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SYSTEMATIC REVIEW

Association of conflicts of interest with the results and conclusions of goal-directed hemodynamic therapy research: a systematic review with meta-analysis

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Abstract

Purpose: The association between conflicts of interest (COI) and study results or article conclusions in goal-directed hemodynamic therapy (GDHT) research is unknown.

Methods: Randomized controlled trials comparing GDHT with usual care were identified. COI were classified as industry sponsorship, author conflict, device loaner, none, or not reported. The association between COI and study results (complications and mortality) was assessed using both stratified meta-analysis and mixed effects meta-regression. The association between COI and an article's conclusion (graded as GDHT-favorable, neutral, or unfavorable) was investigated using logistic regression.

Results: Of the 82 eligible articles, 43 (53%) had self-reported COI, and 50 (61%) favored GDHT. GDHT significantly reduced complications on the basis of the meta-analysis of studies with any type of COI, studies declaring no COI, industry-sponsored studies, and studies with author conflict but not on studies with a device loaner. However, no significant relationship between COI and the relative risk (GDHT vs. usual care) of developing complications was found on the basis of meta-regression ($p = 0.25$). No significant effect of GDHT was found on mortality. COI had a significant overall effect ($p = 0.016$) on the odds of having a GDHT-favorable vs. neutral conclusion based on 81 studies. Eighty-four percent of the industry-sponsored studies had a GDHT-favorable conclusion, while only 27% of the studies with a device loaner had the same conclusion grade.

Conclusions: The available evidence does not suggest a close relationship between COI and study results in GDHT research. However, a potential association may exist between COI and an article's conclusion in GDHT research.

Keywords: Conflicts of interest, Goal-directed hemodynamic therapy, Study results, Article conclusions, Association

Introduction

Goal-directed hemodynamic therapy (GDHT) is the management of global and/or regional blood flow guided by predetermined hemodynamic parameters with specified goals for intervention. Since pioneering work in 1988 [1] and 1995 [2], GDHT has revolutionized hemodynamic care in patients receiving anesthesia and surgery or admitted to the intensive care unit.

The efficacy of GDHT among different randomized controlled trials (RCTs) has been inconsistent. For example, in patients with sepsis, one GDHT protocol comprised of maintaining the central venous pressure

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between 8 and 12 mmHg, the mean arterial pressure between 65 and 90 mmHg, and the central venous blood oxygen saturation ≥ 70% significantly reduced mortality from 46.5% to 30.5% ($n = 263$) [3]; however, one decade later, three different RCTs failed to replicate this result using almost the same GDHT protocol in the same patient population with a much larger sample size ($n = 1260–1600$) [4–6]. Similar discrepancies are widespread in GDHT research [7].

The cause of these inconsistencies across GDHT research is unclear but may be related to factors such as the heterogeneity of the patient population [8, 9], the parallel use of the Enhanced Recovery After Surgery (ERAS) protocol [10, 11], the different GDHT protocols used by different studies [12–14], and the timing and type of antibiotics administered to septic patients [15]. However, other causes likely exist that contribute to the inconsistency of the results.

Modern GDHT is characterized by the use of innovative technologies that are noninvasive or minimally invasive and emphasize the monitoring of intravascular volume and cardiac output. These monitors are manufactured by competing companies and incur definite costs. For reasons including but not limited to the competition among different manufacturers and the costs incurred by these novel devices, different types of conflicts of interest (COI) are widespread in GDHT research.

The recent editorials published in *Science* [16] and *Intensive Care Medicine* [17] highlight the concern over the potential confounding effect of COI on biomedical research. A robust body of literature demonstrates that industry-sponsored studies tend to have proindustry results and/or conclusions [18–21]. However, these previous investigations primarily focused on research related to drugs, smoking, alcoholism, and nutrition [18–20], while the association between COI and research related to medical devices has not been adequately studied. Given the rapid implementation of contemporary hemodynamic monitors in acute care, an urgent need exists to understand the influence of COI on GDHT research.

We hypothesize that GDHT research is confounded by COI. RCTs that had specifically compared GDHT with usual care in adult patients under acute care were identified and analyzed to understand the association between COI and GDHT research. We herein differentiate between study results and article conclusions because results are based on objective data, while conclusions can be influenced by personal opinions.

Methods

Literature search

A systematic literature search of published RCTs comparing GDHT with usual care was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22]. A medical librarian (A.B.) performed the systematic search of multiple databases after consultation with lead authors and a medical subject heading (MeSH) analysis of key articles provided by the research team. The formal search used relevant controlled vocabulary terms and synonymous free-text words and phrases to capture the concepts of RCT and GDHT. The electronic databases OVID Medline, OVID Embase, PubMed, and Cochrane Trials were searched on October 12, 2017 and July 6, 2018. The strategy used for the last search is presented in Supplemental file 1. Additional studies were identified nonsystematically by screening the reference lists of relevant articles and searching Google Scholar and PubMed.

Study selection

Two investigators (L.Z. and L.M.) independently screened identified references and then performed full-article reviews; conflicts were resolved by consulting a third investigator (Y.A.). The inclusion criteria were as follows: (1) adult patients (≥ 18 years old); (2) comparison between GDHT and usual care; (3) complications, mortality, or length of hospital stay reported as outcome; (4) perioperative or critical care setting; and (5) randomized controlled trial. A study was excluded if it (1) was not a randomized study, (2) was not published in a full-text article, (3) compared two different forms of GDHT instead, and (4) did not report the outcome of interest. GDHT was defined as the management of global and/or regional blood flow or oxygen delivery guided by predetermined hemodynamic parameters with specified goals for intervention. Usual care was defined as the hemodynamic management that is widely accepted as the standard of care but without guidance based on advanced volume or flow monitoring.

Definition of outcomes

Complication was defined as any deviation from the normal postoperative course or organ dysfunction [23–25]. Organ-specific complications include myocardial infarction, congestive heart failure, cardiac arrest, atrial fibrillation or other types of arrhythmia, pulmonary embolus, pneumonia treated with antibiotics, respiratory failure requiring intubation, respiratory insufficiency requiring physiotherapy or oxygen therapy, stroke, transient ischemic attack, postoperative delirium or cognitive decline, renal insufficiency requiring dialysis, acute kidney injury, urinary tract infection requiring antibiotics, hepatic insufficiency, gut hypoperfusion, ileus, disseminated intravascular coagulation, and sepsis. Surgery-related complications refer to surgical site bleeding, infection, anastomotic leakage, stenosis, ischemia, or tissue necrosis. In-study mortality was defined as the mortality reported

by the study, referring to the rate of death in the hospital or at any time point specified by the study. The longest follow-up was used in the meta-analysis when different mortalities at different time points were reported. The length of hospital stay was defined as the total days from admission until the actual day of discharge or the day the patient was deemed fit for discharge.

Classification of conflicts of interest

All eligible articles were independently investigated by two investigators (L.Z. and L.M.) to determine the presence and type of self-reported COI in each article, with special attention focused on disclosure, acknowledgments, and the author's work place. The COI was classified as industry sponsorship, author conflict, device loaner, none, or not reported (Table 1). If an article had different types of COI, the following priority order was used for classification: industry sponsorship > author conflict > device loaner.

Grading of an article's conclusion

The conclusion of each eligible article was graded as GDHT-favorable, neutral, or unfavorable by two investigators (L.Z. and L.M.) independently. An article was determined to have a favorable conclusion if it favored GDHT over usual care, an unfavorable conclusion if it favored usual care over GDHT, and a neutral conclusion otherwise.

Data extraction

The following data were extracted from each eligible article: (1) setting of acute care, (2) number of patients, (3) classification of COI, (4) protocols involving hemodynamic parameters and specific goals, (5) complications, (6) mortality, (7) length of hospital stay, (8) article conclusion grade, (9) study origin, and (10) monitoring device used.

Quality assessment of selected studies

The risk of bias of each study was assessed by the tool established by the Cochrane Collaboration [26]. The following domains were assessed: (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding of participants and personnel (performance bias), (4) blinding of outcome assessment (detection bias), (5) incomplete data outcome (attrition bias), (6) selective reporting (reporting bias), and (7) other bias. A study was rated as having a high risk of bias overall if more than one domain was rated as having a high risk of bias. Publication bias was assessed by visual inspection of the funnel plot, with a symmetrical plot indicating the absence of bias, and an asymmetrical plot indicating the presence of bias.

Synthesis of evidence

The effects of GDHT on complications and mortality were assessed by meta-analysis using RevMan 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The I^2 statistic [27] was calculated to measure the extent of heterogeneity, and the Cochrane Q test statistic was used to assess the statistical significance. A random effects model was used if significant heterogeneity was identified, and a fixed effects model was used otherwise. To quantify the magnitude of the effect size for dichotomous outcomes of complications and mortality, the risk ratio (RR) with a 95% confidence interval (CI) was calculated. A two-sided p value less than 0.05 was considered statistically significant. Forest plots were constructed to help visualize both the result of a single study and the pooled result.

The association between COI and study results, or more specifically whether the therapeutic effect of GDHT varies with different classes of COI, was investigated by both stratified meta-analysis and mixed effects meta-regression analysis. The metafor package [28] implemented in R software was used to perform meta-regression analysis, in which we investigated whether the heterogeneity of complications or mortality among eligible studies (log RR as the dependent outcome variable) is explainable by the COI classification or other study-level factors, including the study publication year, study setting, patient number, device used for hemodynamic monitoring, GDHT protocol, and origin of the study.

Table 1 Classification of self-reported conflicts of interest (COI) in goal-directed hemodynamic therapy research

Self-reported COI	Definition
Industry sponsorship	The entirety or part of the research was funded by industry
Author conflict	One or more coauthor played a role as a paid consultant, advisory board member, speaker, lecturer, or shareholder of the relevant industry
Device loaner	The research devices or supplies were loaned by industry
None	The article declared no COI
Not reported	A statement of COI was not included in the article

The association between COI and an article's conclusion was investigated by logistic regression, in which COI classifications and other study-level factors were treated as independent variables, and the article's conclusion was treated as the dependent outcome variable. The results are expressed in odds ratios (OR) and 95% CIs to indicate the effect of COI on the conclusion (favorable vs. neutral).

Results

Results of literature search

The systematic search yielded 2174 references, and the nonsystematic search identified 15 additional records. Following de-duplication and screening of the title/abstract, 139 studies were retained and underwent a subsequent full-text review. On the basis of the selection criteria, 82 articles were retained for the final synthesis of evidence [2–6, 24, 29–104]. The selection process is detailed in Fig. 1.

Characteristics of eligible articles

The setting, number of patients, monitor used, intervention protocol, and main conclusion of each study are presented in Table 2. These 82 eligible articles were published between 1993 and 2018, with 71 studies being conducted in the perioperative setting, and 11 studies being conducted in the critical care setting. Most studies originated from Europe ($n=46$, 56%). The risks of bias, expressed as the percentages of low, unclear, and high risks of the different domains of all studies included in the meta-analysis, are presented in Fig. 2, while the risks of bias of different domains of each study based on review authors' judgments are detailed in Supplemental file 2. We detected no obvious evidence of publication bias in the studies included in the meta-analysis based on visual assessment of the funnel plots (Supplemental files 3 and 4).

Prevalence of COI

Of the 82 eligible articles, 43 (53%) reported COI (industry sponsorship = 19; author conflict = 13; device loaner = 11), 33 (40%) declared no COI, and 6 (7%) did not include a COI statement (Supplemental file 5). None of the coauthors among these 82 articles were employed by a related industry.

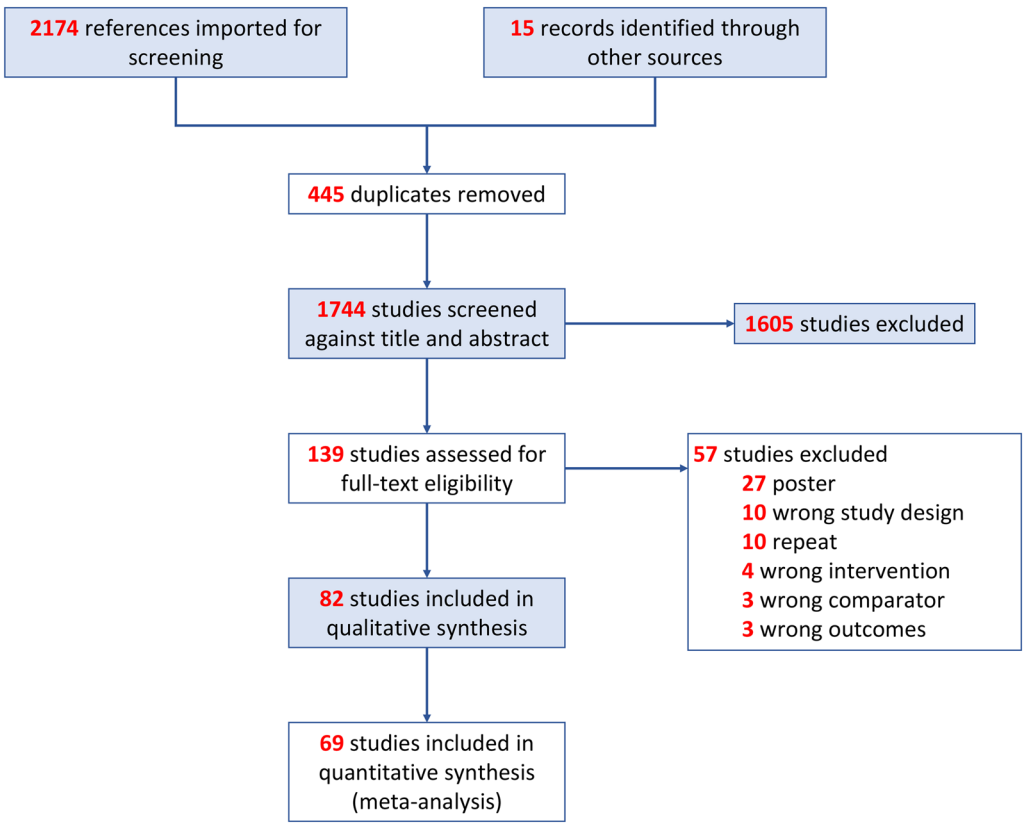

Fig. 1 Article selection process

Table 2 Randomized controlled trials ($n = 82$) comparing goal-directed hemodynamic therapy (GDHT) with usual care in acute care

Year (authors)	Setting	Patients (*n*)		Monitoring device	Parameters	Protocol (specific goals)		Conclusions (GDHT vs. control)
		GDHT	Control			GDHT	Control	
Perioperative setting								
1993 (Boyd et al.) [24]	High-risk surgery	53	54	PAC	DO_2I	$DO_2I > 600$ ml/min/m^2	Usual care	Lower mortality and morbidity
1995 (Mythen and Webb) [2]	Cardiac surgery	30	30	EDM (Deltex)	CVP, SV	CVP increase > 3 mmHg, SV maximization	Usual care	Lower incidence of gut hypoperfusion, fewer complications, and shorter ICU time and LOH
1997 (Bender et al.) [29]	Vascular surgery	51	53	PAC	PCWP, CI, SVRI	PCWP 8–14 mmHg, CI ≥ 2.8 l/min/m^2, SVR ≤ 1100 dyn s/cm^5	Usual care	No benefits
1997 (Sinclair et al.) [30]	Femoral fracture repair	20	20	EDM (Abbott)	△SV, FTc	△SV < 10%, FTc > 0.35	Usual care	Faster recovery and shorter LOH
2002 (Bonazzi et al.) [31]	Vascular surgery	50	50	PAC	PCWP, CI, SVRI, DO_2I	PCWP 10–18 mmHg, CI ≥ 3.0 l/min/m^2, SVR < 1450 dyn s/cm^5, $DO_2I > 600$ ml/min/m^2	Usual care	No benefits
2002 (Gan et al.) [32]	Major abdominal surgery	50	50	EDM (Deltex)	△SV, FTc	△SV < 10%, FTc > 0.35	Usual care	Earlier return of GI function, less PONV, and shorter LOH
2002 (Conway et al.) [33]	Major bowel resection	29	28	EDM (Medicina)	△SV, FTc	△SV < 10%, FTc > 0.35	Usual care	Fewer ICU admissions
2002 (Venn et al.) [34]	Hip fracture repair	30	29	EDM (Deltex)	CVP, △SV, FTc	CVP increase > 3 mmHg, △SV < 10%, FTc 0.35–0.4	Usual care	Faster hospital discharge
2003 (Sandham et al.) [35]	High risk surgery	997	997	PAC	PCWP, CI, HR, MAP, ODI, Hct	PCWP = 18 mmHg, CI 3.5–4.5 l/min/m^2, HR < 120 bpm, MAP > 70 mmHg, ODI 550–600 ml/min/m^2, Hct > 27%	Usual care without PAC use	No benefits
2005 (Wakeling et al.) [36]	Major bowel surgery	64	64	EDM (Deltex)	CVP, △SV	CVP increase > 3 mmHg, △SV < 10%	CVP 12–15 mmHg	Shorter LOH, fewer overall and GI morbidity, and earlier return of GI function
2005 (Pearse et al.) [37]	High-risk general surgery	62	60	LiDCOplus (LiDCO)	△SV, DO_2I	△SV < 10% for > 20 min, $DO_2I > 600$ ml/min/m^2	CVP increase > 2 mmHg for > 20 min	Fewer postoperative complications and shorter LOH

Table 2 continued

Year (authors)	Setting	Patients (*n*)		Monitoring device	Parameters	Protocol (specific goals)		Conclusions (GDHT vs. control)
		GDHT	Control			GDHT	Control	
2006 (Noblett et al.) [38]	Colorectal surgery	51	52	EDM (Deltex)	△SV, FTc	△SV < 10%, FTc > 0.35	Usual care	Shorter LOH, fewer complications, earlier return of GI function
2007 (Lopes et al.) [39]	Major abdominal surgery	17	16	IBPplus (Dixtal)	△PP	△PP < 10%	Usual care	Fewer complications and shorter duration of mechanical ventilation, ICU time, and LOH
2007 (Donati et al.) [40]	High-risk abdominal surgery	68	67	N/A	CVP, MAP, UOP, O_2ERe	CVP = 8–12 cmH_2O, MAP > 80 mmHg, UOP > 0.5 ml/kg/h, O_2ERe ≤ 27%	CVP 8–12 cmH_2O, MAP > 80 mmHg, UOP > 0.5 ml/kg/h	Lower rate of organ failures and shorter LOH
2008 (Harten et al.) [41]	Emergency abdominal surgery	14	15	LiDCOplus (LiDCO)	PPV	PPV < 10%	Usual care	No benefits
2008 (Buettner et al.) [42]	Abdominal surgery	40	40	PiCCOplus (PULSION)	SPV	SPV < 10%	Usual care	No benefits
2008 (Kapoor et al.) [43]	High-risk cardiac surgery	13	14	FloTrac, PreSep (Edwards)	SVV, CI, SVI, SVRI, DO_2I, $ScvO_2$	SVV < 10%, CI 2.5–4.2 l/min/m^2, SVI = 30–65 ml/beat/m^2, SVRI 1500–2500 dyn s/cm^5/m^2, DO_2I 450–600 ml/min/m^2, $ScvO_2$ > 70%	CVP 6–8 mmHg, MAP 90-–100 mmHg, Hct > 30%	Shorter duration of ventilation, ICU stay, and LOH
2009 (Smetkin et al.) [44]	Off-pump coronary surgery	20	20	PiCCOplus (PULSION)	ITBVI, MAP, $ScvO_2$	ITBVI 850–1000 ml/m^2, MAP 60–100 mmHg, $ScvO_2$ > 60%	CVP 6–14 mmHg, MAP 60–100 mmHg	Shorter duration of fit for ICU discharge and postoperative hospital stay
2010 (Van der Linden et al.) [45]	Vascular surgery	20	17	FloTrac (Edwards)	CVP, CI, MAP, Hb	CI > 2.5 l/min/m^2, CVP > 15 mmHg, MAP > 80 mmHg	CVP > 15 mmHg, MAP > 80 mmHg	No benefits
2010 (Benes et al.) [46]	Major abdominal surgery	60	60	FloTrac (Edwards)	CVP, SVV, CI	CVP < 15 mmHg, SVV < 10%, CI > 2.5 l/min/m^2	CVP 8–15 mmHg, MAP > 65 mmHg	Fewer complications
2010 (Jammer et al.) [47]	Colorectal surgery	121	120	N/A	$ScvO_2$	$ScvO_2$ > 75%	Usual care	No benefits
2010 (Mayer et al.) [48]	Major abdominal surgery	30	30	FloTrac (Edwards)	SVV, CI, SVI	SVV < 12%, CI > 2.5 l/min/m^2, SVI > 35 ml/beat/m^2	CVP 8–12 mmHg, MAP > 65 mmHg	Shorter LOH and fewer complications
2011 (Pillai et al.) [49]	Radical cystectomy	32	34	EDM (Deltex)	△SV, FTc	△SV < 10%, FTc > 0.35	Usual care	Better GI outcomes, fewer wound infections

Table 2 continued

Year (authors)	Setting	Patients (*n*)		Monitoring device	Parameters	Protocol (specific goals)		Conclusions (GDHT vs. control)
		GDHT	Control			GDHT	Control	
2011 (Cecconi et al.) [50]	Elective hip surgery	20	20	FloTrac (Edwards)	SV, HR, MAP, DO_2I, SaO_2, Hb	SV maximization, HR < 100 bpm, MAP 60–100 mmHg, DO_2I > 600 ml/min/m^2, SaO_2 > 95%, Hb > 8 mg/dl	MAP > 65 mmHg	Fewer complications
2012 (Brandstrup et al.) [51]	Colorectal surgery	71	79	EDM (Deltex)	△SV	△SV < 10%	Restrictive care (zero balance)	No benefits
2013 (Bartha et al.) [52]	Proximal femoral fracture	70	72	LiDCOplus (LiDCO)	△SV, DO_2I	△SV < 10%, DO_2I > 600 ml/min/m^2	Usual care	No benefits
2013 (Scheeren et al.) [53]	High risk surgery	32	32	FloTrac (Edwards)	△SV, SVV	△SV < 10%, SVV < 10%	Usual care	Less postoperative organ dysfunction
2013 (Salzwedel et al.) [54]	General, gynecological, or urological surgery	79	81	ProAQT (PULSION)	PPV, CI, MAP	PPV < 10%, CI > 2.5 l/min/m^2, MAP > 65 mmHg	Usual care	Fewer complications
2013 (Bisgaard et al.) [55]	Abdominal aortic surgery	32	32	LiDCOplus (LiDCO)	△SVI, DO_2I	△SV < 10% for > 20 min, DO_2I > 600 ml/min/m^2	CVP 8–16 mmHg, HR < 100 bpm or < 20% above baseline, MAP 60–100 mmHg, SaO_2 > 94%, Hb ≥ 9.3 g/dl, T > 36.5 °C	No benefits
2013 (Bisgaard et al.) [56]	Lower limb arterial surgery	20	20	LiDCOplus (LiDCO)	△SVI, DO_2I	△SV < 10% for > 20 min, DO_2I > 600 ml/min/m^2	CVP 8–16 mmHg, HR < 100 bpm or < 20% above baseline, MAP 60–100 mmHg, SaO_2 > 94%, Hb ≥ 9.3 g/dl, *T* > 36.5 °C	Fewer complications
2013 (Bundgaard-Nielsen et al.) [57]	Open radical prostatectomy	21	21	EDM (Deltex)	△SV	△SV < 10%	Usual care	No benefits
2013 (Ramsingh et al.) [58]	Abdominal surgery	18	20	FloTrac (Edwards)	SVV	SVV < 12%	Usual care	Faster return of GI function and shorter LOH
2013 (McKenny et al.) [59]	Major gynecological surgery	51	50	EDM (Deltex)	△SV	△SV < 10%	Usual care	No benefits
2013 (Srinivasa et al.) [60]	Elective colectomy	37	37	EDM (Pharmaco NZ)	△SV, FTc	△SV < 10%, FTc > 0.35	ERAS	No benefits
2013 (Zakhaleva et al.) [61]	Bowel surgery	32	42	EDM (Deltex)	△SV, FTc	△SV < 10%, FTc > 0.35	ERAS	Fewer complications

Table 2 continued

Year (authors)	Setting	Patients (*n*)		Monitoring device	Parameters	Protocol (specific goals)		Conclusions (GDHT vs. control)
		GDHT	Control			GDHT	Control	
2013 (Zheng et al.) [62]	GI surgery	30	30	FloTrac (Edwards)	SVV, CI, SVI, MAP	SVV < 12%, CI > 2.5 l/min/m^2, SVI > 35 ml/beat/m^2, MAP > 65 mmHg	Usual care	Shorter ICU time and LOH, faster return of GI function
2013 (Goepfert et al.) [63]	Cardiac surgery	50	50	PiCCOplus (PULSION)	SVV, CI, ELWI	SVV < 10%, CI > 2.0 l/min/m^2, ELWI ≤ 12 ml/kg	CVP > 8 mmHg, HR 50–110 bpm, MAP > 65 mmHg	Fewer complications and earlier ICU discharge
2013 (Zhang et al.) [64]	Thoracoscopic lobectomy	40	40	FloTrac (Edwards)	SVV, CI	SVV < 10% ± 1%, CI > 2.5 l/min/m^2	HR 60–100 bpm, MAP 65–90 mmHg, UOP > 0.5 ml/kg/h	Less PONV
2014 (Phan et al.) [65]	Colorectal surgery	50	50	EDM	△SVI, FTc	△SVI < 10%, FTc > 0.35	Usual care	No benefits
2014 (Pearse et al.) [66]	Major GI surgery	366	364	LiDCOrapid (LiDCO)	SV	SV maximization	Usual care	No benefits
2014 (Peng et al.) [67]	Major orthopedic surgery	40	40	FloTrac (Edwards)	SVV	SVV < 10% (supine), SVV < 14% (prone)	CVP 8–14 mmHg, HR < 100 bpm, MAP > 65 mmHg, UOP > 0.5 ml/kg/h	Better GI outcomes
2014 (Pestaña et al.) [68]	Major abdominal surgery	72	70	NICOM (Cheetah)	CI, MAP	CI ≥ 2.5 l/min/m^2, MAP ≥ 65 mmHg	Usual care	No benefits
2014 (van Beest et al.) [69]	Major abdominal surgery	20	20	NIRS (Hutchinson), PreSep (Edwards)	CVP, MAP, StO_2 (thenar eminence)	CVP > 8 mmHg, MAP > 65 mmHg, StO_2 ≥ 80%	CVP > 8 mmHg, MAP > 65 mmHg	No benefits
2015 (Lai et al.) [70]	Major abdominal surgery	109	111	LiDCOrapid (LiDCO)	SVV, △SV	SVV < 10%, △SV < 10%	Usual care	No benefits
2015 (Mikor et al.) [71]	Abdominal surgery	38	41	CeVOX (PULSION)	MAP, $ScvO_2$, △ $ScvO_2$	MAP > 60 mmHg, $ScvO_2$ > 75% or $ScvO_2$ decrease < 3%	CVP > 8 mmHg, MAP > 60 mmHg	Fewer complications, improved 28-day survival
2015 (Parke et al.) [72]	Cardiac surgery	70	74	FloTrac and EV-1000 (Edwards)	SVV, CI, MAP	SVV ≤ 13%, CI > 2.5 l/min/m^2, MAP > 65 mmHg	Usual care	Reduced fluid intake, no effect on AKI
2015 (Fellahi et al.) [73]	CABG	43	49	ECOM (ECOM)	SVV, CI	SVV ≤ 11%, CI ≥ 2.4 l/min/m^2	Usual care	Earlier extubation
2015 (Moppett et al.) [74]	Femur fracture repair	51	63	LiDCO (LiDCO)	△SV	△SV < 10%	Usual care	No benefits
2015 (Ackland et al.) [75]	High-risk surgery	95	92	LiDCOplus (LiDCO)	SV, HR, SpO_2, Hb	SV maximization, HR < 100 bpm, SpO_2 ≥ 94%, Hb > 80 g/l, *T* ≥ 36 °C	HR < 100 bpm, SpO_2 ≥ 94%, Hb > 80 g/l, *T* ≥ 36 °C	Similar morbidity but reduced parasympathetic activity postoperatively

Table 2 continued

Year (authors)	Setting	Patients (*n*)		Monitoring device	Parameters	Protocol (specific goals)		Conclusions (GDHT vs. control)
		GDHT	Control			GDHT	Control	
2015 (Correa-Gallego et al.) [76]	Liver resection	69	66	FloTrac (Edwards)	SVV, SBP, Hb, UOP	SVV ≤ 2 SD of baseline measurements, SBP > 90 mmHg, Hb > 7 g/dl, UOP > 25 ml/h	SBP > 90 mmHg, Hb > 7 g/dl, UOP > 25 ml/h	No benefits
2015 (Kumar et al.) [77]	High-risk abdominal surgery	20	20	FloTrac (Edwards)	CI, O_2ER	CI ≥ 2.5 l/min/m^2, O_2ER ≤ 27%	Usual care	No benefits
2015 (Funk et al.) [78]	Abdominal aortic aneurysm repair	20	20	FloTrac (Edwards)	SVV, CI	SVV < 13%, CI > 2.2 l/min/m^2	Usual care	Fewer complications
2015 (Stens et al.) [79]	Elective abdominal surgery	13	18	Nexfin (Edwards)	PPV, CI, MAP	PPV < 12%, CI > 2.5 l/min/m^2, MAP > 70 mmHg	Usual care	No benefits
2015 (Hand et al.) [80]	Head and neck surgery	47	47	FloTrac and EV-1000 (Edwards)	SVV, CI, SVR, MAP	SVV ≤ 13%, CI > 3.0 l/min/m^2, SVR > 800 dyn/s/cm^5, MAP > 75 mmHg or within 110% of baseline	MAP > 70 mmHg or within 80–120% of baseline	Shorter ICU stay
2016 (Broch et al.) [81]	Major abdominal surgery	38	40	Nexfin (Edwards)	PPV, CI, MAP, Hb	PPV ≤ 10%, CI ≥ 2.5 l/min/m^2, MAP ≥ 65 mmHg, Hb ≥ 8 g/dl	CVP < 12 mmHg, MAP ≥ 65 mmHg, Hb ≥ 8 g/dl	No benefits
2016 (Kapoor et al.) [82]	CABG	60	60	FloTrac (Edwards)	SVV, CI, SVI, SVRI, ODI, $ScvO_2$	SVV < 10%, CI 2.5–4.2 l/min/m^2, SVI 30–65 ml/beat/m^2, SVRI 1500–2500 dyn s/cm^5/m^2, ODI 450–600 ml/min/m^2, $ScvO_2$ > 70%	CVP 6–8 mmHg, MAP 90–105 mmHg, UOP > 1 ml/kg/h, SpO_2 ≥ 95%	Shorter duration of ventilator dependency, ICU stay, and LOH
2016 (Osawa et al.) [83]	Cardiac surgery	62	64	LiDCOrapid (LiDCO)	CI, SVI, Hct	CI > 3 l/min/m^2, SVI > 35 ml/beat/m^2, Hct > 28%	Usual care	Fewer major complications and shorter ICU and LOH
2016 (Schmid et al.) [84]	Major abdominal surgery	92	88	PiCCO2 (PULSION)	GEDI, CI, MAP, ELWI	MAP > 70 mmHg, CI > 2.5 l/min/m^2, GEDI > 640 ml/m^2, ELWI < 10 ml/kg	Usual care	No benefits
2017 (Luo et al.) [85]	Craniotomy	73	72	FloTrac (Edwards)	SVV, CI	SVV < 15%, CI > 2.5 l/min/m^2	Usual care	Shorter ICU stay and fewer complications
2017 (Stens et al.) [86]	Moderate-risk abdominal surgery	81	94	ccNexfin (Edwards)	PPV, CI, MAP	PPV < 12%, CI > 2.5 l/min/m^2, MAP > 70 mmHg	Usual care	No benefits

Table 2 continued

Year (authors)	Setting	Patients (*n*)		Monitoring device	Parameters	Protocol (specific goals)		Conclusions (GDHT vs. control)
		GDHT	Control			GDHT	Control	
2017 (Weinberg et al.) [87]	Pancreaticoduodenectomy	26	26	FloTrac, EV1000 (Edwards)	SVV, CI, HR, PaO_2, Hb	SVV < 20%, CI > 2.0 l/min/m^2, HR > 60 bpm, PaO_2 > 100 mmHg, Hb > 8 g/dl, *T* > 36 °C	Usual care	Shorter LOH
2017 (Kaufmann et al.) [88]	Thoracic surgery	48	48	EDM (Deltex)	SVV, CI, MAP	SVV < 10%, CI > 2.5 l/min/m^2, MAP > 70 mmHg	Usual care	Fewer pulmonary complications and shorter LOH
2017 (Elgendy et al.) [89]	Abdominal surgery	43	43	FloTrac (Edwards)	SVV, CI, MAP	SVV < 12%, CI ≥ 2.5 l/min/m^2, MAP > 65 mmHg	CVP 8–12 mmHg, MAP 60–90 mmHg, UOP > 0.5 ml/kg/h	Fewer complications and shorter LOH
2017 (Kapoor et al.) [90]	CABG	66	76	FloTrac, EV-1000 (Edwards)	SVV, CI	SVV < 10%, CI 2.0–4.5 l/min/m^2	CVP > 6–8 mmHg, MAP > 90 mmHg, UOP > 1 ml/kg/h, SpO_2 > 95%, Hct > 30%	Shorter LOH
2017 (Xu et al.) [91]	Thoracotomy with one-lung ventilation	84	84	FloTrac (Edwards)	SVV, CI, MAP	SVV 10–13%, CI > 2.5 l/min/m^2, MAP > 65 mmHg	Usual care	Fewer complications and shorter LOH
2017 (Gómez-Izquierdo et al.) [92]	Laparoscopic colorectal surgery	56	59	EDM (Deltex)	△SV	△SV < 10%	Usual care	No benefits
2018 (Kim et al.) [93]	Head and neck surgery	31	31	FloTrac (Edwards)	SVV, CI, MAP	SVV < 12%, CI ≥ 2.5 l/min/m^2, MAP ≥ 65 mmHg	CVP ≥ 14 mmHg, MAP ≥ 65 mmHg, UOP > 0.5 ml/kg/h	Increase flap survival and shorter ICU stays
2018 (Szturz et al.) [94]	Gastrointestinal surgery	71	69	EDM (Deltex)	CI	CI 2.5–3.8 l/min/m^2	Usual care	Fewer complications
2018 (Gerent et al.) [95]	Cancer surgery	64	64	FloTrac (Edwards)	CI, SVI	CI ≥ 2.5 l/min/m^2, SVI > 35 ml/beat/m^2	HR 70–100 bpm, MAP ≥ 65 mmHg, UOP > 0.5 ml/kg/h, $ScvO_2$ > 70%, Hct > 28%	No benefits
2018 (Corbella et al.) [96]	Kidney transplantation	26	24	EDM (Deltex)	△SV	△SV < 10%	CVP ≤ 12–15 mmHg, SBP > 100 mmHg	No benefits
2018 (Calvo-Vecino et al.) [97]	Low- to moderate-risk surgery	209	211	EDM (Deltex)	△SV, CI, MAP	△SV < 10%, CI > 2.5 l/min/m^2, MAP > 65 mmHg	Usual care	Fewer complications and shorter LOH
Critical care setting								
2001 (Rivers et al.) [3]	Septic shock	130	133	Edwards products (Edwards)	CVP, MAP, UOP, SaO_2, Hct, $ScvO_2$,	CVP ≥ 8–12 mmHg, MAP 65–90 mmHg, UOP ≥ 0.5 ml/kg/h, SaO_2 ≥ 93%, Hct ≥ 30%, $ScvO_2$ ≥ 70%,	CVP ≥ 8–12 mmHg, MAP ≥ 65 mmHg, UOP ≥ 0.5 ml/kg/h	Reduced mortality

Table 2 continued

Year (authors)	Setting	Patients (*n*)		Monitoring device	Parameters	Protocol (specific goals)		Conclusions (GDHT vs. control)
		GDHT	Control			GDHT	Control	
2004 (Holm et al.) [98]	Shock after burn	25	25	Fiberoptic monitoring system (Pulsion)	ITBVI, CI	ITBVI > 800 ml/m^2, CI > 3.5 l/min/m^2	Usual care	No benefits
2006 (Lin et al.) [99]	Septic shock	108	116	N/A	CVP, MAP, UOP	CVP ≥ 8–12 mmHg, MAP ≥ 65 mmHg, UOP ≥ 0.5 ml/kg/h	Usual care	Quicker reversal of shock, reduced mortality, fewer complications
2007 (Chytra et al.) [100]	Multi-trauma	80	82	EDM (Arrow International)	△SV, FTc	△SV < 10%, FTc > 0.35	Usual care	Fewer complications and shorter LOH
2011 (Takala et al.) [101]	Hemodynamically unstable patients	199	187	FloTrac (Edwards)	N/A	N/A	N/A	No benefits
2014 (Andrews et al.) [102]	Sepsis	49	54	N/A	CVP, MAP, Hb	CVP > 3 mmHg, MAP > 65 mmHg, Hb > 7 g/dl	Usual care	Increased mortality in patients with hypoxemic respiratory failure
2014 (ARISE) [4]	Septic shock	793	798	Edwards products (Edwards)	CVP, MAP, $ScvO_2$, Hct	CVP 8–12 mmHg, MAP 65–90 mmHg, $ScvO_2$ ≥ 70%, Hct > 30%	Usual care	No benefits
2014 (ProCESS) [6]	Septic shock	439	456	Edwards products (Edwards)	CVP, MAP, $ScvO_2$, Hct	CVP 8–12 mmHg, MAP 65–90 mmHg, $ScvO_2$ ≥ 70%, Hct > 30%	Usual care	No benefits
2015 (Zhang et al.) [103]	Septic shock and/or ARDS	168	182	PiCCO (PULSION)	GEDI, CI, MAP, ELWI	MAP > 60 mmHg, CI > 2.5 l/min/m^2, GEDI < 850 ml/m^2, ELWI < 10 ml/kg	CVP ≥ 8–12 mmHg, MAP 60–100 mmHg	No benefit
2015 (ProMISe) [5]	Septic shock	626	620	Edwards products (Edwards)	CVP, MAP, SBP, $ScvO_2$	CVP ≥ 8 mmHg, MAP > 65 mmHg, SBP > 90 mmHg, $ScvO_2$ ≥ 70%	Usual care	No benefits
2017 (Yu et al.) [104]	COPD with septic shock	34	37	PiCCO (PULSION)	GEDI, MAP	GEDI > 800 ml/m^2, MAP ≥ 65 mmHg	CVP > 12 mmHg, MAP ≥ 65 mmHg	Reduced duration of ICU stay

PAC pulmonary artery catheter, DO_2 oxygen delivery, DO_2I oxygen delivery index, *EDM* esophageal Doppler monitor, *CVP* central venous pressure, *SV* stroke volume, *ICU* intensive care unit, *LOH* length of hospital stay, *PCWP* pulmonary capillary wedge pressure, *CI* cardiac index, *SVRI* systemic vascular resistance index, *FTc* corrected flow time, *GI* gastrointestinal, *PONV* postoperative nausea and vomiting, *ODI* oxygen delivery index, *MAP* mean arterial pressure, *HR* heart rate, *LiDCO* lithium dilution cardiac output, *ΔPP* variation in arterial pulse pressure induced by mechanical ventilation, O_2ERe oxygen extraction estimate, *UOP* urinary output, *PPV* pulse pressure variation, *SPV* systolic pressure variation, *SVI* stroke volume index, $ScvO_2$ central venous blood oxygen saturation, *Hct* hematocrit, *ITBVI* intrathoracic blood volume index, *N/A* information not available, *SVV* stroke volume variation, *SVI* stroke volume index, *ELWI* extravascular lung water index, *NICOM* noninvasive cardiac output monitor, *NIRS* near-infrared spectroscopy, StO_2 tissue oxygen saturation, *CABG* coronary artery bypass grafting, *ECOM* endotracheal cardiac output monitor, SpO_2 pulse oxygen saturation, *Hb* hemoglobin, *T* temperature, *SD* standard deviation, *SVR* systemic vascular resistance, *GEDI* global end-diastolic volume index, SaO_2 arterial blood oxygen saturation, PaO_2 arterial blood oxygen partial pressure, *ARDS* acute respiratory distress syndrome, *COPD* chronic obstructive pulmonary disease, *ERAS* enhanced recovery after surgery

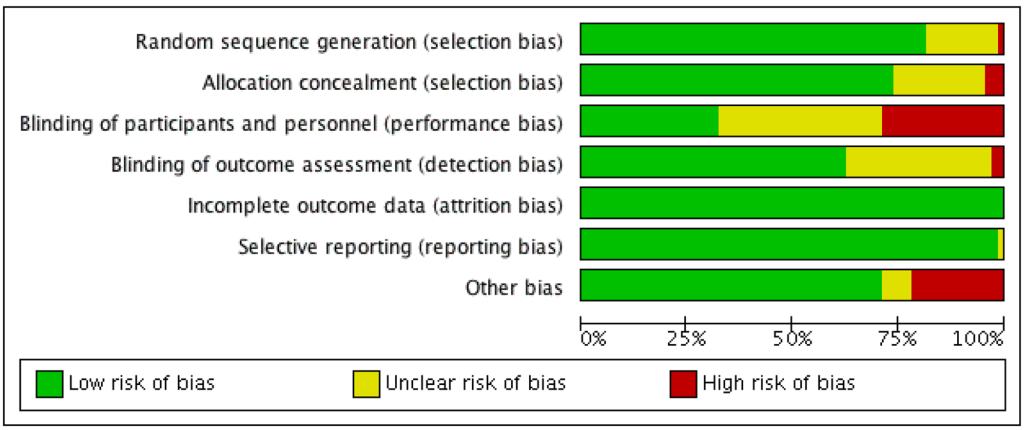

Fig. 2 Risks of bias expressed as percentages of different risks (low, unclear, and high) across all studies included in the meta-analysis

Effects of GDHT on complications per COI classification

Fifty-one studies reported the number of patients with complications, with 3555 patients being managed by GDHT, and 3592 patients being managed by usual care (Supplemental file 5). Compared with usual care, GDHT significantly reduced the risk of developing complications based on these 51 studies (RR = 0.81, 95% CI 0.74–0.88; $p = 0.0001$; Fig. 3a), based on 31 studies with any type of COI (RR = 0.85, 95% CI 0.77–0.93; $p = 0.006$; Fig. 3b), based on 17 studies declaring no COI (RR = 0.76, 95% CI 0.64–0.90; $p = 0.002$; Fig. 3c), based on 12 industry-sponsored studies (RR = 0.83, 95% CI 0.75–0.92; $p = 0.006$; Fig. 3d), and based on 11 studies with author conflict (RR = 0.77, 95% CI 0.64–0.93; $p = 0.007$; Fig. 3e) but not based on eight studies with a device loaner (RR = 1.01, 95% CI 0.86–1.20; $p = 0.90$; Fig. 3f). These effects are comparable as indicated by the overlapping 95% CI ranges.

Effects of GDHT on mortality per COI classification

Forty-six studies reported in-study mortality, with 5942 patients being managed by GDHT, and 6003 patients being managed by usual care (Supplemental file 5). No statistically significant heterogeneity was identified among the various studies. Compared with usual care, GDHT led to a statistically significant change in mortality based on these 46 studies (RR = 0.91, 95% CI 0.85–0.99; $p = 0.02$; Fig. 4a) but not based on 25 studies with any type of COI (RR = 0.93, 95% CI 0.85–1.03; $p = 0.15$; Fig. 4b), 17 studies declaring no COI (RR = 0.89, 95% CI 0.78–1.01; $p = 0.07$; Fig. 4c), eight industry-sponsored studies (RR = 0.92, 95% CI 0.75–1.12; $p = 0.39$; Fig. 4d), seven studies with author conflict (RR = 0.77, 95% CI 0.47–1.26; $p = 0.30$; Fig. 4e), or 10 studies with a device loaner (RR = 0.94, 95% CI 0.85–1.03; $p = 0.20$; Fig. 4f). These effects are comparable as indicated by the overlapping 95% CI ranges.

Results of meta-regression analysis

The raw data used for meta-regression analysis are presented in Supplemental file 6. As there was no significant heterogeneity in the effect of GDHT on mortality among the 46 eligible studies ($I^2 = 0\%$, Fig. 4a), meta-regression was performed to analyze only the effects of GDHT on complications based on the pooled evidence from 51 eligible studies ($I^2 = 53\%$, Fig. 3a). The results (Supplemental file 7) did not identify a significant effect of the COI classification ($p = 0.25$), study setting ($p = 0.55$), patient number ($p = 0.40$), device used ($p = 0.94$), GDHT protocol ($p = 0.99$), or study origin ($p = 0.20$) on the observed study heterogeneity. The only factor that had a significant correlation with the RR of GDHT vs. usual care was the year of study publication ($p = 0.0012$, Fig. 5). As indicated by the significant p values from the tests of residual heterogeneity, it is highly likely that other study-level factors exist that were not considered in our meta-regression but influence the effect of GDHT on complications.

Association between COI and article conclusions

Among the 82 eligible articles, 50 (61%) had a GDHT-favorable conclusion, 31 (38%) had a GDHT-neutral conclusion, and 1 (1%) had a GDHT-unfavorable conclusion (Supplemental file 5). The percentages of articles with specific conclusion grades per COI classification are presented in Fig. 6. Industry-sponsored studies had the highest percentage (84%) of GDHT-favorable conclusions, followed by studies with author conflict (77%), studies declaring no COI (55%), studies including no COI disclosure (50%), and studies with a device loaner (27%). Logistic regression analysis showed that only COI ($p = 0.016$)

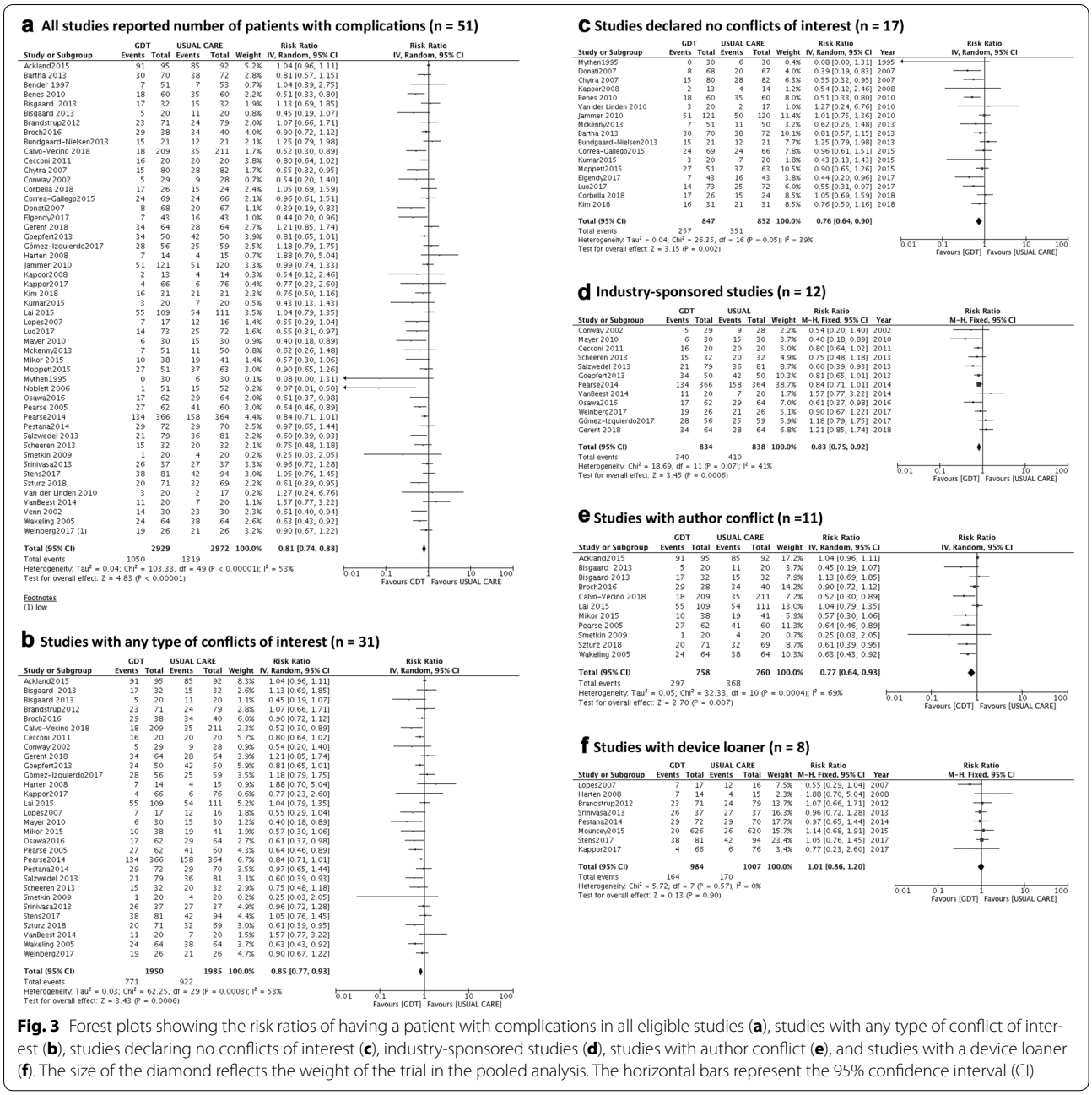

Fig. 3 Forest plots showing the risk ratios of having a patient with complications in all eligible studies (**a**), studies with any type of conflict of interest (**b**), studies declaring no conflicts of interest (**c**), industry-sponsored studies (**d**), studies with author conflict (**e**), and studies with a device loaner (**f**). The size of the diamond reflects the weight of the trial in the pooled analysis. The horizontal bars represent the 95% confidence interval (CI)

and the GDHT protocol ($p=0.022$) were significantly associated with an article's conclusion (GDHT-favorable vs. neutral) in GDHT research (Supplemental file 8).

Discussion

Our study demonstrated that (1) more than half (53%) of RCTs comparing GDHT with usual care have COI; (2) GDHT reduces complications in studies with any type of COI, studies declaring no COI, industry-sponsored studies, and studies with author conflict but not in studies with a device loaner; (3) the heterogeneity of complications among eligible studies cannot be explained by COI, i.e., the therapeutic effect of GDHT on complications does not appear to vary with different classes of COI; (4) GDHT has no effect on mortality on the basis of the meta-analysis of studies with different COI; (5) COI might have a significant overall effect on the odds of having a GDHT-favorable vs. neutral conclusion; and (6) the majority of industry-sponsored studies have a GDHT-favorable conclusion (84%), while the majority of

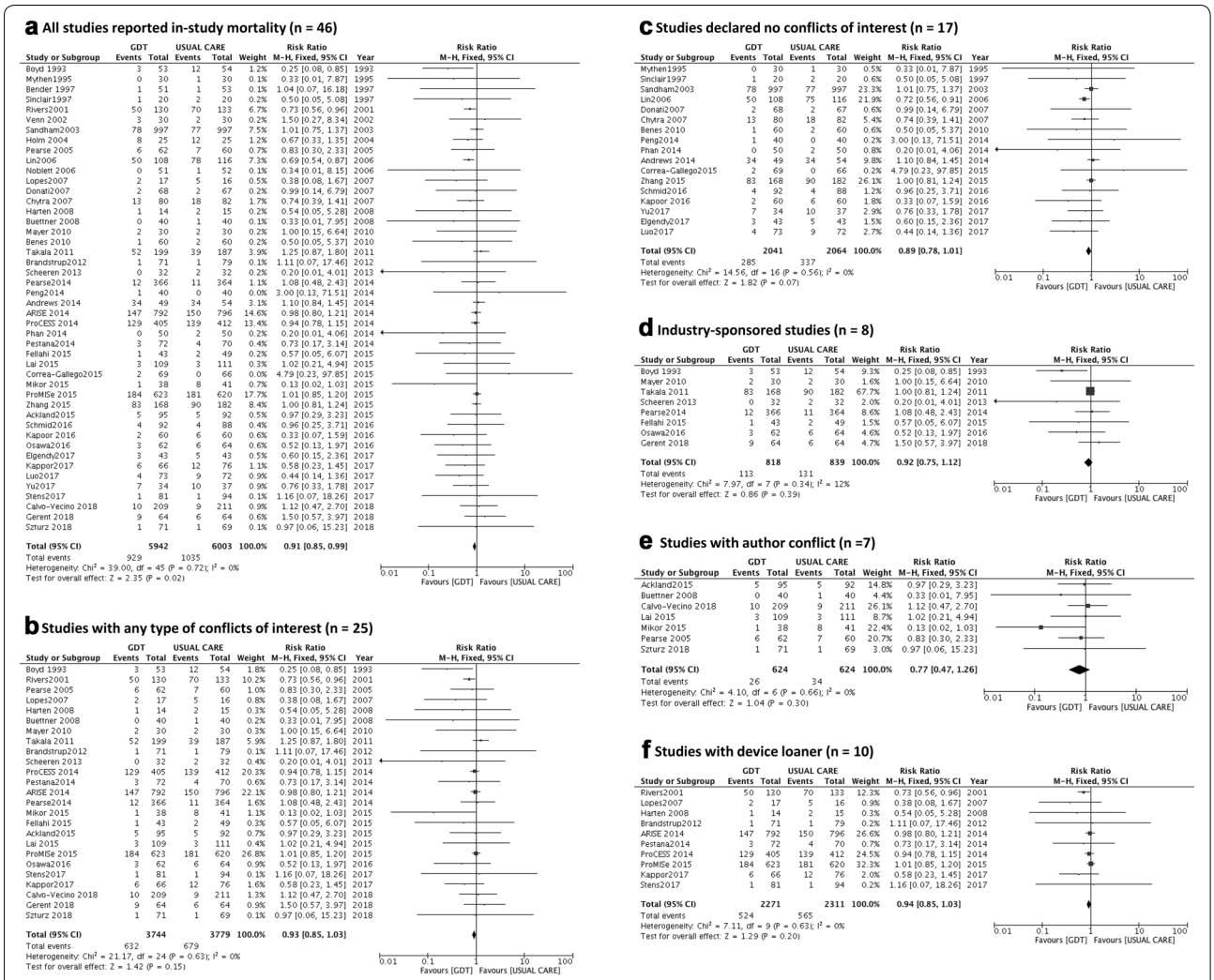

Fig. 4 Forest plots showing the risk ratios of mortality in all eligible studies (**a**), studies with any type of conflict of interest (**b**), studies declaring no conflicts of interest (**c**), industry-sponsored studies (**d**), studies with author conflict (**e**), and studies with a device loaner (**f**). The size of the diamond reflects the weight of the trial in the pooled analysis. The horizontal bars represent the 95% confidence interval (CI)

studies with a device loaner have a GDHT-neutral conclusion (73%). Taken together, the available evidence does not suggest a close relationship between COI and study results; however, it does suggest a potential association between COI and an article's conclusion in GDHT research.

The influence of industry relationships on the outcomes of original research has been scrutinized in various fields of biomedical research [18, 19]. Although the findings diverge, these efforts do highlight concern regarding the potential confounding effect of industry relationships on biomedical research. This concern is corroborated by one recent cumulative meta-analysis concluding that compared with nonindustry-related studies, industry-related studies are more likely to have both favorable efficacy results, based on 25 papers that included 2923 studies (RR = 1.27, 95% CI 1.17–1.37), and favorable conclusions, based on 29 papers that included 4583 studies (RR = 1.34, 95% CI 1.19–1.51) [18]. Aggregation of the results of eight systematic reviews also concluded that the odds of industry-sponsored studies having a proindustry conclusion is 3.60 (95% CI 2.63–4.91) [19].

However, the majority of these previous investigations were based on drug studies, while only a few reports were based on device studies [105–107]. The influence of industry relationships on GDHT research, a field dependent on advanced hemodynamic monitoring devices, has not been reported. One difference between drug and device studies is that devices and reusable supplies can be loaned, which generates a COI different from

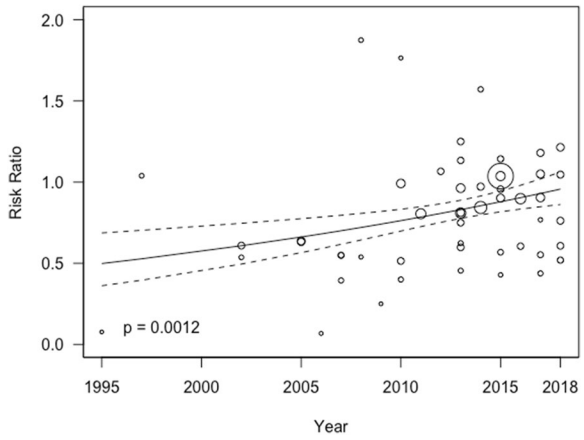

Fig. 5 Bubble plot of the risk ratio of complications vs. the year of study publication

those of industry sponsorship and author conflict. On the basis of this consideration, we classified COI into industry sponsorship, author conflict, and device loaner in our investigation, an approach that differs from that used in previous investigations in which studies were dichotomized into only the industry-sponsored and unsponsored categories. This differentiation is important because our findings suggest that different types of COI may have different associations with the results and conclusions of GDHT research.

Study results and article conclusions are different. Conclusions can be influenced by personal opinions and may or may not be supported by results [21], and differentiating results and conclusions is prudent when investigating the influence of COI on biomedical research. Methods for analysis also differ. In our study, the association between COI and the study results of GDHT research (i.e., complications and mortality) was assessed by stratified meta-analysis and meta-regression, whereas the association between COI and a GDHT research article's conclusion was assessed by logistic regression, which is in accordance with the fact that study results are quantitative, while an article's conclusions are qualitative.

Our investigation revealed that COI are widespread in GDHT research. Although GDHT is a landmark event in intensive hemodynamic care, the inconsistent results and conclusions of GDHT research as well as the associated costs hinder its wide clinical adoption [7]. In addition to industry influence, resource constraints, and the pressure of academic productivity, the urgent need for more evidence may be responsible for the high prevalence of COI in GDHT research. Our investigation found a self-reported incidence of 53%; however, the true incidence might be higher because of underreporting [108]. In our investigation, 55% of the studies declaring no COI had a GDHT-favorable conclusion, which was lower than that of industry-sponsored studies (84%) and studies with author conflict (77%) but higher than that of studies with a device loaner (27%). Although the cause

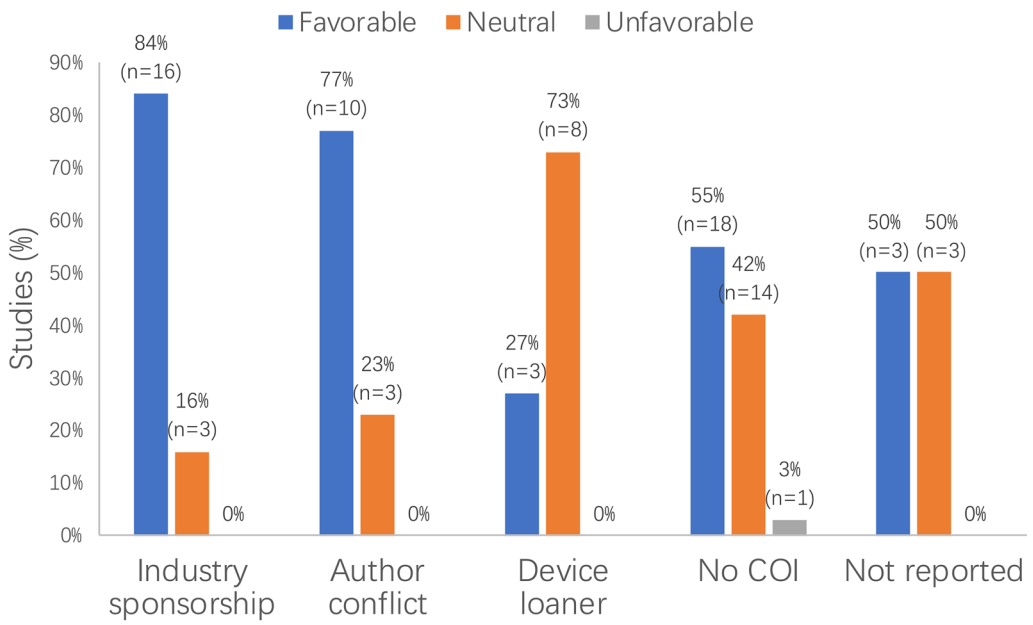

Fig. 6 Percentages of different grades of article conclusions based on the classification of conflicts of interest (COI)

of this discrepancy remains to be elucidated, the possibility of unreliable COI disclosure in GDHT research is suggested.

We found that GDHT can reduce complications but has only a marginal effect on mortality based on the overall evidence. The exact cause of this discrepancy is unknown but may be partially attributable to the difference between outcome measures (i.e., an outcome-dependent effect). The reporting of a complication not only depends on its definition but also on the accuracy and completeness of the information needed for the diagnosis. The diagnosis of a complication made by one investigator may not be made by a different investigator. This potential discrepancy does not exist when using death or survival as the end point, suggesting that the use of objective measures, such as mortality, may result in fewer inconsistencies.

Our meta-analysis did not include studies that reported complications as total events per patient or group instead of the number or percentage of patients in whom complications occurred. Moreover, we were not able to perform a meta-analysis of the length of hospital stay because of the diverse reporting methods (e.g., median vs. mean, whole range vs. interquartile range vs. 95% CI). The differing criteria for the length of hospital stay, variably defined as the time from admission to the actual day of discharge vs. the day the patient was deemed fit for discharge, added another source of heterogeneity.

There are a number of limitations in this study. It should first be noted that the cause–effect relationship between COI and the results or conclusions of GDHT research cannot be determined by this investigation. With the use of meta-analysis, we are able to calculate the pooled estimate of the therapeutic effect with improved precision compared to that of an individual study; however, we cannot guarantee that our estimates have improved accuracy (i.e., less bias) because the number of eligible studies was limited, and we had no access to the raw data from these studies. Our investigation could not determine the influence of nonfinancial COI, such as strongly held beliefs, personal relationships, and desire for career advancement, on GDHT research [109]. This factor in addition to the limited number of quality studies and the potentially missing or inaccurate disclosure of COI may confound the estimation of the association between COI and GDHT research.

It should be noted that multiple tests were performed in our investigation, and we recognize that the family-wise error rate in our study was not necessarily controlled at the 0.05 level, as we did not adjust for raw p values from multiple meta-analyses, meta-regression, or logistic regression. As a result, the statistical significance should be interpreted with caution. Nevertheless, measures such as RRs and 95% CIs should be relied upon to interpret the magnitude of any effects identified in the current study.

In summary, more than half of the RCTs comparing GDHT with usual care are related to industry in the forms of industry sponsorship, author conflict, or device loaner. The available evidence does not suggest a close relationship between COI and study results; however, it does suggest a potential association between COI and an article's conclusion in GDHT research.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-018-5345-z) contains supplementary material, which is available to authorized users.

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Compliance of ethical standards

Conflicts of interest
L. Meng is a consultant for CAS Medical Systems, Inc. The other authors declare no competing interests.

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