h 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 mm Hg using an α -adrenoceptor agonist or vasodilator as required. Postoperative analgesia was provided by epidural infusion (bupivacaine and fentanyl) or intravenous infusion (morphine or fentanyl). With the exception of the interventions described below, all other treatment decisions were at the discretion of and undertaken by senior clinicians.

Hemodynamic Therapy Algorithm Group

Intervention group patients received intravenous fluid and inotropes according to a cardiac output-guided hemodynamic therapy algorithm (eAppendix 1 in the Supplement). The algorithm was developed for OPTIMISE by an expert group. It was designed to be delivered in the operating room/postanesthetic care unit by both medical and nursing staff, ensuring that critical care admission was not necessary for protocol adherence. A cardiac output monitor was chosen that could be used in conscious (extubated) patients (LiDCOrapid, LiDCO Ltd). This technology has been extensively evaluated and in clinical use for more than 10 years.¹³ The hemodynamic therapy algorithm was supported by high-quality clinical and mechanistic evidence and had a good cardiovascular safety profile.^{6,7,14-16} Intravenous colloid solution was administered in 250-mL boluses 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 µg/kg/min through either a peripheral or a central venous catheter (Cephalon Ltd). The choice and dose of inotrope was based on the findings of a previous meta-regression analysis.¹⁵ The dose of dopexamine was reduced if the heart rate increased to 120% of baseline or 100/min (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

The usual care group received usual perioperative 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 a patient's health deterioration.

Trial End Points

The primary effect estimate was the relative risk (RR) of a composite of 30-day postsurgical mortality and predefined moderate or major postoperative complications (pulmonary embolism, myocardial ischemia or infarction, arrhythmia, cardiac or respiratory arrest, limb or digital ischemia, cardiogenic pulmonary edema, acute respiratory distress syndrome, gastrointestinal bleeding, bowel infarction, anastomotic breakdown, paralytic ileus, acute psychosis, stroke, acute kidney injury, infection [source uncertain], urinary tract infection, surgical site infection, organ/space infection, bloodstream infection, nosocomial pneumonia, and postoperative hemorrhage; see study protocol in the Supplement). Secondary outcomes were morbidity on postsurgical day 7 as defined by the Post-Operative Morbidity Survey (POMS)¹⁷; 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 postoperative critical care was categorized according to standard criteria.¹⁸ Patients were followed up for 30 days by visit and through local computerized records while in the hospital. All patients were contacted at 30 days either by telephone for those who had left the hospital or by visit for those who had not. When neces-

sary, 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.

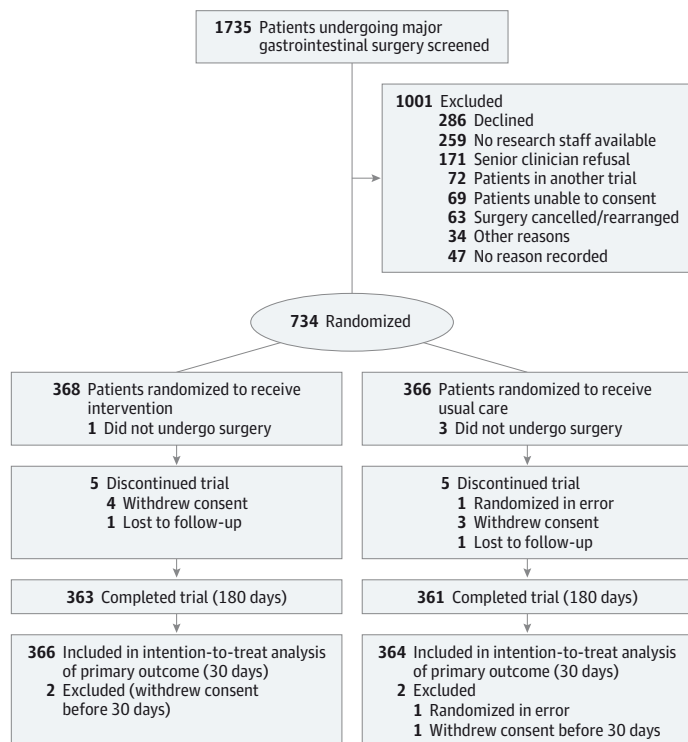
Statistical Analysis

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 predefined moderate or major postoperative complications and mortality at 30 days following surgery from 50% in the usual care group to 37.5% in the intervention group (absolute risk reduction, 12.5%; relative risk reduction, 25%).¹⁴ Allowing for a 3% 1-way crossover 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 the halfway point. Predefined stopping guidelines permitted early termination of the trial for harm but not for effectiveness.

Analyses were performed according to an a priori statistical analysis plan including all patients on an intention-to-treat basis. Categorical data were compared using the Fisher 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, sex, urgency of surgery, surgical procedure category, American Society of Anesthesiology 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 RRs with 95% confidence intervals. Results for the primary outcome are additionally reported as absolute risk reductions with 95% confidence intervals. Results of the logistic regression model are reported as adjusted odds ratios (ORs) with 95% confidence intervals, with unadjusted ORs for comparison.

Prespecified secondary analyses were a modified intention-to-treat analysis excluding patients who did not undergo surgery, an adherence-adjusted analysis, and scenario-based sensitivity analyses for missing primary outcomes. The modified intention-to-treat analysis excluded patients who did not undergo surgery. In the adherence-adjusted analysis, patients whose treatment did not adhere to allocation were assumed to have the same outcome as if they had been assigned to the alternative treatment group.¹⁹ This approach uses the underlying principle of randomization to assume that for each non-adherent case, there would be an equivalent patient in the alternative treatment group whose care would have been nonadherent had their allocations been reversed; therefore, unlike a per-protocol or as-treated analysis, this approach can

Figure 1. Participant Flow



give an unbiased estimate of the treatment effect among patients whose care adhered to their allocated treatment. The scenario-based sensitivity analyses considered 2 extreme scenarios for the outcomes of patients with missing data for the primary outcome variable: a best-case 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. Prespecified subgroup analyses were performed by urgency of surgery, by surgical procedure category, and by timing of recruitment (comparing the first 10 patients recruited at each site with those recruited subsequently (sites recruiting <10 patients were excluded). Continuous variables are presented as means with standard deviations for normally distributed data or medians (interquartile ranges) for non-normally distributed data. Categorical variables are presented as number and percentage of participants. Analyses were performed using Stata SE, version 10.1 (Stata Corp). The 2-tailed statistical significance level was set at $P < .05$.

Systematic Review

Using identical methods, we updated the previous Cochrane systematic review of published randomized trials of “perioperative 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.¹⁰ Detailed methods are presented in Appendix 2 in the Supplement. CENTRAL (Cochrane Library 2014), MEDLINE (1966 to February 2014), and EMBASE (1982 to February 2014) were searched for randomized trials involving adult

patients (aged ≥ 16 years) undergoing surgery in an operating room wherein the intervention met the following criteria: perioperative administration of fluids, with or without inotropes/vasoactive drugs, targeted to increase blood flow (relative to control) against explicit measured goals. *Perioperative* was defined as initiated within 24 hours before surgery and lasting up to 6 hours 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 systematic review), and 28-day, 30-day, or hospital mortality (as reported by authors). Treatment effects were reported as RRs with 95% confidence intervals for clinical variables or weighted mean differences with standard deviations for length of hospital stay. Analyses were performed using RevMan version 5.2.8 using fixed-effects models with random-effects models for comparison.

Results

A total of 734 patients were enrolled between June 2010 and November 2012; 368 patients were allocated to the hemodynamic therapy algorithm and 366 to usual care. In the usual care group, 1 patient who was enrolled in another trial was randomized in error and excluded before surgery (Figure 1).

Table 1. Baseline Patient Characteristics^a

Characteristics	Cardiac Output-Guided Hemodynamic Therapy Algorithm (n = 368)	Usual Care (n = 365)
Age, mean (SD), y	71.3 (8.4)	72.2 (8.6)
Age, y ^b		
50-64	68 (18.5)	57 (15.6)
≥65	300 (81.5)	308 (84.4)
Sex		
Male	237 (64.4)	229 (62.7)
Female	131 (35.6)	136 (37.3)
Urgency of surgery ^{b,c}		
Elective	356 (96.7)	352 (96.4)
Emergency	12 (3.3)	13 (3.6)
Baseline risk factors ^{b,d}		
Renal impairment	26 (7.1)	12 (3.3)
Diabetes mellitus	57 (15.5)	65 (17.8)
Predefined risk factor for cardiac or respiratory disease	117 (31.8)	118 (32.3)
Planned surgical procedure category ^c		
Upper gastrointestinal tract	110 (29.9)	114 (31.2)
Lower gastrointestinal tract	167 (45.4)	163 (44.7)
Small bowel with/without pancreas	86 (23.4)	84 (23.0)
Urological or gynecological surgery involving gut	5 (1.4)	4 (1.1)
American Society of Anesthesiology grade ^e		
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)
Postsurgical recovery unit	4 (1.1)	7 (1.9)
Ward	56 (15.2)	49 (13.4)

^a Data are presented as No. (%) of participants unless otherwise indicated. Data do not include 1 patient in the usual care group who was randomized in error.

^b Eligibility criterion.

^c Minimization criterion.

^d Patients may have more than 1 risk factor.

^e American Society of Anesthesiology grades are defined as follows (grade 5 patients were not eligible for inclusion): 1, a healthy patient; 2, a patient with mild systemic disease that does not limit physical activity; 3, a patient with severe systemic disease that limits physical activity; and 4, a patient with severe systemic disease that is a constant threat to life.

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 (9 patients). Clinical care outside the trial intervention was also similar (Table 2), including critical care admission. Overall volumes of intravenous fluid (colloid and crystalloid combined) administered during the intervention period were similar (intervention, 4190 mL, vs

Table 2. Clinical Management of Patients During Intervention Period (During Surgery and for 6 Hours Following Surgery)^a

Characteristics	Cardiac Output-Guided Hemodynamic Therapy Algorithm (n = 367)	Usual Care (n = 362)
Duration of surgery, median (IQR), min	270 (200-350)	260 (195-360)
Anesthetic technique, No. (%) ^b		
General anesthesia only	107 (29.2)	105 (29.1)
General anesthesia plus epidural	259 (70.8)	256 (70.9)
Intravenous crystalloid, median (IQR), mL ^c		
During surgery	1000 (459-2000)	2000 (1283-3000)
During 6 h following surgery	506 (410-660)	600 (450-800)
Intravenous colloid, median (IQR), mL ^c		
During surgery	1250 (1000-2000)	500 (0-1000)
During 6 h following surgery	500 (250-1000)	0 (0-500)
Blood products, mean (SD), mL ^c		
During surgery	141 (723)	95 (542)
During 6 h following surgery	80 (555)	10 (66)
Bolus vasopressor or inotrope agent used during intervention period, No. (%) ^d	301 (82.2)	270 (74.8)
Infusion of vasopressor or inotrope (other than dopexamine) used during intervention period, No. (%) ^d	103 (28.1)	108 (30.0)
Actual location of care following surgery, No. (%)		
Critical care unit, level 3	258 (70.3)	246 (68.0)
Critical care unit, level 2	42 (11.4)	40 (11.0)
Postsurgical recovery unit	10 (2.7)	9 (2.5)
Ward	57 (15.5)	67 (18.5)

Abbreviation: IQR, interquartile range.

^a Data do not include 1 patient in the usual care group who was randomized in error and 4 patients (3 in the usual care group and 1 in the hemodynamic therapy group) who did not undergo surgery.

^b Two patients (1 in each group) were missing data on anesthetic technique.

^c Two patients (both in the usual care group) were missing data on fluids both during surgery and during the 6 hours following surgery; 1 patient in the hemodynamic therapy group was missing data on fluids during the 6 hours following surgery; 1 patient in the hemodynamic therapy group was missing data on fluids during surgery; 1 patient in the usual care group was missing data on crystalloid use during the 6 hours following surgery; and 1 patient in the hemodynamic therapy group was missing data on blood products during the 6 hours following surgery.

^d Two patients (1 in each group) were missing data on vasopressor or inotrope agents (both bolus and infusion); 1 patient in the usual care group was missing data on vasopressor or inotrope infusion.

usual care, 4024 mL). In the usual care group, more intravenous fluid was administered during than after surgery, while for the intervention group, similar volumes were administered during surgery and during the 6 hours following surgery. The intervention group received more colloid and less crystalloid than the usual care group. With the exception of dopexamine, use of vasopressor and inotropic agents was similar between the groups. Less than 10% of patients in each group had care that was nonadherent to

Table 3. Results for the Primary Outcome^a

Outcomes	Cardiac Output-Guided Hemodynamic Therapy Algorithm, No. (%) (n = 366)	Usual Care, No. (%) (n = 364)
Composite of predefined moderate or major postoperative complications and mortality at 30 d following surgery ^b	134 (36.6)	158 (43.4)
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 bleeding	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
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 ^c	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)
Postoperative hemorrhage	6 (1.6)	4 (1.1)
Self-assessment of blinding for outcome assessment ^d		
Assessor suitably blinded	342 (94.2)	349 (96.7)
Assessor may have known allocation	9 (2.5)	6 (1.7)
Assessor knew allocation ^e	12 (3.3)	6 (1.7)

^a Reports complications; some patients developed more than 1 complication. Data do not include 1 patient in the usual care group who was randomized in error and 3 patients (1 in the usual care group and 2 in the hemodynamic therapy group) who withdrew consent. The predefined complication of other infections of the urinary tract did not occur in any patient.

^b Relative risk, 0.84; 95% CI, 0.71-1.01; $P = .07$.

^c Superficial and deep surgical site infection are presented as a single data point.

^d Six patients (3 in the hemodynamic therapy group and 3 in the usual care group) were missing data on self-assessment of blinding of outcome assessment.

^e Includes 3 patients (2 in the hemodynamic therapy group and 1 in the usual care group) who died within 30 days.

their allocated treatment (eTable 1 in the Supplement). This was achieved through the presence of trained investigators, when necessary, to observe, advise, or deliver the intervention (eTable 2 in the Supplement). Investigator self-assessment of blinding for determination of outcomes also indicated a high rate of adherence to trial procedures (Table 3).

The primary outcome, a composite of predefined moderate or major postoperative complications and mortality at 30 days following surgery, was met by 36.6% of patients (134/366) in the intervention group and by 43.4% (158/364) in the usual care group (RR, 0.84 [95% CI, 0.71-1.01]; absolute risk reduction, 6.8% [95% CI, -0.3% to 13.9%]; $P = .07$) (Table 3). Following adjustment for baseline risk factors, the observed treatment effect remained nonsignificant, with an adjusted OR of 0.73 (95% CI, 0.53-1.00; $P = .05$) (Wald $\chi^2_{16} = 27.6$ for model fit; $P = .04$; unadjusted OR, 0.75 [95% CI, 0.56-1.01]; $P = .07$). The prespecified modified intention-to-treat analysis, in which 3 patients (all in the usual care group) who did not undergo surgery were excluded, had little effect on the primary outcome (RR, 0.84; 95% CI, 0.70-1.00; $P = .06$). In the prespecified adherence-adjusted analysis conducted using established methods,¹⁹ the observed treatment effect was strengthened when the 65 patients whose care was nonadherent (eTable 1 in the Supplement) were assumed to experience the same outcome as if they had been allocated to the alternative group (RR, 0.80; 95% CI, 0.61-0.99; $P = .04$). Scenario-based sensitivity analyses demonstrated that the 4 patients with missing primary outcome data had minimal influence on treatment effect (RRs, 0.84 [95% CI, 0.70-1.00] to 0.85 [95% CI, 0.71-1.02]).

Five patients in the intervention group (1.4%) experienced serious adverse cardiac events within 24 hours of the end of the intervention period (2 tachycardias, 2 myocardial infarctions, and 1 arrhythmia) compared with none in the usual care group ($P = .06$). At 30 days following surgery, however, the incidence of cardiovascular events (myocardial infarction, arrhythmia, and cardiogenic pulmonary edema) 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 (unadjusted OR, 1.09 [95% CI, 0.48-2.45]; adjusted OR, 1.20 [95% CI, 0.51-2.82]; $P = .68$; Wald $\chi^2_{16} = 15.3$ for model fit; $P = .50$); all-cause mortality at 180 days following surgery (unadjusted OR, 0.63 [95% CI, 0.39-1.04]; adjusted OR, 0.61 [95% CI, 0.36-1.04]; $P = .07$; Wald $\chi^2_{16} = 41.8$ for model fit; $P < .001$); and duration of acute hospital length of stay (Table 4 and Figure 2). No interaction was found for urgency of surgery; the intervention was associated with a slight reduction in the primary outcome for the elective surgery subgroup. 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 surgery with or without pancreas surgery. A significant interaction ($P = .02$) was found for timing of recruitment; the intervention was associated with a reduction in the primary outcome for patients recruited later (RR, 0.59 [95% CI, 0.41-0.84]) compared with earlier at each site (RR, 1.51 [95% CI, 0.75-3.01]) (eTable 3 in the Supplement).

The updated literature search identified 7 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 (eFigure 1 in the Supplement). Detailed results are provided

Table 4. Results for Secondary Outcomes^a

Outcomes	Cardiac Output-Guided Hemodynamic Therapy Algorithm	Usual Care	Relative Risk (95% CI)	P Value
POMS-defined morbidity at 7 d following surgery, No./total (%) ^b	182/275 (66.2)	195/287 (67.9)	0.97 (0.87-1.09)	.72
Infectious complications at 30 d following surgery, No./total (%)	87/366 (23.8)	108/364 (29.7)	0.80 (0.63-1.02)	.08
Critical care-free days at 30 d following surgery, median (IQR)	27 (26-29)	28 (25-29)		.98
All-cause mortality at 30 d following surgery, No./total (%) ^c	12/366 (3.3)	11/364 (3.0)	1.08 (0.48-2.43)	>.99
All-cause mortality at 180 d following surgery, No./total (%) ^d	28/363 (7.7)	42/361 (11.6)	0.66 (0.42-1.05)	.08
Duration of postoperative hospital stay, median (IQR), d	10 (7-14)	11 (7-17)		.05
Survivors	10 (7-14)	11 (7-17)		
Nonsurvivors	7 (3-33)	16 (9-36)		

Abbreviations: IQR, interquartile range; POMS, Post-Operative Morbidity Survey.

^a Reports patients; some patients developed more than 1 complication.

^b Among patients alive and in the hospital on day 7 following surgery.

^c Odds ratios for all-cause mortality at 30 days following surgery: unadjusted, 1.09 (95% CI, 0.48-2.45); adjusted, 1.20 (95% CI, 0.51-2.82); *P* = .68.

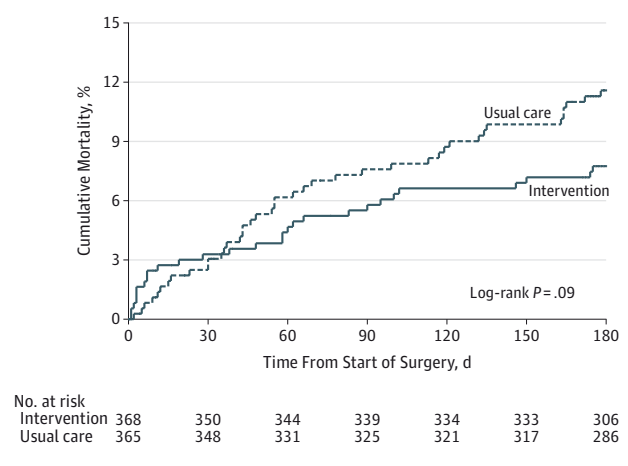
^d Odds ratios for all-cause mortality at 180 days following surgery: unadjusted, 0.63 (95% CI, 0.39-1.04); adjusted, 0.61 (95% CI, 0.36-1.04); *P* = .07.

in eAppendix 2 in the Supplement. The addition of the findings of OPTIMISE and other recent trials does not substantially alter the findings of the recent Cochrane meta-analysis. Complications were less frequent among patients treated according to a hemodynamic therapy algorithm (intervention, 488/1548 [31.5%] vs control, 614/1476 [41.6%]; RR, 0.77 [95% CI, 0.71-0.83]) (Figure 3).^{6,14,20-38} The intervention was associated with a reduced incidence of postoperative infection (intervention, 182/836 [21.8%] vs control, 201/790 [25.4%]; RR, 0.81 [95% CI, 0.69-0.95]) and a reduced duration of hospital stay (mean reduction, 0.79 days [95% CI, 0.96-0.62]) (eFigures 2 and 3 in the Supplement). There was a nonsignificant reduction in hospital, 28-day, or 30-day mortality (intervention, 159/3215 [4.9%] vs control, 206/3160 [6.5%]; RR, 0.82 [95% CI, 0.67-1.01]) and a nonsignificant reduction in mortality at longest follow-up (intervention, 267/3215 deaths [8.3%] vs control, 327/3160 deaths [10.3%]; RR, 0.86 [95% CI, 0.74-1.00]) (eFigures 4 and 5 in the Supplement). These results were strengthened through the use of random-effects models (eAppendix 2 in the Supplement).

Discussion

The principal finding of the OPTIMISE trial was that among patients undergoing major abdominal surgery involving the gastrointestinal tract, when compared with usual care, use of this cardiac output-guided, hemodynamic therapy algorithm was not associated with a significant reduction in the composite primary outcome of moderate or major postoperative complications at 30 days following surgery. However, after incorporating the results of this large trial into an updated systematic review and meta-analysis, there was evidence that this intervention was associated with a clinically important reduction in the number of patients who develop complications after surgery. 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 find-

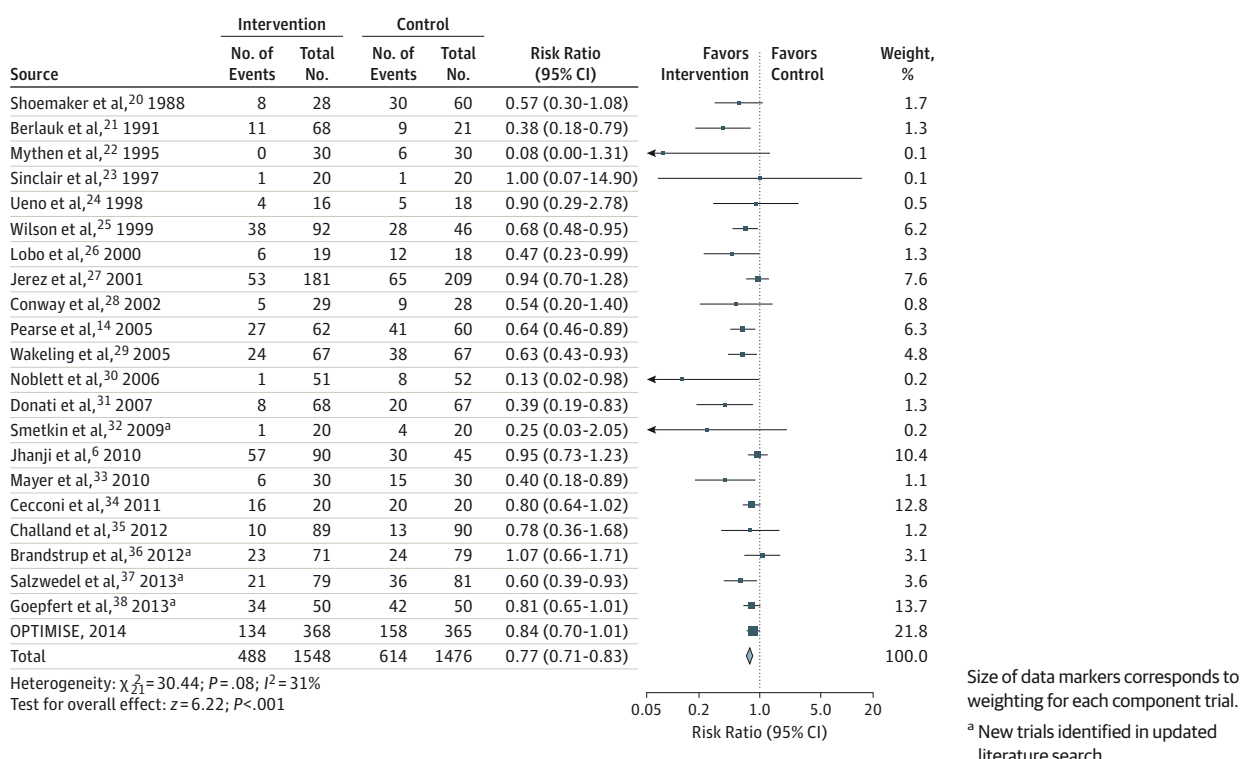
Figure 2. Cumulative Incidence of Mortality Up to 180 Days After Surgery Using a Cardiac Output-Guided Hemodynamic Therapy Algorithm Intervention vs Usual Care



ings of the updated systematic review suggest that this treatment approach is associated with a significant reduction in the number of patients who develop postoperative infection as well as in duration of hospital stay. The findings of the mortality analyses provide borderline evidence but remain consistent with benefit.

To the best of our knowledge, this is the largest trial of a perioperative, cardiac output-guided hemodynamic therapy algorithm to date. OPTIMISE was designed to address several limitations in the previous trials.³⁹ The large sample size allowed for comparison of the cardiac output-guided hemodynamic therapy algorithm with usual perioperative care, avoiding problems associated with alternative “control” treatment algorithms, which do not reflect typical practice.¹² 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 high-quality clinical and mechanistic evidence and a good cardiovascular safety

Figure 3. Meta-analysis of Number of Patients Developing Complications After Surgery



profile.^{6,7,10,14-16} 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 postanesthetic care unit by both medical and nursing staff and particularly to ensure that admission to critical care was not necessary for adherence to the intervention. Importantly, the high rate of adherence to the hemodynamic therapy algorithm used in this trial suggests that this treatment approach is feasible for use in routine clinical practice. A widely used cardiac output monitoring technology was used (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.^{40,41} Although we do not have individual patient data describing the use of starch, a post hoc survey of investigators suggested that 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.⁴²

A potential weakness of OPTIMISE may be the use of a primary outcome that was a composite of moderate or major postoperative 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 adherence to blinding for patient outcome assessment. Finally, the event rate in the usual care group was slightly lower than expected and crossover 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 a failure to achieve statistical significance for the primary outcome. Although emergency surgery was one of our inclusion criteria, we were able to recruit only 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. Although 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 suggest 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 required. A prespecified 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.⁴³

The systematic review represents an up-to-date and robust summary of the literature but also has limitations. Most of the component trials are small single-center trials that lack statistical power and may have an elevated risk of bias; there is evidence of small-studies effects. Addition of the OPTIMISE trial findings improves the quality of this evidence synthesis, but the reporting of outcomes remains inconsistent among trials, with diverse criteria for complications reported over a variety of time frames. More than half the included studies were published more than 10 years ago and may not be representative of current practice.

Conclusions

In a randomized trial of high-risk patients undergoing major gastrointestinal surgery, the use of a cardiac output-guided hemodynamic therapy algorithm did not reduce a composite outcome of complications and 30-day mortality compared with usual care. However, inclusion in an updated meta-analysis indicates that the intervention was associated with a reduction in complication rates.

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