EDITORIAL

Hemodynamic Goal-Directed Therapy in High-Risk Surgical Patients

Elliott Bennett-Guerrero, MD

Most clinicians agree that during stress, such as acute critical illness or surgery, maintaining adequate perfusion and oxygen delivery reduces the risk of injury to vital organs. However, the best way to achieve these general goals remains controversial. A growing body of evidence suggests that "goal-directed therapy" (GDT) to increase blood flow can reduce postoperative complications and cost.[1] Goal-directed therapy typically uses a monitoring tool to continuously assess cardiac performance, and through a set of protocolized instructions, fluid administration and vasoactive agents are titrated to optimize cardiac performance. A central tenet of many of these studies is that GDT should not be defined by the presence or absence of a monitoring device but rather by explicit goals of care, such as maintenance of sustained maximal stroke volume. In other words, a GDT protocol should clearly define how data from the monitor trigger specific changes in care.

Related article page 2181

Pearse and colleagues[2] report the results of OPTIMISE, a pragmatic multicenter trial conducted at 17 hospitals that randomized 734 high-risk patients undergoing gastrointestinal surgery to receive usual care or GDT intraoperatively and for 6 hours after surgery. Consistent with the core principles of GDT, the intervention tested in this study consisted of an infusion of dopexamine plus administration of 250-mL boluses of colloid to maintain maximal stroke volume during the study period. Stroke volume was determined by a cardiac output monitor, which required an arterial catheter for pulse pressure analysis. The incidence of the primary outcome—a composite of prespecified postoperative complications through 30 days after surgery—was lower in the GDT group (36.6% vs 43.4%). This reduction, while consistent with benefit observed in many previous trials (eFigures 2-5 in the article),[2] was not statistically significant (P = .07), even after adjusting for baseline risk factors.

This study has numerous strengths, including a large number of patients and participating sites. Self-assessment of blinding by outcome evaluators further enhances the quality of the study. In addition, several important prespecified secondary analyses were performed, including adjustment for protocol adherence and adjustment for a learning curve; ie, exclusion of the first 10 patients at each of the 17 sites. Both of these analyses yielded a more robust treatment effect, which might be expected for an intervention that requires experience and training.

The study is further strengthened because study team members were present during the intervention period in more than 80% of the cases (eTable 2 in the article), which probably improved adherence to the protocol. Of note, study team members were also present during surgery in almost half of the usual care cases, which may have increased the presence of senior anesthesia or surgical staff and may have improved the care and outcomes of the control group. Greater attention to detail, such as avoidance of hypovolemia and hypotension, also may have played a role, as the clinicians were aware that they were being monitored. Thus, study team presence may account in part for the lower composite event rate in the control group (43.4%) compared with the higher value (68%) from preliminary data, which was used to calculate the sample size for the trial. Another factor that may have lowered the occurrence of the primary outcome rate in the control group was the protocol recommendation that patients in the usual care group receive dynamic central venous pressure–guided fluid administration. These data were not presented, but if used frequently, they may have minimized hypovolemia/tissue hypoperfusion and related complications in the control group.

Adherence to the protocol is important in this setting, where the presence of a monitor does not ensure that it is used correctly or actually triggers changes in care. The investigators report adherence in more than 90% of patients in each group (eTable 1 in the article). However, nonadherence focused largely on the administration of dopexamine. Nonadherence to the fluid algorithm was defined as "failure to monitor," which does not provide information about whether monitoring resulted in sustained maximal stroke volume. No objective data are provided regarding cardiac output and stroke volume at different time points. Analysis of the colloid and crystalloid fluid volumes (Table 2 in the article) does not directly shed light on whether maximal stroke volume was achieved. The extent to which dopexamine and additional colloid boluses increased blood flow (ie, cardiac output) was not reported. Thus, the observed benefit from GDT may be less than was expected if the protocol for the intervention was not followed.

Initial studies in GDT focused on critically ill patients (often with sepsis), and augmentation of global oxygen delivery was often achieved with high doses of dobutamine guided by a pulmonary artery catheter. In many of these studies, however, investigators concluded that GDT provided no benefit and may even cause potential harm.[3] Thus, many speculated that in these very sick patients, organs were already too injured to respond to care and that future studies should focus on prevention of organ injury. This led to the concept of early GDT for patients with sepsis[4]; however, a recent large multicenter trial (ProCESS) showed no benefit.[5] In contrast, since 1988, more than 30 randomized trials have tested GDT in high-risk surgery patients and yielded encouraging results.[2]

An evolution in the choice of monitors used to optimize patient hemodynamics has led to a move away from pulmon-

ary artery catheters toward minimally invasive monitors of cardiac output. These include esophageal Doppler, bioreactance/bioimpedance, and pressure waveform analysis, which uses an arterial catheter or finger probe.[6] Goal-directed therapy is easier to implement with these newer technologies because they require less training and, in most cases, are easily interpreted by a wide range of caregivers. However, their comparative effectiveness to guide fluid administration is unclear, so results from trials using one monitor cannot necessarily be generalized to other monitors.

Goal-directed therapy requires a monitor and an intervention, usually intravenous fluid with or without a vasoactive agent. Although colloid has generally been promoted over crystalloid as the intravenous fluid because colloid has more sustained volume expansion and possibly lower risk of edema,[7] the optimal choice of fluid has been unclear. Clinical trials are only now beginning to address this question.[8] The OPTIMISE trial did not standardize the type of colloid used and, other than reporting the volumes administered, did not analyze for possible effects of colloid type on the primary outcome.

The use of vasoactive agents in GDT is controversial, especially the choice of agent and the need for it. Dopexamine is a reasonable choice; however, clinicians in countries that do not have this drug (eg, the United States) will be unsure as to what drug (and dose) is the best substitute. Some clinicians will wonder why dopexamine was infused in all intervention patients in the OPTIMISE trial and not titrated to explicit targets of cardiac performance. A simple response may be that this was a pragmatic trial, and it was easier to give the drug to all patients. Furthermore, since dopexamine is an inotrope and selective vasodilator, there may be no simple explicit goal to titrate against. Some staunch supporters of GDT will argue that fluid alone should be used to begin hemodynamic optimization and that an inotropic agent should be added only if necessary. Indeed, some data suggest that adding dopexamine may not provide incremental benefit for patients who are already receiving GDT.[9] Future studies are needed to determine which tools (monitor, fluid, drugs) and targets are best for balancing safety, effectiveness, cost, and practical considerations.

There was little evidence to suggest that the intervention was harmful to patients. As an inotrope and vasodilator, dopexamine can potentially cause myocardial ischemia, arrhythmias, and hypotension. However, cardiovascular adverse events occurred in only a small percentage of patients in the intervention group (1.4%), and these events did not appear to translate into increased cardiovascular mortality. This favorable safety profile was perhaps due in part to exclusion of patients at higher risk of cardiac events; eg, recent acute myocardial ischemia or aortic stenosis. The volumes of fluid administered to intervention patients were modest (median of 1250 mL more colloid) and not associated with pulmonary edema (Table 3 in the article).

As recommended by many in the field of evidence-based medicine, the authors conducted an additional analysis, the inclusion of the OPTIMISE results in an updated systematic review.[2] These results further strengthen the overall conclusion that GDT of some type is probably beneficial for high-risk patients and has few documented adverse effects. Compared with the previous review,[10] this updated analysis added 7 additional trials and reported statistically significant reductions in complications, infections, and hospital stay for patients who received GDT. These findings are consistent with reports by the Centers for Medicare & Medicaid Services[11] and the National Institute for Health and Care Excellence,[12] which recommend the use of hemodynamic therapy algorithms. The extent to which GDT will be translated into routine practice is difficult to predict and will depend on many factors. Goal-directed therapy is best achieved in environments that emphasize a multidisciplinary team approach to patient care, including anesthesiologists, surgeons, intensivists, and nurses. This approach is exemplified in the "perioperative surgical home," which is gaining momentum as a model to improve outcome and reduce costs.[13]

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Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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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Editorial page 2177

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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 Services[8] 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 guidelines[11]); 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 mellitus; 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 ≥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 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.

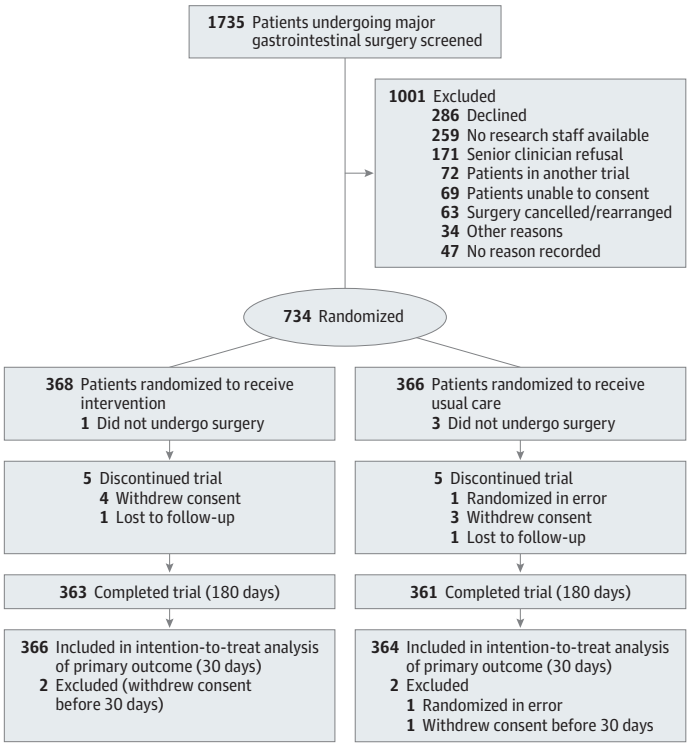
Statistical Analysis

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 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 nonadherent 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 eAppendix 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.

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.

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 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] 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 χ^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 χ^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 χ^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

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 (%)[a]	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 (%)[b]	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 (%)[c]	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.

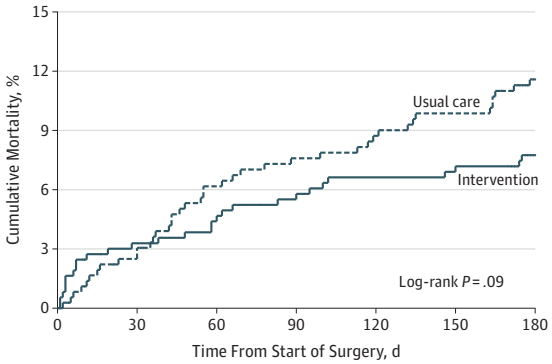
[a] Among patients alive and in the hospital on day 7 following surgery.

[b] 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.

[c] 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).

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



No. at risk

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

Discussion

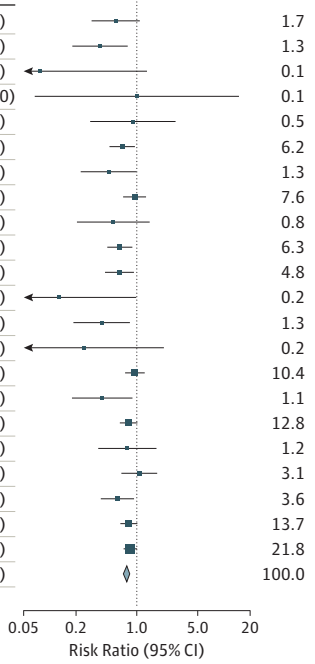
The principal finding of the OPTIMISE trial was that among patients undergoing major abdominal surgery involving the gastrointestinal tract, when compared with usual care, use of this cardiac output-guided, hemodynamic therapy algorithm was not associated with a significant reduction in the composite 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 findings 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

Source	Intervention No. of Events	Intervention Total No.	Control No. of Events	Control Total No.	Risk Ratio (95% CI)	Weight, %
Shoemaker et al,[20] 1988	8	28	30	60	0.57 (0.30-1.08)	1.7
Berlauk et al,[21] 1991	11	68	9	21	0.38 (0.18-0.79)	1.3
Mythen et al,[22] 1995	0	30	6	30	0.08 (0.00-1.31)	0.1
Sinclair et al,[23] 1997	1	20	1	20	1.00 (0.07-14.90)	0.1
Ueno et al,[24] 1998	4	16	5	18	0.90 (0.29-2.78)	0.5
Wilson et al,[25] 1999	38	92	28	46	0.68 (0.48-0.95)	6.2
Lobo et al,[26] 2000	6	19	12	18	0.47 (0.23-0.99)	1.3
Jerez et al,[27] 2001	53	181	65	209	0.94 (0.70-1.28)	7.6
Conway et al,[28] 2002	5	29	9	28	0.54 (0.20-1.40)	0.8
Pearse et al,[14] 2005	27	62	41	60	0.64 (0.46-0.89)	6.3
Wakeling et al,[29] 2005	24	67	38	67	0.63 (0.43-0.93)	4.8
Noblett et al,[30] 2006	1	51	8	52	0.13 (0.02-0.98)	0.2
Donati et al,[31] 2007	8	68	20	67	0.39 (0.19-0.83)	1.3
Smetkin et al,[32] 2009[a]	1	20	4	20	0.25 (0.03-2.05)	0.2
Jhanji et al,[6] 2010	57	90	30	45	0.95 (0.73-1.23)	10.4
Mayer et al,[33] 2010	6	30	15	30	0.40 (0.18-0.89)	1.1
Cecconi et al,[34] 2011	16	20	20	20	0.80 (0.64-1.02)	12.8
Challand et al,[35] 2012	10	89	13	90	0.78 (0.36-1.68)	1.2
Brandstrup et al,[36] 2012[a]	23	71	24	79	1.07 (0.66-1.71)	3.1
Salzwedel et al,[37] 2013[a]	21	79	36	81	0.60 (0.39-0.93)	3.6
Goepfert et al,[38] 2013[a]	34	50	42	50	0.81 (0.65-1.01)	13.7
OPTIMISE, 2014	134	368	158	365	0.84 (0.70-1.01)	21.8
Total	488	1548	614	1476	0.77 (0.71-0.83)	100.0

Heterogeneity: $\chi^2_{21} = 30.44$; $P = .08$; $I^2 = 31\%$
Test for overall effect: $z = 6.22$; $P < .001$



Size of data markers corresponds to weighting for each component trial.

[a] New trials identified in updated literature search.

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 predefined 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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In Reply Dr Fleischhacker suggests that high dropout rates limit the generalizability of our findings. This effectiveness study included participants that clinicians selected as candidates for long-acting injectable antipsychotic medications (ie, they were expected to benefit from depot treatment because they were at risk of poor outcomes due to a history of poor adherence or substance abuse). Thus the findings should be generalizable to typical patients for whom treatment with long-acting injectable antipsychotics is considered.

Fleischhacker speculates that some differences in extrapyramidal symptom ratings did not reach statistical significance due to low power. With a large enough sample, all such differences become statistically significant; however, we agree that small differences in adverse events may be clinically important for individuals. Any results that did not meet statistical significance must be considered relative to clinically and statistically significant differences (eg, the mean 2 kg weight gain with paliperidone palmitate vs the 1 kg weight loss with haloperidol decanoate). We plan to investigate possible differences in injection site pain, but it is already clear that any effect favoring one of the drugs did not result in an overall effectiveness advantage.

Fleischhacker correctly points out that oral haloperidol rather than oral haloperidol decanoate was the comparator in the haloperidol-risperidone trial mentioned in our article. A correction accompanies this letter.

Dr Suzuki suggests that the mean doses of paliperidone used for maintenance treatment in our trial may have been too high. His analysis, which initiated from a study about relative doses of antipsychotics that did not include paliperidone palmitate, suggests that the mean maintenance dose of paliperidone palmitate in our study should have been approximately 50 mg per month. We are aware of no evidence to support this as a typical maintenance dose, which is less than half the recommended maintenance dose found in the paliperidone palmitate package insert.

Because our study was not restricted to people with an acute exacerbation, it is not surprising that the participants were on average moderately ill. We used randomization to address measured and unmeasured factors, including baseline medications, that might theoretically advantage one group. Adjunctive psychotropics, excluding the sustained need for antipsychotic medications after 8 weeks, were allowed throughout the trial, and we found similar rates of starting new medications in the 2 groups for the following indications: anxiety (16.6% for paliperidone vs 15.2% for haloperidol); depression (19.3% for paliperidone vs 17.2% for haloperidol); agitation, excitement, or mania (8.3% for paliperidone vs 4.8% for haloperidol); aggression or violence (1.4% for paliperidone vs 0.7% for haloperidol); and insomnia (22.1% for paliperidone vs 24.8% for haloperidol).

The study found that paliperidone palmitate and haloperidol decanoate were similar in avoiding efficacy failure. We could not rule out a clinically meaningful difference favoring one of the drugs, but did find significant differences in akathisia favoring paliperidone palmitate and in weight and prolactin levels favoring haloperidol decanoate.

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Use of Hemodynamic Algorithm After Gastrointestinal Surgery

To the Editor The pragmatic, multicenter, randomized, observer-blinded Optimisation of Cardiovascular Management to Improve Surgical Outcome (OPTIMISE) trial[1] found that a cardiac output–guided hemodynamic treatment algorithm did not result in a statistically significant improvement in outcomes compared with usual care in high-risk patients undergoing major gastrointestinal surgery. An updated meta-analysis on perioperative goal-directed therapy, which was part of the same article, came to the opposite conclusion.

We believe the reason for this diversity is a misinterpretation of pragmatic. The main determinants of hemodynamic goal-directed therapy are fluids and pharmacological

manipulation of cardiovascular function; ie, the application of catecholamines and vasopressors. However, those 2 determinants were handled pragmatically in this trial.

First, the choice of colloids used for maximizing stroke volume remained at the discretion of the treating physician, and in light of the controversy surrounding the use of different colloids in high-risk patients,[2,3] this choice is difficult to understand.

Second, every patient in the intervention group received a vasoactive and inotropic drug, dopexamine, whose use in high-risk patients is debatable,[4] particularly at a fixed, predefined dose. Neither the indication nor any adjustment of dosage was made based on advanced measures of cardiac function such as stroke volume or cardiac output, although these were key measures in the trial and the central part of the treatment protocol.

Concerns regarding manageability must not lead to an oversimplification of treatment algorithms, ignoring the complexity of pathophysiology in high-risk patients. Furthermore, such concerns must not lead to standardization of treatment that ignores the individuality of each patient. We disagree that this is pragmatic.[1,5]

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To the Editor The main result of the OPTIMISE randomized clinical trial was that goal-directed therapy using fluids and inotropes to achieve noninvasive cardiac output goals did not significantly alter any of the primary or secondary morbidity or mortality end points.[1]

Dr Pearse and colleagues[1] also performed a systematic review and meta-analysis, combining their data along with data from a few small trials with the results of a recent Cochrane review,[2] and reported that complications after surgery were significantly reduced by goal-directed therapy. Based on the updated meta-analysis, the authors of the OPTIMISE study and accompanying editorialist[3] concluded that goal-directed therapy is an effective strategy to decrease perioperative complication rates.

Several issues are worthy of note. First, data from the largest (n=1994 patients) randomized clinical trial to date on perioperative goal-directed therapy[4] were not included in the composite outcome of complications described in the OPTIMISE meta-analysis. These data were not included because the unit of analysis for the publicly available data was not compatible with the OPTIMISE composite end point; however, Sandham et al[4] did not find significant improvements in the rate of any single postoperative complication in patients treated with goal-directed therapy.

Second, as described in the Cochrane report,[2] the meta-analysis was subject to significant small-study bias, and small studies also constituted the majority of studies in the OPTIMISE meta-analysis.

Third, as also noted in the Cochrane review,[2] the overall quality of the data included in the meta-analysis was low and the results were highly sensitive to the analytic methods, increasing uncertainty of the conclusions.

Fourth, a mechanism that can plausibly explain any difference in complication rates due to goal-directed therapy, given all the different protocols used among studies, is lacking. Do Pearse et al[1] advocate the fluid/dopexamine protocol used in the OPTIMISE study or will any of the previously described protocols that bolster cardiac performance suffice?

The benefits, if any, of perioperative goal-directed therapy have been controversial for the past 25 years. Although it remains possible that goal-directed therapy is useful in this setting, particularly with regard to reducing hospital length of stay, the objective data are far murkier than suggested.

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1. Pearse RM, Harrison DA, MacDonald N, et al; OPTIMISE Study Group. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. *JAMA*. 2014;311(21):2181-2190.

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In Reply Drs Saugel and Reuter challenge the description of the OPTIMISE trial as a pragmatic trial. As applied to clinical trials, the term *pragmatic* has a particular meaning. Pragmatic trials are designed to evaluate the clinical effectiveness of a treatment in the context of routine clinical practice.[1] This distinguishes them from explanatory trials, which are designed to evaluate the efficacy of a treatment under ideal conditions.

However, rather than describing dichotomous alternatives, the 2 terms represent different ends of a qualitative continuum.[2] Investigators designing pragmatic trials are faced with the challenge of balancing competing pressures to maintain internal validity (efficacy of the intervention) and the feasibility of implementation into widespread clinical use, the latter ensuring external validity (generalizability of findings).

The OPTIMISE intervention was developed from an evidence base consisting of several clinical trials and other supporting data, which were described in the article. We evaluated this intervention in an explanatory pilot trial, the findings of which indicate a clear mechanistic basis through improvements in systemic oxygen delivery, tissue microvascular flow, and tissue oxygenation.[3]

Our laboratory studies also suggest that dopexamine may have important anti-inflammatory actions.[4] Given the evidence available when the trial was designed, the high levels of protocol adherence, and our findings, we are satisfied that we achieved an appropriate balance between efficacy and feasibility in the design of this trial.

Drs Latif and Faraday raise questions relating to the systematic review incorporated into the OPTIMISE article. They correctly describe unit-of-analysis issues that were highlighted in our discussion. These relate to evaluation of the primary outcome measure (number of patients developing complications), which was not reported for the trial by Sandham et al.[5] However, mortality data were reported for this trial and were included both in the previous Cochrane systematic review[6] and in analyses of mortality reported in the main text of our article.

The results of the systematic review in detail are presented in the supplementary material. Comments in the report of the Cochrane review regarding sensitivity to analytical technique[6] relate to the choice of methods of meta-analysis and not to the design or outcome measures of component trials.

The findings of the OPTIMISE trial and our systematic review require careful interpretation. The contrasting views of these correspondents highlight that uncertainty remains regarding the benefits of this treatment. They also reinforce the importance of pragmatic studies, such as the OPTIMISE trial, and emphasize the need for much larger trials to address this and other key uncertainties in perioperative medicine.

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Primary Care Physician–Led Health Reform

To the Editor Dr Mostashari and colleagues[1] described a vexing problem—creating incentives that encourage efficiency, not volume. Invoking an ambiguous role model, the corporate CEO, they postulated that primary care physicians, who account for 5% of health care spending, should make the tough calls on the rest.

Supporting their solution proves hard. To set primary care's contribution equal to estimated avoidable costs, they ignored a key finding: there is an association between costs and primary care physician supply.[2] To support physician-led over hospital-led accountable care organizations (ACOs), which must absorb volume-related revenue declines that are off practice balance sheets, they cited similar cost-reduction success rates. The authors asserted that primary care physicians can best pick specialists, diagnostics, and institutions "that provide evidence-based high-value care."

Putting primary care physicians in charge of reducing costs is neither new nor supported by experience. As gatekeepers in both earlier health maintenance organization and more recent payer-driven cost containment efforts, they had, at best, modest success in improving outcomes[3] and reducing costs.[4] So why again nominate them as quality change agents?

How does primary care prepare one for, say, comparing cancer treatment pathways or reducing surgical errors? Treating specialists are better informed about processes, outcomes, and tradeoffs.