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REVIEW ARTICLE

Intraoperative goal directed hemodynamic therapy in noncardiac surgery: a systematic review and meta-analysis

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KEYWORDS
Goal directed fluid therapy;
Meta-analysis;
Hemodynamic goal;
Noncardiac surgery

Abstract
Background: The goal directed hemodynamic therapy is an approach focused on the use of cardiac output and related parameters as end-points for fluids and drugs to optimize tissue perfusion and oxygen delivery. Primary aim: To determine the effects of intraoperative goal directed hemodynamic therapy on postoperative complications rates.
Methods: A meta-analysis was carried out of the effects of goal directed hemodynamic therapy in adult noncardiac surgery on postoperative complications and mortality using Preferred Reporting Items for Systematic Reviews and Meta-Analyses methodology. A systematic search was performed in Medline PubMed, Embase, and the Cochrane Library (last update, October 2014). Inclusion criteria were randomized clinical trials in which intraoperative goal directed hemodynamic therapy was compared to conventional fluid management in noncardiac surgery. Exclusion criteria were trauma and pediatric surgery studies and that using pulmonary artery catheter. End-points were postoperative complications (primary) and mortality (secondary). Those studies that fulfilled the entry criteria were examined in full and subjected to quantifiable analysis, predefined subgroup analysis (stratified by type of monitor, therapy, and hemodynamic goal), and predefined sensitivity analysis.

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Results: 51 RCTs were initially identified, 24 fulfilling the inclusion criteria. 5 randomized clinical trials were added by manual search, resulting in 29 randomized clinical trials in the final analysis, including 2654 patients. A significant reduction in complications for goal directed hemodynamic therapy was observed (RR: 0.70, 95% CI: 0.62–0.79, $p < 0.001$). No significant decrease in mortality was achieved (RR: 0.76, 95% CI: 0.45–1.28, $p = 0.30$). Quality sensitive analyses confirmed the main overall results.
Conclusions: Intraoperative goal directed hemodynamic therapy with minimally invasive monitoring decreases postoperative complications in noncardiac surgery, although it was not able to show a significant decrease in mortality rate.

PALAVRAS-CHAVE
Fluidoterapia alvo-dirigida;
Metaanálise;
Objetivo hemodinâmico;
Cirurgia não cardíaca

Terapia hemodinâmica alvo-dirigida no intraoperatório de cirurgia não cardíaca: revisão sistemática e meta-análise

Resumo
Justificativa: A terapia hemodinâmica alvo-dirigida (THAD) é uma abordagem focada no uso do débito cardíaco (DC) e parâmetros relacionados, como desfechos para fluidos e medicamentos para otimizar a perfusão tecidual e o fornecimento de oxigênio. Objetivo primário: determinar os efeitos da THAD sobre as taxas de complicações no pós-operatório.
Métodos: Meta-análise dos efeitos da THAD em cirurgias não cardíacas de adultos sobre as complicações pós-operatórias e mortalidade, usando a metodologia PRISMA. Uma busca sistemática foi realizada no Medline PubMed, Embase e Biblioteca Cochrane (última atualização, outubro de 2014). Os critérios de inclusão foram estudos clínicos randômicos (ECRs) nos quais a THAD no intraoperatório foi comparada com a terapia convencional de reposição de líquidos em cirurgia não cardíaca. Os critérios de exclusão foram traumatismo e estudos de cirurgia pediátrica e aqueles usando cateter de artéria pulmonar. Os desfechos, primário e secundário, foram complicações pós-operatórias e mortalidade, respectivamente. Os estudos que atenderam aos critérios de inclusão foram examinados na íntegra e submetidos à análise quantitativa, análise de subgrupo pré-definido (estratificada por tipo de monitor, terapia e objetivo hemodinâmico) e análise de sensibilidade pré-definida.
Resultados: 51 ECRs foram identificados inicialmente, 24 atenderam aos critérios de inclusão. Cinco ECRs foram adicionados por busca manual, resultando em 29 ECRs para análise final, incluindo 2.654 pacientes. Uma redução significativa das complicações para a THAD (RR: 0,70, IC de 95%: 0,62-0,79, $p < 0{,}001$). Nenhuma diminuição significativa na mortalidade foi observada (RR: 0,76, IC de 95%: 0,45-1,28, $p = 0{,}30$). Análises de sensibilidade qualitativa confirmaram os principais resultados gerais.
Conclusões: THAD no intraoperatório com monitoração minimamente invasiva diminui as complicações no pós-operatório de cirurgia não cardíaca, embora não tenha mostrado uma redução significativa da taxa de mortalidade.

Introduction

The perioperative management of high-risk surgical patients continues to be a challenge for the anesthesiologists. Despite advances in perioperative management, the incidence of serious complications after major surgery remains high.[1,2] A decrease in perioperative oxygen transport is closely related to the development of organ failure and death.[3] It has also been demonstrated that a large high-risk surgical population accounts for 12.5% of surgical procedures and for more than 80% of deaths.[4] Surgical patients can be classified as high risk based on surgical factors or patient-related factors.[5] Goal directed hemodynamic therapy (GDHT) is based on the optimization of preload with the use of algorithms based on fluids, inotropes and/or vasopressors to achieve a certain goal in stroke volume (SV), cardiac index (CI), or oxygen delivery (DO_2). The ultimate goal of this optimization is to avoid fluid overload, tissue hypoperfusion, and hypoxia.[6] All the studies of perioperative hemodynamic optimization had the same starting point, fluid loading, and the same endpoint, achieving adequate DO_2. However, clinical heterogeneity between studies of GDHT cannot be ignored, with regard to type of surgery, patient's characteristics, therapeutic goals, methods for achieving these goals and monitoring. The pulmonary arterial catheter (PAC) has been considered to be the ''gold standard'' for monitoring preload, afterload, contractility, and tissue oxygenation. The invasiveness and high rate of complications associated with this device render it as unsuitable for routine use in most cases. The use of minimally invasive monitoring has gained popularity in the past few years; these devices have been validated intraoperatively. Currently PAC is not recommended in most surgeries, and for this reason it was not analyzed in this meta-analysis. There are no data to support the practice of using central venous pressure to guide fluid therapy,[7] therefore, central venous pressure-guided fluid therapy was not included in analysis.

Yet there are no studies in which different algorithms or different objectives are compared. The best method for assessing tissue oxygenation and intravascular volume has not yet been defined. The present review was designed to update the published evidence and determine the effectiveness of intraoperative GDHT with regard to complications and mortality with different types of algorithms and monitors used.

Material and methods

Selection criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology[8] was used to identify the studies, based on the following inclusion criteria:

1. *Participants*: Adult patients (over 18 years) undergoing elective noncardiac surgery were included. The studies were not limited in terms of surgical risk.
2. *Types of intervention*: Intraoperative goal directed hemodynamic therapy: defined as hemodynamic monitoring that allows to perform a hemodynamic optimization algorithm based on the use of fluids, inotropes and/or vasopressors to achieve normal or supranormal hemodynamic values. GDHT guided by pulmonary artery catheter, transesophageal echocardiography or central venous pressure-guided GDHT were excluded.
3. *Types of comparison*: The studies that were selected for analysis included those that compared GDHT with conventional fluid management (monitoring of blood pressure, electrocardiogram, heart rate, urine output and/or central venous pressure).
4. *Results:* RCTs reporting any of the following outcomes: postoperative complications and/or mortality.
5. *Types of studies*: RCTs where intraoperative GDHT was performed in adult patients scheduled for noncardiac major surgery. Only peer-reviewed manuscripts were included.

Sources of information

Following the PRISMA protocol[8] different search strategies (last updated in October 2014) were used to identify relevant studies that met inclusion criteria using EMBASE, MEDLINE and the Cochrane Library. There were no restrictions on the publication date or language. In addition to electronic searching, industry representatives were contacted for additional material. All identified review articles and evidence-based guidelines were hand-searched for additional references.

Search items

The search was conducted using the following key words: surgery, fluid, goal directed, end point, hemodynamic, target, goal and randomized controlled trial.

Study selection and data extraction

Two independent investigators assessed each title and abstract in order to discard any irrelevant RCTs and identify those potentially relevant. These RCTs were analyzed selecting those that met the inclusion criteria outlined above. RCT data extraction was performed by two different investigators and any discrepancy required further analysis and confirmation by a third investigator. The authors reviewed the data analysis in order to avoid errors in data transcription.

Assessment of risk of bias in included studies

Bias assessment risk was performed using the Cochrane risk of bias tool. From this tool, we used seven domains to assess the methodological quality of the studies included in the analysis.

Outcome variables

The primary outcome was the overall postoperative complications. The results were stratified according to the following variables: monitor utilized, therapy used to reach a hemodynamic goal and the hemodynamic goal. For the predefined subgroup analysis, studies were grouped:

(1) *Monitor*: (a) Arterial pulse contour analysis methods (Vigileo/Flotrac®, Edwards Lifesciences Corporation, USA; ProAQT®, Pulsion medical systems SE, Germany; LiDCO Plus®, LiDCO Ltd., UK); (b) oesophageal Doppler Monitoring-ODM (CardioQ®, Deltex Medical, UK); (c) noninvasive methods (Masimo®, Masimo Corporation; CNAP® PPV, CNSystems Medizintechnik AG) and (d) measures of oxygen delivery and extraction methods.
(2) *Therapy*: (a) Fluids; (b) fluids and inotropes; (c) vasopressors and fluids and (4) fluids, inotropes and vasopressors.
(3) *Hemodynamic goals*: (a) SV maximization; (b) $CI > 2.5\,mL/min/m^2$; (c) preload responsiveness (including stroke volume variation, Pulse pressure variation and Pleth Variability Index®) and (d) $ScvO_2$.

The secondary outcome was mortality.

Statistical analysis

Review manager (''Revman'') 10 for MAC (Cochrane collaboration, Oxford, UK) was used for statistical analysis. Meta-analysis was carried out using the Mantel—Haenszel

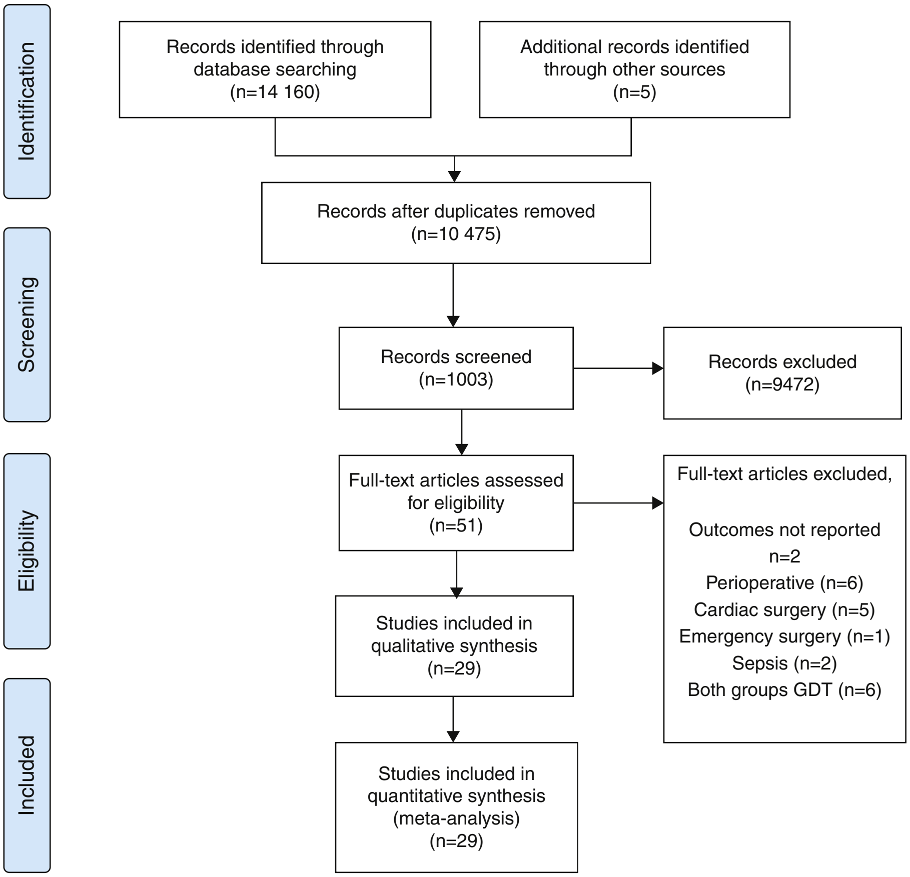


Figure 1 Flow diagram illustrating search strategy.

random-effects model, with results presented as risk ratio (RR) with a 95% confidence interval (CI). Forest plots were then constructed, considering $p < 0.050$ as statistically significant effect. Statistical heterogeneity was evaluated using I^2 statistics; I^2 values of less than 25% were defined as low heterogeneity, 25–50% as moderate heterogeneity and greater than 50% as high heterogeneity. A χ^2 test for heterogeneity was performed, with $p < 0.100$ regarded as statistically significant. *A priori* sensitivity analyses were conducted on both the primary and the secondary outcomes by restricting the analysis to high quality trials: to those studies that showed no allocation bias and those without randomization/allocation bias. Publication bias was assessed using funnel plot techniques.

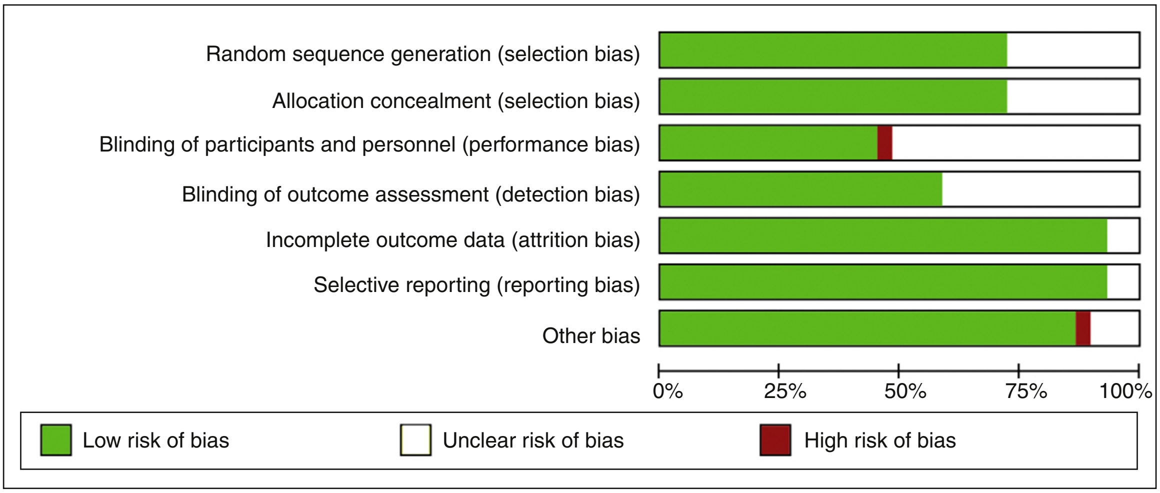


Figure 2 Review authors' judgements about each risk of bias item presented as percentages across all included studies. Green, low risk of bias; white, unclear risk of bias; red, high risk of bias.

Results

Study selection

There were 14,160 references in electronic databases, of which 1003 were screened. Of those, 55 RCTs were analyzed and 24 of them were included for systematic review and meta-analysis, excluding those who did not meet the inclusion criteria. Finally a total of 29 RCTs were included[9–37]; 5 RCTs were added by manual search. 2654 patients were included. Fig. 1 shows the flowchart used for item selection.

Assessment of risk of bias in individual studies

Bias risk was analyzed with the Cochrane tool. This was performed by two authors independently and we resolved any disparity by discussion and the involvement of a third person. We present the methodological quality in a summary table and a graph (Figs. 2 and 3).

Characteristics of the studies included in the analysis

The selected articles describe the results of RCTs that evaluated the use of intraoperative GDHT in noncardiac elective surgery, and that included postoperative complications and/or mortality as outcome. The characteristics of the included RCTs are shown in Table 1.

Primary results

1. *Total complications*
   Analyzing the 29 RCTs, 26 describe the total associated complications[10–37] GDHT was associated with a significant reduction in overall complication compared with patients treated in the control group (RR: 0.70, 95% CI: 0.62–0.79, $p < 0.001$) (Fig. 4).
2. *Complications by monitor*
   A significant decrease in complications was found in subgroup based on pulse contour analysis (RR: 0.78, 95% CI: 0.59–0.99, $p = 0.04$) and subgroup ODM (RR: 0.67, 95% CI: 0.53–0.85, $p < 0.001$). However, it was not shown in the subgroup of noninvasive monitoring (RR: 0.57, 95% CI: 0.28–1.15, $p = 0.12$) and was based on measures of oxygen delivery and extraction methods (RR: 0.59, 95% CI: 0.20–1.80, $p = 0.36$) (Fig. 5).
3. *Complications by hemodynamic therapy*
   A significant decrease in complications was observed in the fluids as monotherapy subgroup (RR: 0.69, 95% CI: 0.57–0.84, $p < 0.001$), fluids and vasopressors subgroup (RR: 0.76, 95% CI: 0.68–0.85, $p < 0.001$), and fluids, vasopressors and inotropes subgroup (RR: 0.54, 95% CI: 0.32–0.89, $p = 0.02$). However, the use of fluids and inotropes showed no decrease in complications (RR. 0.66, 95% CI: 0.34–1.28, $p = 0.22$) (Fig. 6).
4. *Complications by hemodynamic goal*
   A decrease in complications was associated with the use of GDHT in the following subgroups: Svmaximization (RR: 0.73, 95% CI: 0.61–0.89, $p < 0.001$), in the subgroup preload responsiveness (RR: 0.73, 95% CI: 0.59–0.95),

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bartha et al. 2012	+	+		+	+	+	+
Benes et al. 2010	+	+	+	+	+	+	+
Brandstrup et al. 2012	+	+		+	+	+	+
Buettner et al. 2008		+	+	+		+	+
Cecconi et al. 2011	+	+	+		+	+	+
Challand et al. 2012	+	+	+	+	+	+	+
Conway et al. 2002			+		+	+	+
Donati et al. 2007	+	+			+		
Forget et al. 2010				+	+	+	+
Forget et al. 2013	+		−		+	+	+
Gan et al. 2002	+	+			+	+	+
Jammer et al. 2010	+			+	+	+	+
Lopes et al. 2007	+			+	+	+	+
Mayer et al. 2010		+		+	+	+	−
McKenny et al. 2013	+	+	+	+	+	+	+
Nobblet et al. 2006			+	+	+	+	
Peng et al. 2014	+	+			+	+	+
Salzwedel et al. 2013		+		+	+	+	+
Scheeren et al. 2013	+	+		+	+	+	+
Senagore et al. 2009	+		+	+	+	+	+
Sinclair et al. 1997		+	+		+	+	+
Srinivasa et al. 2013	+	+	+	+	+	+	+
Van der Linden et al. 2010	+	+	+	+	+	+	+
Venn et al. 2002	+	+	+		+	+	+
Walkening et al. 2005	+	+	+		+	+	
Zakhaleva et al. 2013	+	+			+	+	+
Zhang et al. 2012	+				+	+	+
Zhang et al. 2013		+					+
Zheng et al. 2013	+	+		+	+	+	+

Figure 3 Review authors' judgements about each risk of bias item for each included study.

Table 1 PICO characteristic of included studies.

Study	Year	Patients	Intervention	Comparator	Outcomes	Study design
Sinclair et al.	1997	Patients over 55 years undergoing hip replacement surgery	CardioQ-guided GDHT by optimizing SV and cFT with fluids *n* 20	Standard care *n* 20	Length of stay, hemodynamic parameters	RCT
Conway et al.	2002	ASA I–III patients undergoing colorectal surgery	CardioQ-guided GDHT by optimizing SV with fluids *n* 29	Standard care *n* 28	Hemodynamic parameters, bowel function parameters, complications	RCT
Gan et al.	2002	ASA I–III patients undergoing major surgery	CardioQ-guided GDHT by optimizing SV with fluids *n* 50	Standard care *n* 50	Length of stay, complications	RCT
Venn et al.	2002	Patients undergoing hip replacement surgery	CardioQ-guided GDHT by optimizing SV with fluids *n* 30	Standard care *n* 29	Length of stay, hemodynamic parameters	RCT
Walkeling et al.	2005	ASA I–III patients undergoing colorectal surgery in an ERAS protocol	CardioQ-guided GDHT by optimizing SV with fluids *n* 64	Standard care (CVP 12–15 mmHg) *n* 64	Length of stay, oral tolerance, complications, quality of recovery	RCT
Nobblet et al.	2006	Patients undergoing colorectal surgery	CardioQ-guided GDHT by optimizing SV with fluids *n* 54	Standard care *n* 54	Length of stay, complications, bowel function recovery	RCT
Donati et al.	2007	High-risk patients undergoing major abdominal surgery	GDHT by optimizing ERO2 with fluids and inotropes *n* 68	Standard care *n* 67	Hemodynamic parameters, complications, length of stay	RCT
Lopes et al.	2007	High-risk patients undergoing major abdominal surgery	CNAP-guided GDHT by optimizing $\triangle PP < 10\%$ *n* 17	Standard care *n* 16	Hemodynamic parameters, complications, ICU stay, length of stay	RCT
Buettner et al.	2008	ASA I–III patients undergoing major abdominal surgery (general, gynecological)	PPV-guided GTHD with fluids and vasopressors *n* 40	Standard care *n* 40	Tissue oxygenation parameters, hemodynamic parameters, length of stay	RCT
Senagore et al.	2009	Low- and moderate-risk patients undergoing laparoscopic bowel resection in an ERAS protocol	CardioQ-guided GDHT by optimizing SV with fluids n 21(LR) or HES 6% *n* 21	Standard care *n* 22	Complications, length of stay	RCT
Jammer et al.	2010	Patients undergoing colorectal surgery	$ScvO_2$-guided GDHT with fluids *n* 121	Standard care *n* 120	Complications	RCT
Van der Linden et al.	2010	ASA II–III patients undergoing low limb arterial by-pass	Flotrac-guided GDHT maintaining a $CI > 2.5\,mL/min/m^2$ and $CVP < 15\,mmHg$ with fluids and inotropes. Sevoflurane anesthesia *n* 20	Standard care guided by APm and CVP *n* 17	Hemodynamic parameters, Complications, length of stay	RCT

Table 1 (*Continued*)

Study	Year	Patients	Intervention	Comparator	Outcomes	Study design
Forget et al.	2010	Patients undergoing major abdominal surgery	Masimo-guided GDHT by optimizing PVI with fluids and vasopressors *n* 41	Standard care *n* 41	Amount of fluid administered, lactate levels, complications, length of stay, mortality	RCT
Mayer et al.	2010	High-risk patients undergoing major abdominal surgery	Flotrac-guided GDHT maintaining a $CI > 2.5\,mL/min/m^2$ with fluids, inotropes and vasopressors *n* 30	Standard care (restrictive) *n* 30	Length of stay, complications	RCT
Benes et al.	2010	High-risk patients (ASA III–IV) undergoing major abdominal surgery	Flotrac-guided GDHT by optimizing SVV with fluids and inotropes *n* 60	Standard care *n* 60	Complications, length of stay, ICU stay, mortality	RCT
Cecconi et al.	2011	Patients undergoing hip replacement. Regional Anesthesia	Flotrac-guided GDHT by optimizing SV and $DOI > 600\,mL/min/m^2$ with fluids, inotropes and vasopressors *n* 20	Standard care *n* 20	Amount of fluids administered, vasoactive use, complications, length of stay	RCT
Challand et al.	2012	Patients undergoing colorectal surgery in an ERAS protocol. All patients	CardioQ-guided GDHT by optimizing SV with fluids *n* 89	Standard care *n* 90	Length of stay, readmission, complications	RCT
Brandstrup et al.	2012	ASA I–III patients undergoing colorectal surgery	CardioQ-guided GDHT by optimizing SV with fluids *n* 71	Standard care. Zero balance *n* 79	Complications, length of stay	RCT
Bartha et al.	2013	Patients over 70 years undergoing hip replacement in an ERAS protocol	LiDCO plus guided GDHT by optimizing SV and $DOI > 600\,mL/min/m^2$ with fluids and inotropes *n* 74	Standard care *n* 75	Complications, amount of fluids administered, hemodynamic response, length of stay	RCT
Zhang et al.	2013	ASA I–II patients undergoing gastrointestinal surgery	PPV-guided GDHT with fluids: LR *n* 20; and HES 6% *n* 20	Standard care *n* 20	Length of stay, bowel function parameters, complications, hemodynamic parameters	RCT
Salzwedel et al.	2013	ASA II–III patients undergoing major abdominal surgery	ProAQT-guided GDHT maintaining a $CI > 2.5\,mL/min/m^2$ with fluids, inotropes and vasopressors *n* 79	Standard care *n* 81	Complications, length of stay	RCT
Scheeren et al.	2013	ASA III–IV undergoing major abdominal surgery	Flotrac-guided GDHT by optimizing SV and SVV with fluids *n* 26	Standard care *n* 26	Complications, SOFA score, ICU stay, mortality	RCT

Table 1 (*Continued*)

Study	Year	Patients	Intervention	Comparator	Outcomes	Study design
Zhang et al.	2013	ASA I–II undergoing lobectomy surgery	Flotrac-guided GDHT by optimizing SVV and maintaining a $CI > 2.5\,mL/min/m^2$ with fluids and inotropes *n* 30	Standard care *n* 30	Length of stay, complications	RCT
Forget et al.	2013	Low- and moderate-risk patients undergoing colorectal surgery in an ERAS protocol	Masimo-guided GDHT by optimizing PVI with fluids ($IPV < 13$) *n* 10	Standard care *n* 11	Amount of fluids administered, complications, mortality, length of stay	RCT
Zakhaleva et al.	2013	Patients undergoing colorectal surgery in an ERAS protocol	CardioQ-guided GDHT by optimizing SV and cFT with fluids *n* 32	Standard care *n* 40	Time of surgery, amount of fluids administered, bowel function recovery, complications, length of stay, mortality	RCT
Srinivasa et al.	2013	ASA I–III patients undergoing colorectal surgery without an ERAS protocol	CardioQ-guided GDT by optimizing SV and cFT with fluids *n* 37	Standard care *n* 37	Hemodynamic parameters, complications	RCT
McKenny et al.	2013	Patients undergoing major gynecological surgery	CardioQ-guided GDHT by optimizing SV and cFT with fluids *n* 51	Standard care *n* 50	Complications, length of stay	RCT
Zheng et al.	2013	Elderly high-risk patients undergoing major abdominal surgery	Flotrac-guided GDHT by maintaining a $CI > 2.5\,mL/min/m^2$ with fluids and vasopressors *n* 30	Standard care *n* 30	Cardiovascular complications, bowel function parameters, ICU stay, length of stay	RCT
Peng et al.	2014	Adult patients undergoing major orthopedic surgery	Flotrac-guided GDHT to maintain $SVV < 10$ or <14% in prone position *n* 40	Standard care *n* 40	Splanchnic organ functions, postoperative complications	RCT

GDHT, goal directed hemodynamic therapy; SV, stroke volume; Cft, corrected flow time; RCT, randomized controlled trial; ASA, American Society of Anesthesiologist; CVP, central venous pressure; ERAS, enhanced recovery after surgery; ERO_2, oxygen extraction index; △PP, increment of pulse pressure; PPV, pressure pulse variation; LR, lactate of ringer; HES, hydroxyethyl starch; CI, cardiac index; PVI, plethysmography variation index; SVV, stroke volume variation; DOI, oxygen delivery index; SVI, indexed stroke volume; PP, pulse pressure; $ScvO_2$, central venous oxygen saturation.

$p < 0.001$), and with a CI target, $CI > 2.5\,mL/min/m^2$ (RR: 0.58, 95% CI: 0.44–0.76, $p < 0.001$), whereas in the subgroup that utilized measures of oxygen delivery and extraction methods no significant decrease was observed (Fig. 7).

Mortality

No significant differences were found with regard to mortality (RR: 0.76, 95% CI: 0.45–1.28, $p = 0.30$) (Fig. 8).

Sensitivity analysis, assessment risk of bias across studies and publication bias

No changes in the results with regard to complications ([RR: (CI 95%) 0.71 (0.61–0.82), $p < 0.01$]) or mortality ([RR: (CI 95%) 0.77 (0.42–1.40), $p = 0.39$]) were observed when restricting the analysis to those studies that had no allocation bias; or when restricting the analysis to those that had no allocation and/or randomization bias in the results with regard to complications [RR (CI 95%) 0.69 (0.59–0.81), $p < 0.01$] and mortality ([RR (CI 95%) 0.95 (0.45–1.85), $p = 0.87$]) On the other hand, a prespecified group analysis

Study	GDHT Events	GDHT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Gan et al. 2002	21	60	38	59	4.7%	0.54 [0.37, 0.81]	2002
Venn et al. 2002	11	30	21	29	3.5%	0.51 [0.30, 0.85]	2002
Conway et al. 2002	5	29	9	28	1.4%	0.54 [0 .20, 1.40]	2002
Walkening et al. 2005	24	64	38	64	5.0%	0.63 [0.43 , 0.92]	2005
Nobblet et al. 2006	1	54	8	54	0.3%	0.13 [0.02, 0.97]	2006
Donati et al. 2007	9	68	27	67	2.4%	0.33 [0 .17, 0.64]	2007
Lopes et al. 2007	7	17	12	16	2.6%	0.55 [0 .29, 1.04]	2007
Senagore et al. 2009	8	42	4	44	1.0%	2.10 [0.68, 6.44]	2009
Mayer et al. 2010	6	30	15	30	1.9%	0.40 [0.18, 0.89]	2010
Forget et al. 2010	32	41	41	41	7.9%	0.78 [0.66, 0.93]	2010
Jammer et al. 2010	51	121	51	120	6.0%	0.99 [0.74, 1.33]	2010
Van der Linden et al. 2010	3	20	2	17	0.5%	1.27 [0 .24, 6.76]	2010
Benes et al. 2010	18	60	35	50	4.4%	0.43 [0.28, 0.66]	2010
Cecconi et al. 2011	16	20	20	20	7.0%	0.80 [0 .64, 1.02]	2011
Zhang et al. 2012	12	40	10	40	2.2%	1.20 [0.59, 2.45]	2012
Brandstrup et al. 2012	23	71	24	71	3.9%	0.96 [0.60, 1.53]	2012
Challand et al. 2012	10	89	13	90	2.0%	0.78 [0 .36, 1.68]	2012
Bartha et al. 2012	44	74	43	75	6.4%	1.04 [0 .79, 1.36]	2012
Zhang et al. 2013	9	30	16	30	2.6%	0.56 [0.30, 1.07]	2013
McKenny et al. 2013	8	51	15	50	2.0%	0.52 [0.24 , 1.12]	2013
Scheeren et al. 2013	12	36	16	26	3.2%	0.54 [0.31, 0.94]	2013
Salzwedel et al. 2013	52	79	72	81	7.8%	0.74 [0.62, 0.88]	2013
Forget et al. 2013	1	10	7	10	0.4%	0.14 [0 .02, 0.96]	2013
Srinivasa et al. 2013	26	37	27	37	6.2%	0.96 [0.72 , 1.28]	2013
Zakhaleva et al. 2013	7	32	19	40	2.1%	0.46 [0.22, 0.96]	2013
Zheng et al. 2013	19	30	30	30	6.3%	0.64 [0.49, 0.84]	2013
Peng et al. 2014	25	40	32	40	6.2%	0.78 [0.59, 1.04]	2014
Total (95% CI)		1275		1259	100.0%	0.70 [0.62, 0.79]	
Total events	460		645				

Heterogeneity: Tau^2=0.04 ; Chi^2=54.70, df=26 (*P*=.0008); I^2=52%
Test for overall effect: Z=5.71 (*P*<.00001)

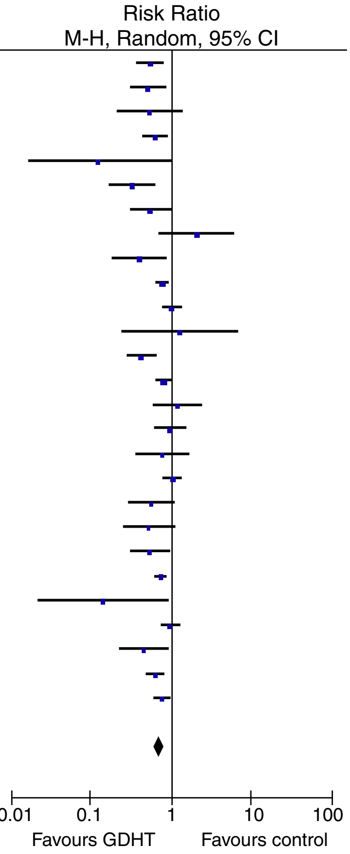


Figure 4 Effect of GDHT in the protocol group vs control group on overall complications.

has been conducted and described above. A funnel plot was drawn for the primary outcome comparison to explore the possibility of publication bias. The symmetry of the funnel plot was assessed visually and did not suggest publication bias (Fig. 9).

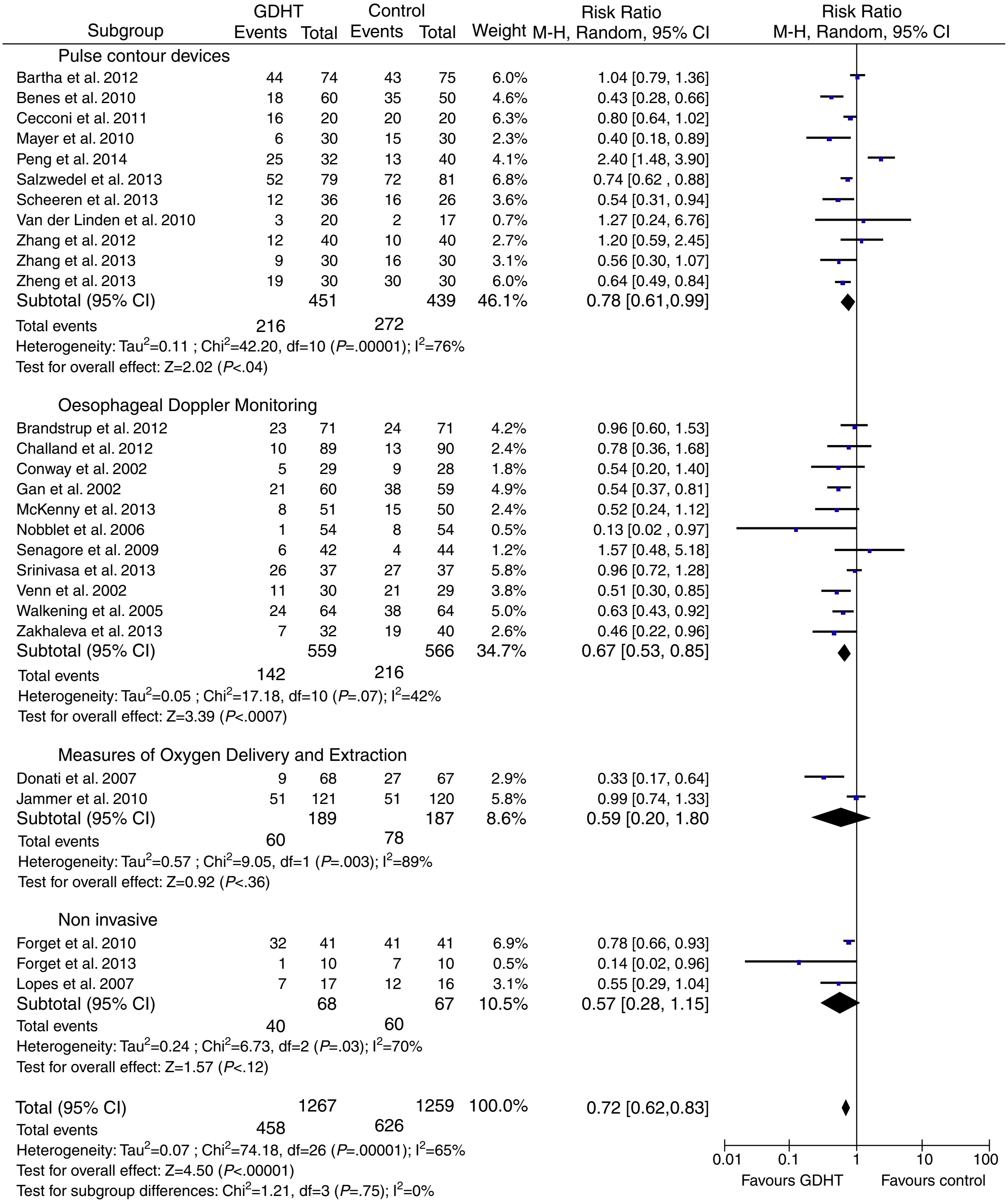
Discussion

Numerous studies have reported differences between technologies, especially in their response to typical surgical interventions such as fluid and vasoactive drug administration.[38] The results obtained with one type of monitoring cannot be extrapolated to those obtained with other monitors.[39] RCTs using noninvasive monitors were limited both in number of patients studied and methodological quality. How minimal invasive cardiac output monitoring techniques can be used to guide individualized fluid management[40] needs to be sustained by validation studies that adhere to the proposed methodological considerations[41] as well as large-scale clinical outcome studies.

There is some evidence that SV maximization strategies could be harmful in aerobically fit patients by leading to volume overload,[25] and recent evidence suggests that this goal does not provide the benefits previously described.[42]

However, the results of our meta-analysis show that this hemodynamic goal remains valid. The use of dynamic response parameters to volume may decrease the risk of volume overload. A CI > 2.5 mL/min/m^2 as hemodynamic target within algorithms in which fluids, vasopressors and inotropes are used avoid the risk of hypotension due to decreased vasomotor tone. The use of inotropes increases the CO in situations where the patient is nonresponsive to the volume and does not present a reduced vasomotor tone. Inotropic support with dobutamine can result in changes in microvascular flow related to direct effects on the microcirculation as well as global CO.[43] With the exception of ScvO$_2$, that was only evaluated in one RCT,[19] and was not associated with better outcomes, this meta-analysis has not been able to detect significant differences between subgroups. Therefore it seems reasonable to adapt GDHT to risk patient, type of surgery as well as its duration[44] as recommended by recent European Society of Anaesthesiology guidelines.[45] A multicenter observational trial in patients with intra-abdominal surgery found that low ScvO$_2$ was associated with an increased risk of postoperative complications in high-risk surgery. In this trial, the optimal value of mean ScvO$_2$ to discriminate between patients who did or did not develop complications was 73% (sensitivity 72%, specificity 61%)[46] One of the major limitations of venous oximetry is that, as a global marker of demand-supply balance, it does not reflect organ-specific malperfusion. Whether ScvO$_2$ monitoring improves outcomes in surgical patients remains to be proven in large RCTs.

Unlike our results, a recent meta-analysis has shown a significant benefit of GDHT in patients receiving fluids and



Subgroup	GDHT Events	GDHT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Pulse contour devices						
Bartha et al. 2012	44	74	43	75	6.0%	1.04 [0.79, 1.36]
Benes et al. 2010	18	60	35	50	4.6%	0.43 [0.28, 0.66]
Cecconi et al. 2011	16	20	20	20	6.3%	0.80 [0.64, 1.02]
Mayer et al. 2010	6	30	15	30	2.3%	0.40 [0.18, 0.89]
Peng et al. 2014	25	32	13	40	4.1%	2.40 [1.48, 3.90]
Salzwedel et al. 2013	52	79	72	81	6.8%	0.74 [0.62 , 0.88]
Scheeren et al. 2013	12	36	16	26	3.6%	0.54 [0.31, 0.94]
Van der Linden et al. 2010	3	20	2	17	0.7%	1.27 [0.24, 6.76]
Zhang et al. 2012	12	40	10	40	2.7%	1.20 [0.59, 2.45]
Zhang et al. 2013	9	30	16	30	3.1%	0.56 [0.30, 1.07]
Zheng et al. 2013	19	30	30	30	6.0%	0.64 [0.49, 0.84]
Subtotal (95% CI)		451		439	46.1%	0.78 [0.61,0.99]
Total events	216		272			
Oesophageal Doppler Monitoring						
Brandstrup et al. 2012	23	71	24	71	4.2%	0.96 [0.60, 1.53]
Challand et al. 2012	10	89	13	90	2.4%	0.78 [0.36, 1.68]
Conway et al. 2002	5	29	9	28	1.8%	0.54 [0.20, 1.40]
Gan et al. 2002	21	60	38	59	4.9%	0.54 [0.37, 0.81]
McKenny et al. 2013	8	51	15	50	2.4%	0.52 [0.24, 1.12]
Nobblet et al. 2006	1	54	8	54	0.5%	0.13 [0.02 , 0.97]
Senagore et al. 2009	6	42	4	44	1.2%	1.57 [0.48, 5.18]
Srinivasa et al. 2013	26	37	27	37	5.8%	0.96 [0.72, 1.28]
Venn et al. 2002	11	30	21	29	3.8%	0.51 [0.30, 0.85]
Walkening et al. 2005	24	64	38	64	5.0%	0.63 [0.43, 0.92]
Zakhaleva et al. 2013	7	32	19	40	2.6%	0.46 [0.22, 0.96]
Subtotal (95% CI)		559		566	34.7%	0.67 [0.53, 0.85]
Total events	142		216			
Measures of Oxygen Delivery and Extraction						
Donati et al. 2007	9	68	27	67	2.9%	0.33 [0.17, 0.64]
Jammer et al. 2010	51	121	51	120	5.8%	0.99 [0.74, 1.33]
Subtotal (95% CI)		189		187	8.6%	0.59 [0.20, 1.80
Total events	60		78			
Non invasive						
Forget et al. 2010	32	41	41	41	6.9%	0.78 [0.66, 0.93]
Forget et al. 2013	1	10	7	10	0.5%	0.14 [0.02, 0.96]
Lopes et al. 2007	7	17	12	16	3.1%	0.55 [0.29, 1.04]
Subtotal (95% CI)		68		67	10.5%	0.57 [0.28, 1.15]
Total events	40		60			
Total (95% CI)		1267		1259	100.0%	0.72 [0.62,0.83]
Total events	458		626			

Pulse contour devices:
Heterogeneity: Tau^2=0.11 ; Chi^2=42.20, df=10 (*P*=.00001); I^2=76%
Test for overall effect: Z=2.02 (*P*<.04)

Oesophageal Doppler Monitoring:
Heterogeneity: Tau^2=0.05 ; Chi^2=17.18, df=10 (*P*=.07); I^2=42%
Test for overall effect: Z=3.39 (*P*<.0007)

Measures of Oxygen Delivery and Extraction:
Heterogeneity: Tau^2=0.57 ; Chi^2=9.05, df=1 (*P*=.003); I^2=89%
Test for overall effect: Z=0.92 (*P*<.36)

Non invasive:
Heterogeneity: Tau^2=0.24 ; Chi^2=6.73, df=2 (*P*=.03); I^2=70%
Test for overall effect: Z=1.57 (*P*<.12)

Total (95% CI):
Heterogeneity: Tau^2=0.07 ; Chi^2=74.18, df=26 (*P*=.00001); I^2=65%
Test for overall effect: Z=4.50 (*P*<.00001)
Test for subgroup differences: Chi^2=1.21, df=3 (*P*=.75); I^2=0%

Figure 5 Effect of GDHT in the protocol group vs control group on overall complications grouped by monitor. Pulse contour devices: Vigileo/Flotrac®, ProAQT, and LiDCO Plus®. No invasive: CNAP® PPV and Masimo®.

inotropes in order to achieve supraphysiological targets for oxygen delivery in high-risk patients.[47]

This meta-analysis was unable to demonstrate a significant reduction in mortality. There are a number of reasons to explain why the control mortality may have decreased over time. These include: (1) better overall care thus decreasing mortality for similar patients; (2) clinicians' awareness, learning from previous early published studies and therefore drifting their practice toward lower risk groups; (3) improvement in technology, that has become less invasive and therefore, gaining more credibility.[48] Another reason for this may be that the most recent studies are not powered to assess mortality; in earlier studies, mortality was considered the most relevant endpoint, but this has changed to

Subgroup	GDHT Events	GDHT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Fluids							
Gan et al. 2002	21	60	38	59	4.7%	0.54 [0 .37, 0.81]	2002
Venn et al. 2002	11	30	21	29	3.4%	0.51 [0.30, 0.85]	2002
Conway et al. 2002	5	29	9	28	1.3%	0.54 [0 .20, 1.40]	2002
Walkening et al. 2005	24	64	38	64	5.0%	0.63 [0.43, 0.92]	2005
Nobblet et al. 2006	1	54	8	54	0.3%	0.13 [0.02, 0.97]	2006
Lopes et al. 2007	7	17	12	16	2.6%	0.55 [0.29, 1.04]	2007
Senagore et al. 2009	6	42	4	44	0.9%	1.57 [0.48 , 5.18]	2009
Jammer et al. 2010	51	121	51	120	6.1%	0.99 [0 .74, 1.33]	2010
Brandstrup et al. 2012	23	71	24	71	3.9%	0.96 [0.60, 1.53]	2012
Challand et al. 2012	10	89	13	90	1.9%	0.78 [0 .36, 1.68]	2012
Zhang et al. 2012	12	40	10	40	2.2%	1.20 [0.59, 2.45]	2012
Scheeren et al. 2013	12	36	16	26	3.2%	0.54 [0 .31, 0.94]	2013
Zakhaleva et al. 2013	7	32	19	40	2.1%	0.46 [0.22, 0.96]	2013
Forget et al. 2013	1	10	7	10	0.4%	0.14 [O.Q2 , 0.96]	2013
McKenny et al. 2013	8	51	15	50	2.0%	0.52 [0 .24, 1.12]	2013
Srinivasa et al. 2013	26	37	27	37	6.2%	0.96 [0.72, 1.28]	2013
Subtotal (95% CI)		783		778	46.3%	0.69 [0.57, 0.84]	
Total events	225		312				
Heterogeneity: Tau^2= 0.06 ; Chi^2=27.25, df=15 (*P*=.02); I^2=46%							
Test for overall effect: Z=3.65 (*P*=.0003)							
Fluids and inotropes							
Donati et al. 2007	9	68	27	67	2.4%	0.33 [0 .17, 0.64]	2007
Van der Linden et al. 2010	3	20	2	17	0.5%	1.27 [0.24, 6.76]	2010
Bartha et al. 2012	44	74	43	75	6.4%	1.04 [0.79, 1.36]	2012
Zhang et al. 2013	9	30	16	30	2.6%	0.56 [0 .30, 1.07]	2013
Subtotal (95% CI)		192		189	11.9%	0.66 [0.34, 1.28]	
Total events	65		88				
Heterogeneity: Tau^2=0.31 ; Chi^2=12.69, df=3 (*P*=.005); I^2=76%							
Test for overall effect: Z=1.22 (*P*=.22)							
Fluids and vasopressor							
Forget et al. 2010	32	41	41	41	8.1%	0.78 [0.66, 0.93]	2010
Cecconi et al. 2011	16	20	20	20	7.0%	0.80 [0 .64, 1.02]	2011
Zheng et al. 2013	19	30	30	30	6.4%	0.64 [0.49, 0.84]	2013
Peng et al. 2014	25	40	32	40	6.2%	0.78 [0.59, 1.04]	2014
Subtotal (95% CI)		131		131	27.7%	0.76 [0.68, 0.85]	
Total events	92		123				
Heterogeneity: Tau^2=0.00 ; Chi^2=1.98, df=3 (*P*=.58); I^2=0%							
Test for overall effect: Z=4.77 (*P*<.00001)							
Fluids, inotropes and vasopressor							
Benes et al. 2010	18	60	35	50	4.3%	0.43 [0.28, 0.66]	2010
Mayer et al. 2010	6	30	15	30	1.8%	0.40 [0.18, 0.89]	2010
Salzwedel et al. 2013	52	79	72	81	7.9%	0.74 [0.62, 0.88]	2013
Subtotal (95% CI)		169		161	14.1%	0.54 [0.32, 0.89]	
Total events	76		122				
Heterogeneity: Tau^2=0.14 ; Chi^2=8.64, df=2 (*P*=.01); I^2=77%							
Test for overall effect: Z=2.41 (*P*=.02)							
Total (95% CI)		1275		1259	100.0%	0.70 [0.62,0.79]	
Total events	458		645				
Heterogeneity: Tau^2=0.04 ; Chi^2=53.21, df=26 (*P*=.001); I^2=51%							
Test for overall effect: Z=5.82 (*P*<.00001)							
Test for subgroup differences: Chi^2=2.31, df=3 (*P*=.51); I^2=0%							

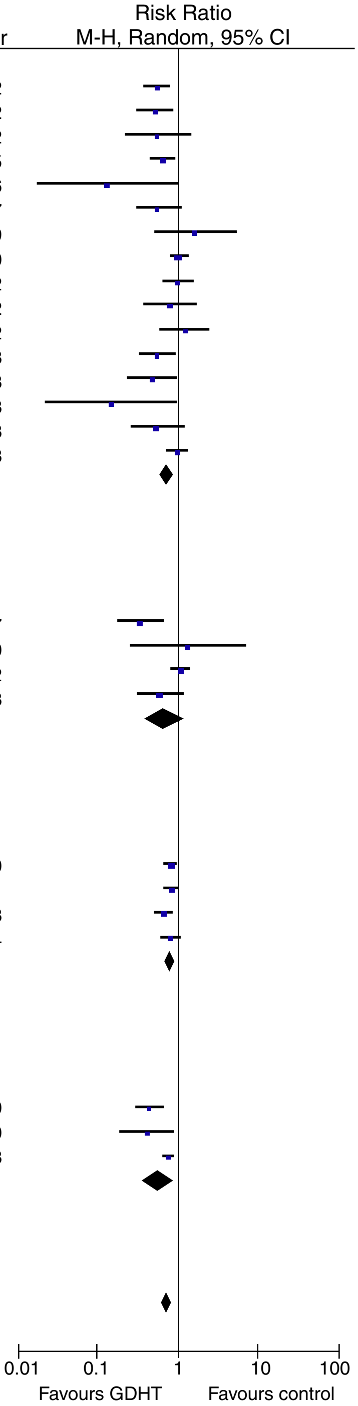


Figure 6 Effect of GDHT in the protocol group vs control group on overall complications grouped by therapy.

length of stay and morbidity endpoints with less high-risk patient group, and as a result, have very low or no mortality. However, a reduction in mortality associated with GDHT was demonstrated in groups of extremely high-risk patients (baseline mortality rate of >20%)[49] as well as with long-term follow-up.[50]

Unlike previous meta-analysis, we have not included those studies in which PAC was used, since these studies were published over 10 years, and do not reflect current practice. Grocott et al. meta-analysis[51] included 31 studies with 5292 participants. The results are dominated by a single large RCT with a weight of more than 60% of the overall population in which PAC was used.[52] The present meta-analysis confirms that the use of minimally invasive monitoring is effective and reduces postoperative complications. Postsurgical complications have a dramatic

Subgroup	GDHT Events	GDHT Total	Control Events	Control Total	Weight	Risk ratio M–H, Random, 95% CI	Year
SV maximization							
Conway et al. 2002	5	29	9	28	1.3%	0.54 [0.20, 1.40]	2002
Gan et al. 2002	21	60	38	59	4.8%	0.54 [0.37, 0.81]	2002
Venn et al. 2002	11	30	21	29	3.4%	0.51 [0.30, 0.85]	2002
Walkening et al. 2005	24	64	38	64	5.0%	0.63 [0.43, 0.92]	2005
Nobblet et al. 2006	1	54	8	54	0.3%	0.13 [0.02, 0.97]	2006
Senagore et al. 2009	6	42	4	44	0.9%	1.57 [0.48, 5.18]	2009
Cecconi et al. 2011	16	20	20	20	7.3%	0.80 [0.64, 1.02]	2011
Challand et al. 2012	10	89	13	90	1.9%	0.78 [0.36, 1.68]	2012
Brandstrup et al. 2012	23	71	24	71	4.0%	0.96 [0.60, 1.53]	2012
Bartha et al. 2012	44	74	43	75	6.6%	1.04 [0.79, 1.36]	2012
Srinivasa et al. 2013	26	37	27	37	6.3%	0.96 [0.72, 1.28]	2013
McKenny et al. 2013	8	51	15	50	2.0%	0.52 [0.24, 1.12]	2013
Zakhaleva et al. 2013	7	32	19	40	2.1%	0.46 [0.22, 0.96]	2013
Subtotal (95% CI)		653		661	46.0%	0.73 [0.61, 0.89]	
Total events	202		279				
Heterogeneity: Tau^2=0.05; Chi^2=23.67, df=12 (P=.02); I^2=49%							
Test for overall effect: Z=3.21 (P=.001)							
Preload responsiveness (SVV, PPV, PVI)							
Lopes et al. 2007	7	17	12	16	2.6%	0.55 [0.29, 1.04]	2007
Forget et al. 2010	32	41	41	41	8.4%	0.78 [0.66, 0.93]	2010
Zhang et al. 2012	12	40	10	40	2.2%	1.20 [0.59, 2.45]	2012
Scheeren et al. 2013	12	36	16	26	3.2%	0.54 [0.31, 0.94]	2013
Forget et al. 2013	1	10	7	10	0.4%	0.14 [0.02, 0.96]	2013
Peng et al. 2014	25	40	32	40	6.4%	0.78 [0.59, 1.04]	2014
Subtotal (95% CI)		184		173	23.1%	0.73 [0.59, 0.91]	
Total events	89		118				
Heterogeneity: Tau^2=0.02; Chi^2=7.76, df=5 (P=.17); I^2 =36%							
Test for overall effect: Z=2.78 (P=.005)							
CI>2.5m/min/m^2							
Donati et al. 2007	9	68	27	67	2.4%	0.33 [0.17, 0.64]	2007
Van der linden et al. 2010	3	20	2	17	0.5%	1.27 [0.24, 6.76]	2010
Mayer et al. 2010	6	30	15	30		Not estimable	2010
Benes et al. 2010	18	60	35	50	4.4%	0.43 [0.28, 0.66]	2010
Zheng et al. 2013	19	30	30	30	6.6%	0.64 [0.49, 0.84]	2013
Zhang et al. 2013	9	30	16	30	2.6%	0.56 [0.30, 1.07]	2013
Salzwedel et al. 2013	52	79	72	81	8.2%	0.74 [0.62. 0.88]	2013
Subtotal (95% CI)		287		275	24.6%	0.58 [0.44, 0.76]	
Total events	110		182				
Heterogeneity: Tau^2=0.06; Chi^2=12.59, df=5 (P=.03); I^2 =60%							
Test for overall effect: Z=3.90 (P<.0001)							
ScVO2>75%							
Jammer et al. 2010	51	121	51	120	6.2%	0.99 [0.74, 1.33]	2010
Subtotal (95% CI)		121		120	6.2%	0.99 [0.74, 1.33]	
Total events	51		51				
Heterogeneity: Not applicable							
Test for overall effect: Z=0.06 (P=.96)							
Total (95% CI)		1245		1229	100.0%	0.71 [0.63.0.80]	
Total events	452		630				
Heterogeneity: Tau^2=0.04; Chi^2=50.42, df=25 (P=.002); I^2=50%							
Test for overall effect: Z=5.66 (P<.00001)							
Test for subgroup differences: Chi^2=6.94, df=3 (P=0.07), I^2=56.8%							

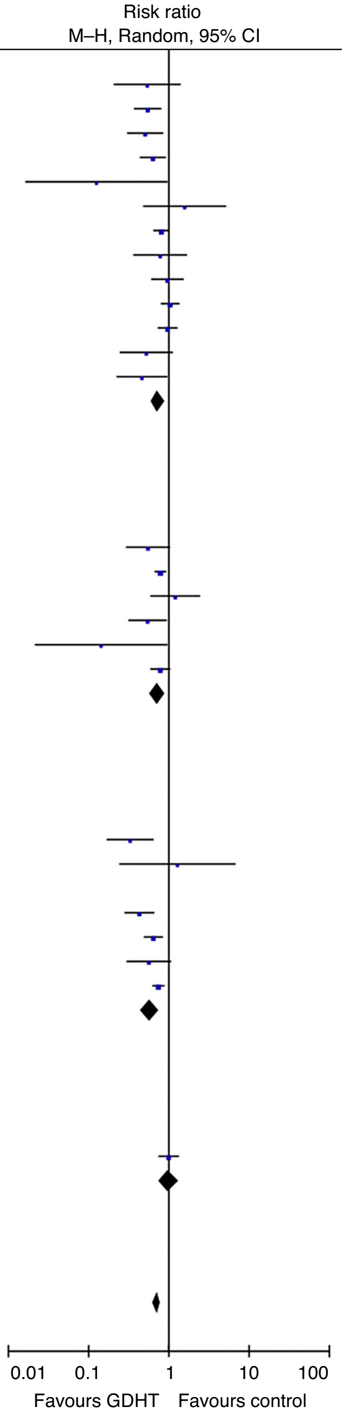
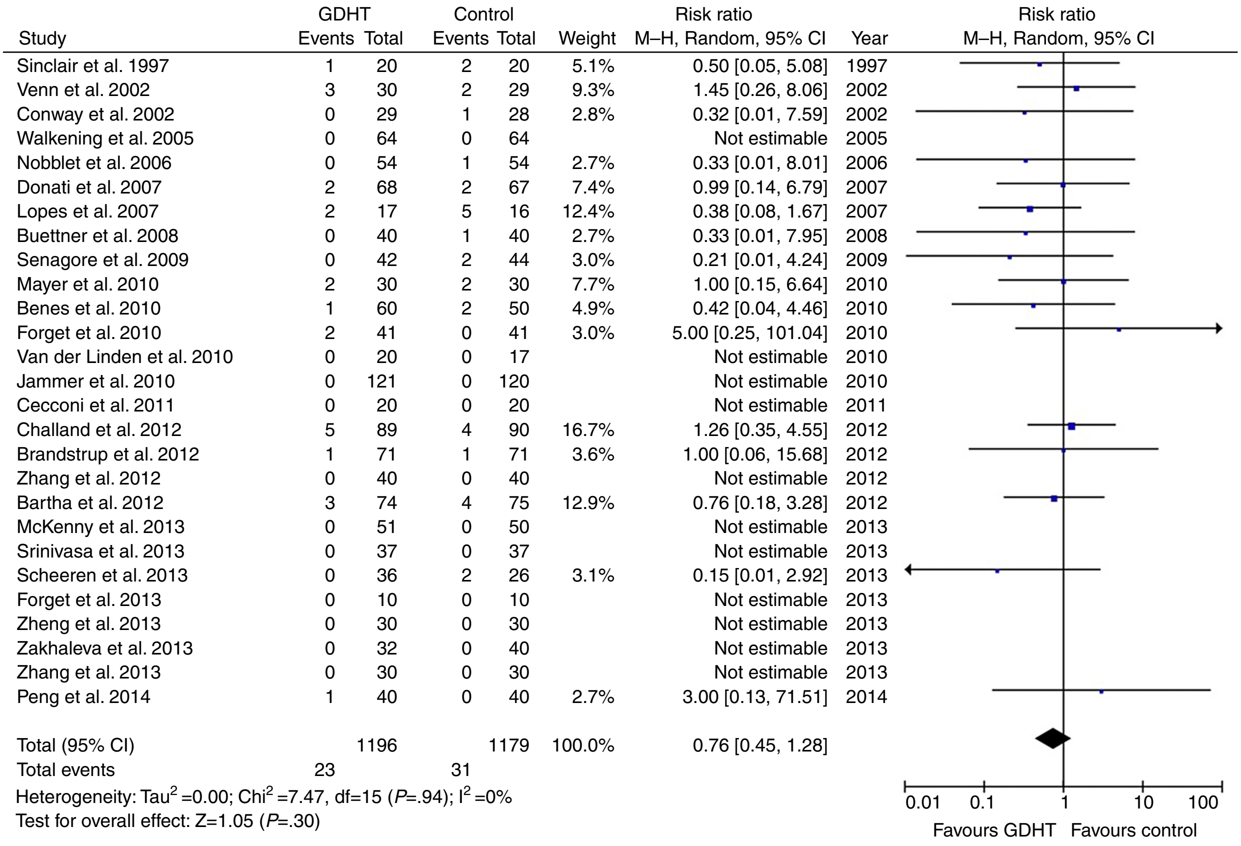


Figure 7 Effect of GDHT in the protocol group vs control group on overall complications grouped by hemodynamic goal. (SV, stroke volume; CI, cardiac index, SVV, stroke volume variation; PPV, pulse pressure variation, PVI®, Pleth Variability Index).

impact on costs. Potential costs savings resulting from GDHT are substantial[53] and seem to be cost effective even with moderate clinical effect.[54] Particularly, ODM technology has been considered favorably by both the NHS Center for evidence-based purchasing in the United Kingdom and United States Agency for Healthcare Research and Quality.[55,56]

Research implications

More studies in which different types of monitoring and different types of algorithms and hemodynamic therapies are compared in patients with different risk in order to achieve optimal hemodynamic goals are needed. In addition, outcome report should be standardized. In this regard,



Study	GDHT Events	GDHT Total	Control Events	Control Total	Weight	Risk ratio M–H, Random, 95% CI	Year
Sinclair et al. 1997	1	20	2	20	5.1%	0.50 [0.05, 5.08]	1997
Venn et al. 2002	3	30	2	29	9.3%	1.45 [0.26, 8.06]	2002
Conway et al. 2002	0	29	1	28	2.8%	0.32 [0.01, 7.59]	2002
Walkening et al. 2005	0	64	0	64		Not estimable	2005
Nobblet et al. 2006	0	54	1	54	2.7%	0.33 [0.01, 8.01]	2006
Donati et al. 2007	2	68	2	67	7.4%	0.99 [0.14, 6.79]	2007
Lopes et al. 2007	2	17	5	16	12.4%	0.38 [0.08, 1.67]	2007
Buettner et al. 2008	0	40	1	40	2.7%	0.33 [0.01, 7.95]	2008
Senagore et al. 2009	0	42	2	44	3.0%	0.21 [0.01, 4.24]	2009
Mayer et al. 2010	2	30	2	30	7.7%	1.00 [0.15, 6.64]	2010
Benes et al. 2010	1	60	2	50	4.9%	0.42 [0.04, 4.46]	2010
Forget et al. 2010	2	41	0	41	3.0%	5.00 [0.25, 101.04]	2010
Van der Linden et al. 2010	0	20	0	17		Not estimable	2010
Jammer et al. 2010	0	121	0	120		Not estimable	2010
Cecconi et al. 2011	0	20	0	20		Not estimable	2011
Challand et al. 2012	5	89	4	90	16.7%	1.26 [0.35, 4.55]	2012
Brandstrup et al. 2012	1	71	1	71	3.6%	1.00 [0.06, 15.68]	2012
Zhang et al. 2012	0	40	0	40		Not estimable	2012
Bartha et al. 2012	3	74	4	75	12.9%	0.76 [0.18, 3.28]	2012
McKenny et al. 2013	0	51	0	50		Not estimable	2013
Srinivasa et al. 2013	0	37	0	37		Not estimable	2013
Scheeren et al. 2013	0	36	2	26	3.1%	0.15 [0.01, 2.92]	2013
Forget et al. 2013	0	10	0	10		Not estimable	2013
Zheng et al. 2013	0	30	0	30		Not estimable	2013
Zakhaleva et al. 2013	0	32	0	40		Not estimable	2013
Zhang et al. 2013	0	30	0	30		Not estimable	2013
Peng et al. 2014	1	40	0	40	2.7%	3.00 [0.13, 71.51]	2014
Total (95% CI)		1196		1179	100.0%	0.76 [0.45, 1.28]	
Total events	23		31				

Heterogeneity: Tau^2 =0.00; Chi^2 =7.47, df=15 (*P*=.94); I^2 =0%

Test for overall effect: Z=1.05 (*P*=.30)

Figure 8 Effect of GDHT in the protocol group vs control group on mortality.

recommendations for the evaluation and standardization of perioperative complications have been recently published.[57] In summary, more studies are needed to demonstrate a significant reduction in mortality associated with GDHT.

Weaknesses in study

The study by Mayer et al.[22] has been under investigation for ethical reasons, the manuscript has not been withdrawn and remains part of the scientific record at the time we searched the literature. To verify potential biases in our results, both the primary and the secondary outcome were re-examined without including the Mayer et al.[22] manuscript and no differences were found.

Many trials were single center trials and only one has investigated more than 100 patients per group.[19] Differences in methodological quality may cause heterogeneity. Smaller studies tend to be conducted and analyzed with less methodological rigor than larger studies, and trials of lower quality also tend to show larger intervention effects.

The major limitation of our analysis is that overall complications were analyzed, regardless of the severity of these and their impact on length of stay and/or mortality. Furthermore, the use of different surgical interventions, different monitoring systems and algorithms adds more heterogeneity to the analysis. Thus, study heterogeneity may reduce the precision of treatment effect estimates and reduce the generalizability of the results of this meta-analysis.

The present meta-analysis is based on studies that describe the incidence of postoperative complications. It has to be recognized that the reporting of complications is not consistent and that the definitions used can differ in type, definition and importance between studies, limiting the applicability of some of our findings.

Furthermore, and unlike previous meta-analysis, the present meta-analysis conducted a global analysis of total

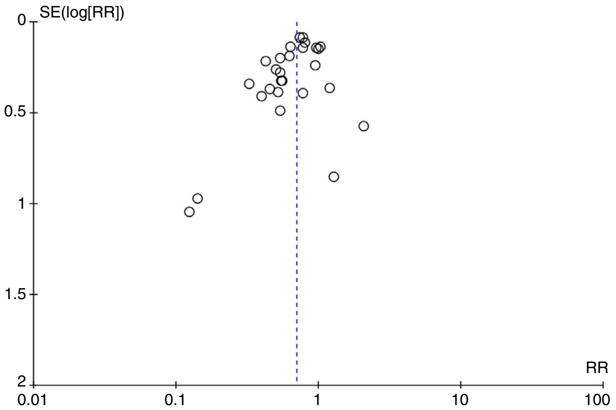


Figure 9 Funnel plot of the published studies in relation to the primary outcome. The measure of precision used is the standard error (SE) of the log RR.

complications, without conducting an organ-specific[47,58] or stratified by risk[49] analysis. Despite these limitations, the results are consistent in most subgroups analyzed and even when the analysis is restricted to those studies with higher quality.

Conclusions

The results of this meta-analysis show that the use of intraoperative GDHT with minimally invasive monitoring decreases postoperative complications in noncardiac surgery, although it was not possible to show a significant decrease in mortality rate. $ScvO_2$ monitoring was not able to decrease the frequency of complications.

Conflicts of interest

The authors declare no conflicts of interest.

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