

REVIEW

Clinical review: Goal-directed therapy - what is the evidence in surgical patients? The effect on different risk groups

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Abstract

Patients with limited cardiac reserve are less likely to survive and develop more complications following major surgery. By augmenting oxygen delivery index (DO_2I) with a combination of intravenous fluids and inotropes (goal-directed therapy (GDT)), postoperative mortality and morbidity of high-risk patients may be reduced. However, although most studies suggest that GDT may improve outcome in high-risk surgical patients, it is still not widely practiced. We set out to test the hypothesis that GDT results in greatest benefit in terms of mortality and morbidity in patients with the highest risk of mortality and have undertaken a systematic review of the current literature to see if this is correct. We performed a systematic search of Medline, Embase and CENTRAL databases for randomized controlled trials (RCTs) and reviews of GDT in surgical patients. To minimize heterogeneity we excluded studies involving cardiac, trauma, and paediatric surgery. Extremely high risk, high risk and intermediate risks of mortality were defined as >20%, 5 to 20% and <5% mortality rates in the control arms of the trials, respectively. Meta-analyses were performed and Forest plots drawn using RevMan software. Data are presented as odd ratios (OR; 95% confidence intervals (CI), and *P*-values). A total of 32 RCTs including 2,808 patients were reviewed. All studies reported mortality. Five studies (including 300 patients) were excluded from assessment of complication rates as the number of patients with complications was not reported. The mortality benefit of GDT was confined to the extremely high-risk group (OR = 0.20, 95% CI 0.09 to 0.41; *P* < 0.0001). Complication rates were reduced in all subgroups (OR = 0.45, 95% CI 0.34 to 0.60; *P* < 0.00001). The morbidity benefit was greatest amongst patients in the extremely high-risk subgroup (OR = 0.27, 95% CI 0.15 to 0.51; *P* < 0.0001), followed by the intermediate risk subgroup (OR = 0.43, 95% CI 0.27 to 0.67; *P* = 0.0002), and the high-risk subgroup (OR 0.56, 95% CI 0.36 to 0.89; *P* = 0.01). Despite heterogeneity in trial quality and design, we found GDT to be beneficial in all high-risk patients undergoing major surgery. The mortality benefit of GDT was confined to the subgroup of patients at extremely high risk of death. The reduction of complication rates was seen across all subgroups of GDT patients.

Introduction

A significant number of patients who undergo major surgery suffer postoperative complications, many of which may be avoidable [1,2]. The associated health and financial loss is significant, especially considering patients who suffer from postoperative complications suffer long-term morbidity [3]. A significant proportion of patients undergoing surgery suffer from postoperative complications, and identification of this cohort of patients may enable appropriate preventative measures

to be taken [4]. Perioperative goal-directed therapy (GDT) aims to match the increased oxygen demand incurred during major surgery, by flow-based haemodynamic monitoring and therapeutic interventions to achieve a predetermined haemodynamic endpoint. When carried out early, in the right patient cohort, and with a clearly defined protocol, GDT has been shown to reduce postoperative mortality and morbidity [5].

Despite this, postoperative GDT is not carried out widely, perhaps due to the lack of evidence for its benefit from large multicenter randomized clinical trials. Scepticism about GDT may exist for a number of reasons: many of the studies performed may be considered outdated; the high mortality rates in some of the studies performed are not representative of current clinical

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practice; and pulmonary artery catheters (PACs) are used in many of the clinical trials but have been largely superseded by less invasive haemodynamic monitors. A recent meta-analysis has demonstrated that although studies prior to 2000 demonstrate a benefit in mortality, studies conducted after 2000 demonstrate a significant reduction in complication rates [5]. Furthermore, the reduction in complication rates is significant regardless of the type of haemodynamic monitor used.

We hypothesized that the benefits of GDT are greater in patients who are at higher risk of mortality. We defined risk by the mortality rate of the study population undergoing major surgery. We conducted this meta-analysis to determine if GDT in high-risk surgical patients undergoing major non-cardiac surgery improves postoperative mortality and morbidity, and if this was affected by the mortality risk among the population studied.

Methods

Eligibility criteria

We reported only randomized controlled trials, that reported morbidity (complications) and mortality as primary or secondary outcomes. GDT was defined as the term encompassing the use of haemodynamic monitoring and therapies aimed at manipulating haemodynamics during the perioperative period to achieve a predetermined haemodynamic endpoint(s). Studies with GDT started pre-emptively in the perioperative period (24 hours before, intraoperative or immediately after surgery) were included. The GDT must have an explicit protocol, defined as detailed step-by-step instructions for the clinician based on patient-specific haemodynamic data obtained from a haemodynamic monitor or surrogates (for example, lactate, oxygen extraction ratio), and predefined interventions carried out by the clinician in an attempt to achieve the goal(s). Interventions included fluid administration alone or fluids and inotropes together. As the use of inotropic agents was aimed at a specific haemodynamic goal(s) and titrated accordingly, fixed dose studies of inotropes were excluded. Only studies involving adult general surgical populations were included, and studies involving cardiac, trauma and paediatric surgery were excluded.

Information sources

A systematic literature search of MEDLINE (via Ovid), EMBASE (via Ovid) and the Cochrane Controlled Clinical trials register (CENTRAL, issue 4 of 2012) was conducted to identify suitable studies. Only articles written in English were considered. Date restrictions were not applied to the CENTRAL and MEDLINE searches. EMBASE was restricted to the years 2009 to 2012 [6]. The last search update was in April 2012.

Search strategy

We included the following search terms: goal-directed therapy, optimization, haemodynamic, goal oriented, goal targeted, cardiac output, cardiac index, oxygen delivery, oxygen consumption, cardiac volume, stroke volume, fluid therapy, fluid loading, fluid administration, optimization, supranormal, lactate and extraction ratio. Search terms were entered into the electronic databases using search strategy methods validated by the Cochrane collaboration (see Box 1 for search strategies used) [7]. In addition to searching electronic databases, previous review articles on the subject were hand-searched for further references.

Methodological quality of included studies

Methodological quality of included studies was assessed using criteria described by Jadad and colleagues [8]. The Jadad scale analyzes methods used for random assignment, blinding and flow of patients in clinical trials. The range of possible scores is 0 (lowest quality) to 5 (highest quality). Studies were not excluded based on Jadad scores.

Analysis of outcomes

Three investigators independently screened both the titles and abstracts to exclude non-pertinent studies. Relevant full text articles were then retrieved and analysed for eligibility against the pre-defined inclusion criteria. Information from selected studies was extracted using a standardized data collection form. Data were collected independently by three different investigators (GA, NA and CC) and discrepancies resolved by a fourth author (MC).

Hospital mortality was reported in all the included articles and was the primary outcome of our study. Morbidity, expressed as number of patients with complications, was the secondary outcome. Mortality risk groups were based on the definition of the high-risk surgical patient by Boyd and Jackson, such that patients whose risk of mortality was 5 to 19% and $\geq 20\%$ were classified as high-risk and extremely high-risk, respectively [9]. We therefore performed subgroup analyses based on the control group mortality in each study. We created three subgroups based on the mortality rate of the control group. Mortality rates of 0 to 4.9%, 5 to 19.9%, and $\geq 20\%$ were considered intermediate, high risk, and extremely high risk, respectively. Mortality and complications were analyzed according to the above subgroups. Studies were also analyzed according to the type of monitor used, type of interventions, the therapeutic goals, and the use of 'supranormal' physiological goals.

Statistical analysis

Dichotomous data outcomes were analysed using the Mantel-Haenszel random effects model and results

Box 1. Search strategies

1. MEDLINE database (OVID interface): the Cochrane highly sensitive search strategy was used:

- #1. randomized Controlled Trials as Topic/
- #2. randomized controlled trial/
- #3. random Allocation/
- #4. double Blind Method/
- #5. single Blind Method/
- #6. clinical trial/
- #7. controlled clinical trial.pt.
- #8. randomized controlled trial.pt.
- #9. multicenter study.pt.
- #10. clinical trial.pt.
- #11. exp Clinical Trials as topic/
- #12. or/1-11
- #13. (clinical adj trial\$).tw.
- #14. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.
- #15. randomly allocated.tw.
- #16. (allocated adj2 random\$).tw.
- #17. or/13-16
- #18. 12 or 17
- #19. case report.tw.
- #20. letter/
- #21. historical article/
- #22. or/19-21
- #23. 18 not 22
- #24. exp surgery/
- #25. surgery.tw.
- #26. surgery.mp.
- #27. 24 or 25 or 26
- #28. exp goal directed/ or goal directed.tw. or goal directed.mp.
- #29. exp goal oriented/ or goal oriented.tw. or goal oriented.mp.
- #30. exp goal target/ or goal target.tw. or goal target.mp.
- #31. exp cardiac output/ or cardiac output.tw. or cardiac output.mp.
- #32. exp cardiac index/ or cardiac index.tw. or cardiac index.mp.
- #33. exp oxygen delivery/ or oxygen delivery.tw. or oxygen delivery.mp.
- #34. exp oxygen consumption/ or oxygen consumption.tw. or oxygen consumption.mp.
- #35. exp cardiac volume/ or cardiac volume.tw. or cardiac volume.mp.
- #36. exp stroke volume/ or stroke volume.tw. or stroke volume.mp.
- #37. exp fluid therapy/ or fluid therapy.tw. or fluid therapy.mp.
- #38. exp fluid loading/ or fluid loading.tw. or fluid loading.mp.
- #39. exp fluid administration/ or fluid administration.tw. or fluid administration.mp.
- #40. exp optimization/ or optimization.tw. or optimization.mp.
- #41. exp optimisation/ or optimisation.tw. or optimisation.mp.
- #42. exp supranormal/ or supranormal.tw. or supranormal.mp.
- #43. exp lactate/ or lactate.tw. or lactate.mp.
- #44. exp extraction ratio/ or extraction ratio.tw. or extraction ratio.mp.
- #45. #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44
- #46. #23 and #27 and #45

2. Embase (OVID interface): search restricted to the years 2009 to 2012:

- #1. Clinical trial/
- #2. Randomized controlled trial/
- #3. Randomization/
- #4. Single blind procedure/
- #5. Double blind procedure/
- #6. Crossover procedure/
- #7. Placebo/
- #8. Randomi?ed controlled trial\$.tw.
- #9. Rct.tw.
- #10. Random allocation.tw.
- #11. Random allocated.tw.

- #12. Allocated randomly.tw.
- #13. (allocated adj2 random).tw.
- #14. Single blind\$.tw.
- #15. Double blind\$.tw.
- #16. Placebo\$.tw
- #17. Prospective study/
- #18. Or/1-17
- #19. Case study/
- #20. Case report.tw.
- #21. Abstract report/or letter/
- #22. Or/19-21
- #23. 18 not 22
- #24. surgery
- #25. exp surgery/or surgery
- #26. surg\$
- #27. 24 or 25 or 26
- #28. exp heart/ or heart.mp.) and output.mp.
- #29. exp heart output/ or heart output.mp.
- #30. goal directed
- #31. goal oriented
- #32. goal target
- #33. exp heart index/ or heart index.mp.
- #34. exp heart stroke volume/ or heart stroke volume.mp.
- #35. exp oxygen consumption/ or oxygen consumption.mp.
- #36. oxygen delivery.mp.
- #37. exp fluid therapy/
- #38. fluid administration.mp
- #39. fluid loading.mp.
- #40. hemodynamic.mp
- #41. supranormal.mp.
- #42. optimisation.mp.
- #43. optimization.mp.
- #44. exp lactate/
- #45. extraction ratio.mp
- #46. #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45
- #47. #23 and #27 and #46

3. Cochrane clinical trials database (CENTRAL):

- #1. surgery in Trials
- #2. surgical* in Trials
- #3. surgery* in Trials
- #4. #1 OR #2 OR #3
- #5. cardiac near output* in trials
- #6. cardiac near volume* in Trials
- #7. cardiac near index* in Trials
- #8. oxygen near delivery* in Trials
- #9. oxygen near consumption* in Trials
- #10. supranormal* in Trials
- #11. stroke near volume* in Trials
- #12. fluid near therapy* in Trials
- #13. fluid near administration* in Trials
- #14. fluid near loading* in Trials
- #15. extraction near ratio* in Trials
- #16. lactate* in Trials
- #17. goal near directed* in Trials *
- #18. goal near oriented* in Trials
- #19. goal near target* in Trials
- #20. Hemodynamic near optimization* in trials
- #21. Haemodynamic near optimization * in trials
- #22. Optimization* in trials
- #23. Optimisation* in trials
- #24. #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
- #25. #4 AND#24

presented as an odds ratio (OR) with 95% confidence intervals (CI). The meta-analysis was carried out using review manager ('Revman') for MAC (version 5.1, Cochrane collaboration, Oxford, UK). Statistical heterogeneity was assessed using the I^2 methodology. When an I^2 value of >50% was present heterogeneity and inconsistency were considered significant, and when it was >75% these were considered highly significant [10]. All P -values were two-tailed and considered statistically significant if <0.05.

Results

Included trials

The search strategy used in this study produced 12,938 potential titles (Figure 1). After screening of titles and abstracts, 307 references were identified as relevant to perioperative GDT. After further screening of titles and abstracts against our inclusion criteria, 85 references were retrieved for full text analysis. Detailed full text evaluation excluded 13 studies, as they were not randomized controlled trials [11-23]. Analysis of the remaining 72 randomized controlled trials produced the following exclusions: studies focusing on fluid management strategies (that is, liberal versus restrictive) [24-33], use of 'fixed dose' inotropic agents not titrated to a pre-determined goal [34-38], cardiac surgery [39-44], trauma [45-52], paediatric surgery [53] and critically ill medical populations [54-62]. A study not using protocols to direct application of GDT was also excluded [63]. The quality of the trials was analysed using the Jadad score. The median Jadad score was 3.

Description of studies

A total of 32 studies were included in the meta-analysis (Table 1) [64-95]. These 32 studies included a total of 2,808 patients, 1,438 in the GDT arm and 1,370 in the control treatment arm. Five studies included patients who were considered extremely high risk, 12 included patients who were high risk, and 15 included patients who were intermediate risk. The intermediate-risk, high-risk, and extremely high-risk mortality subgroups included 1,569, 924, and 315 patients, respectively. There were similar numbers of patients in the GDT and control arms. Twenty studies initiated GDT at start of surgery, whilst the other studies initiated GDT before or immediately after surgery.

Mortality

Three studies did not report any deaths in the control or intervention group. All 32 studies included mortality rates (Figure 2). Although there was an overall benefit on mortality (OR 0.52, 95% CI 0.36 to 0.74; $P = 0.003$), subgroup analyses revealed that mortality benefit was seen only in studies that included extremely high risk

patients (OR 0.20, 95% CI 0.09 to 0.41; $P < 0.0001$) but not for the intermediate-risk patients (OR 0.83, 95% CI 0.41 to 1.69; $P = 0.62$). There was a trend towards a reduction in mortality in the high risk group (OR 0.65, 95% CI 0.39 to 1.07; $P = 0.09$; Figure 2). Further subgroup analyses of mortality as an endpoint revealed that mortality was reduced in the studies using a pulmonary artery catheter (OR 0.3, 95% CI 0.15 to 0.60; $P = 0.0007$), fluids and inotropes as opposed to fluids alone (OR 0.41, 95% CI 0.23 to 0.73; $P = 0.002$), cardiac index or oxygen delivery index as a goal (OR 0.36, 95% CI 0.21 to 0.36; $P = 0.0003$), and a supranormal resuscitation target (OR 0.27, 95% CI 0.15 to 0.47; $P < 0.00001$) (Table 2).

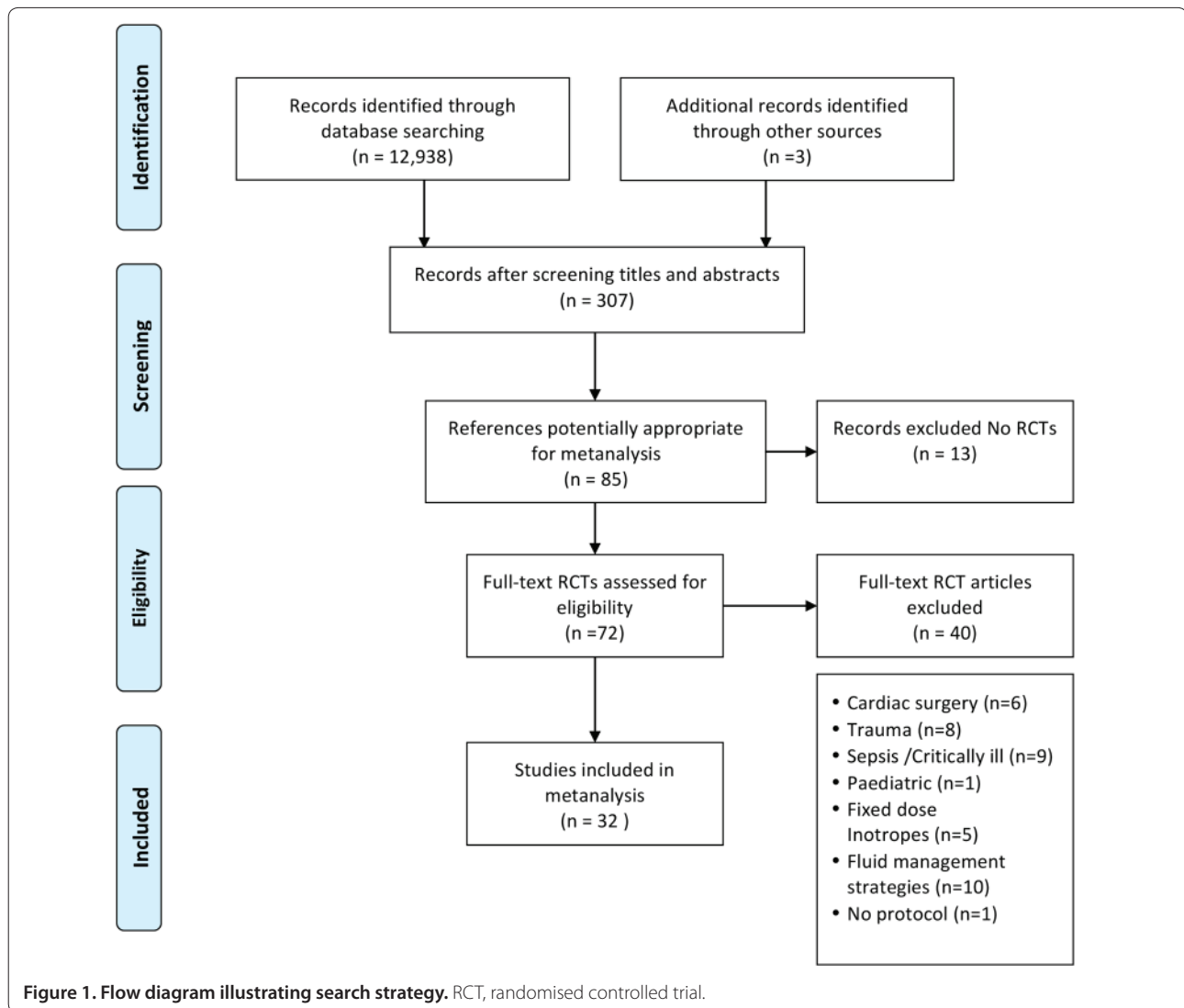
Morbidity

Twenty-seven studies (including 2,477 patients) reported the number of patients with postoperative complications. Meta-analysis of these studies revealed an overall significant reduction in complication rates (OR 0.45, 95% CI 0.34 to 0.60; $P < 0.00001$; Figure 3). Consistent with the mortality benefits, the reduction in morbidity was greatest in the extremely high-risk group (OR 0.27, 95% CI 0.15 to 0.51; $P < 0.0001$). However, there was also a significant morbidity benefit in the intermediate risk group (OR 0.43, 95% CI 0.27 to 0.67; $P = 0.0002$) and the high-risk groups (OR 0.56, 95% CI 0.36 to 0.89; $P = 0.01$) (Figure 3). The reduction in the number of patients suffering postoperative complications was seen across all subgroups, apart from studies that did not use the oxygen delivery index (DO_2I ; ml/minute/ m^2), the cardiac index (CI; ml/minute/ m^2), stroke volume (SV; ml), or corrected flow time (FTc) as a goal (OR 0.48, 95% CI 0.22 to 1.04; $P = 0.06$), although this approached statistical significance (Table 3).

Discussion

We believe that GDT in high-risk surgical patients is likely to have the greatest benefit if carried out early, in the right patient cohort and with a clearly defined protocol. We performed this meta-analysis to test the hypothesis that patients with the highest perioperative risk gain the greatest benefits from GDT. Studies without clearly defined GDT protocols and studies that initiated GDT late in the postoperative course were therefore excluded from our meta-analysis. Studies were stratified into different risk groups based on the mortality rate of the control group in the study. Heterogeneity in the year of study, patient demographics, type and urgency of surgery, and health care facilities among the different studies are likely to account for the difference in mortality rates.

A reduction in mortality associated with GDT was seen only in the extremely high-risk group of patients (baseline mortality rate of >20%). A baseline mortality rate of >20%



is unusual in current practice [4,96]; in this sense it is interesting to note that two of five studies with a baseline mortality rate of >20% were carried out within the past decade. Neither of these studies demonstrated a survival benefit with GDT [80,97]. One of these studies demonstrated a reduction in complication rates [97], whilst the other demonstrated a trend towards a reduction in complication rates [80].

Supranormal physiological targets, targeting DO_2I or CI , the use of inotropes in addition to fluids, and the use of a PAC were also associated with an improvement in survival. As first demonstrated by Shoemaker and colleagues [19], a supranormal physiological target of global oxygen delivery to ameliorate the oxygen deficit incurred during major surgery is associated with a survival benefit. This is likely to explain the other associations with an improvement in morbidity across all risk groups. The combination of fluids and inotropes is

more likely to achieve a supranormal physiological target, as opposed to fluids alone. All eight studies using the oesophageal doppler used fluids alone, reflected by the lack of mortality benefit with the use of FTc or SV as a target. The survival benefit associated with the use of PACs is unlikely to be due to the use of the PACs *per se*. The survival benefit associated with PAC use may be explained by a number of factors. These include the ability to measure and therefore achieve supranormal DO_2I , and the use of inotropes in addition to fluids in all studies using a PAC.

The reduction in the number of patients suffering post-operative complications was seen across all subgroups, apart from studies that did not use DO_2I , CI , SV, or FTc as a goal. However, there was a trend towards fewer complications among the GDT cohort in these studies. Goals used by these studies included lactate, pulse pressure variation, plethysmographic variability index,

Table 1. Summary of included studies

Study	Year	Jadad score	Type of surgery	Number of patients of GDT group	Number of patients of control group	Type of monitor in GDT group	Intervention type	Goals in GDT group	Goals in control group	Mortality GDT (%)	Mortality control (%)	Complications GDT (%)	Complications control (%)
Bender <i>et al.</i> [64]	1997	1	Elective vascular/aortic	51	53	PAC	Fluid and inotropes	CI ≥2.8 PAWP 8-14 SVR <1100	Standard care	1.96	1.9	13.73	13.21
Benes <i>et al.</i> [65]	2010	3	Elective abdominal	60	60	Flotrac	Fluid and inotropes	SW <10% CI ≥2.5	MAP >65 HR <100 CVP 8-12	1.67	3.3	30	58.33
Berlauk <i>et al.</i> [66]	1991	2	Peripheral vascular surgery	68	21	PAC	Fluid and inotropes	CI ≥2.8 PAWP 8-14 SVR <1100	Standard care	1.47	9.5	16.7	42.8
Bonazzi <i>et al.</i> [67]	2002	2	Elective vascular	50	50	PAC	Fluid and inotropes	CI >3.0 PAWP 10-18 SVR <1,450 DO ₂ >600	Standard care	0	0	4	8
Boyd <i>et al.</i> [68]	1993	1	Abdominal/vascular	53	54	PAC	Fluid and inotropes	MAP 80-110 PAWP 12-14 SpO ₂ >94% Hb >12 UO >0.5ml/kg/h DO ₂ >600	MAP 80-110 PAWP 12-14 SpO ₂ >94% Hb >12 UO >0.5ml/kg/h	5.66	22.2	NS	NS
Buettner <i>et al.</i> [69]	2008	2	Major abdominal or gynaecological	40	40	PICCO	Fluids	SPV <10% Hct >23% Normal clotting	Standard care	0	2.5	NS	NS
Cecconi <i>et al.</i> [70]	2011	4	Total hip replacement	20	20	Flotrac	Fluid and inotropes	SV change DO ₂ >600	Standard care	0	0	80	100
Chaland <i>et al.</i> [71]	2012	5	Major open/laparoscopic colorectal	89	90	OD	Fluids	SV change	Standard care	5.62	4.4	33.71	28.89
Conway <i>et al.</i> [72]	2002	2	Major bowel resection	29	28	OD	Fluids	FTc >0.35 SV change	Standard care	0	3.6	17.24	32.14
Donati <i>et al.</i> [73]	2007	3	Elective major abdominal/aortic	68	67	CVC	Fluids	O ₂ ER <27% MAP >80 UO >0.5 CVP 8-12 Hb >10	MAP >80 UO >0.5 CVP 8-12 Hb >10	2.94	3	13.24	40.3
Forget <i>et al.</i> [74]	2010	2	Major intrabdominal	41	41	Masimo pulsioximeter	Fluids	PVI <13%	Standard care	4.88	0	78.05	100

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Table 1. Continued

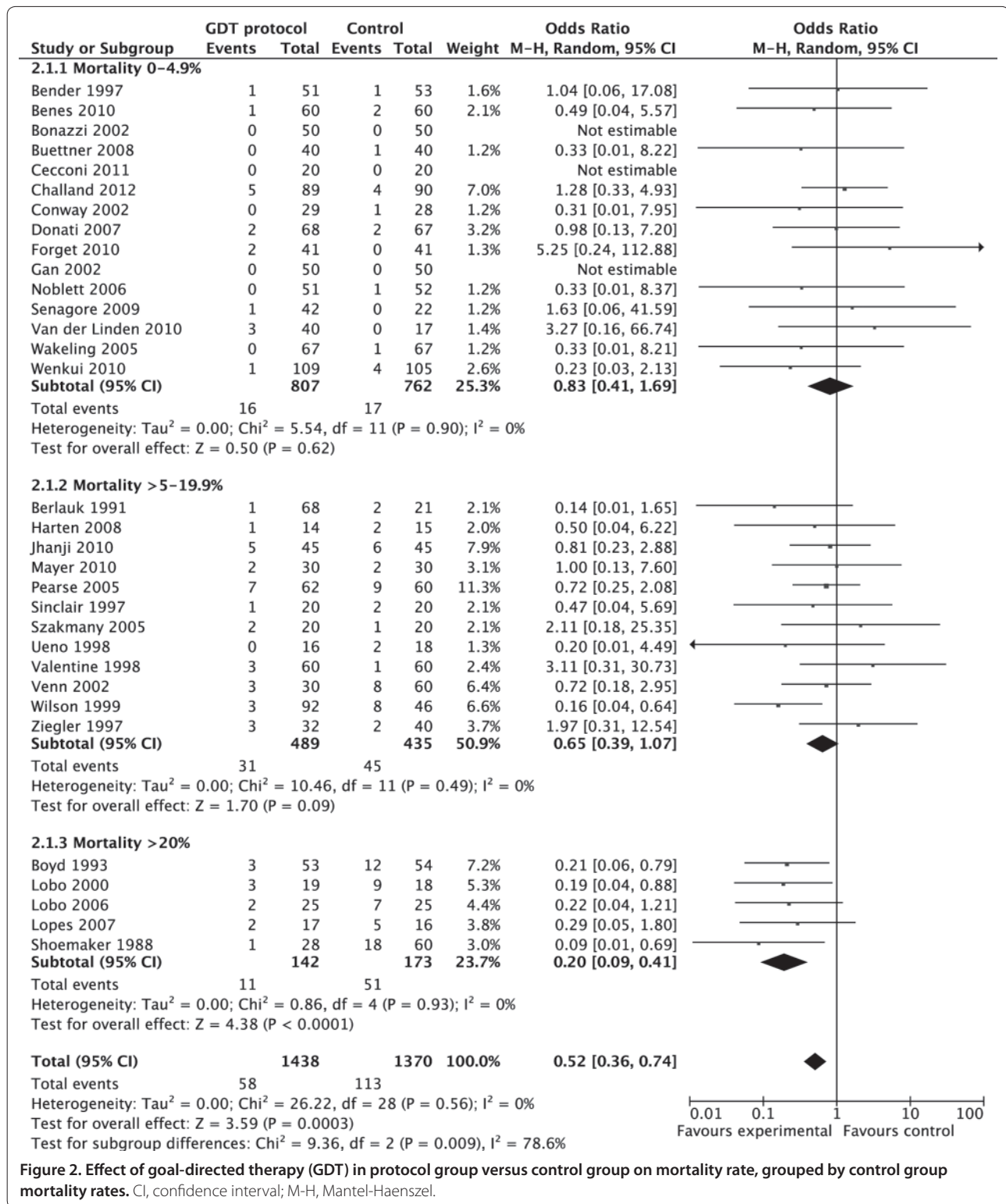
Study	Year	Jadad score	Type of surgery	Number of patients in GDT group	Number of patients in control group	Type of monitor in GDT group	Intervention type	Goals in GDT group	Goals in control group	Mortality GDT (%)	Mortality control (%)	Complications GDT (%)	Complications control (%)
Gan <i>et al.</i> [75]	2002	5	Elective general, urological, gynaecologic	50	50	OD	Fluids	FTc >0.35 SV change	Increase HR >20% baseline sBP <90 or CVP <20% baseline	0	0	42	76
Harten <i>et al.</i> [76]	2008	3	Emergency abdominal	14	15	Lidco	Fluids	PPV	Standard care	7.14	13.3	50	26.67
Jhanji <i>et al.</i> [77]	2010	3	Major surgery	45	45	LIDCO	Fluids	SV	CVP standard care	11.11	13.3	57.58	66.67
Lobo <i>et al.</i> [78]	2000	3	Major surgery	19	18	PAC	Fluid and inotropes	DO ₂ >600	Standard care	15.79	50	31.58	66.67
Lobo <i>et al.</i> [79]	2006	3	Major surgery	25	25	PAC	Fluid and inotropes	PWP 12-16 MAP 70-110 Hct >30%, SAO ₂ >94% UO >0.5 DO ₂ >600 ΔPP <10%	PAWP 12-16 MAP 70-110 Hct >30% SaO ₂ >94% UO >0.5	8	28	16	52
Lopes <i>et al.</i> [80]	2007	2	Major surgery	17	16	IBPplus; Dixtal	Fluids		Standard care	11.76	31.3	41.18	75
Mayer <i>et al.</i> [81]	2010	2	Major gastrointestinal surgery	30	30	Flotrac	Fluid and inotropes	CI >2.5 SW <12%	CVP 8-12 MAP >65 UO >0.5	6.67	6.7	20	50
Noblett <i>et al.</i> [82]	2006	5	Colorectal	51	52	OD	Fluids	FTc >0.35 SV change	Standard care	0	1.9	1.96	15.38
Pearse <i>et al.</i> [83]	2005	3	Major surgery	62	60	LIDCO	Fluid and inotropes	DO ₂ >600	SaO ₂ ≥94% Hb >8 Temp >37°C HR <100 or <20 above baseline MAP 60-100 CI ≥2.5	11.29	15	43.55	68.33
Senagore <i>et al.</i> [84]	2009	3	Elective lap colorectal	42	22	OD	Fluids	SV response	Standard care	2.38	4.7	NS	NS
Shoemaker <i>et al.</i> [85]	1988	2	Major surgery	28	60	PAC	Fluid and inotropes	CI >4.5 VO ₂ >170 DO ₂ >600	Standard care	3.57	30	28.5	50
Sinclair <i>et al.</i> [86]	1997	2	Neck of femur repair	20	20	OD	Fluids	FTc >0.35 SV change	Standard care	5	10	NS	NS

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Table 1. Continued

Study	Year	Jadad score	Type of surgery	Number of patients in GDT group	Number of patients in control group	Type of monitor in GDT group	Intervention type	Goals in GDT group	Goals in control group	Mortality GDT (%)	Mortality control (%)	Complications GDT (%)	Complications control (%)
Szakmany <i>et al.</i> [87]	2005	3	Major abdominal	20	20	PICCO	Fluids	ITBV 850-950 ml/m ²	CVP Standard care	9.09	5	NS	NS
Ueno <i>et al.</i> [88]	1998	2	Hepatic resection	16	18	PAC	Fluid and inotropes	CI >4.5 VO ₂ >170 DO ₂ >600	SpO ₂ >95% Mean PAOP 11-15 mmHg Hb >10	0	11.1	0	27.78
Valentine <i>et al.</i> [89]	1998	3	Aortic	60	60	PAC	Fluid and inotropes	CI >2.8 PAWP 8-15 SVR <1100	Standard care	5	1.7	25	16.67
Van Der linden <i>et al.</i> [90]	2010	4	Vascular	40	17	LiDCO + CVC	Fluid and inotropes	CI >2.5	Standard care	7.5	0	10	0
Venn <i>et al.</i> [91]	2002	3	Neck of femur repair	30	60	OD	Fluids	FTc >0.35 SV change	Standard care	10	6.9	34.4	72.4
Wakeling <i>et al.</i> [92]	2005	3	Colorectal	67	67	OD	Fluids	SV change	Standard care	0	1.5	35.82	56.72
Wenkui <i>et al.</i> [93]	2010	3	Elective GI Cancer	109	105	Lactate	Fluids	Lactate <1.6	Standard care	0.92	3.8	22.94	33.3
Wilson <i>et al.</i> [94]	1999	4	Major surgery	92	46	PAC	Fluid and inotropes	DO ₂ >600	Standard care	3.26	17.4	41.3	60.87
Ziegler <i>et al.</i> [95]	1997	2	Vascular	32	40	PAC	Fluid and inotropes	PAOP >12	Standard care	9.38	5	25	27.5

CI, cardiac index (ml/minute/m²); CVP, central venous pressure (cmH₂O); CVC, central venous catheter; DO₂, oxygen delivery index (ml/minute/m²); FTc, corrected flow time; GDT, goal-directed therapy; Hb, haemoglobin (g/dl); Hct, haematocrit (%); HR, heart rate (beats/minute); ITBV, intrathoracic blood volume; VO₂, oxygen consumption (ml/minute); MAP, mean arterial pressure (mmHg); NS, not stated; O₂ ER, oxygen extraction ratio (%); OD, oesophageal Doppler; PAC, pulmonary artery catheter; PAOP, pulmonary artery occlusion pressure (mmHg); PAWP, pulmonary artery wedge pressure (mmHg); PP, pulse pressure; PPV, pulse pressure variation; PVI, plethysmographic variability index; SAO₂, arterial oxygen saturation; sBP, systolic blood pressure (mmHg); SpO₂, oxygen saturation (%); SV, stroke volume (ml); SVR, systemic vascular resistance (dynes-s/cm²); SVV, stroke volume variation (%); UO, urine output (ml/kg/h); VO₂, oxygen consumption (ml/minute).



pulmonary artery occlusion pressure, oxygen extraction ratio, and intrathoracic blood volume [73,74,76,80,87, 93,95]. Consistent with the trends seen with mortality, the reduction in complication rates was most profound in

the extremely high-risk group of patients, protocols with supranormal physiological targets, targeting DO₂₁ or CI, and the use of inotropes in addition to fluids. In contrast to the benefits seen in mortality, however, the subgroup

Table 2. Mortality by subgroup analysis

	Number of studies	Number of patients in GDT group	Mortality in GDT group (%)	Number of patients in control group	Mortality in control group (%)	Odds ratio	95% CI	P-value
Risk group								
Intermediate risk	15	807	16 (2.0)	762	17 (2.2)	0.83	0.41-1.69	0.62
High risk	12	489	31 (6.3)	435	45 (10.3)	0.65	0.39-1.07	0.09
Extremely high risk	5	142	11 (7.7)	173	51 (29.5)	0.2	0.09-0.41	<0.0001
Fluid/inotropes								
Fluid	16	732	25 (3.4)	738	38 (5.1)	0.72	0.42-1.23	0.23
Fluid + inotrope	16	706	33 (4.7)	632	75 (11.9)	0.41	0.23-0.73	0.002
Goal								
Supranormal	9	365	19 (5.2)	351	65 (18.5)	0.27	0.15-0.47	<0.00001
Normal	23	1073	39 (3.6)	1,019	48 (4.7)	0.80	0.51-1.27	0.35
Target								
CI/DO ₂ I	15	674	30 (4.5)	592	73 (12.3)	0.36	0.21-0.36	0.0003
FTc/SV	9	423	15 (3.5)	434	23 (5.3)	0.78	0.40-1.52	0.46
Other	8	341	13 (3.8)	344	17 (4.9)	0.78	0.35-1.72	0.54
Type of monitor								
PAC	11	494	20 (4.0)	445	62 (13.9)	0.3	0.15-0.6	0.0007
ODM	8	378	10 (2.6)	389	17 (4.4)	0.77	0.35-1.69	0.51
Other	13	566	28 (4.9)	536	34 (6.3)	0.74	0.43-1.28	0.28

CI, cardiac index (ml/minute/m²); DO₂I, oxygen delivery index (ml/minute/m²); FTc, corrected flow time; ODM, oesophageal doppler monitor; PAC, pulmonary artery catheter; SV, stroke volume (ml).

using the ‘other cardiac output monitors’ had a greater reduction in complication rate than the subgroup using the PAC. This may relate to the complexity and invasive nature of the PAC in comparison to less invasive cardiac output monitors [98-100].

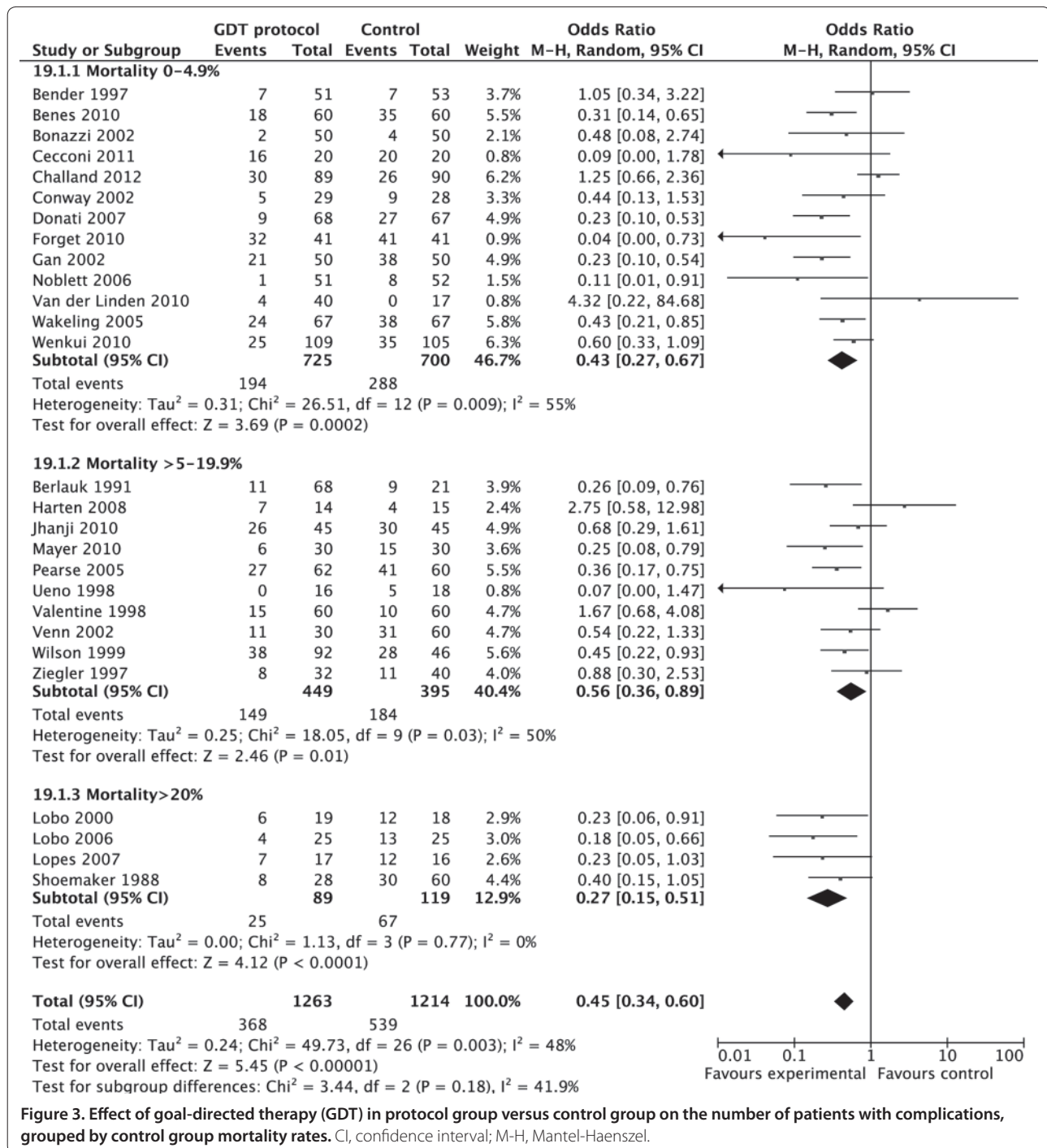
There remains significant heterogeneity in complication rates among postoperative patients in different centres [4,96]. Although differences in patient demographics are not modifiable, optimal management of the high-risk surgical patient during the perioperative phase may improve overall outcomes. Despite a requirement for an increase in healthcare resources to offer early GDT to high-risk surgical patients, reductions in immediate postoperative complications translate to overall benefits in healthcare costs. Any perceived increase in resource allocation results in a lower patient mortality and morbidity, and therefore a financial saving [101]. Furthermore, reduction in immediate postoperative complications has far-reaching effects, with a potential beneficial effect on long-term survival [102].

This meta-analysis includes trials from 1988 to 2011. As surgical techniques, perioperative care, and patient selection have been refined over these years, the overall mortality of patients has reduced. As such, the applicability of historical trials to current day practice may not be valid. This has recently been evaluated in a

meta-analysis of 29 perioperative GDT trials carried out between 1995 and 2008 [5]. There was an approximate halving of mortality rates in the control group every decade (29.5%, 13.5%, 7%). Despite a reduction in mortality rate, the morbidity rate remained constant, with approximately a third of patients experiencing postoperative complications. Perioperative GDT should therefore offer a reduction in complication rates in current practice.

We acknowledge that there is an element of subjectivity in our decision to include trials in this meta-analysis. Many studies were conducted in single centres with limited patient numbers, and not all studies conducted were of a high quality design. This is reflected by the median Jadad score of 3. The effect of study quality on outcomes of GDT trials has been analysed in a recent meta-analysis [5]. Most perioperative GDT trials were single-centre studies, and only a few were conducted in a double-blind manner. In contrast to the lower quality studies, the higher quality studies (defined as a Jadad score of at least 3) did not demonstrate any benefit in mortality reduction. However, the beneficial effect of reduction in perioperative complication rates was evident irrespective of trial quality.

One of the main limitations of this study is the lack of data on the volume and type of fluids given, and the dose of inotropes used due to variation and inconsistencies in



reporting. However, it must be emphasised that the absolute volume of fluids used *per se* is not as important as the way in which fluid is given. Fluid therapy must be titrated against a patient's response to a fluid challenge, with the use of haemodynamic monitoring [103]. Such 'goal-directed' fluid therapy must also be given at the right time, as GDT is not beneficial after complications have already developed [104,105].

One of the other limitations is missing data on the number of patients with complications, due to variations in reporting of complications in the literature, with some studies reporting the number of complications as opposed to the number of patients with complications. Furthermore, we acknowledge that the definitions and coding of complications are likely to vary between studies. We have analysed data extracted from studies,

Table 3. Complications by subgroup analysis

	Number of studies	Number of patients in GDT group	Patients with complications in GDT group (%)	Number of patients in control group	Patients with complications in control group (%)	Odds ratio	95% CI	P-value
Risk group								
Intermediate risk	13	727	194 (26.7)	698	288 (41.3)	0.43	0.27-0.67	0.0002
High risk	10	449	149 (33.2)	395	184 (46.6)	0.56	0.36-0.89	0.01
Extremely high risk	4	89	25 (28.1)	119	67 (56.3)	0.27	0.15-0.51	<0.0001
Fluid/inotropes								
Fluid	12	610	198 (32.5)	636	299 (47.0)	0.47	0.30-0.73	0.0007
Fluid + inotropes	15	653	170 (26.0)	578	240 (41.5)	0.44	0.30-0.64	<0.0001
Goal								
Supranormal	8	312	101 (32.4)	297	153 (51.5)	0.34	0.23-0.51	<0.00001
Normal	19	951	267 (28.1)	917	386 (42.1)	0.51	0.36-0.73	0.0002
Target								
CI/DO ₂ I	14	621	162 (26.1)	538	229 (42.6)	0.41	0.28-0.61	<0.0001
FTc/SV	7	361	118 (32.7)	392	180 (45.9)	0.50	0.30-0.84	0.009
Other	6	281	88 (31.3)	284	130 (45.8)	0.48	0.22-1.04	0.06
Type of monitor								
PAC	10	441	99 (22.4)	391	129 (33.0)	0.49	0.30-0.80	0.005
ODM	6	316	92 (29.1)	347	150 (43.2)	0.46	0.25-0.86	0.01
Other	11	506	177 (35.0)	476	260 (54.6)	0.41	0.26-0.64	0.0001

CI, cardiac index (ml/minute/m²); DO₂I, oxygen delivery index (ml/minute/m²); FTc, corrected flow time; ODM, oesophageal doppler monitor; PAC, pulmonary artery catheter; SV, stroke volume (ml).

rather than data of individual patients. As some of the studies included were carried out several years ago, obtaining data on individual patients would not have been possible. Despite these limitations, the results remain consistent across many subgroups of patients, and are consistent with other recent meta-analyses, supporting our hypothesis [5,106] and the recent EUSOS study which showed a mortality of 4% [107]. The benefit in terms of reduction of complications of GDT in the intermediate risk group may have implications for the majority of the European surgical population.

Conclusion

Despite heterogeneity in trial quality and design, early GDT among high-risk surgical patients has a significant benefit in reducing rates of complications. There is also an associated reduction in mortality among patients at extremely high risk of perioperative death. GDT is of greatest benefit in patients with the highest risk of mortality.

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Abbreviations

CI, cardiac index (ml/minute/m²); DO₂I, oxygen delivery index (ml/minute/m²); FTc, corrected flow time; GDT, goal-directed therapy; PAC, pulmonary artery catheter; SV, stroke volume (ml).

Competing interests

MC: Edwards Lifesciences, LiDCO, Deltex, Applied Physiology, Masimo, Bmeye, Cheetah, Imacor (travel expenses, honoraria, advisory board, unrestricted educational grant, research material). MH: lecture fees from Edwards, Deltex, hutchinson technology and LidCO. AR: honoraria and advisory board for LiDCO. Honoraria for Covidien, Edwards Lifesciences and Cheetah. NA: travel expenses from LiDCO.

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