Targeting Oliguria Reversal in Goal-Directed Hemodynamic Management Does Not Reduce Renal Dysfunction in Perioperative and Critically Ill Patients: A Systematic Review and Meta-Analysis

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BACKGROUND: We investigated whether resuscitation protocols to achieve and maintain urine output above a predefined threshold—including oliguria reversal as a target—prevent acute renal failure (ARF).
METHODS: We performed a systematic review and meta-analysis using studies found by searching MEDLINE, EMBASE, and references in relevant reviews and articles. We included all studies that compared "conventional fluid management" (CFM) with "goal-directed therapy" (GDT) using cardiac output, urine output, or oxygen delivery parameters and reported the occurrence of ARF in critically ill or surgical patients. We divided studies into groups with and without oliguria reversal as a target for hemodynamic optimization. We calculated the combined odds ratio (OR) and 95% confidence intervals (CIs) using random-effects meta-analysis.
RESULTS: We based our analyses on 28 studies. In the overall analysis, GDT resulted in less ARF than CFM (OR, 0.58; 95% CI, 0.44–0.76; $P < 0.001$; $I^2 = 34.3\%$; $n = 28$). GDT without oliguria reversal as a target resulted in less ARF (OR, 0.45; 95% CI, 0.34–0.61; $P < 0.001$; $I^2 = 7.1\%$; $n = 7$) when compared with CFM with oliguria reversal as a target. The studies comparing GDT with CFM in which the reversal of oliguria was targeted in both or in neither group did not provide enough evidence to conclude a superiority of GDT (targeting oliguria reversal in both protocols: OR, 0.63; 95% CI, 0.36–1.10; $P = 0.09$; $I^2 = 48.6\%$; $n = 9$, and in neither protocol: OR, 0.66; 95% CI, 0.37–1.16; $P = 0.14$; $I^2 = 20.2\%$; $n = 12$).
CONCLUSIONS: Current literature favors targeting circulatory optimization by GDT without targeting oliguria reversal to prevent ARF. Future studies are needed to investigate the hypothesis that targeting oliguria reversal does not prevent ARF in critically ill and surgical patients. (Anesth Analg 2016;122:173–85)

IV fluids are administered to compensate for losses during or after surgery and to increase intravascular volume in hypovolemic patients. Textbooks often recommend using urine output to help guide fluid therapy.[1–3] Oliguria is often viewed as a marker of decreased kidney and organ perfusion and as a trigger t o administer fluids to prevent acute renal failure (ARF) and organ damage. However, oliguria may not be caused solely by a suboptimal hemodynamic status but may be attributed to medications or hormonal effects, which reduce its value as a fluid-loading criterion. Large observational studies have found no relation between intraoperative urine output and subsequent ARF.[4–6] Even in the critically ill, oliguria lacks cannot predict subsequent ARF.[7] Thus, fluids may be administered unnecessarily, which in turn could lead to fluid overloading. Several studies suggest that excess fluid administration is associated with adverse clinical outcomes in patients with ARF.[8–11]

Goal-directed therapy (GDT) strategies in the perioperative and critical care settings target specific hemodynamic parameters related to cardiac output or oxygen delivery along with intensive monitoring. In high-risk surgical or critically ill patients, such strategies are increasingly being used to guide fluid therapy and have been associated with less morbidity and mortality.[12–16] This effect may even be greater when hemodynamic targets are not achieved by additional fluid administration but with inotropic agents.[16]

We hypothesized that including oliguria reversal as a target—defined as achieving and maintaining urine output above a predefined threshold—does not prevent ARF, especially when used alongside cardiac output or oxygen delivery-related hemodynamic parameters. In this systematic review and meta-analysis, we focused on whether including oliguria reversal as a target in the protocols of studies comparing GDT strategies with conventional fluid management (CFM) strategies reduced the incidence of renal dysfunction in surgical and critically ill patients.

METHODS

We performed a systematic literature search to identify all studies comparing GDT with CFM that reported ARF. We

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excluded all animal studies, articles not in English, studies unavailable as full text, and studies with pediatric patients.

We defined GDT as any hemodynamic optimization strategy in the perioperative and critical care setting using parameters related to cardiac output and oxygen delivery, regardless of the device or method used to measure these parameters, and either exclusively or in combination with the classical parameters such as blood pressure, heart rate, and urine output. To minimize the bias of protocol effect, the hemodynamic targets used in CFM had to be clearly defined. Because of variability in the definition of renal dysfunction in the studies we evaluated and a very specific definition for the term acute kidney injury defined by the Acute Dialysis Quality Initiative,[17] we used the term ARF to include a relative or absolute increase in serum creatinine, need for renal replacement therapy, any severity and duration of oliguria, or any combination of the previous, as defined in the selected studies. We defined targeting oliguria reversal as using fluids or vasoactive medication to achieve and maintain urine output above a previously defined threshold. The use of diuretics to increase urine output was not considered a resuscitation method to reverse oliguria because of the difficulty in using urine output to assess oxygen delivery or blood flow after the administration of diuretics. We used urine output thresholds as set by the selected studies.

We accessed the MEDLINE (1966 to present) database via PubMed and the EMBASE (1980 to present) database (last search March 2014) with no limits for publication date or language (Table 1, Supplemental Digital Content 1, http://links.lww.com/AA/B265, which shows the search strategy for the MEDLINE database, and a similar strategy was used to search the EMBASE database). We used the "related articles" function in PubMed to identify eligible studies that were not found by the main search queries. References of studies considered for inclusion and references of review articles were hand-searched for eligible studies. We also used the "cited reference search" function of Web of Knowledge (Thomson Reuters) to find potential studies. We screened the title and abstract of the studies found in the search to see whether GDT was compared with CFM and whether the occurrence of ARF was reported. In case of doubt, we screened the full-text article. Using a predefined study form, one author scored the following variables: total study population, group sizes, type of patients, definition of GDT and CFM, treatment targets in both groups, devices used in GDT to assess hemodynamic parameters, timing of intervention, fluid intake and balance during and after the study period, definition of ARF used, and development of ARF. Once included, the studies were scored according to the Jadad scale on the following: reporting whether the study was randomized and by which method; the method and appropriateness of blinding used; and adequate reporting of withdrawals and dropouts.[18]

Statistical Analysis

All included studies were grouped depending on whether oliguria reversal was included as a target in the study protocol. Studies comparing GDT and CFM where neither treatment protocol involved oliguria reversal were designated as GDT− versus CFM−, studies comparing GDT without oliguria reversal as a target with CFM with oliguria reversal as a target as GDT− versus CFM, and studies comparing GDT with CFM where both treatment arms had oliguria reversal as a target as GDT+ versus CFM+. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each study based on their reported treatment arm, specific sample size, and observed frequencies of ARF.

In the primary analysis, we compared the number of patients with ARF in the 2 treatment arms in all studies as well as separately for each of the 3 study protocol groups (GDT− versus CFM−, GDT− versus CFM+, GDT− versus CFM−) using random-effects meta-analysis. To gain further insight into the role of the treatment period in which the protocol was used (pre-, versus intra- or postoperative), we meta-analyzed studies in which the treatment protocol was used during the preoperative or intraoperative setting separately from those in which the protocol was used during the postoperative or intensive care unit (ICU) setting in a secondary analysis. Studies in which the treatment protocol was used during both periods were included in both analyses. Therefore, we performed a sensitivity analysis in which only studies were included that used the treatment protocols during the postoperative and ICU settings only.

To investigate the potential sources of bias, we also identified subgroups of studies, which were defined based on ARF definition, type of monitoring, differences in fluid intake between GDT and CFM, year of publication, and Jadad score. We compared the ARF definition with the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) and Acute Kidney Injury Network (AKIN) criteria and assigned the studies to 1 of the 3 ARF subgroups: studies defining ARF using RIFLE and AKIN criteria ("exact"), studies defining ARF using a relative increase in serum creatinine near 50% or an absolute serum creatinine increase near 0.3 mg/dL (27 μmol/L) ("similar"), and studies using an absolute cutoff value for serum creatinine or the need for renal replacement therapy without other criteria ("other"). The categories for the type of monitoring were "invasive monitoring," which included studies using pulmonary artery catheters or esophageal Doppler to guide therapy, "noninvasive," which included studies using arterial waveform or pulse contour analysis devices to guide therapy, and "metabolic indices," which included studies using oxygen saturation or lactate to guide therapy without using devices from the 2 other groups. Difference in fluid intake between GDT and CFM was specified as 1 of the 3 categories: studies in which more fluids were infused in GDT than in CFM ("more"), studies in which similar volumes of fluids were infused in GDT and in CFM ("similar"), and studies in which less fluids were infused in GDT than in CFM ("less"). In addition, we created a subgroup including all studies in which more colloids were infused in GDT than in CFM. According to the year of publication, studies were divided into 2 subgroups: published before 2004 and published in or after 2004. The year 2004 was chosen as the cutoff point because the consensus definition and RIFLE criteria by the Acute Dialysis Quality Initiative Group were published in that year. Lastly, studies with a Jadad score >2 formed another subgroup.

All meta-analyses were conducted as random-effects meta-analysis in R (version 3.1.3)[19] using the package metafor (version 1.9.5).[20] Specifically, the Sidik-Jonkman estimator[21] was used in combination with the Knapp and Hartung adjustment[22] to get better estimates of the heterogeneity variance. In studies with a count of zero in one of the treatment arms, 0.5 was added to all frequencies of that study. Heterogeneity between studies was analyzed using the I^2 statistic and interpreted using thresholds as defined in the Cochrane Handbook.[23] Funnel plots were analyzed visually to detect possible publication bias. In the subgroup analysis, pooled OR and CI were calculated without considering heterogeneity between studies, and P values were determined using the Fisher exact test. ORs were considered statistically significant when their 95% CI did not include 1.00 and the corresponding P value was <0.05.

RESULTS

Our search strategy resulted in 1062 articles, of which 588 remained after excluding duplicates (Fig. 1). Of those, 525 were animal studies, pediatric studies, not in English, not available as full-text, or compared different fluid types and were excluded. After reading all full-text articles for eligibility, we excluded another 34 studies because either the hemodynamic parameters were not defined in the conventional arm or no data on ARF were presented. One study, which did report ARF,[24] was excluded because it was not possible to distinguish new occurrences of ARF in each group from those with ARF at randomization. Table 1 shows the characteristics of the resulting 28 included studies, and Table 2 shows the hemodynamic monitoring used in each of the selected studies. Twelve studies[25–36] did not include oliguria reversal as a target in either of the treatment protocols, GDT and CFM, and were allocated to the GDT– versus CFM– group; 7 studies in which only the CFM protocol included oliguria reversal were allocated to the GDT– versus CFM+ group[37–43]; and 9 studies that included oliguria reversal as a target in both the GDT and the CFM protocol were assigned to the GDT+ versus CFM+ group.[44–52] We did not find studies comparing GDT with oliguria reversal as a target with CFM without oliguria reversal as a target, studies comparing GDT with and without oliguria reversal as a target, or studies comparing CFM with and without oliguria reversal as a target. Eight of the 28 studies had a score of <3 on the Jadad scale (Table 3). The allocation of the studies to the subgroups is shown in Table 4. None of the selected studies reported the use of nephrotoxic medication, and only 5 reported the use of diuretics for reasons other than oliguria reversal.[36,40,47,49,52]

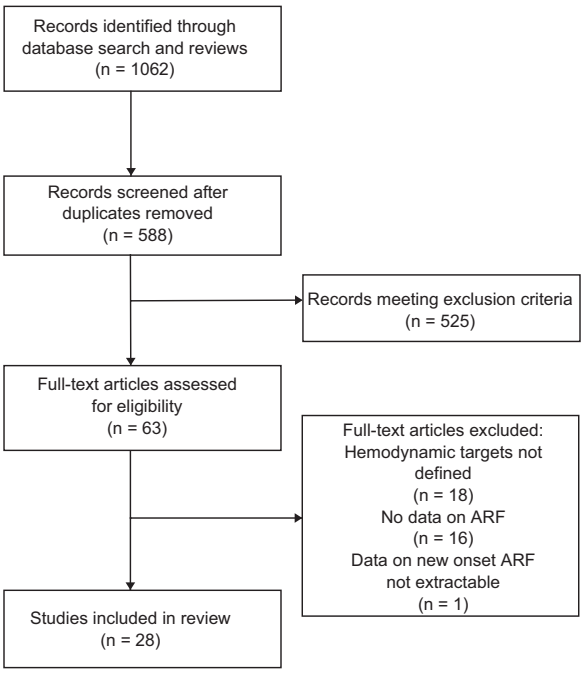

Figure 1. Flowchart of study selection. ARF = acute renal failure.

Primary Analysis

Meta-analysis of all 28 studies showed that overall, GDT was associated with a lower occurrence of ARF than CFM (OR, 0.58; 95% CI, 0.44–0.76; $P < 0.001$; $I^2 = 34.3\%$; $n = 28$). In the GDT– versus CFM+ group, patients who received GDT were less likely to develop ARF than those treated with CFM (OR, 0.45; 95% CI, 0.34–0.61; $P < 0.001$; $I^2 = 7.1\%$; $n = 7$). The studies in the other 2 protocol groups did not provide enough evidence to conclude a superiority of GDT compared with CFM. Forest plots of the primary analysis are shown in Figure 2. The heterogeneity in this analysis ranged from low to moderate. The funnel plot of the overall analysis showed no marked asymmetry, suggesting the absence of publication bias (Figure 1, Supplemental Digital Content 2, http://links.lww.com/AA/B266, showing the funnel plot of studies reporting the occurrence of ARF when comparing GDT with CFM).

Secondary Analysis

Results from the meta-analysis of those studies that targeted oliguria reversal during the pre- and intraoperative setting are shown in Figure 3. Here, the combined analysis showed that GDT was associated with a lower occurrence of ARF compared with CFM (OR, 0.62; 95% CI, 0.42–0.89; $P = 0.01$; $I^2 = 25.1\%$; $n = 21$). All 3 protocol group-specific meta-analyses estimated ORs smaller than 1; however, none of the estimates were significantly different from 1.00.

Meta-analysis of the studies that used fluid management protocols during the postoperative and ICU setting showed that GDT reduced the number of ARF cases (OR, 0.56; 95% CI, 0.39–0.80; $P = 0.004$, $I^2 = 42.6\%$; $n = 14$). The corresponding forest plot is displayed in Figure 4. Here, the OR in the GDT– versus CFM+ group was significantly smaller than 1.00 (OR, 0.46; 95% CI, 0.31–0.70; $P = 0.015$; $I^2 = 1.2\%$; $n = 3$), whereas results in the other 2 groups were inconclusive. Funnel plots for the secondary analyses showed no asymmetry, and hence suggested no publication bias (Figures 2 and 3, Supplemental Digital Content 3 and 4, http://links.lww.com/AA/B267 and http://links.lww.com/AA/B268, showing the funnel plots corresponding to the secondary analysis).

Seven studies[28,37,39,43,46,49,51] in which the treatment protocol was first used in the postoperative or the ICU setting, and not in the pre- or intraoperative setting, were included in the sensitivity analysis. Here, meta-analysis showed that GDT resulted in less ARF than CFM (OR, 0.58; 95% CI,

Table 1. Characteristics of Studies Included

Study	Group	Total number	Type of patient	Exclusion of renal conditions	Timing	Definition of ARF
Berlauk et al. (1991)[25]	GDT– versus CFM–	89	Vascular		Pre	UO <0.5 mL/kg/h for 5 h and/or a change in baseline sCr >44 μmol/L
Valentine et al. (1998)[26]	GDT– versus CFM–	120	Vascular abdominal		Pre, intra, post	Not mentioned in original publication
Wilson et al. (1999)[27]	GDT– versus CFM–	138	General, vascular, abdominal		Pre	Increase in BUN >5 mmol/L from pre- levels
Pölönen et al. (2000)[28]	GDT– versus CFM–	393	Cardiac		Post	UO <750 mL/24 h or increase in sCr >150 μmol/L from previous normal levels
Bonazzi et al. (2002)[29]	GDT– versus CFM–	100	Vascular, abdominal	Yes, advanced CKD	Pre	Worsening of prerenal function with accompanying oliguria requiring high doses of furosemide (>250 mg/d) and/or RRT
Wakeling et al. (2005)[30]	GDT– versus CFM–	128	Abdominal	Yes, renal insufficiency	Intra	UO <500 mL/d, increase in sCr >30%, or urinary catheter in place for a nonsurgical reason
Forget et al. (2010)[31]	GDT– versus CFM–	86	Abdominal	Yes, dialysis	Intra	RRT or UO <0.5 mL/kg for >2 h
WenKui et al. (2010)[32]	GDT– versus CFM–	214	Abdominal		Intra, post	RRT
Cecconi et al. (2011)[33]	GDT– versus CFM–	40	Orthopedic		Intra	UO <500 mL/d, increase in sCr >30%, or urinary catheter in place for a nonsurgical reason
Bartha et al. (2013)[34]	GDT– versus CFM–	149	Orthopedic		Intra	50% increase in baseline sCr and/or UO <0.5 mL/h
Bisgaard et al. (2013)[35]	GDT– versus CFM–	70	Vascular, abdominal	Yes, ESRD	Intra, post	Not mentioned in original publication
Goepfert et al. (2013)[36]	GDT– versus CFM–	92	Cardiac	Yes, dialysis	Intra	AKIN
Bishop et al. (1995)[37]	GDT– versus CFM+	115	Orthopedic		ICU, post	sCr ≥177 μmol/L or with preexisting renal disease a sCr twice that on admission
Gan et al. (2002)[38]	GDT– versus CFM+	100	General, abdominal	Yes, significant renal dysfunction	Intra	UO <500 mL/d, increase in sCr >30%
McKendry et al. (2004)[39]	GDT– versus CFM+	174	Cardiac		Post	Not mentioned in original publication
Benes et al. (2010)[40]	GDT– versus CFM+	120	High risk, abdominal		Intra	UO <500 mL/d or sCr >170 μmol/L or RRT
Mayer et al. (2010)[41]	GDT– versus CFM+	60	High risk		Intra	UO <500 mL/d or RRT
Zhang et al. (2013)[42]	GDT– versus CFM+	80	Pulmonary		Intra	Not mentioned in original publication
ProCESS Investigators (2014)[43]	GDT– versus CFM+	885	Sepsis		ICU	RRT
Shoemaker et al. (1988)[44]	GDT+ versus CFM+	88	High risk		Intra, post	BUN >18 mmol/L, sCr >265 μmol/L
Boyd et al. (1993)[45]	GDT+ versus CFM+	107	High risk	Yes, ARF	Pre, intra, post, ICU	UO <500 mL/24 h
Gattinoni et al. (1995)[46]	GDT+ versus CFM+	762	High risk		ICU	sCr ≥177 μmol/L, RRT, or both
Lobo et al. (2000)[47]	GDT+ versus CFM+	37	High risk, general, abdominal, vascular		Intra, post	Renal SOFA ≥3
Donati et al. (2007)[48]	GDT+ versus CFM+	135	Vascular, abdominal		Intra	sCr >177 μmol/L or RRT
Kapoor et al. (2008)[49]	GDT+ versus CFM+	27	Cardiac		Post	Not mentioned in original publication
Jammer et al. (2010)[50]	GDT+ versus CFM+	241	Abdominal	Yes, sCr >177 μmol/L	Intra	sCr increase >33%
Jhanji et al. (2010)[51]	GDT+ versus CFM+	135	Abdominal		Post, ICU	AKIN
Brandstrup et al. (2012)[52]	GDT+ versus CFM+	150	Abdominal		Intra, post	RRT

GDT– = goal-directed therapy without oliguria reversal as a target; GDT+ = goal-directed therapy with oliguria reversal as a target; CFM– = conventional fluid management without oliguria reversal as a target; CFM+ = conventional fluid management with oliguria reversal as a target; CKD = chronic kidney disease; ESRD = end-stage renal disease; pre = preoperative; intra = intraoperative; post = postoperative; ICU = intensive care unit; ARF = acute renal failure; sCr = serum creatinine; UO = urine output; RRT = renal replacement therapy; SOFA = Sequential Organ Failure Assessment score; BUN = blood urea nitrogen; AKIN = Acute Kidney Injury Network.

0.37–0.90; $P = 0.02$; $I^2 = 30.6\%$; $n = 7$; Figure 4, Supplemental Digital Content 5, http://links.lww.com/AA/B269, which show the forest plot of the sensitivity analysis).

Additional Analysis

Because we did not find any studies directly comparing targeting oliguria reversal with not targeting oliguria reversal

Table 2. Hemodynamic Monitoring Used in Selected Studies

Study	Group	Device	Hemodynamic target	UO criteria	Intervention
Berlauk et al. (1991)[25]	GDT– versus CFM–	PAC	PAOP, CI, SVR		Fluids, vasoactive medication
Valentine et al. (1998)[26]	GDT– versus CFM–	PAC	PCWP, CI, SVR		Crystalloids, dopamine, vasoactive medication
Wilson et al. (1999)[27]	GDT– versus CFM–	PAC	PAOP		Fluids, adrenaline, dopexamine
Pölönen et al. (2000)[28]	GDT– versus CFM–		S_vO_2, lactate		Fluids, dobutamine, vasoactive medication
Bonazzi et al. (2002)[29]	GDT– versus CFM–	PAC	CI, PCWP, SVR, DO_2		Crystalloids, vasoactive medication
Wakeling et al. (2005)[30]	GDT– versus CFM–	Esophageal Doppler	SV		Colloids
Forget et al. (2010)[31]	GDT– versus CFM–	Masimo pulse oximeter	PVI		Colloids, vasoactive medication
WenKui et al. (2010)[32]	GDT– versus CFM–		Lactate		Crystalloids, colloids, dopamine, ephedrine
Cecconi et al. (2011)[33]	GDT– versus CFM–	FloTrac sensor/ Vigileo	SV		Colloids, vasoactive medication, dobutamine
Bartha et al. (2013)[34]	GDT– versus CFM–	LiDCO	SV, DO_2I		Fluids, vasoactive medication
Bisgaard et al. (2013)[35]	GDT– versus CFM–	LiDCO	SVI		Colloids, dobutamine, vasoactive medication
Goepfert et al. (2013)[36]	GDT– versus CFM–	PiCCOplus	SV, GEDI, ELVI, CI		Fluids, vasoactive medication
Bishop et al. (1995)[37]	GDT– versus CFM+	PAC	DO_2I, VO_2I, CI	UO 30–50 mL/h	Volume, dobutamine
Gan et al. (2002)[38]	GDT– versus CFM+	Esophageal Doppler	SV, Ftc	UO <0.5 mL/kg/h	Colloids
McKendry et al. (2004)[39]	GDT– versus CFM+	Esophageal Doppler	SI	UO, no specific goal mentioned	Colloids, blood, vasoactive medication
Benes et al. (2010)[40]	GDT– versus CFM+	FloTrac sensor/ Vigileo	SVV	UO >0.5 mL/kg/h	Colloids, dobutamine
Mayer et al. (2010)[41]	GDT– versus CFM+	FloTrac sensor/ Vigileo	CI, SVI	UO >0.5 mL/kg/h	Crystalloids, colloids, norepinephrine, dobutamine, vasodilators
Zhang et al. (2013)[42]	GDT– versus CFM+	FloTrac sensor/ Vigileo	SVV, CI	UO >0.5 mL/kg/h	Crystalloids, colloids, vasoactive medication
ProCESS Investigators (2014)[43]	GDT– versus CFM+		$S_{cv}O_2$, CVP	UO, no specific goal mentioned	Crystalloids, colloids, vasoactive medication
Shoemaker et al. (1988)[44]	GDT+ versus CFM+	PAC	Hct, P_vO_2, PAP, SVR, PWP, PVR, DO_2, VO_2	UO >30 mL/h	Crystalloids, colloids, vasoactive medication
Boyd et al. (1993)[45]	GDT+ versus CFM+	PAC	DO_2I	UO >0.5 mL/kg/h	Gelatin, dopexamine
Gattinoni et al. (1995)[46]	GDT+ versus CFM+	PAC	CI or S_vO_2	UO >0.5 mL/kg/h	Fluids, vasoactive medication
Lobo et al. (2000)[47]	GDT+ versus CFM+	PAC	DO_2	UO <0.5 mL/kg/h	Fluids, dobutamine
Donati et al. (2007)[48]	GDT+ versus CFM+		S_vO_2, O_2ERe	UO >0.5 mL/kg/h	Fluids, dobutamine
Kapoor et al. (2008)[49]	GDT+ versus CFM+	FloTrac sensor/ Vigileo	CVP, SVV	UO >1 mL/kg/h	Colloids, dopamine or other inotropes
Jammer et al. (2010)[50]	GDT+ versus CFM+		$S_{cv}O_2$	UO >0.5 mL/kg/h	Crystalloids, colloid
Jhanji et al. (2010)[51]	GDT+ versus CFM+	LiDCO	SV	UO >25 mL/h	Fluids, dopexamine
Brandstrup et al. (2012)[52]	GDT+ versus CFM+	Esophageal Doppler	SV	UO >0.5 mL/kg/h	Colloid

GDT– = goal-directed therapy without oliguria reversal as a target; GDT+ = goal-directed therapy with oliguria reversal as a target; CFM– = conventional fluid management without oliguria reversal as a target; CFM+ = conventional fluid management with oliguria reversal as a target PAC = pulmonary artery catheter; PAC+ = pulmonary artery catheter with supranormal hemodynamic targets; pre = preoperative; intra = intraoperative; post = postoperative; SV = stroke volume; DO_2I = oxygen delivery index; PAOP = pulmonary artery occlusion pressure; CI = cardiac index; SVR = systemic vascular resistance; SVI = systemic vascular index; PCWP = pulmonary capillary wedge pressure; DO_2 = oxygen delivery; PVI = pleth variability index; GEDI = global end-diastolic volume index; ELVI = extravascular lung water index; S_vO_2 = mixed venous oxygen saturation; Ftc = corrected flow time; SVV = stroke volume variation; VO_2I = oxygen consumption index; SI = stroke index; O_2Ere = oxygen extraction estimate; $S_{cv}O_2$ = central venous oxygen saturation; CVP = central venous pressure; PvO_2 = venous oxygen pressure; PAP = pulmonary artery pressure; PWP = pulmonary wedge pressure; PVR = pulmonary vascular resistance; Hct = hematocrit; VO_2 = oxygen consumption; UO = urine output.

in each treatment, we conducted additional, pooled analyses based on the subgroups of studies described earlier (Table 4). The results from this analysis are reported in detail in Table 5.

DISCUSSION

In the present study, we performed meta-analyses on 28 studies and found that GDT is superior to CFM with regard to preventing ARF. This effect was the strongest in studies that included oliguria reversal as a target in CFM but not in GDT. Although the comparison of GDT with CFM where both treatments included or excluded oliguria reversal as a target suggested superiority of GDT, available evidence was inadequate to allow a definite conclusion. This lack of clarity may partially be because of the small number of studies that were available for analysis.

In the additional, pooled analysis (Table 5), GDT and CFM strategies targeting oliguria reversal increased the odds of developing ARF when compared with GDT and CFM strategies not targeting oliguria reversal. This finding may partially explain the larger difference between treatments observed in the primary analysis of GDT– versus

Table 3. Risk of Bias Assessment in Selected Studies

Study	Group	Blinding score	Randomization score	Withdrawal score	Score on Jadad scale
Berlauk et al. (1991)[25]	GDT– versus CFM–	0	2	1	3
Valentine et al. (1998)[26]	GDT– versus CFM–	0	2	1	3
Wilson et al. (1999)[27]	GDT– versus CFM–	2	2	0	4
Pölönen et al. (2000)[28]	GDT– versus CFM–	0	2	0	2
Bonazzi et al. (2002)[29]	GDT– versus CFM–	0	2	0	2
Wakeling et al. (2005)[30]	GDT– versus CFM–	2	2	1	5
Forget et al. (2010)[31]	GDT– versus CFM–	0	1	1	2
WenKui et al. (2010)[32]	GDT– versus CFM–	0	2	1	3
Cecconi et al. (2011)[33]	GDT– versus CFM–	0	1	1	2
Bartha et al. (2013)[34]	GDT– versus CFM–	0	2	1	3
Bisgaard et al. (2013)[35]	GDT– versus CFM–	0	2	1	3
Goepfert et al. (2013)[36]	GDT– versus CFM–	0	2	1	3
Bishop et al. (1995)[37]	GDT– versus CFM+	0	1	0	1
Gan et al. (2002)[38]	GDT– versus CFM+	0	2	1	3
McKendry et al. (2004)[39]	GDT– versus CFM+	2	2	1	5
Benes et al. (2010)[40]	GDT– versus CFM+	0	2	1	3
Mayer et al. (2010)[41]	GDT– versus CFM+	0	2	1	3
Zhang et al. (2013)[42]	GDT– versus CFM+	0	2	0	2
ProCESS Investigators (2014)[43]	GDT– versus CFM+	0	2	1	3
Shoemaker et al. (1988)[44]	GDT+ versus CFM+	0	2	0	2
Boyd et al. (1993)[45]	GDT+ versus CFM+	0	1	0	1
Gattinoni et al. (1995)[46]	GDT+ versus CFM+	0	2	1	3
Lobo et al. (2000)[47]	GDT+ versus CFM+	0	2	1	3
Donati et al. (2007)[48]	GDT+ versus CFM+	0	2	1	3
Kapoor et al. (2008)[49]	GDT+ versus CFM+	0	2	1	3
Jammer et al. (2010)[50]	GDT+ versus CFM+	0	2	1	3
Jhanji et al. (2010)[51]	GDT+ versus CFM+	0	2	1	3
Brandstrup et al. (2012)[52]	GDT+ versus CFM+	2	2	1	5

GDT– = goal-directed therapy without oliguria reversal as a target; GDT+ = goal-directed therapy with oliguria reversal as a target; CFM– = conventional fluid management without oliguria reversal as a target; CFM+ = conventional fluid management with oliguria reversal as a target.

Table 4. Allocation of the Selected Studies to Subgroups

Study	Type of monitoring	Relation to RIFLE/AKIN criteria	Colloids infused in GDT relative to CFM	Fluids infused in GDT relative to CFM
Berlauk et al. (1991)[25]	Invasive monitoring	Similar		
Valentine et al. (1998)[26]	Invasive monitoring			More
Wilson et al. (1999)[27]	Invasive monitoring	Other		
Pölönen et al. (2000)[28]	Metabolic indices	Other	More	More
Bonazzi et al. (2002)[29]	Invasive monitoring	Other		More
Wakeling et al. (2005)[30]	Invasive monitoring	Similar	More	More
Forget et al. (2010)[31]	Metabolic indices	Other		Less
WenKui et al. (2010)[32]	Metabolic indices	Other		More
Cecconi et al. (2011)[33]	Noninvasive monitoring	Similar		More
Bartha et al. (2013)[34]	Noninvasive monitoring	Exact		Less
Bisgaard et al. (2013)[35]	Noninvasive monitoring			Similar
Goepfert et al. (2013)[36]	Noninvasive monitoring	Exact	More	More
Bishop et al. (1995)[37]	Invasive monitoring	Other		More
Gan et al. (2002)[38]	Invasive monitoring	Similar	More	More
McKendry et al. (2004)[39]	Invasive monitoring		More	More
Benes et al. (2010)[40]	Noninvasive monitoring	Other	More	More
Mayer et al. (2010)[41]	Noninvasive monitoring	Other	More	Similar
Zhang et al. (2013)[42]	Noninvasive monitoring			Less
ProCESS Investigators (2014)[43]	Metabolic indices	Other		Less
Shoemaker et al. (1988)[44]	Invasive monitoring	Other		
Boyd et al. (1993)[45]	Invasive monitoring	Other		Similar
Gattinoni et al. (1995)[46]	Invasive monitoring	Other		
Lobo et al. (2000)[47]	Invasive monitoring	Other		Similar
Donati et al. (2007)[48]	Metabolic indices	Other		Similar
Kapoor et al. (2008)[49]	Invasive monitoring			More
Jammer et al. (2010)[50]	Metabolic indices	Other		Less
Jhanji et al. (2010)[51]	Noninvasive monitoring	Exact		Similar
Brandstrup et al. (2012)[52]	Invasive monitoring	Other	More	Similar

Invasive monitoring = the use of pulmonary artery catheters or esophageal Doppler; noninvasive monitoring = the use of arterial waveform or pulse contour analysis devices to estimate cardiac parameters; metabolic indices = the use of oxygen saturation or lactate to guide therapy; GDT = goal-directed therapy; CFM = conventional fluid management; AKIN = Acute Kidney Injury Network; RIFLE = Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease.

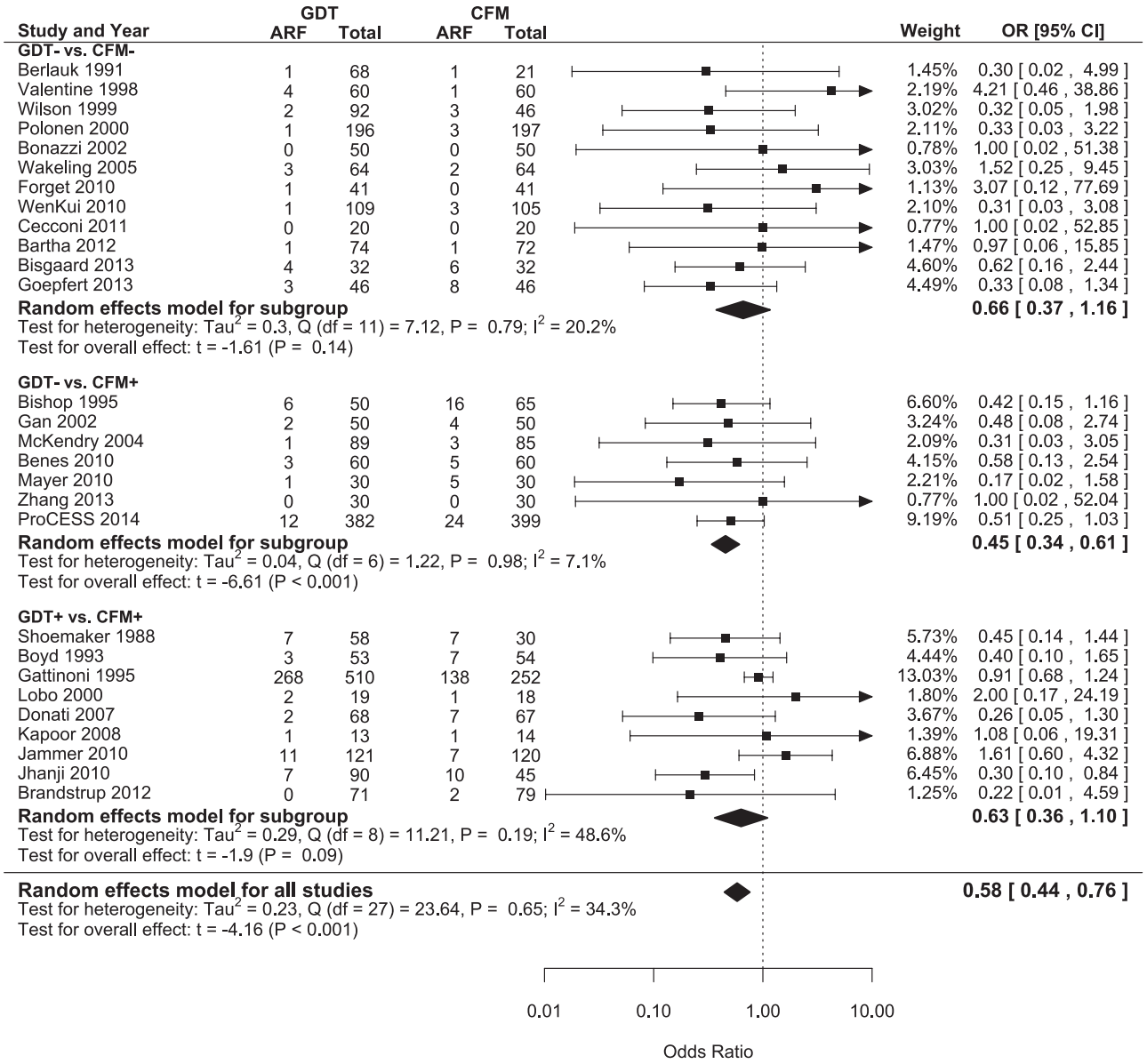

Figure 2. Forest plot of studies reporting occurrence of ARF when comparing goal-directed therapy with CFM. GDT = goal-directed therapy; CFM = conventional fluid management; ARF = acute renal failure; OR = odds ratio; CI = confidence interval; GDT– versus CFM– = goal-directed therapy versus conventional fluid management both without oliguria reversal as a target; GDT– versus CFM+ = goal-directed therapy without oliguria reversal as a target versus conventional fluid management with oliguria reversal as a target; GDT+ versus CFM+ = goal-directed therapy versus conventional fluid management both with oliguria reversal as a target.

CFM+. We found that when GDT– and CFM– groups were compared, the effect on ARF was not different than between GDT+ and CFM+ groups. When combined with the lack of benefit in targeting oliguria reversal in the additional pooled analysis, this difference suggests that targeting oliguria reversal may not reduce the incidence of ARF when compared with strategies that do not target oliguria reversal. Our data support the hypothesis that preventing ARF may not be achieved by striving toward a predefined urine output target.

Several reasons are possible for why urine output may have limited effectiveness as a hemodynamic management goal. Urine output is a parameter that takes time to change and is influenced by factors other than the hemodynamic status. Thus, oliguria can be because of causes that are unaffected by fluid administration or have already been resolved. Therefore, patients may be at risk for fluid overload because of superfluous fluid administration targeted only at urine output. However, strategies that do not target oliguria reversal may limit fluid overload by more precisely targeting variables related to cardiac output or oxygen delivery. Once the hemodynamic status has been optimized, any subsequent occurrence of oliguria is unlikely to be because of hemodynamic causes, favoring the exclusion of oliguria reversal as a target.

GDT patients received a similar or larger volume of fluids than CFM patients in most of the included studies (Table 4); and even in the GDT– versus CFM+ group, most studies

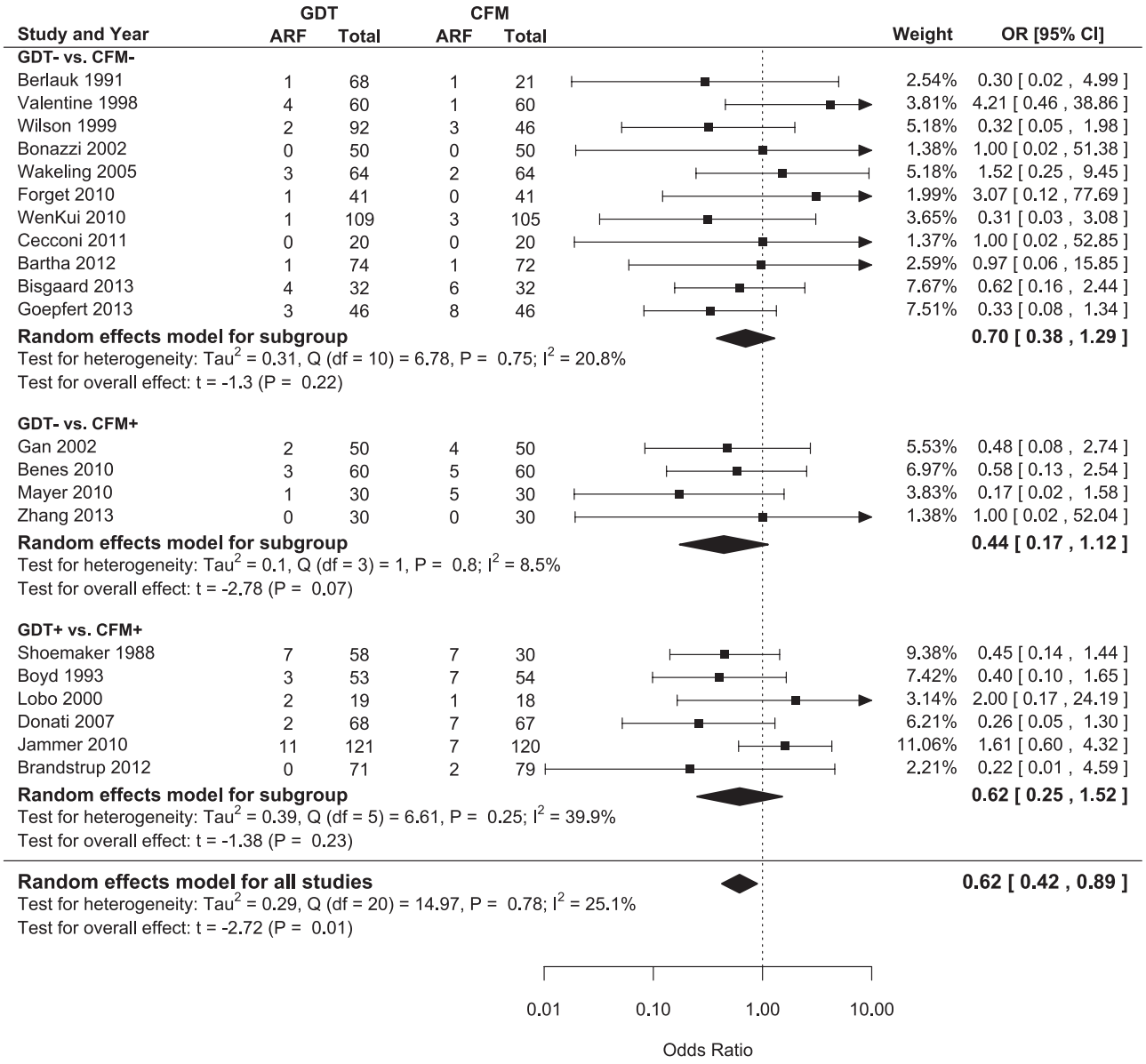

Figure 3. Forest plot of studies reporting the occurrence of ARF when comparing goal-directed therapy with CFM in the preoperative and intraoperative setting. GDT = goal-directed therapy; CFM = conventional fluid management; ARF = acute renal failure; OR = odds ratio; CI = confidence interval; GDT– versus CFM– = goal-directed therapy versus conventional fluid management both without oliguria reversal as a target; GDT– versus CFM+ = goal-directed therapy without oliguria reversal as a target versus conventional fluid management with oliguria reversal as a target; GDT+ versus CFM+ = goal-directed therapy versus conventional fluid management both with oliguria reversal as a target.

used an equal or larger fluid volume in GDT than in CFM. However, in the subset of trials where GDT resulted in less fluid administered than in CFM, targeting oliguria reversal had a larger impact in the CFM than in the GDT group. These data suggest that in GDT trials that focus on limiting fluid administration, targeting oliguria reversal may play a role. For example, additional fluid resuscitation targeted at increasing urine output may result in hypervolemia and subsequent ARF. In contrast, when GDT results in equal or larger fluid volumes than CFM to achieve the predefined hemodynamic targets, any effects of targeting oliguria reversal on the occurrence of ARF may be relatively minor, possibly because of the volume of fluids already administered.

On the basis of our findings, GDT is better suited than CFM for preventing ARF in the preoperative or intraoperative setting. Furthermore, GDT might reduce ARF in the postoperative or ICU setting, but when we excluded studies in which GDT and CFM were already started during the preoperative or intraoperative setting, the data were too limited to draw a definite conclusion. Similar to our findings, the meta-analysis performed by Brienza et al.[12] reported that patients treated with GDT in the postoperative setting had less ARF. However, their meta-analysis differed from ours in several ways. First, they assigned studies according to the commencement of hemodynamic optimization. Second, they pooled the intraoperative and postoperative commencement into one analysis.[12] Finally, they excluded studies with late optimization (i.e., >12 hours postoperative or after the onset of organ failure). It has been suggested that intraoperative and postoperative

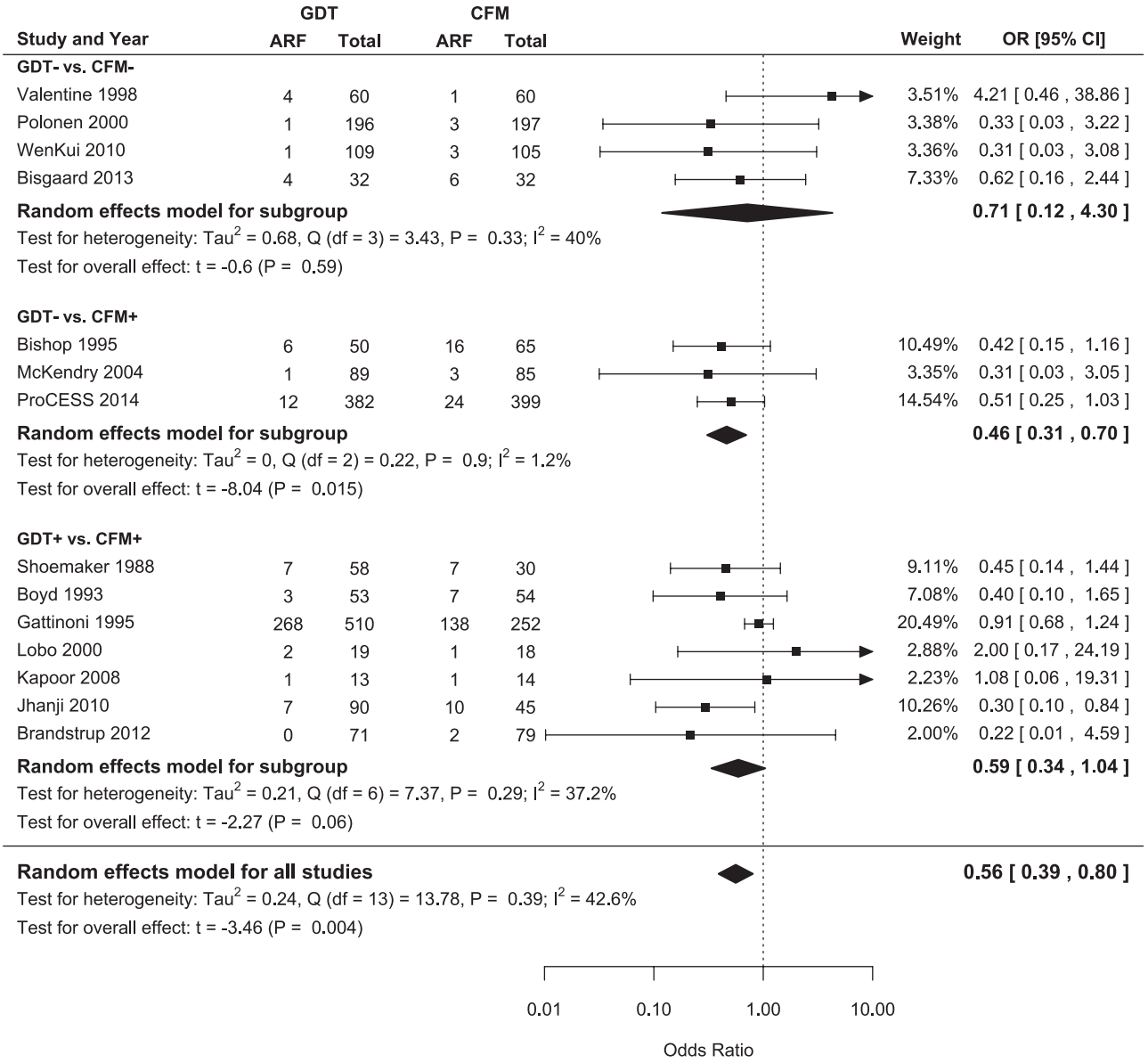

Figure 4. Forest plot of studies reporting the occurrence of ARF when comparing goal-directed therapy with CFM in the postoperative setting and intensive care unit. GDT = goal-directed therapy; CFM = conventional fluid management; ARF = acute renal failure; OR = odds ratio; CI = confidence interval; GDT– versus CFM– = goal-directed therapy versus conventional fluid management both without oliguria reversal as a target; GDT– versus CFM+ = goal-directed therapy without oliguria reversal as a target versus conventional fluid management with oliguria reversal as a target; GDT+ versus CFM+ = goal-directed therapy versus conventional fluid management both with oliguria reversal as a target.

optimization should be separated because of differences in etiology and hemodynamic goals.[53] Consequently, although our study supports the findings of Brienza et al.[12] for the early postoperative phase, our findings also suggest that GDT may prevent ARF when used during the late postoperative phase or in the ICU.

Although we found that GDT was associated with less ARF when oliguria reversal was not included as a target, the effects of such strategies on mortality remain unclear. Because of the relatively low numbers of available studies reporting both ARF and mortality, we considered the risk of selection bias too high and therefore did not perform analyses to investigate the effects of targeting oliguria reversal on mortality.

Our study has several limitations. First, as shown in Table 1, not all the included studies shared the same definition for ARF. Although the heterogeneity found in most of the analyses—as assessed by the I^2 statistic—is low to moderate, most of the included studies are likely to underestimate the occurrence of ARF. Most definitions included an increase in serum creatinine values, a form of oliguria, some form of renal replacement therapy, or a combination of these criteria and thus are quite similar to the RIFLE or AKIN criteria. However, because of the relatively short observation periods, the relatively high cutoff points for serum creatinine, or the need for renal replacement therapy in most studies, smaller increases in serum creatinine may have been overlooked. These small increases are clinically relevant, because of the associated increase in adverse outcomes,[54] and are one of the reasons why the AKIN included small increments in serum creatinine in

Table 5. Direct Comparison Between Targeting and Not Targeting Oliguria Reversal in GDT and CFM

		Targeting oliguria reversal		Not targeting oliguria reversal			
Analysis	**FMS**	**ARF**	**Total**	**ARF**	**Total**	**OR (95% CI)**	***P***
Main[25–52]	GDT	301	1003	46	1543	13.94 (10.05–19.7)	<0.001
	CFM	237	1398	28	754	5.29 (3.52–8.22)	<0.001
Pre-/intraoperative[25–27, 29–36, 38, 40–42, 44, 45, 47, 48, 50, 52]	GDT	25	390	26	826	2.11 (1.15–3.85)	0.013
	CFM	45	538	25	557	1.94 (1.15–3.36)	0.009
Postoperative/ICU[26, 28, 32, 35, 37, 39, 43–47, 49, 51, 52]	GDT	288	814	29	918	16.76 (11.22–25.87)	<0.001
	CFM	209	1041	13	394	7.36 (4.14–14.23)	<0.001
Jadad > 2[25–27, 30, 32, 34–36, 38–41, 43, 46–52]	GDT	291	892	38	1156	14.23 (9.96–20.81)	<0.001
	CFM	207	1219	25	446	3.44 (2.23–5.53)	<0.001
Relation to RIFLE/AKIN definitions							
Exact RIFLE/AKIN definition[34, 36, 51]	GDT	7	90	4	120	2.44 (0.6–11.72)	0.21
	CFM	10	45	9	118	3.43 (1.15–10.4)	0.014
Similar definition[25, 30, 33, 38]	GDT	0	0	6	202		
	CFM	4	50	3	105	2.93 (0.48–20.84)	0.21
Other definitions[27–29, 31, 32, 37, 40, 41, 43–48, 50, 52]	GDT	293	900	27	1010	17.55 (11.64–27.45)	<0.001
	CFM	219	1174	9	439	10.95 (5.59–24.48)	<0.001
Type of hemodynamic monitoring used in the GDT group							
Invasive monitoring[25–27, 29, 30, 37–39, 44–47, 49, 52]	GDT	281	724	19	523	16.8 (10.33–28.79)	<0.001
	CFM	179	647	7	241	12.76 (5.93–32.73)	<0.001
Noninvasive monitoring[33–36, 40–42, 51]	GDT	7	90	12	292	1.96 (0.63–5.62)	0.17
	CFM	20	165	15	170	1.42 (0.66–3.11)	0.37
Metabolic indices[28, 31, 32, 43, 48, 50]	GDT	13	189	15	728	3.5 (1.5–8.06)	0.002
	CFM	38	586	6	343	3.89 (1.61–11.38)	0.001
Difference in fluids infused between GDT and CFM							
More colloids in GDT[28, 30, 36, 38–41, 52]	GDT	0	71	14	535	0.26 (0.015–4.38)	0.39
	CFM	19	304	13	307	1.51 (0.69–3.39)	0.28
Less fluids in GDT[31, 34, 42, 43, 50]	GDT	11	121	14	527	3.65 (1.46–8.93)	0.003
	CFM	31	549	1	113	6.69 (1.09–275.29)	0.029
Similar volume[35, 41, 45, 47, 48, 51, 52]	GDT	14	301	5	62	0.56 (0.18–2.06)	0.34
	CFM	32	293	6	32	0.53 (0.19–1.7)	0.24
More fluids in GDT[26, 28–30, 32, 33, 36–40, 49]	GDT	1	13	24	794	2.67 (0.06–19.47)	0.34
	CFM	29	274	17	542	3.65 (1.9–7.22)	<0.001
Year of publication							
<2004[25–29, 37, 38, 44–47]	GDT	280	640	16	566	26.67 (15.8–48.16)	<0.001
	CFM	173	469	8	374	26.66 (12.94–63.77)	<0.001
≥2004[30–36, 39–43, 48–52]	GDT	21	363	30	977	1.94 (1.04–3.55)	0.025
	CFM	64	929	20	380	1.33 (0.78–2.36)	0.32

For each analysis, the pooled data from all relevant studies targeting oliguria reversal was compared with the pooled data from studies not targeting oliguria reversal—separating data from goal-directed therapy protocols from CFM protocols. OR and 95% CIs were then calculated, and the *P* value was calculated using the Fisher exact test to test whether there was a difference in ARF occurrence between targeting and not targeting oliguria reversal in each protocol. When cells with 0 caused problems in calculating OR or associated CI, 0.5 was added to all cells.

FMS = fluid management strategy; ARF = acute renal failure; OR = odds ratio; CI = confidence interval; ICU = intensive care unit; GDT = goal-directed therapy; CFM = conventional fluid management; AKIN = Acute Kidney Injury Network; RIFLE = Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease.

the RIFLE criteria.[55] We found that the definition used for ARF affects the relation between ARF and targeting oliguria reversal. Studies using the RIFLE and AKIN criteria identified less ARF possibly related to targeting oliguria reversal than using the outdated definitions. It is possible that the RIFLE and AKIN criteria diagnosed more patients with less severe ARF, which would have been missed by the outdated definitions.

Second, the hemodynamic parameters targeted in the GDT protocols and the methods used to evaluate them varied greatly among the included studies (Table 2). This variance was partly because of the large timespan between some studies, which has led to pulmonary artery catheters and esophageal Doppler monitoring being replaced by calibrated or uncalibrated arterial pressure-derived continuous cardiac output devices. Our subgroup analyses suggest that although all these methods assess parameters related to cardiac output or oxygen delivery, the differences between these devices and their practical limitations could have affected patient management and treatment options. Even when using similar devices, the correct interpretation of these indices is also important. Starting treatments based on an erroneous interpretation of hemodynamic parameters could result in more harm to patients in terms of ARF or other outcomes rather than the intended benefit. Furthermore, the potential change in the risk of ARF from earlier studies might also be attributable to improvements in conventional health care practice throughout the decades.

Another limitation of our meta-analysis is the different underlying conditions in the included studies. It is likely, for example, that surgical and septic patients differ regarding goals for hemodynamic optimization. Nevertheless, achieving an optimal hemodynamic state through intensive monitoring of cardiac output or oxygen delivery-derived parameters should result in a similar benefit, despite the underlying conditions. Thus, once hemodynamic status has been optimized, the development of ARF should mostly be determined by risk factors associated with the underlying

condition. Furthermore, any additional fluids given after the hemodynamic status has been optimized can lead to deleterious effects because of fluid overload, which in turn increases the risk of developing ARF.

Finally, the methods used to optimize hemodynamic status differed among the studies. As shown in Table 2, the use of vasopressors and inotropic drugs as well as the type of fluid was not consistent. Colloids such as hetastarch, for example, have been associated with an increased risk for acute kidney injury.[56,57] In most of the selected studies, colloids were used as the primary intervention fluid to achieve and maintain hemodynamic goals, including urine output. Although unlikely, it is possible that asymmetry in colloid use between groups may have affected our results. In recent years, an association between hyperchloremic solutions and an increased risk for acute kidney injury has also been suggested.[58,59] This effect also could have influenced our findings because of differences in fluid compositions used within or between studies. Furthermore, it is important to note that standard random-effects meta-analysis methods may not accurately estimate the between-study variation when only few studies are included in the analysis. We attempted to minimize this problem by using a more robust estimator; nevertheless, results from analyses with only few studies should be interpreted with great care.

Collectively, our data favor targeting circulatory optimization by GDT without targeting oliguria reversal to prevent ARF. This effect of GDT on ARF is present even during the perioperative period or in the ICU. Our findings support the hypothesis that ARF is not prevented by striving toward a predefined urine output target. However, randomized controlled trials are needed to investigate whether targeting oliguria reversal has a deleterious effect on the occurrence of ARF and whether—as our findings suggest—resuscitation protocols that prioritize cardiac output and oxygen delivery are better able to reduce the risk of ARF than those including oliguria reversal as a target.

DISCLOSURES

Name: Mohamud Egal, MD.
Contribution: This author helped design the study, collected data, analyzed the data, and prepared the manuscript.
Attestation: Mohamud Egal attests to the integrity of the original data and the analysis reported in this manuscript and approved the final manuscript.
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Contribution: This author analyzed the data and prepared the manuscript.
Attestation: Nicole S. Erler attests to the analysis reported in this manuscript and approved the final manuscript.
Name: Hilde R. H. de Geus, MD, PhD.
Contribution: This author helped design the study and prepared the manuscript.
Attestation: Hilde R. H. de Geus approved the final manuscript.
Name: Jasper van Bommel, MD, PhD.
Contribution: This author helped design the study, analyzed the data, and prepared the manuscript.
Attestation: Jasper van Bommel is the archival author and approved the final manuscript.
Name: A. B. Johan Groeneveld, MD, PhD, FCCP, FCCM.
Contribution: This author helped design the study, collected data, data analysis, and prepared the manuscript.
Attestation: A. B. Johan Groeneveld attests to the integrity of the original data and the analysis reported in this manuscript and approved the final manuscript.
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