URINE OUTPUT BASED FLUID MANAGEMENT IN THE CRITICALLY ILL:

assessing hypovolemia and preventing hypervolemia

Mohamud Egal

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Urine Output Based Fluid Management in the Critically Ill: assessing hypovolemia and preventing hypervolemia

Urineproductie gebaseerde vochtbeleid in de ernstig zieke patiënt: Beoordelen van ondervulling en voorkomen van overvulling

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CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THESIS

Intravenous fluids have become commonplace since their first use in 1831 during a cholera epidemic (1). In modern times, it is used to hydrate patients who are either not allowed or temporarily unable to eat, restore or maintain intravascular volume, or as a dilutive agent for intravenous medication. In the critically ill patient, intravenous fluid therapy and its management strategies are nothing short of a medical intervention. Nevertheless, fluid type selection, dosage and indication for fluids remain highly variable (2,3), despite two decades of research on fluid type and treatment guidelines.

For fluid type, the discussion revolved around crystalloid versus colloid solutions and balanced versus unbalanced solutions. Crystalloid intravenous solution are generally a water and a salt solution, whereas colloid solutions add an insoluble protein (starch, gelatin, albumin) into a water and salt mixture to increase the colloid osmotic pressure of the intravenous fluid. Colloids were believed to reduce the volume of intravenous fluids needed, though the actual reduction was far less than hypothesized (4-8). Furthermore, governing bodies have issued warnings and discontinued the use of starch-based colloids in critically ill and septic patients due to the increased risk for acute kidney injury (AKI), renal replacement therapy, and mortality (9,10). Balanced solutions – like Ringer's Lactate – consist of a water and salt solution approximating human plasma in concentration, whereas unbalanced solutions – like 0.9% saline, which is the most commonly used intravenous fluid – are considered unphysiological due to their huge variance from human plasma. The high chloride concentration in 0.9% saline is feared to result in AKI, as shown by one before-after study (11). However, more recent studies showed no difference in the occurrence of renal adverse events between a balanced and an unbalanced solution (12).

Ever since the landmark study in 2001 on early goal-directed therapy by Rivers *et al.* (13), aggressive fluid resuscitation has become the foundation for early treatment in septic patients. The Surviving Sepsis Campaign, a collaboration between the European Society of Intensive Care Medicine and the Society of Critical Care Medicine, adapted the treatment algorithm formulated by Rivers *et al.* to decrease mortality in sepsis by streamlining the early management and care (14). In these guidelines, additional fluid challenges are recommended after the initial resuscitation if hemodynamic parameters keep improving i.e. as long as the patient remains fluid responsive. Since then, the fluid management guidelines from the Surviving Sepsis Campaign have become standard care in sepsis, and by extension are used in most – if not all – critically ill patients in some form.

Consequences of fluid management

Despite the reported benefits, this aggressive approach may lead to fluid overload, which has been associated with organ dysfunction and mortality (15-21). Since fluid overload should be avoided, research has focused on targets to guide fluid management and safely administer fluids. Traditional markers such as heart rate, blood pressure have consistently

been shown to be unreliable to guide fluid management, and physical examination suggestive of hypovolemia or inadequate perfusion is a poor predictor of whether a fluid bolus will lead to improvement of these physical signs and restoration of adequate perfusion (22,23). Similarly, central venous pressure is a good indicator of preload, but not whether preload will increase after a fluid bolus (24). Nevertheless, at least 75% of clinicians still use central venous pressure to guide fluid management (3,25).

Since the rationale behind giving fluid boluses to restore or improve perfusion is to increase cardiac output, fluid responsiveness is defined as an increase in cardiac output – or more precisely, stroke volume – after a fluid challenge. To accurately assess the effects of additional fluid boluses, cardiac output, stroke volume and other associated hemodynamic indices need to be measured. Currently, there are various methods to do so, though the transpulmonary thermodilution technique has become the main method due to its relative ease of use and the possibility to measure extravascular lung water, which when elevated signals lung edema. In **chapter 2**, we investigate the effects of positive fluid balance on extravascular lung water formation and whether being fluid responsive protects from increases in extravascular lung water. In **chapter 3**, we analyze whether the occurrence of delayed cerebral ischemia in patients with a subarachnoid hemorrhage is associated with fluid intake and balance, and whether invasive hemodynamic monitoring with the transpulmonary thermodilution technique can reduce the total fluid intake while maintaining adequate cardiac output.

Fluid management guided by targeting urine output

Fluid intake is not the only determinant of fluid balance. Urine output is the only significant physiological method for fluid loss, though in patients with AKI, renal replacement therapy may be used to clear fluids. For this reason, urine output is a widely targeted parameter in the critically ill (3,25), and expert opinion historically advocated to keep urine output above 0.5 ml/kg/h (26). It is viewed as a surrogate marker for renal perfusion by most clinicians, and is commonly used to guide fluid management. The rationale behind this is that when a patient is hypovolemic, renal perfusion decreases, and glomerular filtration pressure drops, leading to less urine output. Neurohormonal systems – i.e. renin-angiotensin-aldosterone, antidiuretic hormone and sympathetic activity – are then activated to restore intravascular volume and maintain glomerular perfusion by increasing renal fluid retention (27). If the hypovolemic state with hypoperfusion persists, this may lead to sustained renal damage and AKI (28). Nevertheless, whether targeting urine output in fluid management strategies has any effect on outcome has not been directly investigated.

In **chapter 4**, we investigate the effects of targeting urine output on AKI occurrence in the available literature on goal-directed fluid management versus conventional fluid management strategies. In **chapter 5**, we investigate what the effects of targeting urine

output are on mortality in the available literature on goal-directed fluid management versus conventional fluid management strategies. To prevent fluid overload, restrictive fluid management strategies have been devised which reduce the total volume of fluids administered to patients. In **chapter 6**, we analyze the effects of targeting urine output on AKI in the available literature on restrictive fluid management versus conventional fluid management strategies.

Fluid management in oliguria

While oliguria may be due to hypovolemia, oliguria in critically ill patients also has other causes which are not responsive to fluids. Physical stress due to pain, surgery or hemodynamic changes may lead to adaptation by neurohormonal changes without the presence of hypovolemia (27). In sepsis, pro-inflammatory cytokines, immune cell activity and tubular stress due to microcirculatory dysfunction may also lead to oliguria (29-31). Simply put, administering fluids without an increase in urine output only further aggravates the disbalance between intake and loss. The inability differentiate between the cause of oliguria at the bedside increases the risk of fluid overload.

For this reason, biomarkers such as neutrophil gelatinase associated lipocalin (NGAL) have been used to determine whether there is actual tubular injury. In **chapter 7**, we assessed whether NGAL can be used to identify treatable oliguric patients within the first few hours of intensive care admission. In **chapter 8**, we address whether fluid therapy affects isolated oliguria in the critically ill, and an increase in urine output after a fluid challenge is associated with cardiac fluid responsiveness or AKI, and the predictors for an increase in urine output and AKI in this population of oliguric critically ill patients.

Aim of the thesis

There appears to be a mismatch between intravenous fluid administration and fluid loss via urine output in the critically ill patient, which leads to fluid overload and related adverse events. The main aim of this thesis is to investigate whether additional fluid administration aimed at improving urine output has the desired effect, whether this effect can be predicted, and whether this effect impacts patients' outcome.

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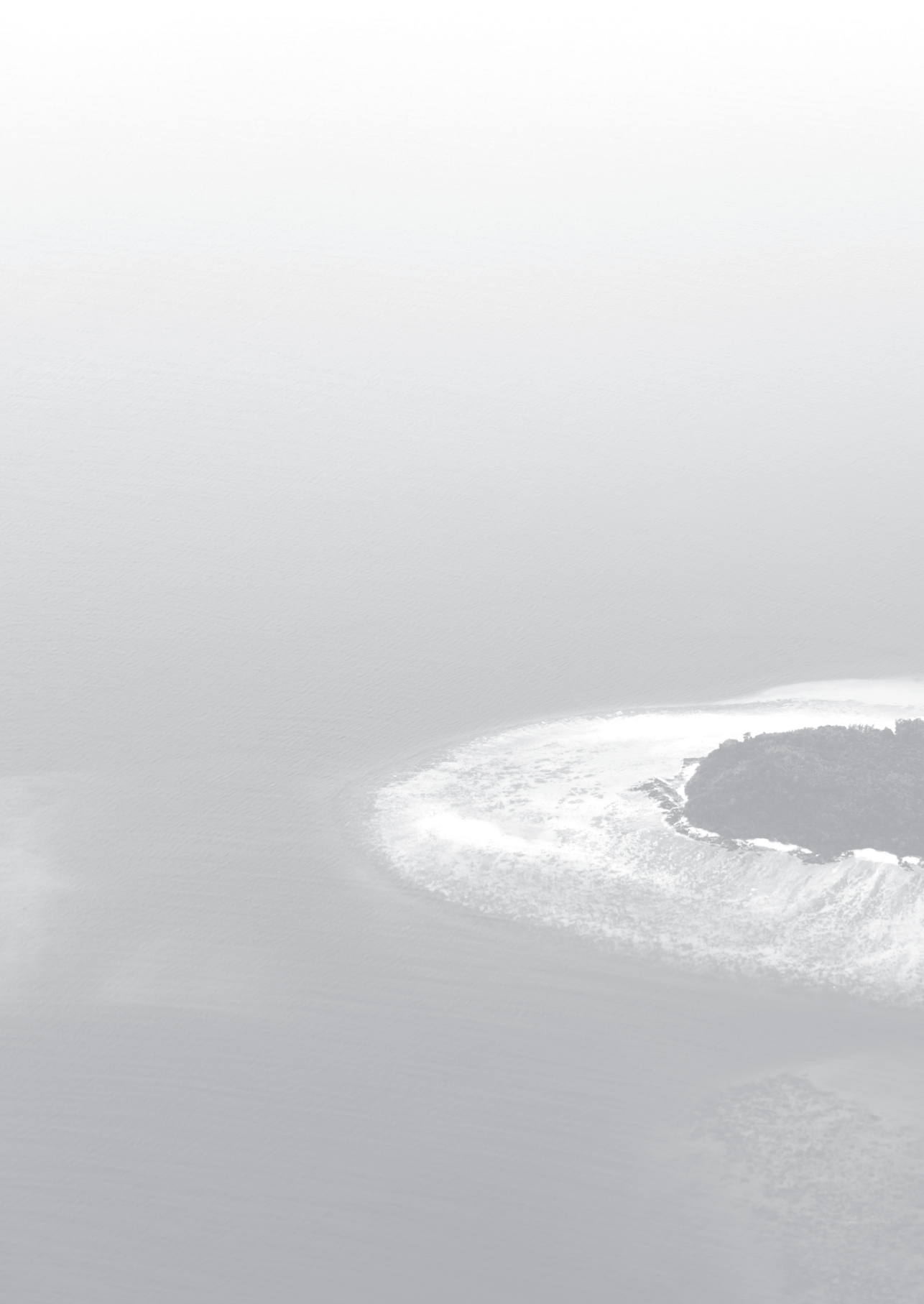
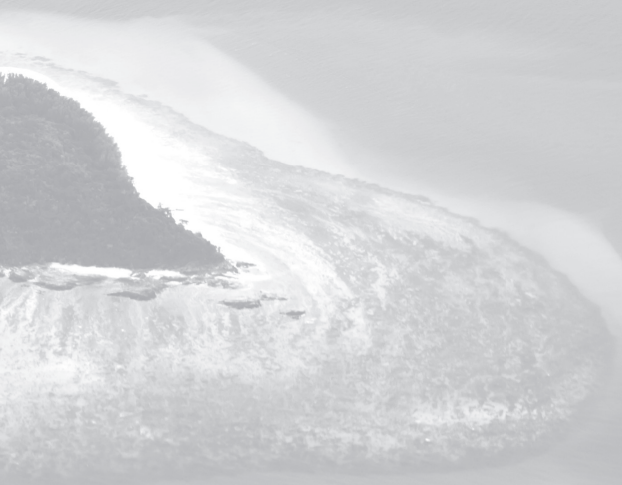


PART I

Consequences of fluid management



CHAPTER 2

Extravascular lung water increases after volume therapy irrespective of the volume status in critically ill patients

CHAPTER 3

High early fluid input after aneurysmal subarachnoid haemorrhage: combined report of association with delayed cerebral ischaemia and feasibility of cardiac output-guided fluid restriction

ABSTRACT

BACKGROUND: Guidelines on the management of patients with aneurysmal subarachnoid haemorrhage (aSAH) recommend maintaining euvolaemia, but fluid loading beyond euvolaemia (hypervolaemia) may occur and has been suggested to cause harm. We aimed to investigate whether high early fluid input and balance are associated with delayed cerebral ischaemia (DCI), and if fluid input can be decreased using transpulmonary thermodilution (TPT) while maintaining adequate preload.

METHODS: We retrospectively included consecutively admitted aSAH patients to an academic intensive care unit (2007–2011; cohort 1) and with aSAH requiring invasive hemodynamic monitoring (2011-2013; cohort 2). Local guidelines recommended a standard fluid input of 3 liters daily. More fluids were administered when daily fluid balance fell below +500 ml. In cohort 2, fluid input in selected high-risk aSAH patients was guided by stroke volume and cardiac output measured by TPT per a strict protocol. Associations of fluid input and balance with DCI were analyzed with multivariable logistic regression (cohort 1) and changes in hemodynamic indices before and after institution of a TPT-protocol were assessed with linear mixed-models (cohort 2).

RESULTS: We included 223 patients in cohort 1. Cumulative fluid input 0-72h after admission was associated with DCI (OR 1.19 per liter; 95% CI 1.07–1.32), whereas cumulative fluid balance was not associated with DCI (OR 1.06 per liter; 95% CI 0.97-1.17). In cohort 2 (23 patients), using TPT fluid input could be decreased (day -2: 6.0±1.0L and day -1: 5.3±0.9L versus day 3: 3.4±0.3L, P=0.012 and P=0.008, respectively), while preload parameters and consciousness remained stable.

CONCLUSIONS: High early fluid input was associated with DCI. Invasive hemodynamic monitoring was feasible to safely and significantly reduce fluid input while maintaining adequate preload. Taken together these results indicate that fluid loading beyond a normal preload is prevalent, may increase DCI risk and can be minimized with a hemodynamic monitoring protocol.

INTRODUCTION

Delayed cerebral ischaemia (DCI) after aneurysmal subarachnoid haemorrhage (aSAH) affects approximately 30% of patients (1). DCI typically develops between days 4 and 14 after ictus (2), and may progress to cerebral infarction which is associated with poor outcome (3,4). Since hypovolemia is associated with DCI, standard management includes maintenance of euvolemia (5,6). Nevertheless, ascertainment of euvolemia is problematic in clinical practice but highly relevant for several reasons. Guidelines recommend using meticulous fluid balance monitoring to guide fluid management. However, fluid balance has been shown to be poorly indicative of volume status (7). In addition, euvolemia as a fluid management goal is subject to interpretation, which is illustrated by highly variable maintenance fluid practices in aSAH across neuro-critical care units (8-10). In clinical practice, many patients with aSAH receive excessive fluids with the aim to maintain a positive fluid balance. However, excessive fluid administration may result in more systemic complications, e.g. congestive heart failure and pulmonary deterioration (11-13). In addition, a recent overview of the current literature suggested that excessive fluids might also be detrimental to neurological outcomes (10). In contrast, hypervolaemic therapy - as part of triple-H therapy - has long been regarded as beneficial rather than potentially harmful in aSAH (10). Hypervolaemia, which may be defined as fluid input exceeding the amount necessary for adequate organ perfusion, may therefore be an ill-recognized cause of harm to the brain. Since fluid management in aSAH still relies importantly on fluid balance, it is clinically relevant to assess whether excessive fluids are beneficial or harmful with regard to neurological clinical course. When “hypervolaemia” as defined above is a frequently occurring and undesirable consequence of aiming for positive fluid balances, one may hypothesize that hemodynamic monitoring may help restricting fluid input without compromising adequate cardiac preload and cerebral blood flow.

The main objective of this study was therefore to investigate whether high early fluid input and fluid balances within 72 hours after admission are associated with the occurrence of DCI in aSAH patients. Our secondary objective was to report on the feasibility to decrease fluid input guided by cardiac output monitoring with transpulmonary thermodilution (TPT).

METHODS

Study design and population

In this report, we describe two thematically related but separate studies. A schematic representation of the design and aims of the separate cohorts is shown in **Figure 3.1**. The first study was a retrospective cohort study of consecutively admitted aSAH patients (cohort 1) to a University hospital’s ICU (Erasmus MC, University Medical Center Rotterdam, the Netherlands) between October 2007 and October 2011 aiming to investigate whether high

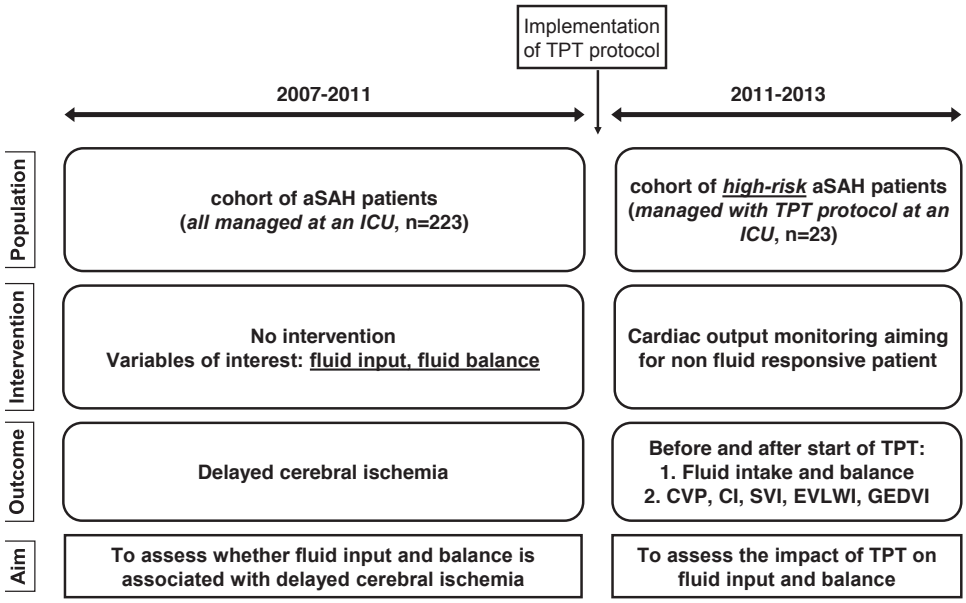


Figure 3.1 Schematic representation of the study design.

TPT: transpulmonary thermodilution; aSAH: acute subarachnoid haemorrhage; ICU: intensive care unit; CVP: central venous pressure; CI: cardiac index; SVI: stroke volume index; EVLWI: extravascular lung water index; GEDVI: global end-diastolic volume index.

early fluid input or positive fluid balances were associated with DCI. Because preliminary analyses of cohort 1 showed that high early fluid input was associated with DCI (14), we instituted a fluid management protocol using fluid responsiveness with TPT using the PiCCO device (Pulsion Medical Systems SE, Feldkirchen, Germany), assuming that a reduction in excessive fluid input while maintaining adequate cardiac preload might be possible.

The second study (cohort 2) concerned the first series of aSAH patients (April 2011 to September 2013, admitted to the same unit) managed with this newly instituted TPT protocol (**Supplement 3.1**) and was aimed at retrospectively assessing changes in fluid input and balances in the days before versus after TPT.

The inclusion criteria for cohort 1 were: 18 years or older, aneurysmal subarachnoid haemorrhage, and admission to hospital ≤ 48 hours after ictus. The exclusion criteria were: heart failure known from medical history, renal insufficiency (creatinine > 150 µmol/L), pregnancy, death within 48 hours after admission. For cohort 2, the inclusion criteria were similar to the indications for TPT monitoring according to the fluid management protocol and concerned high-risk patients (detailed in **Supplement 3.1 and 3.2)**. Briefly, these criteria concerned lower than expected blood pressure or highly negative fluid balance, signs of pulmonary or cardiac dysfunction or progressive neurological deterioration due

to DCI. Patients in both cohorts were identified through a hospital health service code indicating subarachnoid haemorrhage. The Institutional Medical Ethics Committee approval for both cohort studies was obtained and informed consent was not necessary given the observational nature of the studies and anonymization of patient data in accordance with Dutch legislation. Due to the retrospective nature, we did not perform a power analysis and used a sample size of convenience.

Diagnosis and patient management

All patients were routinely managed at an ICU. In both cohorts, patients were evaluated with head CT and CT angiography on admission. When no blood was seen on CT, a lumbar puncture was performed > 12 hours after ictus for spectrophotometric analysis of cerebrospinal fluid (CSF). During the inclusion period for cohort 1, coiling procedures were performed by a regional team of interventional neuroradiologists. Stable patients were temporarily transferred to a different hospital for endovascular treatment when an interventional neuroradiologist was not available within 24 hours in the admitting hospital (Erasmus MC). A detailed description of patient management during the ICU admission in the two cohorts is given in **Supplement 3.2**.

Data collection and outcomes

For both cohorts, data were collected from the ICU patient data management system and electronic patient records. Fluid input included all infusion fluids (including pharmaceuticals, blood products and intraoperative fluids), tube feeding and normal diet. Fluid losses included urine output, intraoperative blood loss, gastric retentions and cerebrospinal fluid from intrathecal drains. Insensible loss was not accounted for in the analyses. Fluid balance was calculated by subtracting fluid loss from input.

In cohort 1, fluid input, loss and balance of the first 3 days after admission (day 1: 0-24 hours, day 2: 24-48 hours, day 3: 48-72 hours) were collected. Admission CT scans were evaluated for Hijdra sum scores (15). The primary outcome was DCI, defined by CT infarction, clinical deterioration or both without other cause, according to recently proposed consensus criteria (1,16). Two authors (LJMV and MvdJ) assessed the primary outcome. During outcome assessments, the authors were blinded to the daily fluid data. Consensus on the outcomes was obtained by discussion in case of initial disagreement. Glasgow Outcome Score (GOS) was assessed between 3 and 6 months after admission to the hospital as a secondary outcome. When GOS could not be retrieved from our electronic patient records, we sent a letter to the general practitioner to request the relevant information.

In cohort 2, fluid data and Glasgow Coma Score (GCS) were collected over a period from up to three days before until three days after initiation of TPT. TPT parameters –

cardiac index (CI), stroke volume index (SVI), global end-diastolic volume index (GEDVI), and extravascular lung water index (EVLWI) – were collected during the study period, and the daily average values recorded. Central venous pressure (CVP) measurements were collected at least from the day before TPT initiation until three days after. In this cohort, DCI was assessed as defined in cohort 1 by one author (ME) who was blinded for other clinical data. In contrast to cohort 1, the primary outcome was the difference in fluid parameters before versus after start of TPT monitoring.

Statistical analysis

Data were summarized as number with percentage (categorical), as median with interquartile range (ordinal), and as mean ± standard error (continuous). Imputation of missing values in the fluid parameters and Hijdra sum scores in cohort 1 was performed with single imputation with regression based on relevant covariates and outcome (Supplement 3.3). Patients with DCI and without DCI in cohort 1 were compared using the student's t-test, Mann-Whitney U test, or Chi2 or Fisher's exact test. In cohort 1, logistic regression models were created with cumulative fluid input or cumulative fluid balance during the first 24, 48 and 72 hours of ICU admission and previously identified independent predictors for DCI as covariables: age, gender, World Federation of Neurosurgical Societies [WFNS] grading score at admission, and Hijdra sum scores on initial CT scan (17,18). Hijdra scores were dichotomized at their median and WFNS was dichotomized in good (WFNS, 1-3) and poor (WFNS, 4-5) grades for the analyses. Sensitivity analyses with cerebral infarction on CT due to DCI with or without clinical signs and a secondary analysis with GOS as outcome were done. Interaction between variables were assessed in each model. To assess whether the relation between fluid input or balance was non-linear, i.e. whether there was a specific cut-off in the effect of fluid on outcome, we did similar analyses with fluid input as covariables dichotomized on a cut-off of 3, 4 and 5 liters daily. In cohort 2, fluid and hemodynamic parameters were compared before and after TPT using linear mixed-models with day 3 after initiation of TPT as the reference. The course of patients' Glasgow Coma Scales before and after TPT was assessed with Wilcoxon signed rank test. A 2-sided P value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 20.0.0 (IBM, Chicago, IL, USA).

RESULTS

Cohort 1

We included 223 consecutive aSAH patients, of whom 91 (41%) developed DCI. General characteristics of patients with and without DCI are reported in **Table 3.1**. In total, 119 observations (18%) of fluid input data, 119 observations (18%) of fluid loss data, 8 (3.6%)

Table 3.1 General characteristics of cohort 1

Variable		No DCI	DCI	P
n		132	91	
Female		82 (62)	61 (67)	0.480
Age (year)		55 ± 1.1	57 ± 1.5	0.289
Loss of consciousness at ictus		53 (41)	55 (61)	0.003
ICU admission within 24 hours		125 (95)	85 (94)	0.761
Admission GCS		14 (13 - 15)	13 (6 - 15)	0.001
Transferred for intervention within 72 hours		59 (45)	29 (32)	0.054
Aneurysm location				
	Anterior circulation	101 (77)	72 (79)	0.744
	Posterior circulation	23 (17)	17 (19)	0.860
	No aneurysm found	8 (6)	2 (2)	0.206
Hijdra cistern sum score		16 (9 - 20)	20 (14 - 23)	0.001
Hijdra ventricular sum score		2 (0 - 4)	3 (0 - 6)	0.010
Treatment day		1.8 ± 0.2	2.0 ± 0.4	0.911
Aneurysm treatment mode				
	Coiling	85 (64)	44 (48)	0.019
	Clipping	31 (24)	25 (28)	0.532
	No occlusion	16 (12)	22 (24)	0.029
Day of DCI diagnosis			8 ± 0.5	
DCI diagnosis based on				
	CT only		34 (37)	
	Clinical signs only		31 (34)	
	Both CT and clinical signs		26 (29)	
Daily mean arterial pressure (mm Hg)				
	Day 1	93.7 ± 1.1	99.3 ± 1.4	0.002
	Day 2	97.2 ± 1.2	101.0 ± 1.8	0.072
	Day 3	101.0 ± 1.3	104.0 ± 1.7	0.170
Mean hemoglobin (mmol/L)				
	Day 1	7.97 ± 0.08	7.82 ± 0.10	0.251
	Day 2	7.45 ± 0.08	7.15 ± 0.13	0.050
	Day 3	7.35 ± 0.09	6.95 ± 0.10	0.009
Mean heart rate (beats per minute)				
	Day 1	71.8 ± 1.1	73.8 ± 1.5	0.303
	Day 2	69.7± 1.1	71.4 ± 1.7	0.389
	Day 3	71.5 ± 1.2	72.8 ± 1.7	0.535

Table 3.1 General characteristics of cohort 1 (continued)

Variable		No DCI	DCI	P
Lowest peripheral oxygen saturation (%)				
	Day 1	89.8 ± 0.95	89.6 ± 0.98	0.875
	Day 2	92.7 ± 0.52	91.7 ± 0.88	0.336
	Day 3	91.6 ± 0.58	91.6 ± 0.58	0.943
GOS follow-up (months)		3.5 ± 0.1	2.8 ± 0.2	0.008
GOS				<0.001
	Death	11 (9)	33 (39)	
	Persistent vegetative state	0	1 (1)	
	Severe disability, dependent	2 (2)	16 (19)	
	Moderate disability, independent	21 (17)	10 (12)	
	Good recovery	88 (72)	25 (29)	
6-month mortality		11 (9)	33 (38)	<0.001

Data is reported as mean ± standard error, median (interquartile range) or number (percentage) where appropriate. DCI: delayed cerebral ischemia; ICU: intensive care unit; GCS: Glasgow Coma

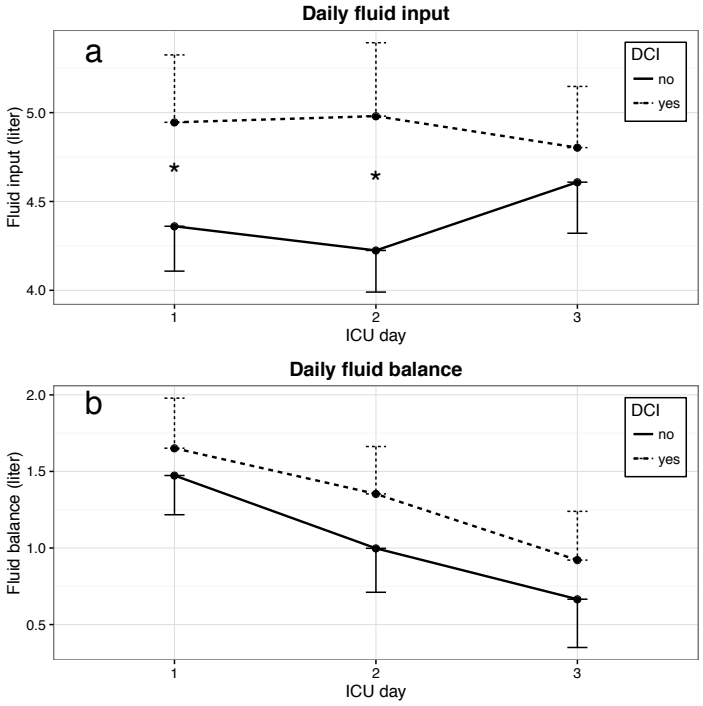


Figure 3.2 Daily fluid parameters in cohort 1.

Data are represented as mean with 95% CI as one-sided error bar. Differences between patients with and without DCI are indicated in Figures: * P<0.01. ICU: intensive care unit; DCI: delayed cerebral ischaemia.

Hijdra cistern sum scores, and 12 (5.4%) of Hijdra ventricle sum scores were missing and imputed. Mean hemoglobin (Hb) level at day 2 and 3 were lower and blood pressure at day 1 and 2 were higher in patients who developed DCI versus those who did not.

In patients who later developed DCI, fluid input was higher on day 1 after admission (DCI: 4.9 ± 0.19 L; no DCI: 4.4 ± 0.13 L; P=0.005) and day 2 (DCI: 5.0 ± 0.21 L; no DCI: 4.2 ± 0.12 L; P=0.004, **Figure 3.2**). Fluid balance did not differ between groups. In multivariable logistic regression models, cumulative fluid input was associated with an increased risk of DCI (0-24h: OR 1.22 per liter, 95% CI 1.01 – 1.46; 0-48h: OR 1.26 per liter, 95% CI 1.10 – 1.44; and 0-72h: OR 1.19 per liter, 95% CI 1.07 – 1.32, **Table 3.2**). There was no association between cumulative fluid balances and DCI (0-24h: OR 1.09 per liter, 95% CI 0.90 – 1.32; 0-48h: OR 1.07 per liter, 95% CI 0.95 – 1.21; and 0-72 hours: OR 1.06 per liter, 95% CI 0.97 – 1.17).

Table 3.2 Multivariable logistic regression models for cumulative fluid input and balance data from cohort 1 with DCI as outcome

	Fluid input			Fluid balance	
Variable	**OR**	**95% CI**	**Variable**	**OR**	**95% CI**
Age (year)	1.01	0.99 – 1.04	Age (year)	1.01	0.99 – 1.03
Gender (female)	1.33	0.73 – 2.43	Gender (female)	1.24	0.69 – 2.24
Admission WFNS (> 3)	2.30	1.24 – 4.27	Admission WFNS (>3)	2.62	1.43 – 4.81
Hijdra Cistern score (≥ 17)	2.23	1.25 – 3.98	Hijdra Cistern score (≥ 17)	2.17	1.22 – 3.86
Hijdra Ventricular score (≥ 2)	1.11	0.60 – 2.05	Hijdra Ventricular score (≥ 2)	1.14	0.62 – 2.10
Fluid input 0 – 24h L	1.22	1.01 – 1.46	Fluid balance 0 – 24h (L)	1.09	0.90 – 1.32
Age (year)	1.01	0.99 - 1.04	Age (year)	1.01	0.99 – 1.03
Gender (female)	1.33	0.72 - 2.45	Gender (female)	1.24	0.68 – 2.23
Admission WFNS (> 3)	2.25	1.21 - 4.20	Admission WFNS (>3)	2.54	1.39 – 4.66
Hijdra Cistern score (≥ 17)	2.22	1.23 - 3.99	Hijdra Cistern score (≥ 17)	2.15	1.21 – 3.81
Hijdra Ventricular score (≥ 2)	1.14	0.61 - 2.12	Hijdra Ventricular score (≥ 2)	1.15	0.63 – 2.10
Fluid input 0 – 48h (L)	1.26	1.10 - 1.44	Fluid balance 0 – 48h (L)	1.07	0.95 – 1.21
Age (year)	1.01	0.99 - 1.04	Age (year)	1.01	0.99 – 1.03
Gender (female)	1.39	0.75 - 2.58	Gender (female)	1.24	0.69 – 2.25
Admission WFNS (> 3)	2.45	1.31 - 4.56	Admission WFNS (>3)	2.50	1.36 – 4.59
Hijdra Cistern score (≥ 17)	2.27	1.26 - 4.08	Hijdra Cistern score (≥ 17)	2.20	1.24 – 3.91
Hijdra Ventricular score (≥ 2)	1.17	0.63 - 2.18	Hijdra Ventricular score (≥ 2)	1.11	0.60 – 2.04
Fluid input 0 – 72h (L)	1.19	1.07 - 1.32	Fluid balance 0 – 72h (L)	1.06	0.97 – 1.17

WFNS: World Federation of Neurosurgical Societies grading score

The logistic regression models including fluid input dichotomized at 3, 4 or 5 liters are reported in **Table 3.3**. Higher fluid input was still associated with increased risk for DCI in these analyses although specific cut-offs were not evident. The univariable analysis for the fluid variables is shown in **Table 3.4**. Adding Hb level and blood pressure as covariables to the multivariable analyses did not change the associations between fluid intake and DCI (data not shown). No significant interactions were found between the independent variables.

Table 3.3 Multivariable logistic regression models (cohort 1) with fluid input, in the first 24 to 72 hours, dichotomized at various cutpoints, as predictors for delayed cerebral ischemia.

Variable	OR	95% CI	OR	95% CI	OR	95% CI
Fluid input cutoff		**3 L**		**4 L**		**5 L**
Age (year)	1.01	0.99 – 1.03	1.01	0.99 – 1.03	1.01	0.99 – 1.04
Gender (female)	1.25	0.69 – 2.26	1.26	0.70 – 2.27	1.32	0.72 – 2.41
Admission WFNS (> 3)	2.54	1.38 – 4.67	2.50	1.36 – 4.61	2.40	1.30 – 4.44
Hijdra Cistern score (≥ 17)	2.15	1.21 – 3.80	2.13	1.20 – 3.76	2.05	1.15 – 3.66
Hijdra Ventricular score (≥ 2)	1.17	0.64 – 2.14	1.16	0.63 – 2.12	1.13	0.61 – 2.09
Fluid input 0 – 24h (L)	1.40	0.56 – 3.52	1.29	0.71 – 2.35	2.18	1.17 – 4.04
Fluid input cutoff		**6 L**		**8 L**		**10 L**
Age (year)	1.01	0.99 – 1.03	1.01	0.99 – 1.04	1.01	0.99 – 1.03
Gender (female)	1.26	0.70 – 2.28	1.26	0.69 – 2.30	1.28	0.70 – 2.32
Admission WFNS (> 3)	2.51	1.37 – 4.61	2.48	1.34 – 4.58	2.51	1.37 – 4.63
Hijdra Cistern score (≥ 17)	2.19	1.23 – 3.89	2.15	1.20 – 3.85	2.13	1.20 – 3.79
Hijdra Ventricular score (≥ 2)	1.17	0.64 – 2.13	1.13	0.61 – 2.09	1.20	0.65 – 2.20
Fluid input 0 – 48h (L)	2.00	0.60 – 6.70	2.30	1.22 – 4.32	2.01	1.10 – 3.69
Fluid input cutoff		**9 L**		**12 L**		**15 L**
Age (year)	1.01	0.99 – 1.04	1.02	0.99 – 1.04	1.01	0.99 – 1.03
Gender (female)	1.23	0.68 – 2.23	1.27	0.70 – 2.31	1.27	0.69 – 2.32
Admission WFNS (> 3)	2.53	1.38 – 4.64	2.55	1.38 – 4.71	2.45	1.32 – 4.54
Hijdra Cistern score (≥ 17)	2.24	1.26 – 3.98	2.21	1.24 – 3.95	2.27	1.26 – 4.09
Hijdra Ventricular score (≥ 2)	1.12	0.61 – 2.05	1.13	0.61 – 2.08	1.24	0.67 – 2.31
Fluid input 0 – 72h (L)	3.89	0.42 – 36.1	1.93	1.02 – 3.65	2.60	1.39 – 4.89

Each set of variables shows the multivariate regression model for the specified cutoff value for cumulative fluid input.
WFNS: World Federation of Neurosurgical Societies grading score; OR: odds ratio; CI: confidence interval.

Table 3.4 Univariable logistic regression models for data from cohort 1 with DCI as outcome

Variable	OR	95% confidence interval
Age (year)	1.01	0.99 – 1.03
Gender (female)	1.24	0.71 – 2.17
Admission WFNS score	2.81	1.59 – 4.96
Hijdra Cistern score	1.06	1.02 – 1.10
Hijdra Ventricular score	1.13	1.04 – 1.23
Fluid input 0–24h (L)	1.25	1.05 – 1.49
Fluid input 0–48h (L)	1.28	1.12 – 1.45
Fluid input 0–72h (L)	1.17	1.06 – 1.29
Fluid balance 0–24h (L)	1.08	0.91 – 1.29
Fluid balance 0–48h (L)	1.10	0.98 – 1.24
Fluid balance 0–72h (L)	1.08	0.99 – 1.18

WFNS: World Federation of Neurosurgical Societies grading score

The sensitivity analysis with DCI infarction as the outcome yielded similar results as those with DCI, but cumulative fluid balances 0-48 hours and 0-72 hours after admission were associated with cerebral infarction due to DCI (0-48h: OR 1.15 per liter, 95% CI 1.00 – 1.33, and 0-72 hours: OR 1.12 per liter, 95% CI 1.01 – 1.25, **Table 3.5**. Secondary outcome analysis for Glasgow Outcome Score showed similar results as the analysis for fluid input and DCI (**Table 3.6**).

Cohort 2

We included the first 23 patients with aSAH who had an indication for TPT according to the protocol (**Appendix 3.1**). **Table 3.7** shows some pertinent characteristics on demographics, aneurysm management and outcomes. Eleven patients (48%) died within 30 days after ICU admission and this high mortality relates to the inclusion of high-risk patients for TPT, including those with recent signs of DCI. Fluid data from day -3 until day 3 relative to TPT initiation were available for 11, 10, 21, 23, 21, 20 and 20 patients, respectively (e.g. only 11/23 patients had been admitted with available fluid data, 3 days before TPT initiation).

Daily fluid parameters and daily GCS are shown in **Figure 3.3**. Compared to day 3 (reference) after TPT initiation (fluid input: 3.4 ± 0.3 L), fluid input was higher on day -2 (6.0 ± 1.0 L; P=0.012) and day -1 (5.3 ± 0.9 L; P=0.008). Daily fluid loss was lower on day -3 when compared to day 3 (2.7 ± 0.5 L versus 3.4 ± 0.4 L; P=0.049). As a result, daily fluid balance was higher on day -3 (1.8 ± 0.6 L; P=0.003), day -2 (2.9 ± 1.4 L; P<0.001) and day -1 (1.4 ± 0.4 L; P=0.014) when compared to day 3 (0.0 ± 0.2 L). Median daily GCS on day -1 was not significantly lower than the median daily GCS on day 3 (GCS of 7 [5.5 – 7.5] versus 9 [6 – 14]; P=0.18). Most hemodynamic parameters as measured during TPT (CVP,

CI, SVI) remained within the range of normal values in spite of significant reductions of fluid input and balances after start of TPT, except GEDVI and EVLWI which were higher than the normal ranges of 650-800 ml/m^2 and 3.0-7.0 ml/kg respectively (**Figure 3.4**).

Table 3.5 Multivariable logistic regression models for cumulative fluid input and balance data with DCI infarction as outcome from cohort 1.

	Fluid input			Fluid balance	
Variable	**OR**	**95% CI**	**Variable**	**OR**	**95% CI**
Age (year)	0.97	0.95 – 1.00	Age (year)	0.97	0.95 – 1.00
Gender (female)	0.98	0.51 – 1.91	Gender (female)	0.91	0.47 – 1.74
Admission WFNS (> 3)	3.25	1.66 – 6.35	Admission WFNS (>3)	3.81	1.97 – 7.39
Hijdra Cistern score (≥ 17)	1.60	0.83 – 3.07	Hijdra Cistern score (≥ 17)	1.57	0.82 – 3.00
Hijdra Ventricular score (≥ 2)	1.12	0.56 – 2.24	Hijdra Ventricular score (≥ 2)	1.10	0.55 – 2.20
Fluid input 0 – 24h (L)	1.24	1.02 – 1.51	Fluid balance 0 – 24h (L)	1.16	0.94 – 1.45
Age (year)	0.97	0.95 – 1.00	Age (year)	0.97	0.95 – 1.00
Gender (female)	0.98	0.50 – 1.91	Gender (female)	0.89	0.46 – 1.72
Admission WFNS (> 3)	3.26	1.66 – 6.40	Admission WFNS (> 3)	3.63	1.87 – 7.05
Hijdra Cistern score (≥ 17)	1.52	0.79 – 2.94	Hijdra Cistern score (≥ 17)	1.57	0.82 – 3.00
Hijdra Ventricular score (≥ 2)	1.14	0.56 – 2.29	Hijdra Ventricular score (≥ 2)	1.09	0.54 – 2.19
Fluid input 0 – 48h (L)	1.26	1.08 – 1.47	Fluid balance 0 – 48h (L)	1.15	1.00 – 1.33
Age (year)	0.97	0.95 – 1.00	Age (year)	0.97	0.95 – 1.00
Gender (female)	1.02	0.52 – 1.99	Gender (female)	0.92	0.47 – 1.78
Admission WFNS (> 3)	3.58	1.83 – 7.01	Admission WFNS (> 3)	3.62	1.86 – 7.05
Hijdra Cistern score (≥ 17)	1.55	0.80 – 2.99	Hijdra Cistern score (≥ 17)	1.61	0.84 – 3.09
Hijdra Ventricular score (≥ 2)	1.16	0.58 – 2.33	Hijdra Ventricular score (≥ 2)	1.06	0.53 – 2.13
Fluid input 0 – 72h (L)	1.18	1.05 – 1.32	Fluid balance 0 – 72h (L)	1.12	1.01 – 1.25

WFNS: World Federation of Neurosurgical Societies grading score

Table 3.6 Multivariate logistic regression models for cumulative fluid input and balance data from cohort 1 with Glasgow Outcome Score as outcome.

Fluid input			Fluid balance		
Variable	**OR**	**95% CI**	**Variable**	**OR**	**95% CI**
Age (year)	1.04	1.01 – 1.07	Age (year)	1.04	1.01 – 1.07
Gender (female)	1.24	0.62 – 2.47	Gender (female)	1.16	0.59 – 2.29
Admission WFNS (> 3)	3.55	1.78 – 7.10	Admission WFNS (> 3)	4.05	2.06 – 7.95
Hijdra Cistern score (≥ 17)	1.51	0.77 – 2.94	Hijdra Cistern score (≥ 17)	1.43	0.74 – 2.77
Hijdra Ventricular score (≥ 2)	1.07	0.53 – 2.17	Hijdra Ventricular score (≥ 2)	1.16	0.58 – 2.33
Fluid input 0 – 24h L	1.22	1.00 – 1.49	Fluid balance 0 – 24h (L)	0.96	0.77 – 1.19
Age (year)	1.04	1.01 – 1.07	Age (year)	1.04	1.01 – 1.07
Gender (female)	1.18	0.59 – 2.35	Gender (female)	1.16	0.59 – 2.29
Admission WFNS (> 3)	3.67	1.84 – 7.30	Admission WFNS (> 3)	4.04	2.05 – 7.95
Hijdra Cistern score (≥ 17)	1.46	0.75 – 2.84	Hijdra Cistern score (≥ 17)	1.44	0.74 – 2.79
Hijdra Ventricular score (≥ 2)	1.12	0.55 – 2.26	Hijdra Ventricular score (≥ 2)	1.14	0.57 – 2.29
Fluid input 0 – 48h (L)	1.14	1.01 – 1.29	Fluid balance 0 – 48h (L)	1.00	0.87 – 1.15
Age (year)	1.05	1.02 – 1.08	Age (year)	1.04	1.02 – 1.07
Gender (female)	1.22	0.61 – 2.46	Gender (female)	1.12	0.56 – 2.23
Admission WFNS (> 3)	3.86	1.94 – 7.67	Admission WFNS (> 3)	3.96	1.99 – 7.84
Hijdra Cistern score (≥ 17)	1.47	0.75 – 2.89	Hijdra Cistern score (≥ 17)	1.50	0.77 – 2.92
Hijdra Ventricular score (≥ 2)	1.12	0.55 – 2.27	Hijdra Ventricular score (≥ 2)	1.07	0.53 – 2.16
Fluid input 0 – 72h (L)	1.12	1.00 – 1.25	Fluid balance 0 – 72h (L)	1.00	0.89 – 1.11

WFNS: World Federation of Neurosurgical Societies grading score
N=207, for 16 patients the outcome could not be retrieved.

Table 3.7 General characteristics at start of invasive hemodynamic monitoring in cohort 2.

Variable	
n	23
Female	19 (83)
Age (year)	55 ± 3.4
GCS	8 (6 - 13)
DCI (infarction, clinical and both)	10 (44)
Hijdra cistern sum score	14.6 ± 1.2
Hijdra ventricular sum score	4.4 ± 0.9
Treatment mode	
Coiling	9 (39)
Clipping	11 (48)
No occlusion	3 (13)
IHM initiated (days after admission)	1.4 ± 0.4
30-day mortality	11 (48)

Data is reported as mean ± standard error, median (interquartile range) or number (percentage) where appropriate. DCI: delayed cerebral ischemia; GCS: Glasgow Coma Score; IHM: invasive hemodynamic monitoring by transpulmonary thermodilution.

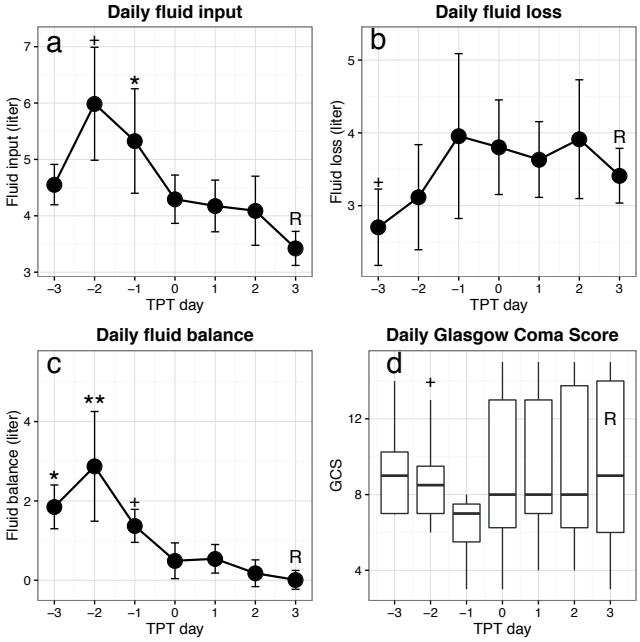


Figure 3.3 Daily fluid parameters and associated course of Glasgow Coma Scale in cohort 2.

Data are represented as mean with standard error as one-sided error bar and median with interquartile range for GCS. TPT day 3 is used as the reference value (R) for the comparisons. + P<0.05; * P<0.01; ** P<0.001. TPT: transpulmonary thermodilution. GCS: Glasgow Coma Scale

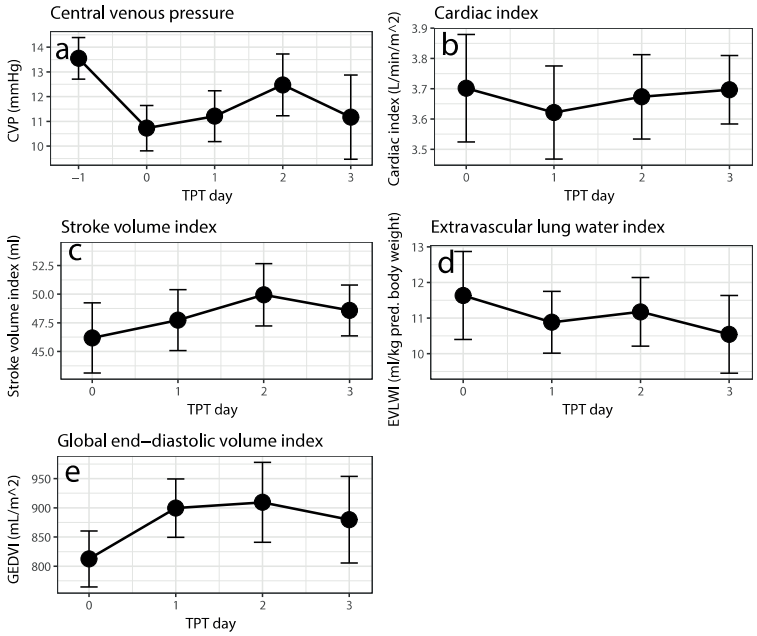


Figure 3.4 Hemodynamic data in cohort 2.

Data is represented as mean with standard error as two-sided error bar. TPT day 3 is used as the reference value (R) for the comparisons: there were no significant differences over time. Because the placement of a jugular or subclavian central venous catheter at admission for aSAH is not standard practice in our institution, data for central venous pressure is only available from at least TPT day -1 until TPT day 3. TPT: transpulmonary thermodilution.

DISCUSSION

The main finding of this study in patients with aSAH is that early high daily fluid input was independently associated with DCI and poor outcome. In addition, we showed that fluid loading beyond normal preload occurred in clinical practice and that it was feasible to significantly restrict fluid input while maintaining adequate preload with TPT in selected high-risk aSAH patients. Taken together, these results corroborate the potential harm from fluid overload in aSAH patients with regard to DCI and support further study on potential benefit of fluid restriction guided by hemodynamic monitoring.

We found that early high fluid input was associated with DCI. However, our cohort data, and specifically the analyses for fluid input of 3, 4 or 5 liters daily, did not indicate a specific cut-off for fluid input beyond which DCI-risk was increased. Therefore, firm conclusions about upper limits of fluid input for this cohort are not possible in spite of the robust finding that more fluids associate with DCI-risk, indicating that fluid titration in aSAH should still be individualized. In a sensitivity analysis with cerebral infarction on CT as the outcome,

positive net fluid balances also showed an association. Furthermore, the hemodynamic data in cohort 2 seem to indicate a state of hypervolaemia, since GEDVI was higher than reference values. There are several possible explanations why high fluid input is associated with DCI (10). First, increased "fluid throughput" may cause fluids to accumulate in the interstitial space when the blood-brain-barrier is damaged, which may impede local oxygen diffusion to neurons (19-21). Second, haemodilution as a consequence of fluid loading may decrease shear-stress in the cerebral arteries, which may be detrimental to the integrity of the blood-brain-barrier (22), and lower hemoglobin levels may contribute to DCI due to decrease oxygen transport capacity of the blood, in line with our findings. Lastly, in cohort 1, as fluid input increased, fluid loss did not increase equally to match the higher fluid input (data not shown). Conversely, in cohort 2, when fluid input decreased, diuresis seemed to increase. Both observations may theoretically be explained by (renal) venous congestion (i.e. high CVP) (23). It has been postulated that venous congestion may also impede cerebral venous outflow and lead to intracranial pressure increase (24). Furthermore, several studies in brain injured critically ill patients have found CVP to be higher in patients with worse neurological outcomes (11,13,25). Similarly, a recent study found that higher CVP was associated with lower brain tissue oxygen saturation and worse outcome in post-cardiac arrest patients (26). We acknowledge that these data do not provide proof and should be regarded as hypothesis-generating regarding the pathophysiologic role of venous congestion in DCI due to excessive fluids.

Our findings substantiate previous findings. Several investigators have described early mean daily fluid input varying from 3.3 to 6.6 liters and daily fluid balances varying from -0.6 to +2.1 liters (7,25,27-30). However, studies investigating the relation between fluid management and DCI are scarce (25,29,31,32). Two studies investigating the effect of early goal-directed hemodynamic management reported that mean daily fluid input was 2.7 liters in the first three days with mean fluid balances between -0.5 to 0.5 liters when using TPT (33,34). Using goal-directed hemodynamic management, less fluid was infused and fewer patients suffered from DCI than in the conventional treatment group in line with our findings (34). The association of fluid input but not fluid balance with DCI is also in line with previous reports (23,28).

Some limitations of our study should be considered. Due to the retrospective nature, potential unmeasured confounding factors and retrieval of relevant patient data are an inherent threat to the associations found in cohort 1. Consequently, causality between high fluid input and DCI cannot be proven with this retrospective study. Another limitation is the fact that we did not differentiate between or adjust for crystalloids versus synthetic colloids, since DCI has been associated with use of synthetic colloids (29,35). However, these compounds were administered mainly in case of clinical deteriorations due to DCI as per out protocol at the time of the study period and not typically in the first three

days when fluid data were collected for this study. Furthermore, we did not adjust fluid parameters for weight. In cohort 2, due to the variable start of the TPT protocol, in relation to clinical admission, missing/unavailable values were unavoidable (e.g. when TPT was initiated soon after admission). Finally, our institutional fluid management protocol used in cohort 2 is based on our best clinical practice and the scarce literature available (33,34), but has not been validated outside our ICU. The patients in cohort 2 are those more likely to develop DCI, so the generalizability of our protocol to low risk aSAH patients is uncertain. Because both cohorts are from a single center and due to the sample size used, the overall generalizability may be limited.

The strengths of our study include a consecutive series of patients managed at an ICU with detailed data on fluid management and prognostic factors, as well as assessment of the primary outcome (DCI) according to recently proposed criteria (1,16). Second, we imputed missing data with multiple imputations enhancing the statistical power. Finally, our data are in line with the recent notion that excessive fluid input is an established risk factor for adverse outcome in non-neurological critically ill patients(36) and aSAH patients in particular (11,29,33,34,37).

A guideline endorsed by the American Heart Association advised to maintain euvolemia (5). However, establishing euvolemia is difficult when clear definitions are absent. This is reflected by the fact that mean daily fluid input and fluid balance in cohort 1 exceeded the predefined targets in our institutional protocol. Similarly, the hemodynamic data in cohort 2 suggested patients were hypervolemic when TPT was initiated. A multi-disciplinary consensus statement recommended use of hemodynamic monitoring devices in aSAH, only in hemodynamically unstable patients (38). A practical approach based on previous literature (10,39) and our results may be to aim for euvolemia by giving 2.5-3.5 L/day in most patients with a fluid balance around zero. Invasive monitoring may then be considered in patients in whom deviations from euvolemia are suspected and considered highly detrimental, or in case of signs of stress cardiomyopathy, neurogenic pulmonary edema, excessive diuresis or progressive DCI. Of note, when monitoring is applied, the ambiguous term “euvolemia” might best be replaced by “adequate preload”.

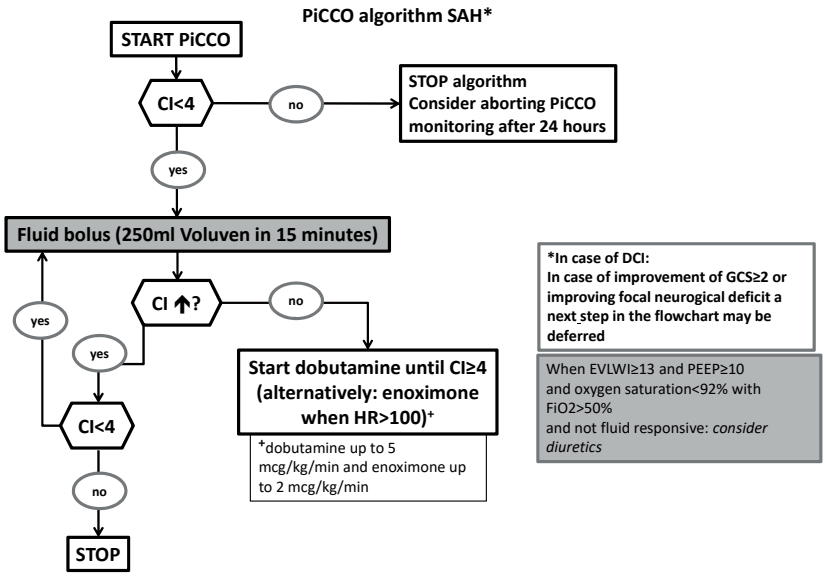
CONCLUSION

High early daily fluid input is associated with DCI after aSAH. We showed the feasibility of a protocol using TPT to significantly reduce fluid input and balance without negatively impacting on preload parameters and Glasgow Coma Scale. Further study seems warranted to determine whether and when hemodynamic monitoring can help establishing both restricted fluid management and improved clinical outcomes.

Supplement 3.1 Invasive hemodynamic monitoring protocol using transpulmonary thermodilution.

SAH fluid management protocol with transpulmonary thermodilution. Basic tenets underlying the protocol:

- Hypovolemia is to be avoided and increases DCI risk.
- Cardiac wall motion abnormalities (CWMA) are frequent but clinically evident signs of heart failure much less so.
- Hypotension after SAH (systole<100mmHg or MAP<65mmHg) is unusual and requires an investigation into its cause and prompt management.
- Neurogenic pulmonary edema (NPE) and cardiac wall motion abnormalities pose risks to adequate CBF and oxygenation and are associated with worse outcomes and occurrence of DCI.
- In general a diagnosis of NPE or CWMA requires invasive hemodynamic monitoring (IHM).
- IHM to assess volume status after SAH is focused on fluid responsiveness as a primary dynamic hemodynamic parameter, instead of only static parameters.
- It is not advised to start inotropes in case of NPE or CWMA without the concurrent initiation of IHM to guide their use.
- In patients with a Glasgow Coma Scale (GCS) >8, improvements of consciousness are also an important end-point of fluid management next to the hemodynamic parameters.
- Considering the previous point, a perfectly awake patient with a GCS=15 is considered to be “euvolemic” with regard to CBF.



Supplement 3.2 Appendix on patient management in each cohort.

Cohort 1:

Routine fluid input at the ICU was started at a total of 3 liters of fluid per 24 hours as per the local SAH management protocol. This included all oral fluids plus, if necessary, 0.9% saline intravenously. Additional fluids were given (6% hydroxyethyl starch 130/0.4 or 0.9% saline), when fluid balance became less than +500 ml daily or when body temperature exceeded 38°C (0.5 liters of 0.9% saline for every degree Celsius per 24 hours). All patients were treated with oral nimodipine 6 x 60 mg for 21 days. When endovascular coiling of the ruptured aneurysm was feasible this was done as soon as possible. Surgical treatment was scheduled when coiling was technically not feasible and as soon as the patient had a World Federation of Neurosurgical Societies (WFNS) grade I or II. Otherwise, surgery was postponed until day 12 after the initial bleed. Immediate treatment of the ruptured aneurysm was postponed when the patient had an admission WFNS grade V and treatment was scheduled as soon as WFNS grade improved.

Cohort 2:

Cohort 2 consisted of patients managed according to a fluid management protocol guided by cardiac output monitoring with transpulmonary thermodilution (Supplemnent 3.1). Briefly, the inclusion criteria for cohort 2 were equal to the entry characteristics for the protocol and were GCS < 15 and at least one of the following characteristics: hypotension (systolic blood pressure < 100 mmHg or MAP < 65 mmHg), not responsive to fluid administration; (neurogenic) pulmonary edema or clinically relevant cardiac dysfunction (as judged by attending ICU physician); negative fluid balance (-1L/day); DCI as judged by attending neurologist and either a persisting negative fluid balance (-500 mL/day) or progressive neurological deterioration despite extra fluid loading (aimed at mean arterial pressure of at least 80 mmHg and positive fluid balance). If cardiac index was < 4.0 L/min/m^2, a fluid bolus of 250 mL 6% hydroxyethyl starch 130/0.4 (Voluven) was infused and repeated until cardiac index increased to > 4.0 L/min/m2 or did not further increase. If cardiac index did not increase after a fluid bolus, dobutamine was started and titrated until cardiac index increased to target or dosage reached 5 µg/kg/min. If a patient had an indication for dobutamine but a heart rate of > 100 beats per minute, enoximone was started and titrated similarly to a maximum dosage of 2 µg/kg/min (Supplement 3.1).

Supplement 3.3 Imputation assumptions and formula used in the Aregimpute function in R

(1) the number of missing values for each variable or the number of complete vs incomplete cases

In total, 119 observations (18%) of fluid input data, 119 observations (18%) of fluid loss data, 8 (3.6%) Hijdra cistern sum scores, and 12 (5.4%) of Hijdra ventricle sum scores were missing and imputed. There were 146 complete cases prior to imputation (65%).

(2) The outcome was available for all patients and the missing number of key exposure variables have already been mentioned. Below is a comparison table between the fluid volumes of the measured values and the imputed values.

	No DCI		DCI	
	Complete cases (n)	**Imputed cases (n)**	**Complete cases (n)**	**Imputed cases (n)**
Fluid input				
day 1	4.4 ± 0.13 (110)	4.4 ± 0.13 (132)	5.0 ± 0.20 (82)	4.9 ± 0.19 (91)
day 2	4.2 ± 0.12 (107)	4.2 ± 0.12 (132)	4.8 ± 0.22 (82)	5.0 ± 0.21 (91)
day 3	4.5 ± 0.17 (92)	4.6 ± 0.15 (132)	4.7 ± 0.18 (77)	4.8 ± 0.17 (90)*
Fluid loss				
day 1	2.8 ± 0.13 (110)	2.9 ± 0.13 (132)	3.3 ± 0.19 (82)	3.3 ± 0.17 (91)
day 2	3.2 ± 0.16 (107)	3.2 ± 0.14 (132)	3.5 ± 0.22 (82)	3.6 ± 0.23 (91)
day 3	3.9 ± 0.18 (92)	3.9 ± 0.15 (132)	3.9 ± 0.21 (77)	3.8 ± 0.19 (90)*
Hijdra sum score				
Cistern	16 (9 - 20) (127)	16 (9 - 20) (132)	20 (14 - 23) (88)	20 (14 - 23) (91)
Ventricular	2 (0 - 4) (124)	2 (0 - 4) (132)	3 (0 - 6) (87)	3 (0 - 6) (91)

Fluid in liters ± standard error. Score with interquartile range. DCI: delayed cerebral ischemia. *One patient died at day 3 and data for this patient was therefore not imputed.

(3) The main reason contributing to occurrence of missing data in cohort 1 is due to the transferral of patients for endovascular interventions, see the methods section. Transferals were at random, based on in which hospital the on-call intervention neuroradiologist was based in.

(4) The data are assumed to be missing at random to allow statistical imputation.

(5) The imputation was performed with the AregImpute function in R statistical software using the following variables in the model: sex, age, admission GCS, aneurysm location, treatment mode, GOS, death within 6 months, Hijdra cistern score, Hijdra ventricle score, intracranial hemorrhage, diastolic/systolic/mean blood pressure at admission, fluid input on day 1 to 3 and fluid loss day 1 to 3. The specific formula used in the Aregimpute function is shown below.

Formula:

sex + age + admissionGCS + as.factor(aneurloc*.m) + as.factor(treatment_mode.m) + I(GOS.m) + death_within_6months.m + HIJDRA_CIST_SUMSCORE.m + HIJDRA_VENTR_SUMSCORE.m + ICH.m + DBPadmission.r + SBPadmission.r + MAPadmission.r + I(TEMPadmission.m) + FL_INTAKE_D1.m + FL_INTAKE_D2.m + FL_INTAKE_D3.m + FL_EXCRETION_D1.m + FL_EXCRETION_D2.m + FL_EXCRETION_D3.m*

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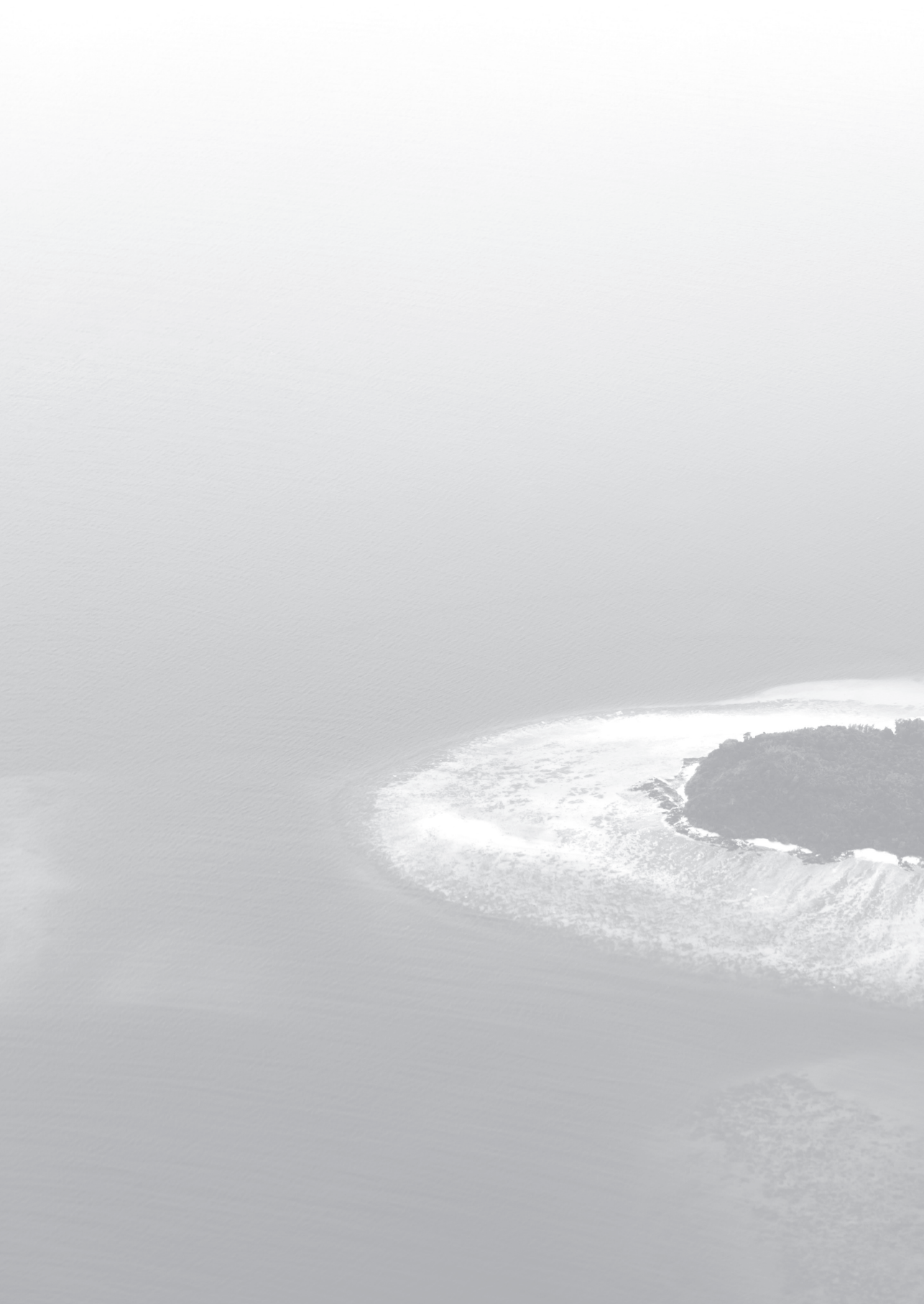
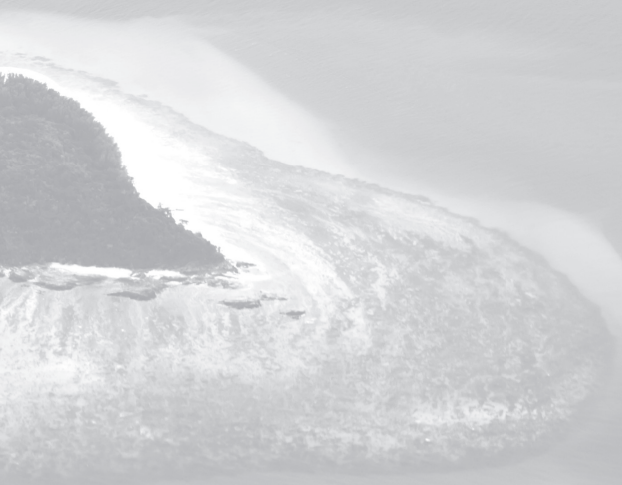


PART II

Fluid management guided by targeting urine output



CHAPTER 4

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

ABSTRACT

BACKGROUND: We investigated whether resuscitation protocols including oliguria reversal as a target – to achieve and maintain urine output above a predefined threshold – 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 which 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 in groups with and without oliguria reversal as a target for hemodynamic optimization. We calculated combined odds ratio (OR) and 95% confidence intervals (CI) 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 to 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 to 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 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 to 1.10; P=0.09; I^2=48.6%; N=9, in neither protocol: OR 0.66; 95% CI 0.37 to 1.16; P=0.14; I^2=20.2%; N=12).

CONCLUSIONS: Collectively, 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.

INTRODUCTION

Intravenous fluids are administered to compensate for losses during or after surgery, and to increase intravascular volume in hypovolemic patients. Textbooks frequently 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 to administer fluids to prevent acute renal failure (ARF) and organ damage. However, oliguria may not solely be caused by a suboptimal hemodynamic status, but may also be attributed to medications or hormonal effects, which reduces 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 utility to 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 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 utilizing parameters related to cardiac output and oxygen delivery, irrespective 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. Due to variability in the definition of renal dysfunction

in the studies we evaluated, and to 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, due to 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 – present) database via PubMed and the EMBASE (1980 – present) database (last search March 2014) with no limits for publication date or language (**Table S4.1**). 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 (M.E.) 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 study period; definition of ARF used; and development of ARF. Once included, the studies were scored according to the Jadad scale on: reporting whether it 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 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- vs. CFM-*, studies comparing GDT without oliguria reversal as a target with CFM with oliguria reversal as a target as *GDT- vs. CFM+* and studies comparing GDT with CFM where both treatment arms had oliguria reversal as a target as *GDT+ vs. CFM+*. Odds ratios (OR) and 95% confidence intervals (CI) 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 two treatment arms in all studies as well as separately for each of the three study protocol

groups (GDT+ vs. CFM+, GDT- vs. CFM+, GDT- vs. CFM-) using random effects meta-analysis. To gain further insights into the role of the treatment period in which the protocol was used (pre-, vs intra-, or postoperative), we meta-analyzed studies in which the treatment protocol was used during the preoperative or intraoperative setting separately from studies 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 protocol only during the postoperative and ICU setting.

To investigate 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 RIFLE and AKIN criteria and assigned the studies to one of three 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 cut-off 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, "non-invasive", which included studies using arterial wave-form or pulse contour analysis devices to guide therapy and "metabolic indices", which included studies using oxygen saturation or lactate to guide therapy without also using devices from the two other groups. Difference in fluid intake between GDT and CFM was specified as one of three 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 CFM ("similar"), and studies in which less fluids were infused in GDT than in CFM ("less"). Additionally, 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 two subgroups: published before 2004 and published in or after 2004. The year 2004 was chosen as cut-off point since the consensus definition and RIFLE criteria by the Acute Dialysis Quality Initiative Group were published in that year. Lastly, studies with a Jadad score greater than 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 & 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 in order to detect possible

publication bias. In the subgroup analysis, pooled OR and CI were calculated without taking heterogeneity between studies into account, and p-values were determined using Fisher's exact test. Odds ratios were considered statistically significant when their 95% CI did not include 1.00 and the corresponding p-value was less than 0.05.

RESULTS

Our search strategy resulted in 1062 articles, of which 588 remained after excluding duplicates (**Figure 4.1**). Of those, 525 were either animal studies, pediatric studies, not in English, not available as full-text, or comparing 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 was presented. One study which did report ARF occurrence (24) was excluded, because it was not possible to distinguish new occurrences of ARF in each group from those with ARF at randomization. **Table 4.1** shows the characteristics of the resulting 28 included studies, and **Table 4.2** shows the hemodynamic monitoring utilized in each of the selected studies.

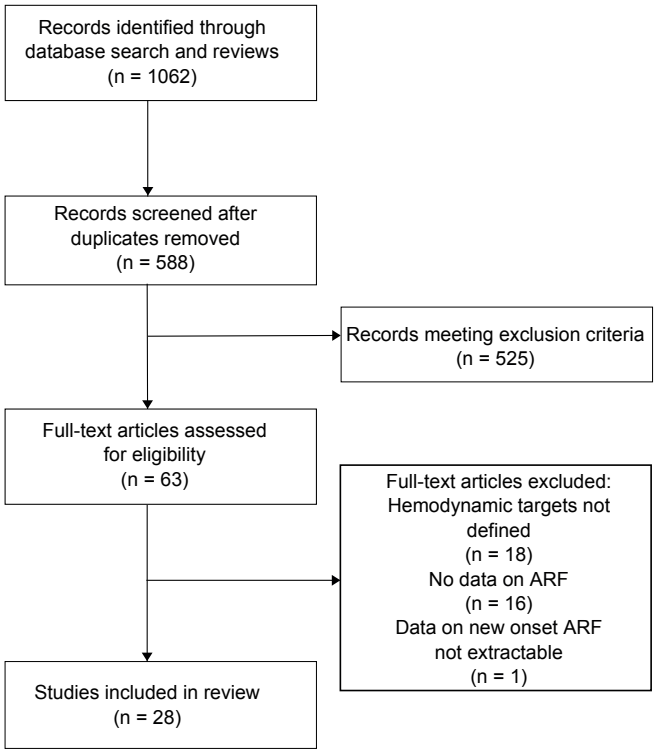


Figure 4.1 Flow chart of study selection.
ARF: acute renal failure.

Table 4.1 Characteristics of studies included

Study	Group	Total number	Type of patient	Exclusion of renal conditions	Timing	Definition of ARF
Berlauk 1991 (25)	GDT-vs.CFM-	89	Vascular		pre	UO < 0.5 mL/kg/hr for 5 hours and/or a change in baseline sCr more than 44 µmol/l.
Valentine 1998 (26)	GDT-vs.CFM-	120	Vascular Abdominal		pre, intra, post	not mentioned in original publication
Wilson 1999 (27)	GDT-vs.CFM-	138	General, Vascular, Abdominal		pre	increase in BUN > 5 mmol / l from pre levels .
Polonen 2000 (28)	GDT-vs.CFM-	393	Cardiac		post	UO < 750 mL/24 h or increase of sCr >150 µmol/l from previous normal levels
Bonazzi 2002 (29)	GDT-vs.CFM-	100	Vascular, Abdominal	Yes, advanced CKD	pre	worsening of pre renal function with accompanying oliguria requiring high doses of furosemide (>250 mg/day) and/or RRT
Wakeling 2005 (30)	GDT-vs.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 2010 (31)	GDT-vs.CFM-	86	Abdominal	Yes, dialysis	intra	RRT or UO <0.5 mL/kg for >2 hours
WenKui 2010 (32)	GDT-vs.CFM-	214	Abdominal		intra, post	RRT
Cecconi 2011 (33)	GDT-vs.CFM-	40	Orthopedic		intra	UO < 500 mL/d, increase in sCr > 30%, or urinary catheter in place for a nonsurgical reason
Bartha 2013 (34)	GDT-vs.CFM-	149	Orthopedic		intra	50% increase of baseline sCr or/and UO < 0.5 ml/h
Bisgaard 2013 (35)	GDT-vs.CFM-	70	Vascular, Abdominal	Yes, ESRD	intra, post	not mentioned in original publication
Goepfert 2013 (36)	GDT-vs.CFM-	92	Cardiac	Yes, dialysis	intra	AKIN

Table 4.1 Characteristics of studies included (continued)

Study	Group	Total number	Type of patient	Exclusion of renal conditions	Timing	Definition of ARF
Bishop 1995 (37)	GDT- vs.CFM+	115	Orthopedic		ICU, post	sCr ≥ 177 µmol/l, or with pre-existing renal disease a sCr 2x that on admission
Gan 2002 (38)	GDT- vs.CFM+	100	General, Abdominal	Yes, significant renal dysfunction	intra	UO < 500 ml/day, increase in sCr > 30%
McKendry 2004 (39)	GDT- vs.CFM+	174	Cardiac		post	not mentioned in original publication
Benes 2010 (40)	GDT- vs.CFM+	120	High Risk, Abdominal		intra	UO < 500 ml/day or sCr > 170 µmol/l or RRT
Mayer 2010 (41)	GDT- vs.CFM+	60	High Risk		Intra	UO < 500 ml/day or RRT
Zhang 2013 (42)	GDT- vs. CFM+	80	Pulmonary		intra	not mentioned in original publication
Pro CI 2014 (43)	GDT- vs. CFM+	885	Sepsis		ICU	RRT
Shoemaker 1988 (44)	GDT+ vs.CFM+	88	High Risk		intra, post	BUN >18 mmol/l, sCr >265 µmol/l
Boyd 1993 (45)	GDT+ vs.CFM+	107	High Risk	Yes, ARF	pre, intra, post, ICU	UO <500 mL/24 h
Gattinoni 1995 (46)	GDT+ vs.CFM+	762	High Risk		ICU	sCr ≥ 177 µmol/l, RRT, or both
Lobo 2000 (47)	GDT+ vs.CFM+	37	High Risk, General, Abdominal, Vascular		intra, post	renal SOFA ≥ 3
Donati 2007 (48)	GDT+ vs.CFM+	135	Vascular, Abdominal		Intra	sCr > 177 µmol/l or RRT
Kapoor 2008 (49)	GDT+ vs.CFM+	27	Cardiac		post	not mentioned in original publication
Jammer 2010 (50)	GDT+ vs.CFM+	241	Abdominal	Yes, sCr > 177 µmol/l	intra	sCr increase > 33%
Jhanji 2010 (51)	GDT+ vs.CFM+	135	Abdominal		post, ICU	AKIN
Brandstrup 2012 (52)	GDT+ vs.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 therapy without oliguria reversal as a target; CFM+: conventional fluid therapy 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.

Table 4.2 Hemodynamic monitoring used in selected studies

Study	Group	Device	Hemodynamic Target	UO criteria	Intervention
Berlauk 1991 (25)	GDT- vs.CFM-	PAC	PAOP, CI, SVR		fluids, vasoactive medication
Valentine 1998 (26)	GDT- vs.CFM-	PAC	PCWP, CI, SVR		crystalloids, dopamine, vasoactive medication
Wilson 1999 (27)	GDT- vs.CFM-	PAC	PAOP		fluids, adrenaline, dopexamine
Polonen 2000 (28)	GDT- vs.CFM-		S_vO_2, Lactate		fluids, dobutamine, vasoactive medication
Bonazzi 2002 (29)	GDT- vs.CFM-	PAC	CI, PCWP, SVR, DO_2		crystalloids, vasoactive medication
Wakeling 2005 (30)	GDT- vs.CFM-	esophageal Doppler	SV		colloids
Forget 2010 (31)	GDT- vs.CFM-	Masimo pulse oximeter	PVI		colloids, vasoactive medication
WenKui 2010 (32)	GDT- vs.CFM-		Lactate		crystalloids, colloids, dopamine, ephedrine
Cecconi 2011 (33)	GDT- vs.CFM-	FloTrac sensor/ Vigileo	SV		colloids, vasoactive medication, dobutamine
Bartha 2013 (34)	GDT- vs.CFM-	LiDCO	SV, DO_2I		fluids, vasoactive medication
Bisgaard 2013 (35)	GDT- vs.CFM-	LiDCO	SVI		colloids, dobutamine, vasoactive medication
Goepfert 2013 (36)	GDT- vs.CFM-	PiCCOplus	SV, GEDI, ELVI, CI		fluids, vasoactive medication
Bishop 1995 (37)	GDT- vs.CFM+	PAC	DO_2I, VO_2I , CI	UO 30-50 ml/h	volume, dobutamine
Gan 2002 (38)	GDT- vs.CFM+	esophageal Doppler	SV, Ftc	UO < 0.5 ml/kg/h	colloids

Table 4.2 Hemodynamic monitoring used in selected studies (continued)

Study	Group	Device	Hemodynamic Target	UO criteria	Intervention
McKendry 2004 (39)	GDT- vs.CFM+	oesophageal Doppler	SI	UO, no specific goal mentioned	colloids, blood, vasoactive medication
Benes 2010 (40)	GDT- vs.CFM+	FloTrac sensor/ Vigileo	SVV	UO > 0.5 ml/kg/h	colloids, dobutamine
Mayer 2010 (41)	GDT- vs.CFM+	FloTrac sensor/ Vigileo	CI, SVI	UO > 0.5 ml/kg/h	crystalloids, colloids, norepinephrine, dobutamine, vasodilators
Zhang 2013 (42)	GDT- vs. CFM+	FloTrac sensor/ Vigileo	SVV, CI	UO > 0.5 ml/kg/h	crystalloids, colloids, vasoactive medication
Pro CI 2014 (43)	GDT- vs. CFM+		$S_{cv}O_2$, CVP	UO, no specific goal mentioned	crystalloids, colloids, vasoactive medication
Shoemaker 1988 (44)	GDT+ vs.CFM+	PAC	Hct, P_vO_2, PAP, SVR, PWP, PVR, DO_2, VO_2	UO > 30 ml/h	crystalloids, colloids, vasoactive medication
Boyd 1993 (45)	GDT+ vs.CFM+	PAC	DO_2I	UO > 0.5 ml/kg/h	gelatin, dopexamine
Gattinoni 1995 (46)	GDT+ vs.CFM+	PAC	CI or S_vO_2	UO > 0.5 ml/kg/h	fluids, vasoactive medication
Lobo 2000 (47)	GDT+ vs.CFM+	PAC	DO_2	UO < 0.5 ml/kg/h	fluids, dobutamine
Donati 2007 (48)	GDT+ vs.CFM+		S_vO_2, O_2ERe	UO > 0.5 ml/kg/h	fluids, dobutamine
Kapoor 2008 (49)	GDT+ vs.CFM+	FloTrac sensor/ Vigileo	CVP,SVV	UO > 1 ml/kg/h	colloids, dopamine or other inotropes
Jammer 2010 (50)	GDT+ vs.CFM+		$S_{cv}O_2$	UO > 0.5 ml/kg/h	crystalloids, colloid
Jhanji 2010 (51)	GDT+ vs.CFM+	LiDCO	SV	UO > 25 ml/h	fluids, dopexamine
Brandstrup 2012 (52)	GDT+ vs.CFM+	esophageal Doppler	SV	UO > 0.5 ml/kg/h	colloid

PAC: pulmonary artery catheter; PAC+: pulmonary artery catheter with supranormal hemodynamic targets; pre: preoperative; intra: intraoperative; post: postoperative; ICU: intensive care unit; 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; PAWP: pulmonary artery wedge pressure; FTc: corrected flow time; PCWP: pulmonary

capillary wedge pressure; 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.

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- vs. CFM- group, seven studies in which only the CFM protocol included oliguria reversal were allocated to the GDT- vs. CFM+ group (37-43), and nine studies which included oliguria reversal as a target in both the GDT and CFM protocol were assigned to the GDT+ vs. 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, or 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 less than 3 on the Jadad scale (**Table 4.3**). The allocation of the studies to the subgroups is shown in **Table 4.4**. None of the selected studies reported the use of nephrotoxic medication and only five studies reported the use of diuretics for reasons other than oliguria reversal (36,40,47,49,52).

Table 4.3 Risk of bias assessment in selected studies

Study	Group	Blinding score	Randomization score	Withdrawal score	Score on Jadad scale
Berlauk 1991 (25)	GDT- vs.CFM-	0	2	1	3
Valentine 1998 (26)	GDT- vs.CFM-	0	2	1	3
Wilson 1999 (27)	GDT- vs.CFM-	2	2	0	4
Polonen 2000 (28)	GDT- vs.CFM-	0	2	0	2
Bonazzi 2002 (29)	GDT- vs.CFM-	0	2	0	2
Wakeling 2005 (30)	GDT- vs.CFM-	2	2	1	5
Forget 2010 (31)	GDT- vs.CFM-	0	1	1	2
WenKui 2010 (32)	GDT- vs.CFM-	0	2	1	3
Cecconi 2011 (33)	GDT- vs.CFM-	0	1	1	2
Bartha 2013 (34)	GDT- vs.CFM-	0	2	1	3
Bisgaard 2013 (35)	GDT- vs.CFM-	0	2	1	3
Goepfert 2013 (36)	GDT- vs.CFM-	0	2	1	3
Bishop 1995 (37)	GDT- vs.CFM+	0	1	0	1
Gan 2002 (38)	GDT- vs.CFM+	0	2	1	3
McKendry 2004 (39)	GDT- vs.CFM+	2	2	1	5
Benes 2010 (40)	GDT- vs.CFM+	0	2	1	3
Mayer 2010 (41)	GDT- vs.CFM+	0	2	1	3
Zhang 2013 (42)	GDT- vs. CFM+	0	2	0	2

Table 4.3 Risk of bias assessment in selected studies (continued)

Study	Group	Blinding score	Randomization score	Withdrawal score	Score on Jadad scale
Pro CI 2014 (43)	GDT- vs. CFM+	0	2	1	3
Shoemaker 1988 (44)	GDT+ vs.CFM+	0	2	0	2
Boyd 1993 (45)	GDT+ vs.CFM+	0	1	0	1
Gattinoni 1995 (46)	GDT+ vs.CFM+	0	2	1	3
Lobo 2000 (47)	GDT+ vs.CFM+	0	2	1	3
Donati 2007 (48)	GDT+ vs.CFM+	0	2	1	3
Kapoor 2008 (49)	GDT+ vs.CFM+	0	2	1	3
Jammer 2010 (50)	GDT+ vs.CFM+	0	2	1	3
Jhanji 2010 (51)	GDT+ vs.CFM+	0	2	1	3
Brandstrup 2012 (52)	GDT+ vs.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 therapy without oliguria reversal as a target; CFM+: conventional fluid therapy with oliguria reversal as a target.

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 to 0.76; $P < 0.001$; $I^2 = 34.3\%$; N = 28). In the GDT- vs. CFM+ group, patients that received GDT were less likely to develop ARF than patients treated with CFM (OR 0.45; 95% CI 0.34 to 0.61; $P < 0.001$; $I^2 = 7.1\%$; N = 7). The studies in the other two protocol groups did not provide enough evidence to conclude a superiority of GDT compared to CFM. Forest plots of the primary analysis are shown in **Figure 4.2**. 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 S4.1**).

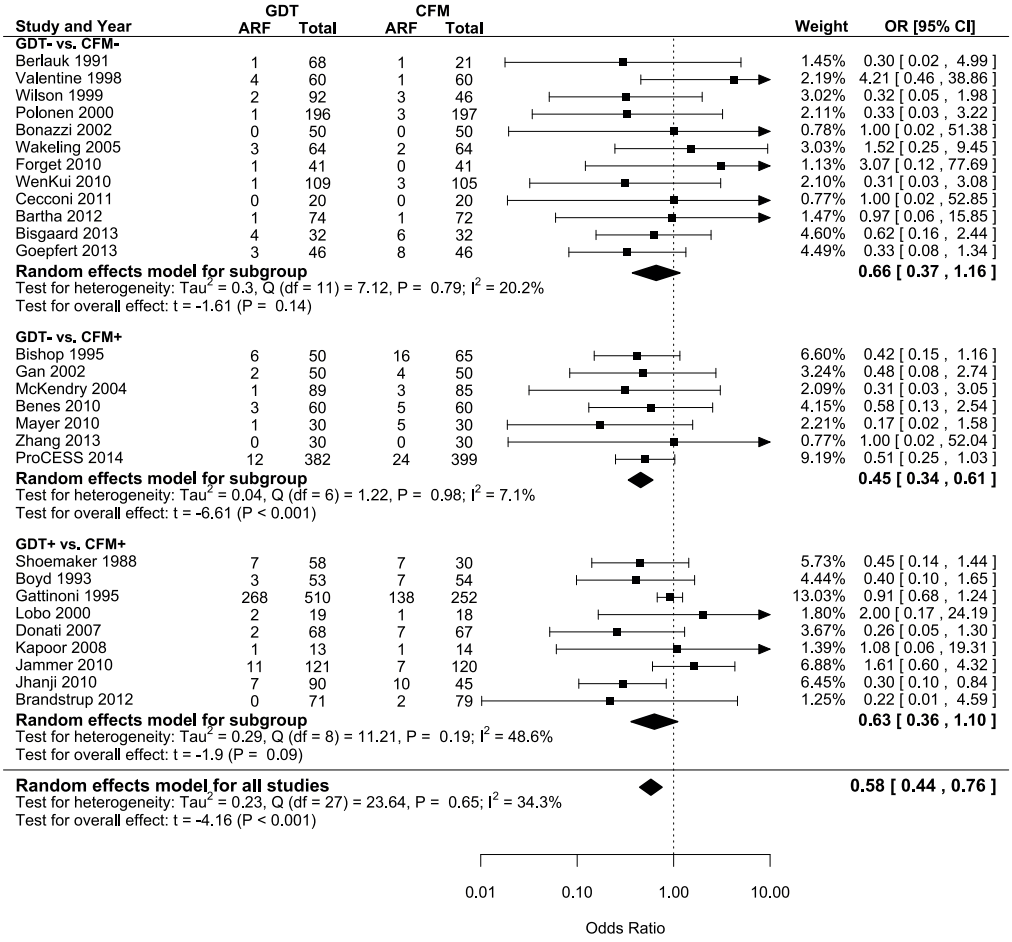


Figure 4.2 Forest plot of studies reporting occurrence of acute renal failure when comparing goal-directed therapy with conventional fluid management.

GDT: goal-directed therapy; CFM: conventional fluid therapy; ARF: acute renal failure; OR: odds ratio; CI: confidence interval; GDT- vs. CFM-: Goal-directed therapy versus conventional fluid therapy both without oliguria reversal as a target; GDT- vs. CFM+: Goal-directed therapy without oliguria reversal as a target versus conventional fluid therapy with oliguria reversal as a target; GDT+ vs. CFM+: Goal-directed therapy versus conventional fluid therapy both with oliguria reversal as a target.

Secondary analysis.

Results from the meta-analysis of those studies that targeted oliguria reversal during the pre- and intraoperative setting are shown in **Figure 4.3**. Here, the combined analysis showed that GDT was associated with a lower occurrence of ARF compared to CFM (OR 0.62; 95% CI 0.42 to 0.89; P = 0.01; I^2 = 25.1%; N = 21). All three protocol group specific meta-analyses estimated ORs smaller than one, however none of the estimates were significantly different from 1.00.

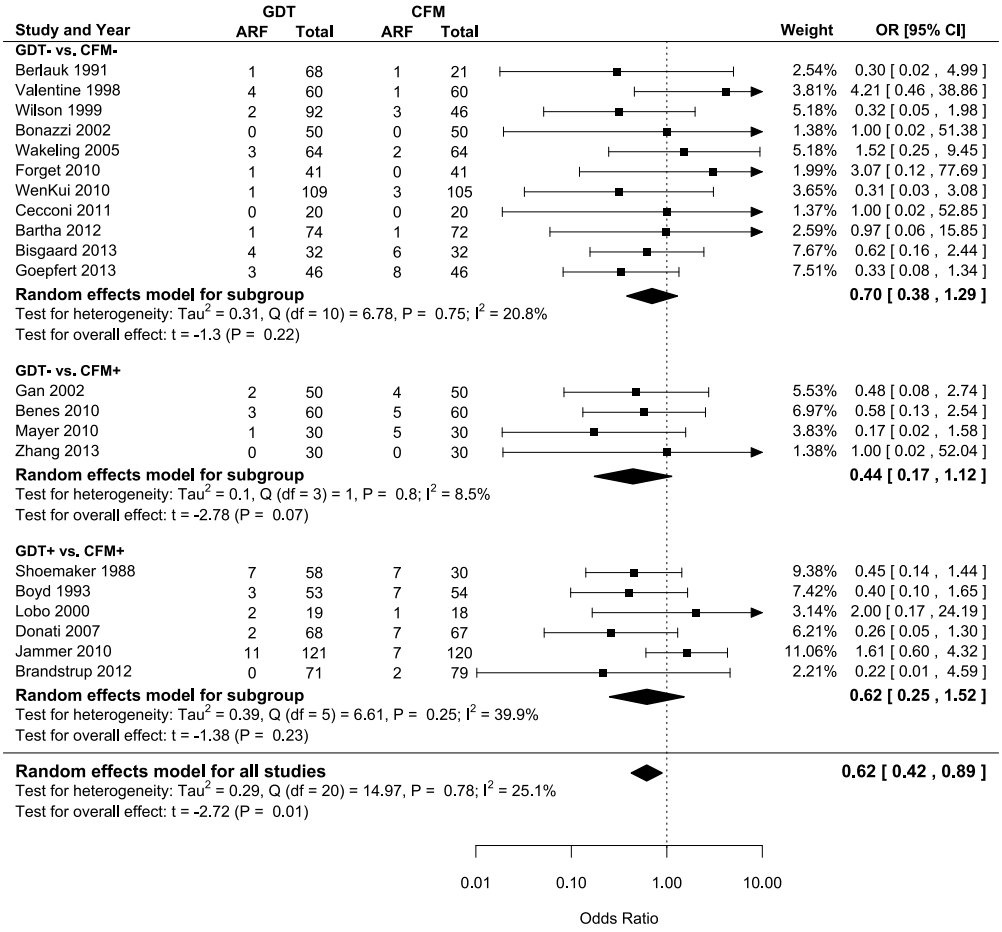


Figure 4.3 Forest plot of studies reporting occurrence of acute renal failure when comparing goal-directed therapy with conventional fluid management in the preoperative and intraoperative setting.

GDT: goal-directed therapy; CFM: conventional fluid therapy; ARF: acute renal failure; OR: odds ratio; CI: confidence interval; GDT- vs. CFM-: Goal-directed therapy versus conventional fluid therapy both without oliguria reversal as a target; GDT- vs. CFM+: Goal-directed therapy without oliguria reversal as a target versus conventional fluid therapy with oliguria reversal as a target; GDT+ vs. CFM+: Goal-directed therapy versus conventional fluid therapy both with oliguria reversal as a target.

Meta-analysis of the studies that used the 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 to 0.80; P = 0.004, I^2 = 42.6%; N = 14). The corresponding forest plot is displayed in **Figure 4.4**. Here, the OR in the GDT- vs. CFM+ group was significantly smaller than 1.00 (OR 0.46; 95% CI 0.31 to 0.70; P = 0.015; I^2 = 1.2%; N = 3), while results in the other two groups were inconclusive. Funnel plots for the secondary analyses showed no asymmetry and hence suggested no publication bias (**Figure S4.2 and S4.3**).

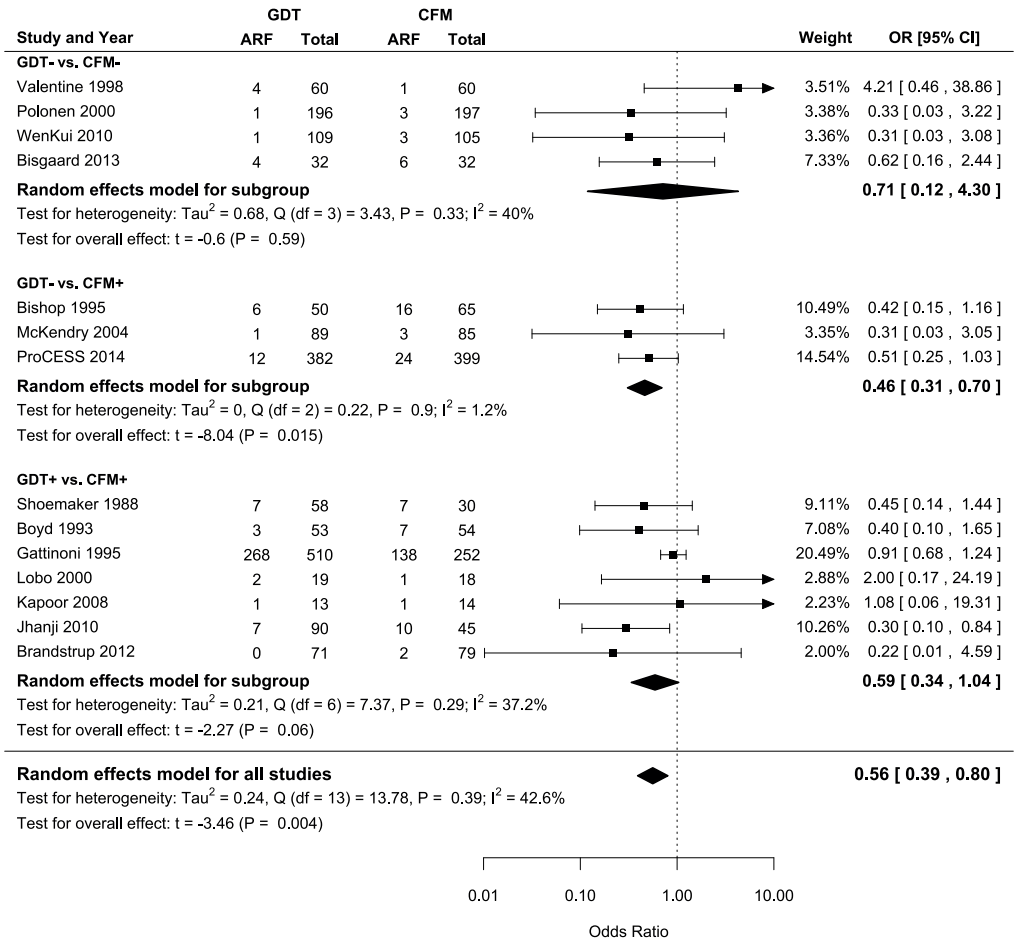


Figure 4.4 Forest plot of studies reporting occurrence of acute renal failure when comparing goal-directed therapy with conventional fluid management in the postoperative setting and intensive care unit.

GDT: goal-directed therapy; CFM: conventional fluid therapy; ARF: acute renal failure; OR: odds ratio; CI: confidence interval; GDT- vs. CFM-: Goal-directed therapy versus conventional fluid therapy both without oliguria reversal as a target; GDT- vs. CFM+: Goal-directed therapy without oliguria reversal as a target versus conventional fluid therapy with oliguria reversal as a target; GDT+ vs. CFM+: Goal-directed therapy versus conventional fluid therapy both with oliguria reversal as a target.

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 0.37 to 0.90; P = 0.02; I^2 = 30.6%; N = 7, **Figure S4**).

Additional analysis.

Since we did not find any studies directly comparing targeting oliguria reversal with not targeting oliguria reversal in each treatment, we conducted additional, pooled analyses based on the subgroups of studies described above (see **Table 4.4**). The results from this analysis are reported in detail in **Table 4.5**.

Table 4.4 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 1991 (25)	Invasive monitoring	Similar		
Valentine 1998 (26)	Invasive monitoring			More
Wilson 1999 (27)	Invasive monitoring	Other		
Polonen 2000 (28)	Metabolic indices	Other	More	More
Bonazzi 2002 (29)	Invasive monitoring	Other		More
Wakeling 2005 (30)	Invasive monitoring	Similar	More	More
Forget 2010 (31)	Metabolic indices	Other		Less
WenKui 2010 (32)	Metabolic indices	Other		More
Cecconi 2011 (33)	Non-invasive monitoring	Similar		More
Bartha 2013 (34)	Non-invasive monitoring	Exact		Less
Bisgaard 2013 (35)	Non-invasive monitoring			Similar
Goepfert 2013 (36)	Non-invasive monitoring	Exact	More	More
Bishop 1995 (37)	Invasive monitoring	Other		More
Gan 2002 (38)	Invasive monitoring	Similar	More	More
McKendry 2004 (39)	Invasive monitoring		More	More
Benes 2010 (40)	Non-invasive monitoring	Other	More	More
Mayer 2010 (41)	Non-invasive monitoring	Other	More	Similar
Zhang 2013 (42)	Non-invasive monitoring			Less
Pro CI 2014 (43)	Metabolic indices	Other		Less
Shoemaker 1988 (44)	Invasive monitoring	Other		
Boyd 1993 (45)	Invasive monitoring	Other		Similar
Gattinoni 1995 (46)	Invasive monitoring	Other		
Lobo 2000 (47)	Invasive monitoring	Other		Similar
Donati 2007 (48)	Metabolic indices	Other		Similar
Kapoor 2008 (49)	Invasive monitoring			More
Jammer 2010 (50)	Metabolic indices	Other		Less
Jhanji 2010 (51)	Non-invasive monitoring	Exact		Similar
Brandstrup 2012 (52)	Invasive monitoring	Other	More	Similar

Invasive monitoring: the use of pulmonary artery catheters or esophageal Doppler. Non-invasive monitoring: the use of arterial wave-form 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.

Table 4.5 Direct comparison between targeting and not targeting oliguria reversal in goal-directed therapy and conventional fluid management.

		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
Non-invasive 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

Table 4.5 Direct comparison between targeting and not targeting oliguria reversal in goal-directed therapy and conventional fluid management. (continued)

		Targeting oliguria reversal		Not targeting oliguria reversal			
Analysis	**FMS**	**ARF**	**Total**	**ARF**	**Total**	**OR (95% CI)**	**P**
Similar volume	GDT	14	301	5	62	0.56 (0.18 - 2.06)	0.34
[35,41,45,47,48,51,52]	CFM	32	293	6	32	0.53 (0.19 - 1.7)	0.24
More fluids in GDT	GDT	1	13	24	794	2.67 (0.06 - 19.47)	0.34
[26,28-30,32,33,36-40,49]	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 to the pooled data from studies not targeting oliguria reversal – separating data from goal-directed therapy protocols from conventional fluid management protocols. Odds ratio and 95% confidence intervals were then calculated and the P-value was calculated using the Fisher's exact test to test whether there was a difference in acute renal failure occurrence between targeting and not targeting oliguria reversal in each protocol. When cells with 0 caused problems in calculating odds ratio or associated confidence interval, 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

DISCUSSION

In the present study, we performed meta-analyses on 28 studies and found that GDT is superior to CFM with regards to preventing ARF. This effect was the strongest in studies that included oliguria reversal as a target in CFM but not in GDT. Even though 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 due to the small number of studies that were available for analysis.

In the additional, pooled analysis (**Table 4.5**), GDT and CFM strategies targeting oliguria reversal increased the odds of developing ARF when compared to 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- vs. 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 to 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 due to causes which are unaffected by fluid administration or have already been resolved. Therefore, patients may be at risk for fluid overload due to superfluous fluid administration targeted only at urine output. On the other hand, 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 already been optimized, any subsequent occurrence of oliguria is unlikely to be due to 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 4.4**), and even in the GDT- vs. CFM+ group most studies 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 due possibly to the volume of fluids already administered.

Based on our findings, GDT is better suited than CFM to prevent ARF in the preoperative or intraoperative setting. Furthermore, GDT might also reduce ARF occurrence 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. Firstly, they assigned studies according to commencement of hemodynamic optimization. Secondly, they pooled the intraoperative and postoperative commencement into one analysis (12). Finally, they excluded studies with late optimization, i.e. more than 12 hours postoperative or after onset of organ failure. It has been previously suggested that intraoperative and postoperative optimization should be separated due to differences in etiology and hemodynamic goals (53). Consequently, while our study supports the findings of Brienza et al. 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.

While 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. Due to 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. Firstly, as shown in **Table 4.1**, not all of the included studies shared the same definition for ARF. While 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 a rise in serum creatinine values; a form of oliguria; some form of renal replacement therapy; or a combination of these criteria, and as such are quite similar to the RIFLE or AKIN criteria. However, due to the relatively short observation periods, the relatively high cut-off 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 due to the associated increase in adverse outcomes (54), and are one of the reasons why the Acute Kidney Injury Network included small increments in serum creatinine in 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.

Secondly, the hemodynamic parameters targeted in the GDT protocols and the methods used to evaluate them varied greatly among the included studies (**Table 4.2**). This variance was due partly to the large time span 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 while 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 the 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 due to 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 4.2**, the use of vasopressors and inotropic drugs as well as 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. While 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 due to differences in fluid compositions used within studies 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.

CONCLUSION

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 which prioritize cardiac output and oxygen delivery are better able to reduce the risk of ARF than those including oliguria reversal as a target.

SUPPLEMENT

Table S4.1 Search strategy

#44	(#36 AND #43)	543
#43	(#39 OR #42)	
#42	(#41 OR #40)	
#41	“controlled trial”	
#40	trial	
#39	(#37 OR #38)	
#38	“randomised”	
#37	“randomized”	
#36	(#35 AND #26)	
#35	(#11 AND #34)	
#34	(#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33)	
#33	fluid	
#32	“fluid resuscitation”	
#31	“fluid loading”	
#30	“fluid administration”	
#29	“fluid management”	
#28	“fluid therapy”	
#27	“fluid therapy”[MeSH]	
#26	(#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25)	
#25	outcome	
#24	“urinary output”	
#23	“urine production”	
#22	“urine output”	
#21	“diuresis”	
#20	“acute renal failure”	
#19	“acute kidney injury”[MeSH]	
#18	“acute kidney injury”	
#17	creatinine	
#16	kidney	
#15	renal	
#14	“organ dysfunction”	
#13	“complications”	
#12	“organ failure”	
#11	(#1 OR #2 OR #3 # OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)	

#10	"supranormal"
#9	"goal-directed therapy"
#8	optimisation
#7	optimization
#6	"cardiac index"
#5	"stroke volume"
#4	"cardiac output"
#3	"hemodynamic target"
#2	"goal-directed"
#1	"goal directed"

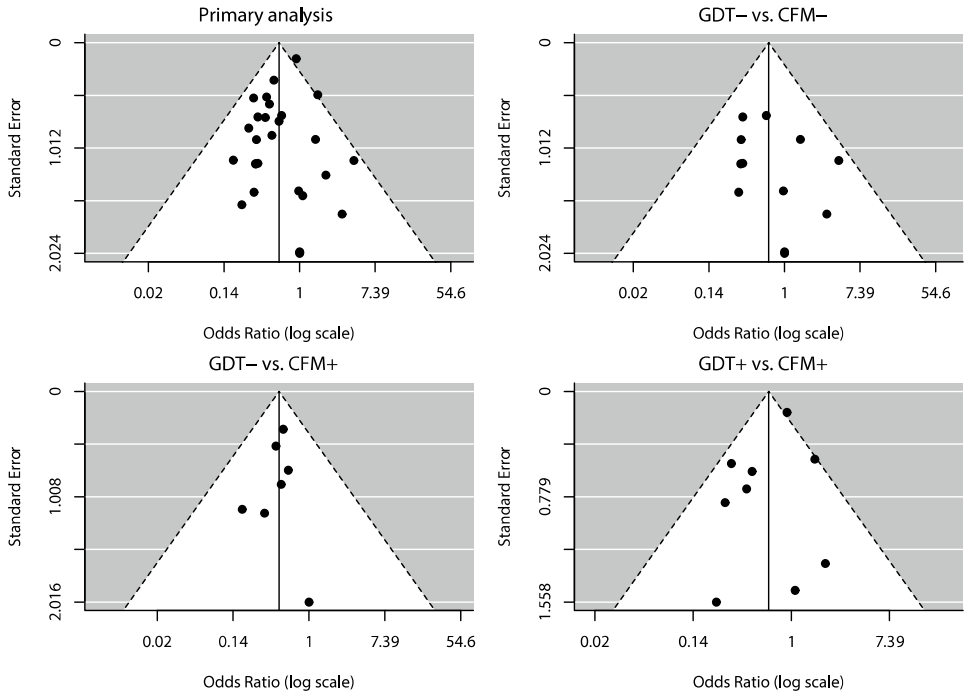


Figure S4.1 Funnel plots used to assess the presence of publication bias in the analysis from Figure 4.2.

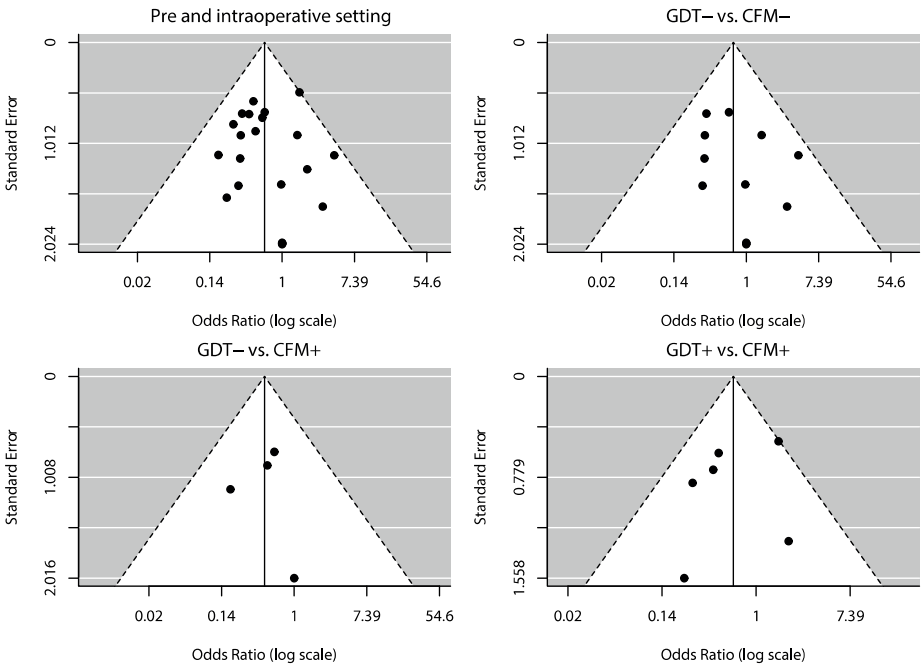


Figure S4.2 Funnel plots used to assess the presence of publication bias in the analysis from Figure 4.3.

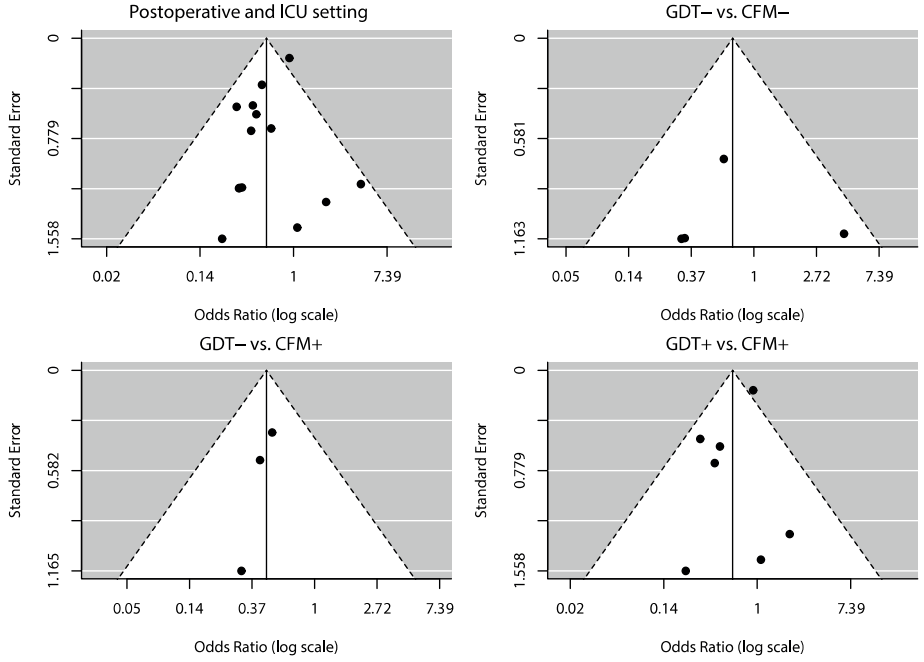


Figure S4.3 Funnel plots used to assess the presence of publication bias in the analysis from Figure 4.4.

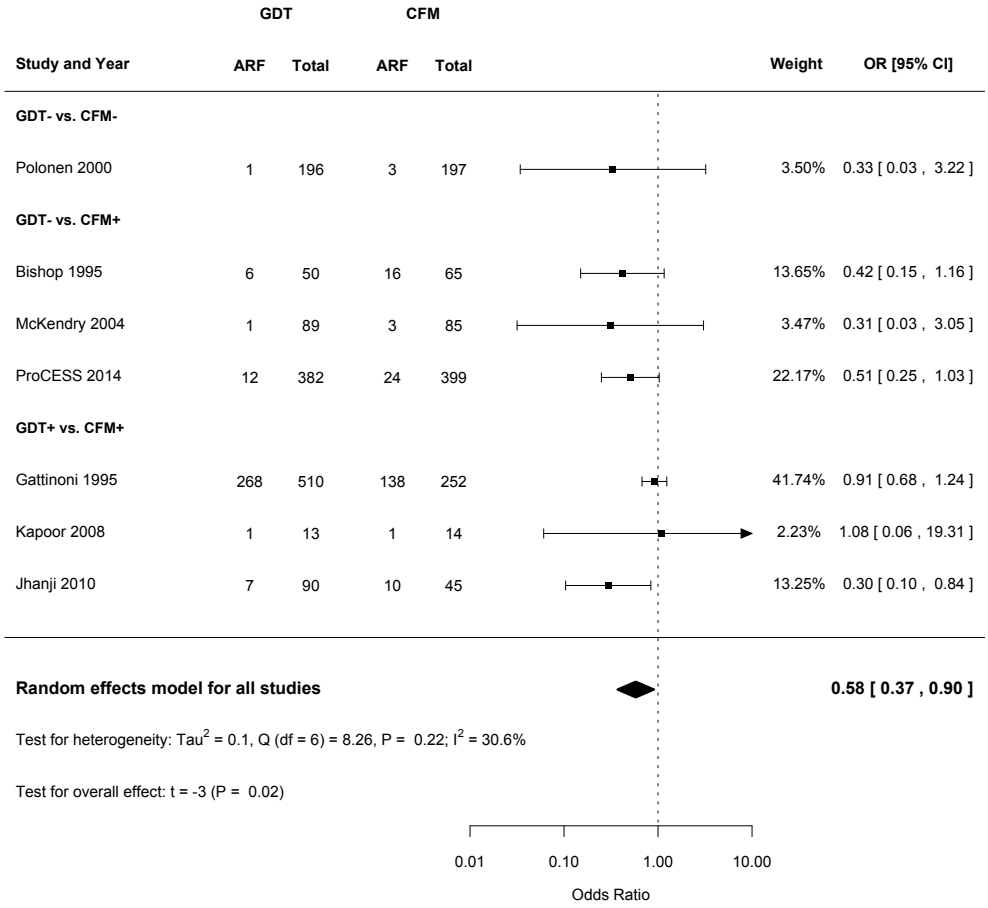


Figure S4.4 Forest plot reporting the sensitivity analysis of GDT and CFM commenced during the postoperative or ICU setting.

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CHAPTER 5

Targeting urine output and 30-day mortality in goal-directed therapy: a systematic review with meta-analysis and meta-regression.

ABSTRACT

BACKGROUND: Oliguria is associated with a decreased kidney- and organ perfusion, leading to organ damage and increased mortality. While the effects of correcting oliguria on renal outcome have been investigated frequently, whether urine output is a modifiable risk factor for mortality or simply an epiphenomenon remains unclear. We investigated whether targeting urine output, defined as achieving and maintaining urine output above a predefined threshold, in hemodynamic management protocols affects 30-day mortality in perioperative and critical care.

METHODS: We performed a systematic review with a random-effects meta-analyses and meta-regression based on search strategy through MEDLINE, EMBASE and references in relevant articles. We included studies comparing conventional fluid management with goal-directed therapy and reporting whether urine output was used as target or not, and reporting 30-day mortality data in perioperative and critical care.

RESULTS: We found 36 studies in which goal-directed therapy reduced 30-day mortality (OR 0.825; 95% CI 0.684-0.995; P=0.045). Targeting urine output within goal-directed therapy increased 30-day mortality (OR 2.66; 95% CI 1.06-6.67; P=0.037), but not in conventional fluid management (OR 1.77; 95% CI 0.59-5.34; P=0.305). After adjusting for operative setting, hemodynamic monitoring device, underlying etiology, use of vasoactive medication and year of publication, we found insufficient evidence to associate targeting urine output with a change in 30-day mortality (goal-directed therapy: OR 1.17; 95% CI 0.54-2.56; P=0.685; conventional fluid management: OR 0.74; 95% CI 0.39-1.38; P=0.334).

CONCLUSIONS: The principal finding of this meta-analysis is that after adjusting for confounders, there is insufficient evidence to associate targeting urine output with an effect on 30-day mortality. The paucity of direct data illustrates the need for further research on whether permissive oliguria should be a key component of fluid management protocols.

BACKGROUND

Textbooks and guidelines frequently recommend urine output as a parameter to guide fluid administration, since decreased organ perfusion may decrease urine output in an attempt to maintain intravascular volume (1-3). However, a suboptimal hemodynamic status is not always the cause of oliguria. In recent years, the concept of an association between intraoperative urine output and postoperative acute kidney injury has been challenged (4-6). As a result, advocacy for permissive oliguria has increased, for example to include permissive oliguria in the early recovery after surgery (ERAS) protocols (7-9).

Our group has previously published meta-analyses concerning the effects of targeting urine output on acute renal failure or acute kidney injury (10,11). A frequent remark on these meta-analyses was that while targeting urine output may not have an effect on preventing acute kidney injury, there is increasing evidence that reduced urine output is a risk factor for mortality (12-16). Especially in critically ill patients, the occurrence and severity of oliguria is associated with an increase in mortality. Whether the association between urine output and outcome is due to a causal relation or rather an epiphenomenon is yet to be determined. Nevertheless, fluids and vasoactive medication are often administered to patients with a decrease in urine output to guarantee and maintain adequate perfusion. However, whether urine output is a useful target for fluid management remains doubtful, especially when direct measures related to cardiac output and oxygen delivery are available.

We hypothesize that including urine output as a target does not decrease 30-day mortality in perioperative and critical care. This study aims to investigate whether including urine output as a target in fluid management protocols reduces 30-day mortality in perioperative and critical care.

METHODS

Search strategy

We conducted a systematic literature search of MEDLINE by using PubMed (1966 – present) and EMBASE (1980 – present). There were no studies directly investigating the effect on 30-day mortality by urine output as fluid management target in a perioperative or critical care protocol. Therefore, to determine the effect of urine output as a target, all studies comparing goal-directed therapy (GDT) and conventional fluid management (CFM) and reporting within 30-day mortality were identified. The last search was performed in May 2016. No limits for publication date or language were used. **Table S5.1 and S5.2** show the strategy for the MEDLINE and EMBASE database. The 'related articles' function in PubMed provided us with the opportunity to identify eligible studies that were not found by the main search queries. All references of the identified articles and review articles were hand

searched to avoid missing relevant trials. We screened the title and abstract of the studies found in the databases to determine whether GDT was compared to CFM and to establish whether mortality was reported. We used the full text of the article in case of uncertainty about the therapy or mortality.

Study selection

The search was performed by two authors (E.Z., M.E.). Disagreements were resolved by consensus or if necessary by a third author (ABJG). We included randomized controlled trials during perioperative or critical care into our main analysis, whereas observational studies have been collected and are reported in the supplement. Animal studies, pediatric trials (<18 years), articles written in another language than English, studies unavailable as full-text, and studies in which mortality data was not clearly described were excluded. Due to the difficulty of using urine output as a parameter after administration of diuretics, the use of diuretic drugs to increase urine output was not allowed during the intervention period. Therefore, studies using diuretics during the intervention period were excluded. Although a full description of the protocol was not required, the hemodynamic targets in the CFM arm had to be clearly reported. We excluded studies which described the CFM arm as 'standard treatment' without further elaboration. Quality assessment was performed using the Cochrane Collaboration's tool for assessing risk of bias (17).

Definitions

Goal-directed therapy was defined as any hemodynamic optimization strategy in the perioperative and critical care setting, utilizing parameters related to cardiac output and oxygen delivery, either exclusively or in combination with classical parameters such as blood pressure and heart rate, irrespective of the device or method used to measure these parameters. Urine output as a target was defined as achieving and maintaining urine output using fluids and vasoactive medication above a predefined threshold. We did not redefine the urine output thresholds and used the thresholds as set by the respective studies. We defined mortality as death by all causes within 30 days after inclusion. In case mortality was reported as 'intensive care mortality' or 'in-hospital mortality', we used the respective length of stay data to determine the survival duration. Studies in which more than 75% of the patients were admitted for less than 30 days were considered for reporting 30-day mortality.

Data collection

Two authors (E.Z., M.E.) extracted the following variables: total study population, size of GDT arm, size of CFM arm, type of patients, timing of the intervention period, definition of

GDT and CFM, urine output target criteria, intraoperative and postoperative urine output data, treatment targets in both study arms, definition of mortality and number of deaths.

Data synthesis

All selected studies were divided into three groups for the main forest plot based on whether oliguria reversal was included as a target in a study protocol: trials comparing GDT and CFM in which both the GDT protocol and the CFM protocol did not include urine output as a target, articles in which urine output was only targeted in the CFM protocol, and articles in which GDT and CFM treatment arms both included urine output as target. We analyzed whether there was a difference in 30-day mortality between the two treatment arms and in the targeting urine output subsets. A funnel plot was conducted to identify asymmetry. If publication bias was detected, possible missing studies were identified by using the 'trim and fill' method.

To investigate the effect of targeting urine output in CFM and in GDT on mortality, a meta-regression model was performed to estimate a regression equation with 30-day mortality as outcome and the use of urine output as a target as a variable for GDT and CFM. This meta-regression model was then adjusted with study setting, hemodynamic monitoring device used, underlying etiology, use of vasoactive medication and year of publication as covariates in the regression equation. The year of publication variable was centered on the mean year of publication, which was 2008.

Due to the various threshold values used as the urine output target, we performed a sensitivity analysis excluding studies utilizing a urine output target different from the conventional standard of 0.5 ml/kg/h. This sensitivity analysis was performed for both the meta-analysis as well as the meta-regression analysis.

Statistical analysis

For each study odds ratios (OR) and 95% confidence intervals (CI) were calculated, based on their sample sizes of the GDT and CFM and the reported mortality in those treatment arms. All meta-analyses were conducted as random effect meta-analyses in R (version 3.2.1) using the metafor package (18,19). The Sidik-Jonkman estimator was used in combination with Knapp & Hartung adjustment to improve estimates of the heterogeneity variance due to the low number of studies included (20,21). In studies with a count of zero in one of the treatment arms, 0.5 was added to all frequencies. Heterogeneity between the trials was analyzed using the I^2 statistic and interpreted using thresholds as defined in the Cochrane Handbook (22). A trial sequence analysis was performed to account for random error. Optimal sample size – i.e. information size – was determined using alpha=0.05 and power of 0.80 for a relative risk reduction of 25%. Due to the Knapp-Hartung adjustment utilizing a t-distribution, we converted the t-value to a z-score using a nominal p-value approach for

the trial sequence analysis. Quality of evidence was assessed using the GRADE system (23). We used a random-effects meta-regression model with targeting urine output, study setting, hemodynamic monitoring device used, underlying etiology, use of vasoactive medication and year of publication as covariates and fluid management protocol (GDT or CFM) as the inner grouping variable and study as the outer grouping variable to test the effect of the moderators on 30-day, using a bivariate approach which has been described earlier (24). This method resulted in separate regression equations for the 30-day mortality risk in GDT and in CFM. For the sensitivity analysis for studies with a urine output target of 0.5 ml/kg/h, we repeated the meta-analysis and meta-regression analysis. Odds ratios were considered statistically significant when their 95% CI did not include 1.00 and the corresponding P-value was less than 0.05.

RESULTS

Our search strategy resulted in 1435 articles. A total of 326 remained after excluding duplicates and irrelevant articles. After removing studies which met our exclusion criteria, 83 articles remained. An additional 41 studies were excluded based on the usage of diuretics, or the absence of a description of the hemodynamic parameters in the CFM arm (**Figure 5.1**).

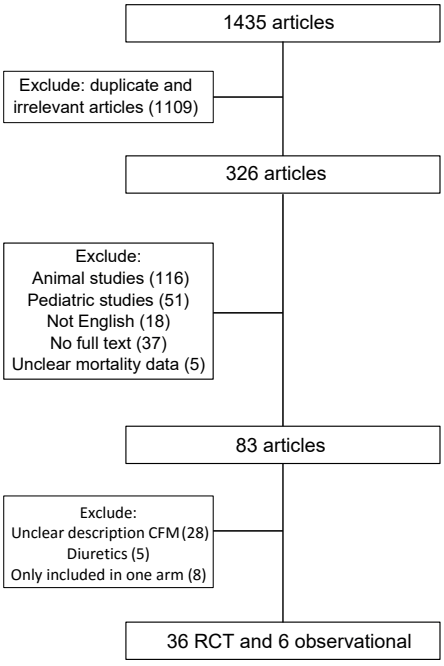

Figure 5.1 Flow chart of study selection
CFM: conventional fluid management; RCT: randomized controlled trial

Table 5.1 shows the characteristics of the remaining 36 randomized controlled trials. Thirteen studies (25-37) did not target urine output in either GDT or CFM; seven studies (38-44) only targeted urine output in the CFM protocol; and sixteen studies (45-60) targeted urine output in both protocols.

Table 5.1 Characteristics of studies included

Study	Total number	Type of patient	Timing	Mortality follow up
Not targeting urine output in either protocol				
Sinclair 1997 [23]	40	Orthopedic	intra	30 days
Polonen 2000 [24]	393	Cardiac	post	28 days
Rhodes 2002 [25]	201	Critically ill	ICU	28 days
Pearse 2005 [26]	122	High risk	post	28 days
Szakmany 2005 [27]	40	Abdominal	Intra	3 days postoperative
Wakeling 2005 [28]	128	Abdominal	intra	30 days
Forget 2010 [29]	86	Abdominal	intra	30 days
WenKui 2010 [30]	214	Abdominal	intra, post	30 days
Cecconi 2011 [31]	40	Orthopedic	intra	28 days
Challand 2012 [32]	236	Abdominal	Intra	30 days
Bartha 2013 [33]	149	Orthopedic	intra	30 days
Bisgaard 2013 [34]	70	Abdominal	intra, post	30 days
Lai 2015 [35]	221	Abdominal	Intra	30 days
Targeting urine output only in CFM				
Bishop 1995 [36]	115	Trauma	post, ICU	in-hospital (95% < 15 days)
McKendry 2004 [37]	174	Cardiac	post	30 days
Benes 2010 [38]	120	High Risk	intra	30 days
Mayer 2010 [39]	60	High Risk	Intra	in-hospital (95% < 30 days)
McKenny 2013 [40]	101	Abdominal	Intra	30 days
Zakhaleva 2013 [41]	74	Abdominal	Intra	30 days
Osawa 2016 [42]	126	Cardiac	Intra, post	30 days
Targeting urine output in both protocols				
Shoemaker 1988 [43]	88	High Risk	intra, post	in-hospital (95% < 29 days)
Boyd 1993 [44]	107	High Risk	pre, intra, post, ICU	28 days
Gattinoni 1995 [45]	762	High Risk	ICU	30 days
Lobo 2000 [46]	37	High Risk	intra, post	28 days,
Rivers 2001 [47]	263	Sepsis	ICU	28 days

Table 5.1 Characteristics of studies included (continued)

Study	Total number	Type of patient	Timing	Mortality follow up
Chytra 2007 [48]	162	Trauma	ICU	n-hospital (75% <29 days)
Donati 2007 [49]	135	Abdominal	Intra	in-hospital (95% < 30 days)
Kapoor 2008 [50]	27	Cardiac	post	in-hospital (95% < 13 days)
Senagore 2009 [51]	43	Abdominal	Intra	2 days
Jammer 2010 [52]	241	Abdominal	intra	30 days
Jansen 2010 [53]	348	Critically ill	ICU	28 days
Jhanji 2010 [54]	135	Abdominal	post, ICU	in-hospital (75% < 28 days)
Bisgaard 2013 [55]	40	Vascular	Intra, post	30 days
Zheng 2013 [56]	60	Abdominal	Pre, intra, post	in-hospital (75% <27 days)
Peng 2014 [57]	80	Orthopedic	Intra	in-hospital (95% <28 days)
Correa-Gallego 2015 [58]	135	Abdominal	Intra, post	30 days

Pre: preoperative; intra: intraoperative; post: postoperative; ICU: intensive care unit.

Hemodynamic monitoring devices and parameters used in the included studies are reported in **Table 5.2**.

Table 5.2 Hemodynamic monitoring used in selected studies

Study	Device	Hemodynamic targets	Urine output threshold	Intervention
Not targeting urine output in either protocol				
Sinclair 1997 [23]	esophageal Doppler	SV		colloids
Polonen 2000 [24]		SvO_2, Lactate		fluids, dobutamine, vasoactive medication
Rhodes 2002 [25]	PAC	PAWP		fluid boluses, vasoactive agents
Pearse 2005 [26]	LiDCO plus	SV, DO_2I		colloid, dopexamine
Szakmany 2005 [27]	PiCCO	ITBVI		crystalloid, colloid
Wakeling 2005 [28]	esophageal Doppler	SV		colloids
Forget 2010 [29]	Masimo pulse oximeter	PVI		colloids, vasoactive medication
WenKui 2010 [30]		Lactate		crystalloids, colloids, dopamine, ephedrine
Cecconi 2011 [31]	FloTrac/Vigileo	SV		colloids, vasoactive medication, dobutamine
Challand 2012 [32]	esophageal Doppler	SV		colloid

Table 5.2 Hemodynamic monitoring used in selected studies (continued)

Study	Device	Hemodynamic targets	Urine output threshold	Intervention
Bartha 2013 [33]	LiDCO	SV, DO_2I		fluids, vasoactive medication
Bisgaard 2013 [34]	LiDCO	SVI		colloids, dobutamine, vasoactive medication
Lai 2015 [35]	LiDCO	SVV		Colloids
Targeting urine output only in CFM				
Bishop 1995 [36]	PAC	DO_2I, VO_2I, CI	30-50 ml/h	volume, dobutamine
McKendry 2004 [37]	esophageal Doppler	SI	no specific goal mentioned	colloids, blood, vasoactive medication
Benes 2010 [38]	FloTrac/Vigileo	SVV	0.5 ml/kg/h	colloids, dobutamine
Mayer 2010 [39]	FloTrac/Vigileo	CI, SVI	0.5 ml/kg/h	crystalloids, colloids, norepinephrine, dobutamine, vasodilators
McKenny 2013 [40]	esophageal Doppler	SV	0.5 ml/kg/h	colloids
Zakhaleva 2013 [41]	esophageal Doppler	SV, SVR, CO, FTc	0.5-1.0 ml/kg/h	colloids
Osawa 2016 [42]	LIDCO	CI, SVI	0.5 ml/kg/h	crystalloid, dobutamine
Targeting urine ouput in both protocols				
Shoemaker 1988 [43]	PAC	Hct, PvO_2, PAP, SVR, PWP, PVR, DO_2, VO_2	30 mL/h	crystalloids, colloids, vasoactive medication
Boyd 1993 [44]	PAC	DO_2I	0.5 mL/kg/h	gelatin, dopexamine
Gattinoni 1995 [45]	PAC	CI or SvO_2	0.5 mL/kg/h	fluids, vasoactive medication
Lobo 2000 [46]	PAC	DO_2	0.5 mL/kg/h	fluids, dobutamine
Rivers 2001 [47]	computerized spectrophotometer	$ScvO_2$, MAP	0.5 mL/kg/h	crystalloid dobutamine, blood transfusions
Chytra 2007 [48]	esophageal Doppler	SV, FTc	1 mL/kg/h	colloids
Donati 2007 [49]		SvO_2, O_2ERe	0.5 mL/kg/h	fluids, dobutamine
Kapoor 2008 [50]	FloTrac/Vigileo	CVP, SVV	1 mL/kg/h	colloids, dopamine or other inotropes
Senagore 2009 [51]	esophageal Doppler	SV	0.5 mL/kg/h	colloid
Jammer 2010 [52]		$ScvO_2$	0.5 mL/kg/h	crystalloids, colloid
Jansen 2010 [53]	CeVOX	Lactate, $ScvO_2$	0.5 mL/kg/h	fluids, vasodilator therapy

Table 5.2 Hemodynamic monitoring used in selected studies (continued)

Study	Device	Hemodynamic targets	Urine output threshold	Intervention
Jhanji 2010 [54]	LiDCO	SV	25 mL/h	fluids, dopexamine
Bisgaard 2013 [55]	LiDCO	DO_2I, SVI	0.5–1.0 mL/kg/h	colloid, dobutamine
Zheng 2013 [56]	FloTrac/Vigileo	CI, SVI, SV	0.5 mL/kg/h	balanced salt solution, colloid, dopamine / norepinephrine, nitroglycerin / ephedrine
Peng 2014 [57]	FloTrac/Vigileo	SVV	0.5 mL/kg/h	Crystalloid, colloid,
Correa-Gallego 2015 [58]	FloTrac/Vigileo	SVV	25 mL/h for 2 consecutive hours	Crystalloid, colloid, albumin bolus infusions

PAC: pulmonary artery catheter; PAC+: pulmonary artery catheter with supranormal hemodynamic targets; pre: preoperative; intra: intraoperative; post: postoperative; ICU: intensive care unit; ITBVI: intrathoracic blood volume index; SV: stroke volume; DO_2I: oxygen delivery index; PAOP: pulmonary artery occlusion pressure; CI: cardiac index; CO: cardiac output; 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; SvO_2: mixed venous oxygen saturation; PAWP: pulmonary artery wedge pressure; FTc: corrected flow time; PAWP: pulmonary artery wedge pressure; SVV: stroke volume variation; VO_2I: oxygen consumption index; SI: stroke index; O_2ERe: oxygen extraction estimate; $ScvO_2$: 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; VO2: oxygen consumption; UO: urine output.

The amount of fluids infused during GDT and CFM in each study is reported in **Table S5.3**. The risk of bias assessment is shown in **Figure 5.2**. Of the 23 studies which included urine output as a target, fifteen studies had a threshold of 0.5 ml/kg/h (**Table 5.2**). For the limited number of studies in which urine output was reported, the urinary data are reported in **Table S5.4**. The data on the six observational studies (61-66) are reported in **Table S5.5 and S5.6**.

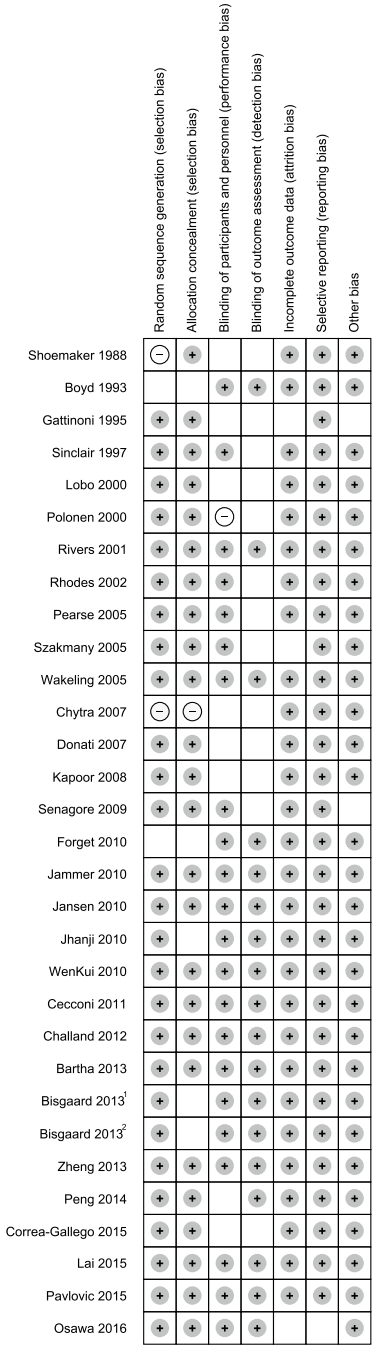

Figure 5.2 Risk of bias assessment

Risk of bias assessment performed with the Cochrane Collaboration tool.(17)
Because there are two studies by Bisgaard et al published in 2013, [1] marks reference (36), and [2] marks reference (57). Gray circle: low risk of bias; blank: unclear risk of bias; white circle: high risk of bias.

Meta-analysis

Because there was no direct data on the effect of targeting urine output on mortality, we first pooled the studies comparing GDT with CFM based on the presence of urine output as a target in either fluid management protocols. Overall, GDT was associated with a decrease in 30-day mortality (OR 0.83; 95% CI 0.68 to 1.00; P = 0.04; I^2 = 28%; N = 36) (**Figure 5.3**).

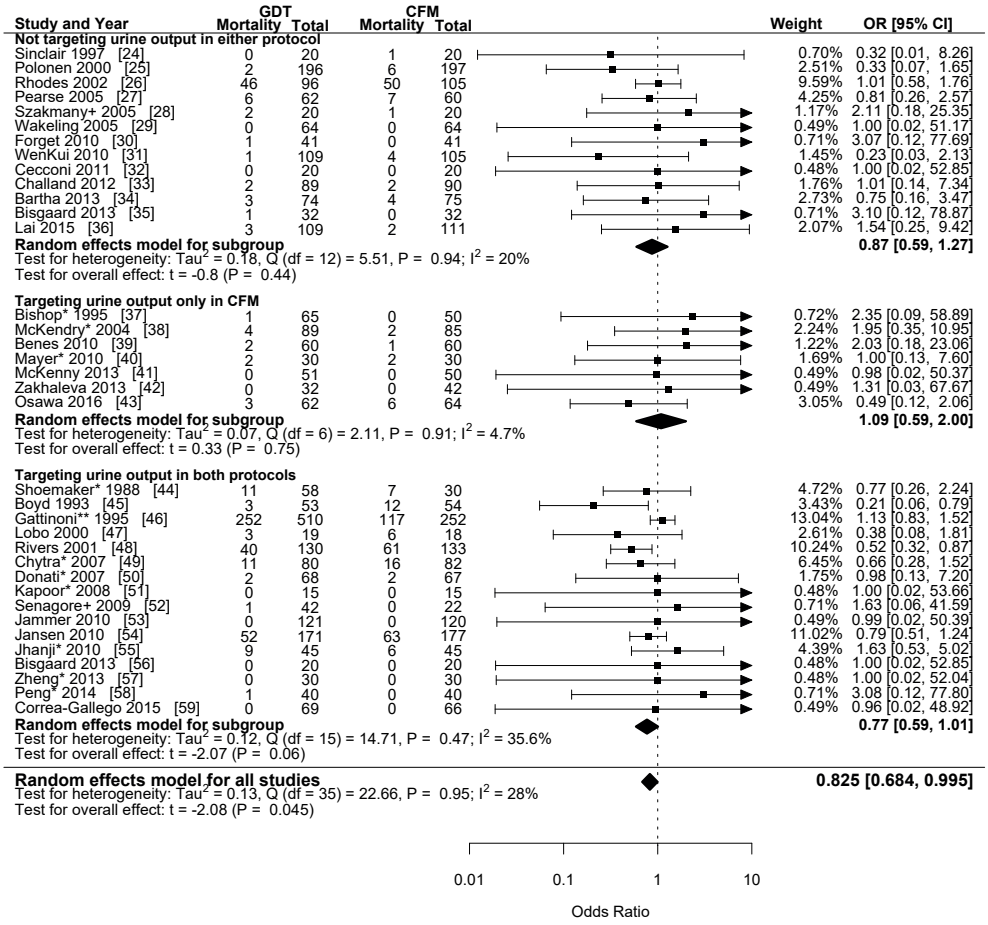

Figure 5.3 Forest plot of 36 studies reporting 30-day mortality when comparing goal-directed therapy with conventional fluid management.

+: mortality follow-up was shorter than 28 days. *: mortality reported as in-hospital mortality. **: mortality data extracted from Kaplan-Meier curve.
GDT: goal-directed therapy; CFM: conventional fluid therapy; OR: odds ratio; CI: confidence interval.

However, there was insufficient evidence for a decrease in 30-day mortality due to GDT in all the subgroups. The heterogeneity was low to moderate. The funnel plot is shown in **Figure S5.1**. A slight asymmetry was detected; and identification of eight possible missing studies altered the point estimate (OR 0.75; 95% CI 0.56 to 1.00; P = 0.05; I^2 = 32.8%). The trial sequential analysis is shown in **Figure S5.2**. Despite reaching statistical significance, the required information size of 7400 was not reached and the cumulative Z-score did not cross the monitoring boundaries. This suggests that the results for the beneficial effects of GDT on mortality in this meta-analysis are inconclusive, and the quality of evidence – as assessed by GRADE – is limited.

Meta-regression analysis

To assess the effects of urine output as a fluid management target from the available data, we performed a meta-regression analysis to estimate a regression line for GDT and CFM with targeting urine output as a secondary variable. There was insufficient evidence to suggest that targeting urine output influences 30-day mortality in a CFM protocol (OR 1.77; 95% CI 0.59-5.34; P=0.305). However, targeting urine output increased 30-day mortality when using GDT (OR 2.66 95% CI 1.06-6.67; P=0.037). After adjusting for study setting, hemodynamic monitoring device, underlying etiology, use of vasoactive medication and year of publication (**Table 5.3**), there was insufficient evidence to associate targeting urine output with an effect on 30-day mortality when using a CFM protocol (OR 0.74; 95% CI 0.39-1.38; P=0.334) and a GDT protocol (OR 1.17; 95% CI 0.54-2.56; P=0.685).

Table 5.3 Meta-regression model with 30-day mortality as outcome for conventional and goal-directed fluid therapy

Variable	CFM	GDT
Targeting urine output	0.74 (0.39-1.38)	1.17 (0.54-2.56)
Intensive Care setting (reference)		
Intraoperative setting	0.15 (0.08-0.28)	0.12 (0.05-0.28)
Postoperative setting	0.06 (0.02-0.15)	0.12 (0.03-0.51)
Transpulmonary thermodilution (reference)		
Esophageal Doppler		0.67 (0.21-2.11)
Pulmonary artery catheter		0.79 (0.27-2.27)
Other monitoring devices		1.27 (0.25-6.35)
Other etiologies (reference)		
Abdominal	0.32 (0.15-0.69)	0.76 (0.32-1.77)
High risk	2.13 (0.94-4.81)	2.19 (0.74-6.51)

Table 5.3 Meta-regression model with 30-day mortality as outcome for conventional and goal-directed fluid therapy (continued)

Variable	CFM	GDT
Inotropic use	1.40 (0.72-2.69)	1.01 (0.4-2.53)
Publication year [a]	0.97 (0.93-1.02)	1.00 (0.91-1.10)

[a]Publication year was inputted as the years from the mean publication year (2008).
Data reported as odds ratio and 95% confidence interval.

Sensitivity analysis

In the sensitivity analysis excluding studies with a urine output threshold different from the conventional standard of 0.5 ml/kg/h in the targeting urine output group, GDT was associated with a decrease in 30-day mortality (OR 0.78; 95% CI 0.63 to 0.97; P = 0.03; I^2 = 31.8%; N = 29, **Figure S5.3**). In the bivariate meta-regression analysis, we found insufficient evidence to suggest that targeting urine output with a threshold of 0.5 ml/kg/h was associated with an increase in 30-day mortality when using a CFM protocol (OR 1.90; 95% CI 0.56 to 6.50; P=0.300) and in a GDT protocol (OR 2.46; 95% CI 0.80 – 7.59; P=0.114). After adjusting for covariates (**Table 5.4**), targeting urine output was not associated with a change in 30-day mortality when using a CFM protocol (OR 0.89; 95% CI 0.41 - 1.91; P=0.756) and a GDT protocol (OR 1.08; 95% CI 0.48 – 2.44; P=0.852).

Table 5.4 Meta-regression model of sensitivity analysis with 30-day mortality for conventional and goal-directed fluid therapy

Variable	CFM	GDT
Targeting urine output	0.56 (0.29-1.11)	0.68 (0.34-1.36)
Intensive Care setting (reference)		
Intraoperative setting	0.16 (0.08-0.30)	0.14 (0.08-0.24)
Postoperative setting	0.07 (0.03-0.16)	0.17 (0.05-0.57)
Transpulmonary thermodilution (reference)		
Esophageal Doppler		0.61 (0.23-1.60)
Pulmonary artery catheter		0.21 (0.07-0.63)
Other monitoring devices		1.80 (0.51-6.33)
Other etiologies (reference)		
Abdominal	0.48 (0.21-1.10)	1.14 (0.54-2.38)
High risk	2.36 (0.99-5.67)	1.19 (0.61-2.30)

Table 5.4 Meta-regression model of sensitivity analysis with 30-day mortality for conventional and goal-directed fluid therapy (continued)

Variable	CFM	GDT
Inotropic use	1.43 (0.67-3.07)	1.15 (0.47-2.81)
Publication year [a]	0.95 (0.9-1.00)	0.95 (0.88-1.03)

The sensitivity analysis excluded studies in which the urine output threshold was not 0.5 ml/kg/h. [a]Publication year was inputted as the years from the mean publication year (2008). Data reported as odds ratio and 95% confidence interval.

DISCUSSION

The principal finding of this meta-analysis is that while GDT might decrease 30-day mortality, including urine output as a target may increase 30-day mortality. However, after adjusting for confounders, there is insufficient evidence to associate targeting urine output with an effect on 30-day mortality. Additionally, using the common urine output threshold of 0.5 ml/kg/h, there was insufficient evidence to suggest that targeting urine output affected 30-day mortality. Considering our previous findings that targeting urine output does not prevent acute renal failure (10,11), our current finding adds further evidence to strongly reconsider the use of urine output as a fluid management target.

Our data shows that GDT is associated with an overall decrease in 30-day mortality, although barely reaching significance. This is partially in agreement with previously published meta-analyses on GDT and mortality. While one meta-analysis in surgical patients reported that GDT was associated with a decrease in mortality (67), another meta-analysis in surgical patients found no such effect (68). The difference in mortality between these two meta-analyses may be due to studies published after the publication of the meta-analysis by Brienza et al (67). The disagreement between the meta-analysis by Corcoran et al. (68) and our meta-analysis may be due to three reasons: the inclusion of newer studies, the addition of critical care studies, and the follow-up period for mortality. Additionally, the meta-analysis by Zhang et al. showed that patients with severe sepsis or septic shock receiving GDT had a similar risk of mortality compared with those in the control group (69). Nevertheless, as the optimal information size metric suggests, the currently available pool of studies may be insufficient to conclusively state any effect of GDT on mortality.

This meta-analysis supports the hypothesis that oliguria is likely an epiphenomenon rather than a modifiable risk factor. In a perioperative setting, low urine output is common in the first 24 hours after surgery and in the absence of other issues it does not reliably reflect fluid status (5). Moreover, urine output is influenced by factors other than the hemodynamic status (70,71). Surgical trauma and physical stress in critical illness cause the release of neuro-hormonal factors which influence glomerular filtration pressure or water reabsorption in the collecting duct, such as catecholamines, arginine vasopressin

and the renin-angiotensin-aldosterone system. While these neuro-hormonal factors are also upregulated in hypovolemia resulting in oliguria, the perioperative or critical care setting itself promote the occurrence of oliguria. Additionally, anesthetic techniques and medication can affect neuro-hormonal factors as well as vasomotor tone. Moreover, using urine output to guide fluid management is inherently flawed due to the delayed response. Evaluating the urinary response to a fluid challenge is generally possible after at least 15-30 minutes and is limited by the lack of a clear dose-response relationship. In contrast, hemodynamic parameters such as cardiac output are dynamic variables which are influenced within a short interval after a fluid challenge is given and for most variables a dose-response relationship has been given. Thus, the primary cause of oliguria may not be affected by fluid administration or may already have been resolved by acting on another target.

In light of this, the use of permissive oliguria has already been advocated in ERAS protocols, primarily to avoid excess fluid loading (7). In patients managed by hemodynamic targets with a better correlation to fluid status, the occurrence of oliguria due to hemodynamic causes is unlikely, which favors the exclusion of urine output as a target for fluid resuscitation. Considering this, the current paradigm that urine output reflects renal injury and – perhaps indirectly – increases mortality needs to be revisited (12,15). In most – if not all – cases, oliguria is most likely an epiphenomenon of an underlying problem. A recent study showed that after adjusting for confounders while intraoperative urine output was not associated with postoperative morbidity, total intraoperative fluid intake and postoperative fluid boluses for hypotension and low urine output were associated with an increase in postoperative morbidity (60). This strongly suggests that urine output should not be a target in a fluid management protocol to improve outcome.

This meta-analysis has several important limitations. The main limitation is the various sources of heterogeneity. The I^2 statistic showed low to moderate heterogeneity in most analyses. However, considering the different hemodynamic targets, fluid types, vasopressor use, monitoring devices, underlying etiologies, clinical settings and mortality follow-up used in these studies, assuming that the heterogeneity is as low as suggested by the I^2 statistic would be imprudent. Because data on fluids infused was not reported as a statistical measure and urinary data was rarely reported at all, further analysis of these data points was not possible. Despite the use of a random-effects model and a bi- and multivariate approach to a meta-regression analysis, the effects of between-trial differences are most likely not completely taken into account (20,21). Since our findings are based on between-trial statistical analyses, given the large differences between the included studies, the interpretation of these findings – even after adjusting for operative setting, underlying etiology and other confounders - should be done with care. Understandably, given the absence of trials primarily investigating the effects of urine output as a target, to account

for all the possible sources of heterogeneity within the currently available literature would be impractical and the inability to do so is currently an inevitable limitation. However, after acknowledging this limitation, our findings are currently the only assessment of the effects of targeting urine output on mortality, and are supported by the observations from various trials (6,60).

Another important limitation is the low number of studies given the available literature on GDT. The potential for robust conclusions by using meta-regression is limited by the number of studies (72). However, to ensure that heterogeneity was limited as much as possible, several of the larger - and perhaps more convincing – trials were excluded. The three recent large studies - ARISE, PROCESS and PROMISE - were not included in this meta-analysis, due to meeting our exclusion criterion of vague CFM protocols (73-75). While their exclusion may limit the generalization of our findings, the strict inclusion and exclusion criteria removes bias caused by some of the heterogeneity. Given that our main objective was to assess the effect of targeting urine output on 30-day mortality, removing as many sources of heterogeneity as possible strengthens our findings. Similarly, despite the absence of these large trials, the mortality rate in most studies is close to the estimated 30-day mortality rate in elective – high risk – surgery (±7%) and critical care (±15%) (76-78). Additionally, a slight asymmetry was found in the funnel plot, and after applying the 'trim and fill' method, the effect size of eight possible missing studies were added to the analysis. In combination with the trail sequential analysis, this suggests insufficient evidence to support a difference in 30-day mortality between GDT and CFM, despite the analysis in **Figure 5.3**, and illustrates the dependence on adequate sample size to establish definite conclusions.

CONCLUSION

In conclusion, based on the currently available literature, we found that GDT might decrease 30-day mortality, including urine output as a target may increase 30-day mortality. However, the principal finding of this meta-analysis is that after adjusting for confounders, there is insufficient evidence to associate targeting urine output with an effect on 30-day mortality. This suggests that oliguria is not a modifiable risk factor for mortality and using diuresis to guide fluid management may not affect survival. However, the paucity of direct data illustrates the need for further research on whether oliguria is just an epiphenomenon and whether 'permissive oliguria' should be a key component of fluid management protocols.

SUPPLEMENTAL

Table S5.1 Search strategy in MEDLINE database through PubMed

#49	((#41 AND #48))	446
#48	((#44 OR #47))	
#47	((#45 OR #46))	
#46	"controlled trial"	
#45	trial	
#44	((#42 OR #43))	
#43	"randomised"	
#42	"randomized"	
#41	((#31 AND #40))	
#40	((#12 AND #39))	
#39	((#32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38))	
#38	fluid	
#37	"fluid resuscitation"	
#36	"fluid loading"	
#35	"fluid administration"	
#34	"fluid management"	
#33	"fluid therapy"	
#32	"fluid therapy"[MeSH]	
#31	((#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30))	
#30	outcome	
#29	"urinary output"	
#28	"urine production"	
#27	"urine output"	
#26	"diuresis"	
#25	"mortality rate"	
#24	"loss of life"	
#23	decease	
#22	lethality	
#21	fatality	
#20	survival	
#19	death	
#18	mortality	
#17	"mortality"[MeSH]	
#16	"acute kidney injury"	

#15	"complications"	
#14	"organ dysfunction"	
#13	"organ failure"	
#12	(#1 OR #2 OR #3 # OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)	
#11	"supranormal"	
#10	"goal directed therapy"	
#9	"goal-directed therapy"	
#8	optimisation	
#7	optimization	
#6	"cardiac index"	
#5	"stroke volume"	
#4	"cardiac output"	
#3	"hemodynamic target"	
#2	"goal-directed"	
#1	"goal directed"	

Table S5.2 Search strategy in EMBASE database

#47	#39 AND #46	890
#46	#42 OR #45	
#45	#43 OR #44	
#44	"controlled trial"	
#43	trial	
#42	#40 OR #41	
#41	"randomised"	
#40	"randomized"	
#39	#30 AND #38	
#38	#12 AND #37	
#37	((#31 OR #32 OR #33 OR #34 OR #35 OR #36))	
#36	fluid	
#35	"fluid resuscitation"	
#34	"fluid loading"	
#33	"fluid administration"	
#32	"fluid management"	
#31	"fluid therapy"	
#30	((#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29))	
#29	outcome	
#28	"urinary output"	
#27	"urine production"	
#26	"urine output"	
#25	"diuresis"	
#24	"mortality rate"	

#23	“loss of life”
#22	decease
#21	lethality
#20	fatality
#19	survival
#18	death
#17	mortality
#16	“acute kidney injury”
#15	“complications”
#14	“organ dysfunction”
#13	“organ failure”
#12	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)
#11	“supranormal”
#10	‘goal-directed’
#9	‘goal directed’
#8	optimisation
#7	optimization
#6	“cardiac index”
#5	“stroke volume”
#4	“cardiac output”
#3	“hemodynamic target”
#2	‘goal-directed therapy’
#1	‘goal directed therapy’

Table S5.3 Amount of fluids infused during the relevant study period.

Study	Total fluid amount GDT (mL)	Total fluid amount CFM (mL)
Not targeting urine output in either protocol		
Sinclair 1997	1475	1000
Polonen 2000	3193	2772
Rhodes 2002	4953	4295
Pearse 2005	2962	2164
Szakmany 2005	5458	5298
Wakeling 2005	5000	4500
Forget 2010	5777	6835
WenKui 2010	2800	2800
Cecconi 2011	6229	3293
Challand 2012	5309	4010
Bartha 2013	1310	1197
Bisgaard 2013	7236	8953
Lai 2015	5369	4532

Table S5.3 Amount of fluids infused during the relevant study period. (continued)

Study	Total fluid amount GDT (mL)	Total fluid amount CFM (mL)
Targeting urine output only in CFM		
Bishop 1995	5496	6165
McKendry 2004	2020	1370
Benes 2010	3746	3729
Mayer 2010	4528	4494
McKenny 2013	2000	2500
Zakhaleva 2013	5300	5600
Osawa 2016	1056	894
Targeting urine output in both protocols		
Shoemaker 1988	-	-
Boyd 1993	5075	4845
Gattinoni 1995	-	-
Lobo 2000	7200	6600
Rivers 2001	4981	3499
Chytra 2007	4516	3599
Donati 2007	4391	4285
Kapoor 2008	-	-
Senagore 2009	3400	3000
Jammer 2010	3875	6490
Jansen 2010	3019	2390
Jhanji 2010	1879	1743
Bisgaard 2013	4314	3616
Zheng 2013	2650	3950
Peng 2014	2100	2600
Correa-Gallego 2015	2000	2900

Pre: preoperative; intra: intraoperative; post: postoperative; ICU: intensive care unit.

Table S5.4 Available urine output data from the selected studies

	Intraoperative urine output			Postoperative urine output		
Study	**GDT**	**CFM**	**P**	**GDT**	**CFM**	**P**
Not targeting urine output						
Szakmany 2005	757 mL ± 533	755 mL ± 528	NS			
Cecconi 2011	1225 mL (IQR 650 - 1375)	300 mL (IQR 100 - 475)	<0.0001			
Challand 2012	655 mL ± 302	388 mL ± 355	<0.001			
Bartha 2013	400 mL (range 0 - 1900)	300 mL (range 0 - 1300)	NS	400 mL (range 0 - 2275)	350 mL (range 25 - 4800)	NS
Targeting urine output						
Gattinoni 1995				95.8 mL ± 50.1	CIG: 102 mL ± 49.5 O_2G: 95.5 mL ± 49.5	0.274
Kapoor 2008				230* mL	140* mL	NS
Jammer 2010	1.1 ml/kg/h ± 1.5	1.5 ml/kg/h ± 1.5	0.020	83 mL 1 ± 445	1104 mL ± 449	<0.001
Zheng 2013	618 mL ± 239	800 mL ± 304	<0.001	518 mL ± 330	870 mL ± 304	<0.001
Peng 2014	1.98 ml/kg/h (IQR 1.29 - 2.63)	2.20 ml/kg/h (IQR 1.53 - 3.25)	NS			
Correa-Gallego 2015	200 mL ± 100	300 mL ± 200	0.10	900 mL ± 600	1000 mL ± 500	0.07

Data as reported by the respective studies as either mean ± standard deviation or median (interquartile range (IQR) or range), in mL or mL/kg/h. *: approximated from figure. GDT: goal-directed therapy; CFM: conventional fluid management; CIG: cardiac index guided group; O_2G: oxygen saturation guided group. NS: not statistically significant.

Table S5.5 Characteristics of observational studies included

Study	Total number	Type of patient	Timing	Mortality (GDT vs CFM), follow up
Not targeting urine output in either protocol				
Hussien 2011	25	Abdominal	intra	1 vs 0, 10 days
See 2014	612	Critically ill	ICU	90 vs 148, 30 days
Thomson 2014	264	Cardiac	Post	0 vs 2 ,30 days
Cannesson 2015	330	Abdominal, pelvic	intra	2 vs 1, 30 days
Targeting urine output in both protocols				
Sivayoham 2012	174	Critically ill	ICU	22 vs 33, 30 days
Reydellet 2013	50	Abdominal	Intra, post	1 vs 4, 30 days

Pre: preoperative; intra: intraoperative; post: postoperative; ICU: intensive care unit.

Table S5.6 Hemodynamic monitoring used in observational studies

Study	Device	Hemodynamic targets	Urine output threshold	Intervention
Not targeting urine output in either protocol				
Hussien 2011	Oesophageal Doppler	SV		colloids
See 2014		PP, SV		crystalloids
Thomson 2014	LiDCOplus	SV		colloids, cystalloids, blood products
Cannesson 2015	EV 1000, Edwards	SV, SVV, CI		crystalloids
Targeting urine output in both protocols				
Sivayoham 2012		SVO_2, CI,	0.5 ml/kg/h	crystalloids, colloids, vasoactive medication
Reydellet 2013	FloTrac-Vigileo	MAP, CO, CI, SV, SVV, ScvO2	no specific goal mentioned	colloids, crystalloids vasoactive medication

SV: stroke volume; PP: pulse pressure; SVV: stroke volume variation; CI: cardiac index; SvO_2: mixed venous oxygen saturation; MAP: mean arterial pressure; CO: cardiac output; $ScvO_2$: central venous oxygen saturation;

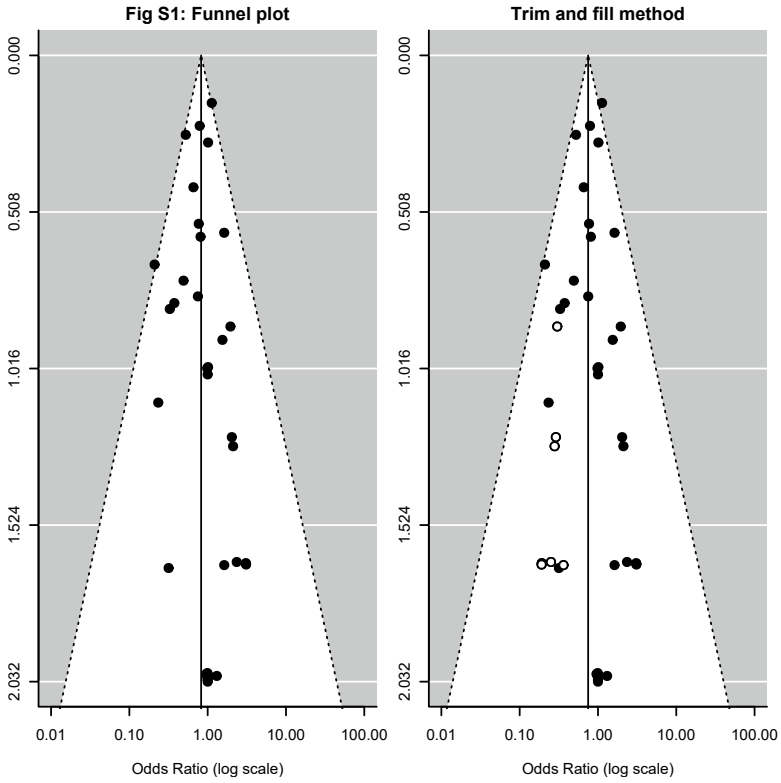

Figure S5.1: Funnel plot used to assess the presence of publication bias in the performed analysis.

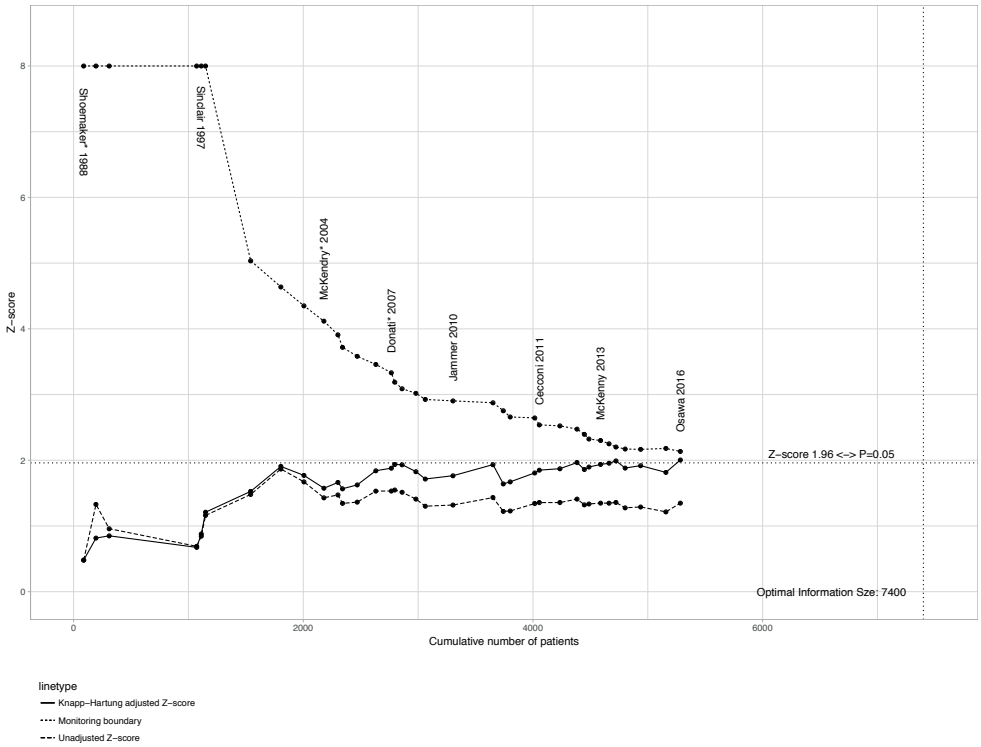

Figure S5.2: Trial sequential analysis for cumulative meta-analysis.

Data is analyzed cumulatively in order of year of publication, and the optimal information size (sample size) is 7400 patients to find a 25% relative risk reduction with a power of 80% and an alpha of 0.05.

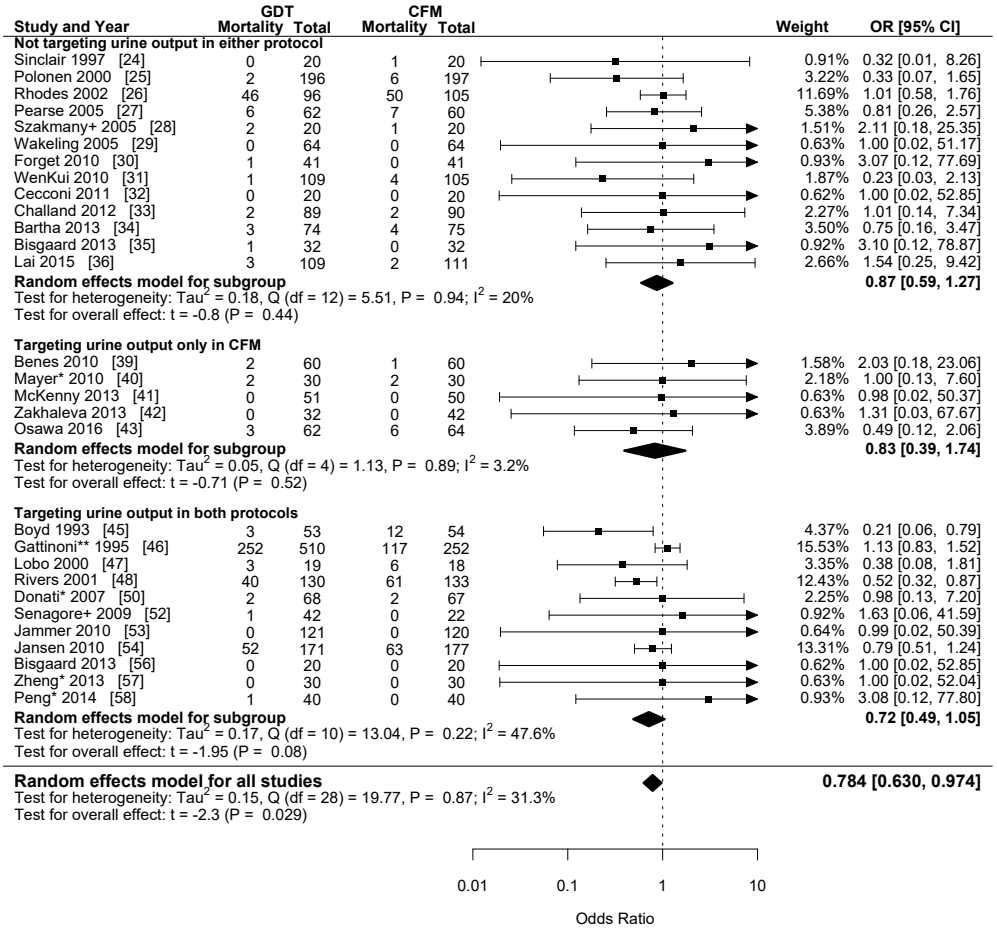

Figure S5.3: Forest plot of sensitivity analysis (urine output threshold 0.5 ml/kg/h) on 30-day mortality when comparing goal-directed therapy with conventional fluid management.
+: mortality follow-up was shorter than 28 days. *: mortality reported as in-hospital mortality. **: mortality data extracted from Kaplan-Meier curve. GDT: goal-directed therapy; CFM: conventional fluid therapy; OR: odds ratio; CI: confidence interval. PDF.

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CHAPTER 6

Targeting oliguria reversal in perioperative restrictive fluid management does not influence the occurrence of renal dysfunction: a systematic review and meta-analysis

ABSTRACT

BACKGROUND: Interest in perioperative fluid restriction has increased, but it could lead to hypovolemia. Urine output is viewed as surrogate for renal perfusion and is frequently used to guide perioperative fluid therapy. However, the rationale behind targeting oliguria reversal - achieving and maintaining urine output above a previously defined threshold by additional fluid boluses - is often questioned.

OBJECTIVE: We assessed whether restrictive fluid management had an effect on the occurrence of oliguria, acute renal failure (ARF), and fluid intake. We also investigated whether targeting oliguria reversal affected these parameters.

DESIGN: Systematic review of randomized controlled trials with meta-analyses. We used the definitions of restrictive and conventional fluid management as provided by the individual studies.

DATA SOURCES: We searched MEDLINE (1966 – present), EMBASE (1980 – present), and relevant reviews and articles.

ELIGIBILITY CRITERIA: We included randomized controlled trials with adult patients undergoing surgery comparing a restrictive fluid management against a conventional fluid management protocol and also reporting the occurrence of postoperative ARF.

RESULTS: We included fifteen studies with a total of 1594 patients. There was insufficient evidence to associate restrictive fluid management with an increase in oliguria (restrictive 83/186 vs conventional 68/230; odds ratio 2.07; 95% confidence interval (CI) 0.97-4.44; P=0.06;I^2=23.7%;$N_{studies}$=5). The frequency of ARF in restrictive and conventional fluid management was 20/795 and 20/799 respectively (odds ratio 1.07;95% CI 0.60-1.92;P=0.8;I^2=17.5%;$N_{studies}$=15). There was no statistically significant difference in ARF occurrence between studies targeting oliguria reversal and not targeting oliguria reversal (odds ratio 0.31;95% CI 0.08-1.22;P=0.088). Intraoperative fluid intake was 1.89 liters lower in restrictive than in conventional fluid management when not targeting oliguria reversal (95% CI -2.59L to -1.20L P<0.001;I^2=96.6%;$N_{studies}$=7), and 1.63 liters lower when targeting oliguria reversal (95% CI -2.52L to -0.74L;P<0.001;I^2=96.6%;$N_{studies}$=6).

CONCLUSIONS: Our data suggests that, even though event numbers are small, perioperative restrictive fluid management does not increase oliguria or postoperative ARF, while decreasing intraoperative fluid intake, irrespective of targeting reversal of oliguria or not.

INTRODUCTION

Interest in restrictive fluid management has increased over the past decade, mainly due to increasing evidence of adverse events associated with positive fluid balances in surgical and critically ill patients (1-4). The large fluid volumes in standard perioperative fluid management were intended to compensate for hypovolemia due to non-anatomical third-space loss and preoperative fasting (5), though in recent years both these concepts have been called into question (6-8). While several meta-analysis have associated restrictive fluid management with lower mortality and complication rates after abdominal and major surgery (9-11), the main argument against reducing intraoperative fluid intake was that it would lead to persistence of hypovolemia and thereby induce or aggravate renal injury. However, a recent meta-analysis by Boland et al. concluded that perioperative fluid restriction in major abdominal surgery had no effect on postoperative acute renal failure (ARF) (12).

Even so, clinicians widely use urine output as surrogate for renal perfusion to guide perioperative fluid therapy (13,14). Many perioperative care protocols include oliguria reversal as a resuscitation target to maintain urine output above a certain predefined threshold and advocate additional fluid boluses when oliguria occurs in an attempt to improve diuresis. However, the relation between perioperative urine output and postoperative ARF is weak at best (15). Oliguria is not always due to a decrease in renal perfusion pressure or glomerular perfusion and therefore will not necessarily benefit from fluid therapy aimed at improving cardiac output and systemic blood pressure. Intra-abdominal pressure during abdominal surgery and neurohormonal regulation due to surgical stress are likely fluid unresponsive causes of oliguria during surgery (16), and administering fluids to increase urine output in these cases may lead to fluid overload without any renal benefits. Conversely, if fluid boluses are withheld when oliguria occurs in a hypovolemic patient, the persistence of renal hypoperfusion may over time induce damage leading to ARF. Even though the rationale behind targeting oliguria reversal is often questioned, especially when hemodynamic monitoring tools which can estimate cardiac output are available, it still remains widely used.

Objectives

We investigated whether perioperative restrictive fluid management had an effect on the occurrence of oliguria, ARF, fluid intake and fluid balance. We also investigated whether targeting oliguria reversal influenced these parameters. We hypothesized that excluding oliguria reversal as target does not affect these parameters when used in a restrictive fluid management protocol.

METHODS

Eligibility criteria

We performed a systematic literature search to identify all studies investigating restrictive fluid management and also reporting the occurrence of ARF. We included studies with adult surgical patients, performed as randomized controlled trials, and comparing restrictive with conventional fluid management in the perioperative period. Studies only using restrictive fluid management in the postoperative setting were also eligible for inclusion; however the intraoperative data - if available - was not pooled with the intraoperative data from the other studies. We excluded articles not in English or unavailable as full-text. We excluded studies directly comparing restrictive fluid management strategy against a goal-directed therapy strategy, because, while goal-directed therapy leads to the infusion of a fluid volume equal to conventional fluid management (17), the additional hemodynamic measurements would introduce bias. However, studies in which both the restrictive and the control group were treated using a goal-directed therapy strategy were included, and the control group was allocated to the conventional fluid management group. We excluded studies with protocols in which diuretics were administered when oliguria occurred to increase urine output; however studies that use diuretic for indications outside the fluid management protocol or for indications not related to the reversal of oliguria were not excluded.

Definitions

We used the definitions of restrictive and conventional fluid management as provided by the individual studies. We defined targeting oliguria reversal as the concept of achieving and maintaining urine output above a previously defined threshold by additional fluid boluses - in combination with vasoactive medication – guided by the occurrence of oliguria. Because the currently used term acute kidney injury is specifically linked to the RIFLE and later criteria (18), we used the term ARF for all definitions using a relative or absolute increase in serum creatinine, need for renal replacement therapy, or any combination of the previous with any severity and length of oliguria - as defined in the selected studies.

Search strategy

We searched the MEDLINE (1966 – present) database via PubMed and the EMBASE (1980 – present) database (last search August 2015) using combinations of the following MESH terms and keywords; a full search strategy for the MEDLINE database is presented in **Supplement Table S6.1** and for the EMBASE database in **Supplement Table S6.2**. We handsearched references of studies considered for inclusion and references of the review articles for eligible studies. We screened the title and abstract of the studies found in the

search to see whether the study fulfilled our inclusion criteria, and if the occurrence of ARF was not reported in the abstract, we screened the full-text article.

Data collection

Using a predefined study form, one author (M.E.) scored the following variables: total study population; group sizes; type of patients; presence or absence of oliguria reversal in treatment protocols; urine output threshold to define oliguria; occurrence of oliguria; definition of ARF; duration of postoperative period in which ARF was assessed; and occurrence of ARF; intraoperative fluid intake; postoperative fluid intake; postoperative fluid balance; operative periods in which the study was performed. Once included, the studies were scored according to the Jadad scale on: reporting whether randomized or not and by which method; the method of blinding used and whether this was appropriate; and adequate reporting of withdrawals and dropouts (19).

Data synthesis

To investigate whether targeting oliguria reversal had an effect on oliguria, ARF occurrence, fluid intake and fluid balance, we assigned all included studies to one of two groups based on whether oliguria reversal was included as a target in the study protocol: restrictive fluid management compared with conventional fluid management without oliguria reversal as a target in both protocols; and restrictive fluid management compared with conventional fluid management with oliguria reversal as a target in both protocols.

We first analyzed whether there was a difference in the occurrence of intraoperative study-defined oliguria between restrictive and conventional fluid management. The second analysis was to investigate the difference in ARF occurrence between restrictive and conventional fluid management. We also performed a sensitivity analysis based on whether ARF was defined as need for renal replacement therapy or as an increase in serum creatinine levels. We then pooled studies reporting intraoperative fluid intake to investigate whether the mean fluid difference between restrictive and conventional fluid management differed between studies targeting and studies not targeting oliguria reversal. We similarly pooled studies reporting postoperative fluid intake and postoperative fluid balance. In studies reporting postoperative fluid balance as a change from preoperative weight, we made the assumption that 1 kilogram of weight gain was equal to a volume increase of 1 liter.

Due to the lack of studies directly comparing the inclusion and exclusion of oliguria reversal as a target in a perioperative restrictive fluid management protocol, we performed an indirect comparison to assess the effects of targeting oliguria reversal. We compared the cumulative ARF occurrence of studies including oliguria reversal as a target with studies

without oliguria reversal as a target, grouped according to the use of either restrictive or conventional fluid management protocols.

Statistical analysis

We calculated the odds ratio (OR) and corresponding 95% confidence interval (CI) of each study for occurrence of ARF using the available dichotomous data. In studies with a count of zero in one of the treatment arms, 0.5 was added to all frequencies of that study. For the continuous data, we used mean with standard deviation (SD). If mean with SD was not present, we calculated it from median and range using the methods described by Hozo et al (20). When only median with interquartile range (IQR) was presented in the study, we assumed a normal distribution in order to approximate mean with SD and used the median as mean. We calculated SD for each side of the IQR as $\mathrm{SD}_{[a,b]} = \frac{(\mathrm{IQR}_{[a,b]}\text{-median})}{0.67}$ where 0.67 is the Z-range for the 25th to 75th percentile where *a* equals the lower IQR value, and *b* equals the upper IQR value. Then we used the formula $SD_{study} = \sqrt{\frac{\mathrm{SD_a}^2 \text{-} \mathrm{SD_b}^2}{2}}$ to calculate the SD of the study population. In an indirect comparison, we calculated an OR and 95% CI for the difference in ARF occurrence in studies with and without oliguria reversal as a target based on the cumulative number of patients with ARF and the cumulative total number of patients in each fluid management protocol. We calculated the respective P value using the Fisher's exact test.

All meta-analyses were performed as a random effects meta-analysis, and due to the expected heterogeneity between studies and the low number of included studies we used the Sidik-Jonkman estimator (21) in combination with the Knapp & Hartung adjustment (22) to get better estimates of the heterogeneity variance. Heterogeneity was analyzed using the I^2 statistics, and the thresholds for interpretation were used as defined in the Cochrane Handbook. We used a random effects meta-regression model with a heteroscedastic compound symmetry variance structure using targeting oliguria reversal as the moderator to test for subgroup differences in ARF occurrence and mean differences in intraoperative fluid intake, and postoperative fluid balance between studies targeting and studies not targeting oliguria reversal. We did not perform a meta-regression analysis for oliguria and postoperative fluid intake due to low number of studies in one group and changes in postoperative fluid management strategies in both groups, respectively. We used R (version 3.2.1) (23) with the metafor package (version 1.9.7) (24) for the analyses and creating the forest and funnel plots. In case the funnel plot for the analysis on ARF occurrence suggested publication bias, we performed a trim and fill analysis to identify missing studies. We subsequently performed a new analysis which compensates for any missing trials identified and compared the results to the analysis on ARF occurrence with a meta-regression model. Pooled outcome data are presented as OR and 95% CI, and exact P

values are given unless P < 0.001. Statistical significance was defined as a 95% CI which did not include 1.00 and a P value less than 0.05.

RESULTS

Study selection and characteristics

We found 477 articles, of which 30 full text articles remained after removing duplicates and articles which met our exclusion criteria, see **Figure 6.1**. We included fifteen studies and the characteristics are reported in **Table 6.1**. Six studies included oliguria reversal as a target in both the restrictive and conventional fluid management protocols (25-30), and nine studies excluded oliguria reversal as target in both protocols (31-39). One study only used restrictive fluid management during the postoperative period (34). Three studies did not exclude patients with chronic kidney disease or preoperative ARF (27,28,32). Only one of the included studies (28) had a score of less than 3 on the Jadad scale (**Table 6.2**).

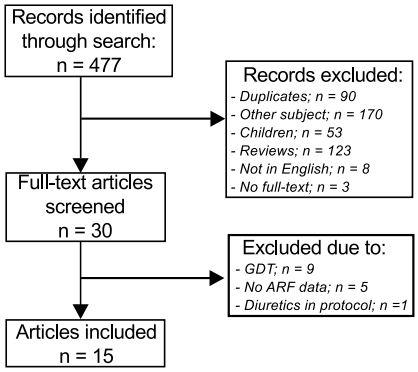

Figure 6.1 Flow chart of study selection.
ARF: acute renal failure, GDT: goal-directed therapy.

Oliguria

Four studies (34,35,37,38) reported no difference in intraoperative urine output between restrictive and conventional fluid management, and in three studies (25,32,36) intraoperative urine output was lower in patients with restrictive fluid management. Five studies reported the occurrence of study-defined oliguria when using restrictive and conventional fluid management, ranging from urine output less than 0.5 ml/kg/h to less than 1.0 ml/kg/h (25,33,34,37,38). There was insufficient evidence to associate restrictive fluid management with an increase in study-defined oliguria, see **Figure 6.2**. Because of the limited number of studies in the targeting oliguria reversal subset, we did not test for differences in oliguria between targeting and not targeting oliguria reversal.

Table 6.1 Characteristics of included studies

Study	Year	Country	Number Total (Restrictive | Conventional)	Type of patient	Timing	Target oliguria reversal	Renal exclusion
Brandstrup	2003	Denmark	141 (69 | 72)	Abdominal Elective	intraoperative	Yes	Renal insufficiency
Nisanevich	2005	Israel	152 (77 | 75)	Abdominal Elective	Intraoperative	Yes	sCr > 97 (female) or > 115 (male) µmol/l
MacKay	2006	UK	80 (39 | 41)	Abdominal Elective	intraoperative, postoperative	No	Significant renal impairment
Holte	2007	Denmark	32 (16 | 16)	Abdominal Elective	intraoperative, postoperative	No	
Gonzalez-Fajardo	2009	Spain	40 (20 | 20)	Vascular / Abdominal Elective	intraoperative, postoperative	No	Impaired renal function
McArdle	2009	Northern Ireland	21 (10 | 11)	Vascular / Abdominal Elective	intraoperative, postoperative	Yes	
Muller	2009	Switzerland	151 (76 | 75)	Abdominal	Intraoperative	Yes	
Vermeulen	2009	Netherlands	62 (30 | 32)	Abdominal Elective	postoperative	No	Impaired renal function

ARF definition	Conventional protocol	Restrictive protocol
Renal replacement therapy	Preloading 500 mL HAES 6%. Third space loss 7 mL/kg/h NS first hour; 5 mL/kg/h NS second and third hour; 3 mL/kg/h NS following hours. Maintenance: 500 mL of normal saline 0.9%	Preloading No preloading. Third space loss No replacement Maintenance: 500 mL of glucose 5%
sCr > 97 (female) or > 115 (male) µmol/l within 3 postoperative days	Before skin incision: 10 ml/kg RL After skin incision; 12 ml/kg/h RL	4 ml/kg/h RL
Not clearly defined in the study	1L 0.9% NS + 2L 5% dextrose per day, until day 3 unless decided otherwise by the consultant.	2L 4% dextrose/0,18% NS per day. All intravenous fluids were stopped on day 1 after operation unless there was a clinical reason to maintain them.
Renal replacement therapy	Preload 10 ml/kg RL During surgery 18 ml/kg/h RL 7 mg/kg Voluven After operation day of surgery: 10 ml/kg RL	Preload None During surgery: 7 ml/kg/h RL first hour 5 ml/kg/h RL subsequent hours 7 mg/kg Voluven After operation day of surgery No fluids
sCr > 97 (female) or > 115 (male) µmol/l ; oliguria not further specified	1000 ml of 5% dextrose and 1500 ml of 0.9% NS per day	1500 ml of 0.9% NS per day
Renal replacement therapy	Preload 10 mL/kg NS During surgery 12 mL/kg/h HM Postoperative (day-of surgery) 125 mL/h HM	Preload No preload During surgery 4 mL/kg/h HM Postoperative (day-of surgery) 83 mL/h HM
Not clearly defined in the study	preoperative loading 2 mL/kg/h RL during surgery. 10 mL/kg/h RL	preoperative loading 1 mL/kg/h RL during surgery. 5 mL/kg/h RL
Renal replacement therapy	1500 ml 0.9% NS and 1000 ml 5% glucose per day	1000 ml 0.9% NS and 500 ml 5% glucose IV per day

Table 6.1 Characteristics of included studies (continued)

Study	Year	Country	Number Total (Restrictive | Conventional)	Type of patient	Timing	Target oliguria reversal	Renal exclusion
Futier	2010	France	70 (36 | 34)	Abdominal Elective	intraoperative	No	sCr > 97 (female) or > 115 (male) µmol/l
Lobo	2011	Brazil	88 (45 | 43)	High Risk	intraoperative	Yes	sCr > 176 µmol/l
Abraham-Nordling	2012	Sweden	161 (79 | 82)	Abdominal Elective	intraoperative, postoperative	No	sCr > 97 (female) or > 115 (male) µmol/l
Matot	2012	Israel	107 (52 | 55)	Abdominal Elective	intraoperative	No	sCr > 97 (female) or > 115 (male) µmol/l
Kalyan	2013	UK	239 (121 | 118)	Abdominal Elective	Intraoperative, postoperative	Yes	sCr > 140 µmol/l
Matot	2013	Israel	102 (51 | 51)	Thoracic Elective	intraoperative	No	sCr > 97 (female) or > 115 (male) µmol/l
Wuethrich	2014	Switzerland	166 (83 | 83)	Urologic / Abdominal Elective	Intraoperative	No	Estimated glomerular filtration rate <60 ml/min

ARF: acute renal failure; sCr: serum creatinine; UO: urine output; NS: normal saline; RL: Ringer's Lactate; RA: Ringer's Acetate; HM: Hartmann's solution; HAES: Hydroxyethyl starch.

ARF definition	Conventional protocol	Restrictive protocol
Within 2 postoperative days: UO < 500ml/d sCr > 30% from preoperative Renal replacement therapy	12 mL/kg/h RL	6 mL/kg/h RL
sCr > 2x baseline value during discharge or 60 days	12 ml/kg/hour RL	4 ml/kg/hour RL
Not clearly defined in the study	before surgery: 500–1000 ml RA during surgery 5 ml/kg/h RA induction of anesthesia: 2 ml/kg/h buffered glucose 2.5% early postoperative period: 1000 ml RA from early after operation until morning after surgery : 1 ml/kg/h glucose 10%	induction of anesthesia: 2 ml/kg/h buffered glucose 2.5% from early after operation until morning after surgery : 1 ml/kg/h glucose 10%
sCr > 97 (female) or > 115 (male) µmol/l within 3 postoperative days	10 mL/kg/h RL	4 mL/kg/h RL
Renal replacement therapy	Preloading 500 mL HM Third space loss 7 mL/kg/h HM first hour; 5 mL/kg/h HM following hours. Maintenance: 1.5 ml/kg/h	Preloading No preloading. Third space loss No replacement Maintenance: 1.5 ml/kg/h during anesthesia 1 ml/kg/h 5% glucose until enteral intake
sCr > 97 (female) or > 115 (male) µmol/l within 3 postoperative days	8 mL/kg/h RL	2 mL/kg/h RL
sCr >50% upper limit of normal value within 90 days	Induction: 6 ml/kg/h RL 6 ml/kg/h RL until end of surgery	1 ml/kg/h RL until bladder removal 3 ml/kg/h RL after bladder removal

Table 6.2 Risk of bias assessment in selected studies

Study	Year	Randomization	Blinding	Withdrawal	Jadad Score	Concealment of allocation
Brandstrup	2003	2	1	1	4	Complications assessed both blinded and unblinded
Nisanevich	2005	2	2	1	5	Study personnel was blinded to allocation
MacKay	2006	2	1	1	4	Allocation concealed for consultant surgeon
Holte	2007	2	2	1	5	Concealment until end of study
Gonzalez-Fajardo	2009	2	1	1	4	Study personnel were blinded to allocation
McArdle	2009	2	0	1	3	Only 1 investigator was blinded to allocation
Muller	2009	2	0	0	2	No concealment of allocation
Vermeulen	2009	2	2	1	5	Disclosure at the end of the operation
Futier	2010	2	1	1	4	Study personnel was blinded to allocation
Lobo	2011	2	0	1	3	Only 1 investigator was blinded to allocation
Abraham-Nordling	2012	2	1	1	4	Only 2 investigator were not blinded to allocation
Matot	2012	2	2	0	4	Clinicians and investigators were blinded to allocation
Kalyan	2013	2	1	1	4	Surgeon: until end of operation.
Matot	2013	2	2	1	5	Clinicians and investigators were blinded to allocation
Wuethrich	2014	2	2	1	5	Clinicians and investigators were blinded to allocation

Acute renal failure

The frequency of ARF in restrictive and conventional fluid management was 2.5% and 2.5%, respectively. In two studies targeting oliguria reversal (25,29) and five studies not targeting oliguria reversal (31,33,35,37,38), serum creatinine did not significantly increase from baseline during the following postoperative days. The overall analysis did not provide enough evidence to conclude that restrictive fluid management increased ARF occurrence (**Figure 6.3**). Though the heterogeneity in this analysis was low, six studies reported no occurrence of ARF in either restrictive or conventional fluid management. The funnel plot suggested possible publication bias (**Figure 6.4**). The trim and fill analysis suggested three missing studies, which are included in the funnel plot and forest plot in **Figure 6.4** and **Figure 6.5**, respectively. The overall OR was

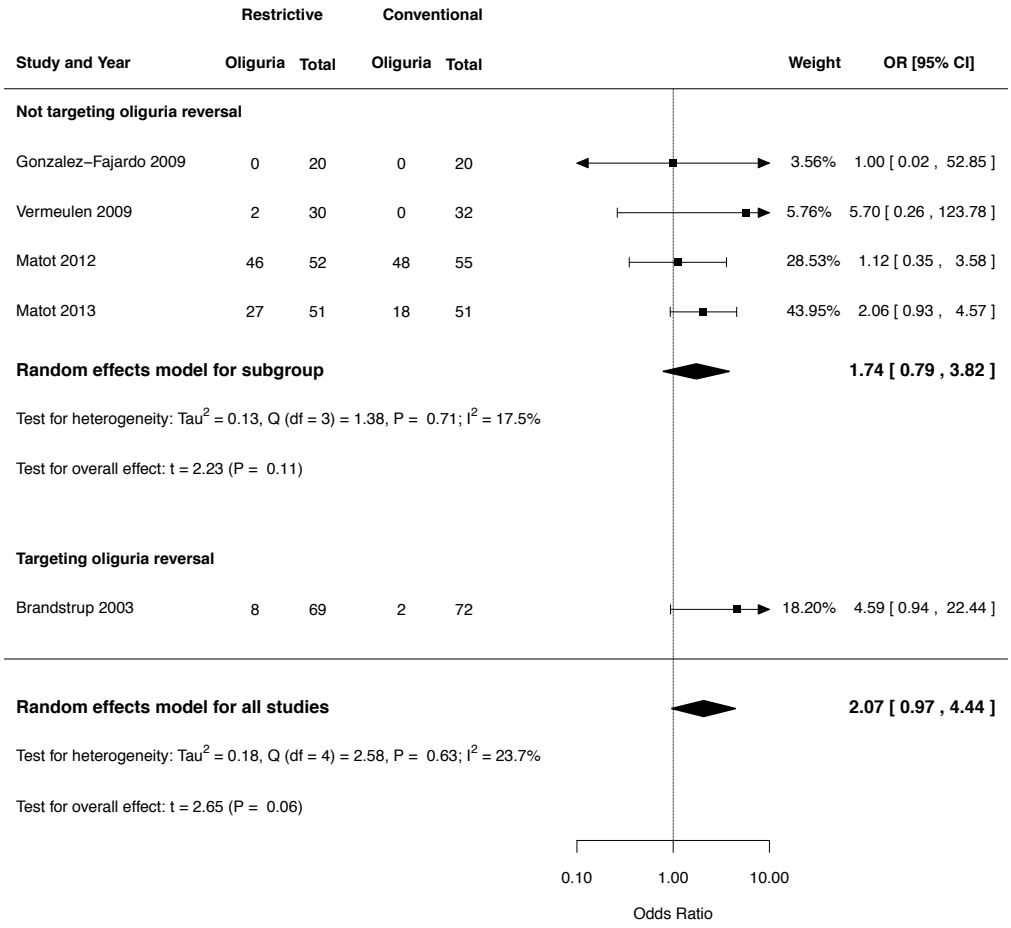

Figure 6.2 Forest plot of studies reporting occurrence of study-defined oliguria when comparing restrictive with conventional fluid management.
IV: inverse variance; CI: confidence interval

1.07 (95% CI 0.60 to 1.92; P=0.84; I^2=17.5%; $N_{studies}$=18), which does not significantly differ from the analysis in **Figure 6.2** (P=1.00).

The sensitivity analysis to investigate whether different ARF definitions influenced the results is reported in **Figure 6.6**. The estimated OR for need for renal replacement therapy was 0.89 (95% CI 0.22 to 3.61; P=0.82; I^2=24.7%; $N_{studies}$=5) and for serum creatinine 0.75 (95% CI 0.19 to 2.96; P=0.62; I^2=22.4%; $N_{studies}$=6) when comparing restrictive with conventional fluid management.

In studies with oliguria reversal as a target, the estimated OR for ARF occurrence was 0.58 favoring restrictive fluid management, and in studies not targeting oliguria reversal

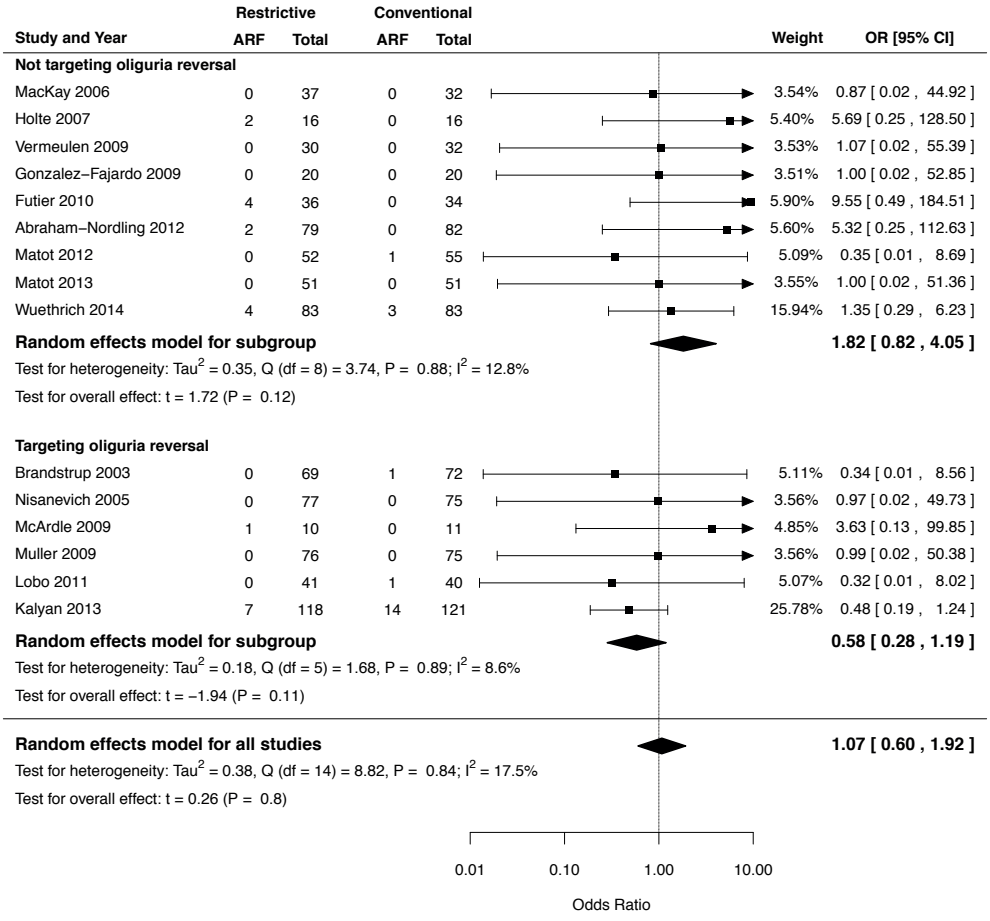

Figure 6.3 Forest plot of studies reporting occurrence of acute renal failure when comparing restrictive with conventional fluid management.
IV: inverse variance; CI: confidence interval.

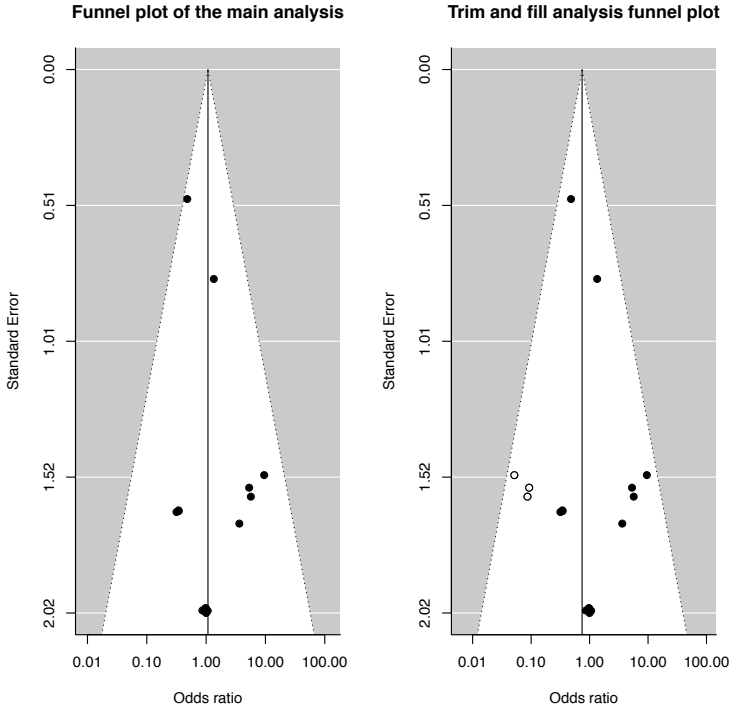

Figure 6.4: Funnel plot of studies reporting occurrence of acute renal failure when comparing restrictive with conventional fluid management, and a funnel plot which includes possible missing studies identified by the trim-and-fill analysis.

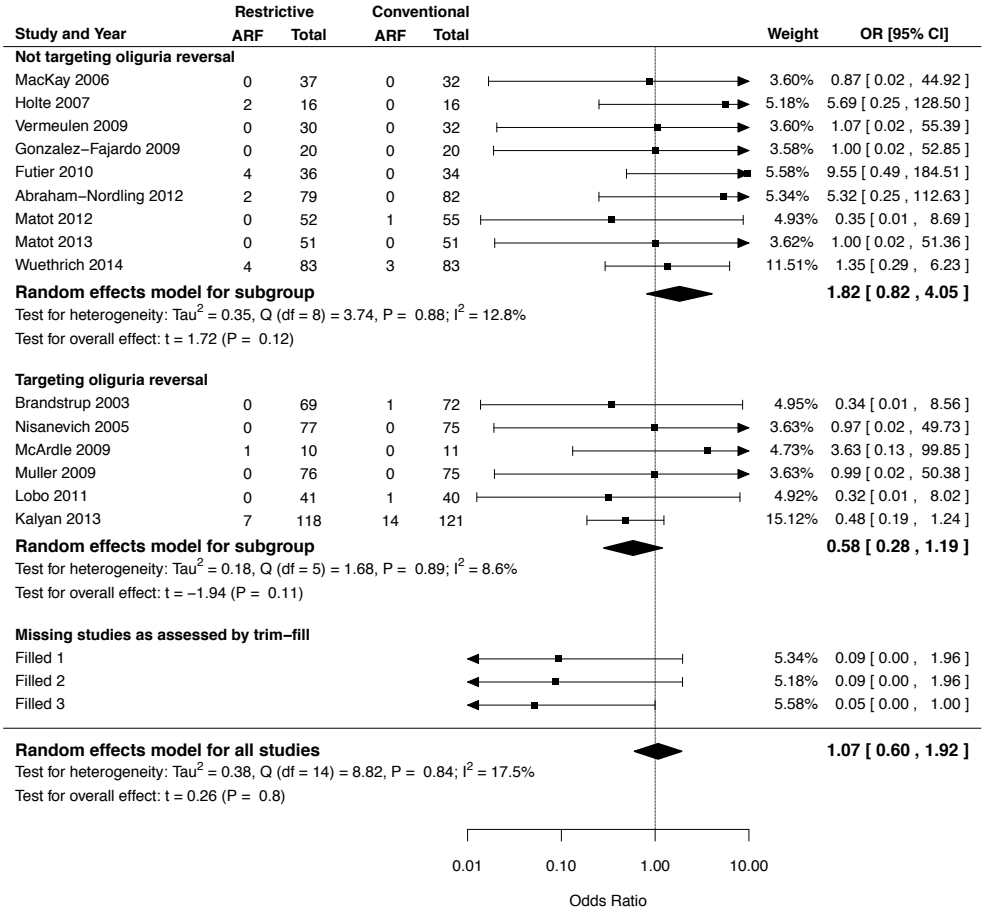

Figure 6.5: Forest plot of studies reporting occurrence of acute renal failure when comparing restrictive with conventional fluid management which includes possible missing studies identified by the trim-and-fill analysis.

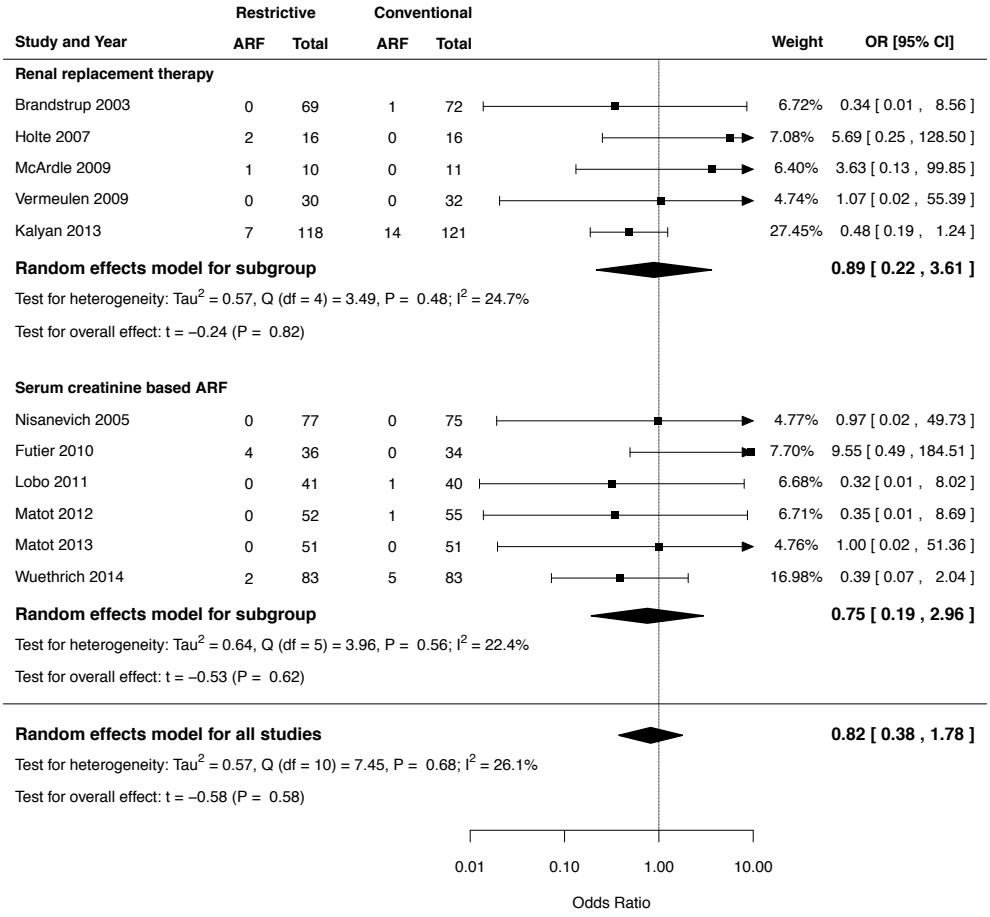

Figure 6.6: Forest plot of studies reporting occurrence of acute renal failure when comparing restrictive with conventional fluid management based on acute renal failure definition.

the estimated OR for ARF occurrence was 1.8 favoring conventional fluid management; however neither was significantly different from 1.00 (**Figure 6.3**). There was also insufficient evidence to suggest that targeting oliguria reversal decreased the occurrence of ARF (OR 0.31; 95% CI 0.08 to 1.22; P=0.088).

Fluid management

The fluid management protocols for each study are presented in **Table 6.1**. Two studies (25,28) reported that respectively 15% and 22% of the patients in the restrictive fluid management protocol had received more fluids than intended, and one study (34) reported that the actual volume administered during surgery was higher than intended in either

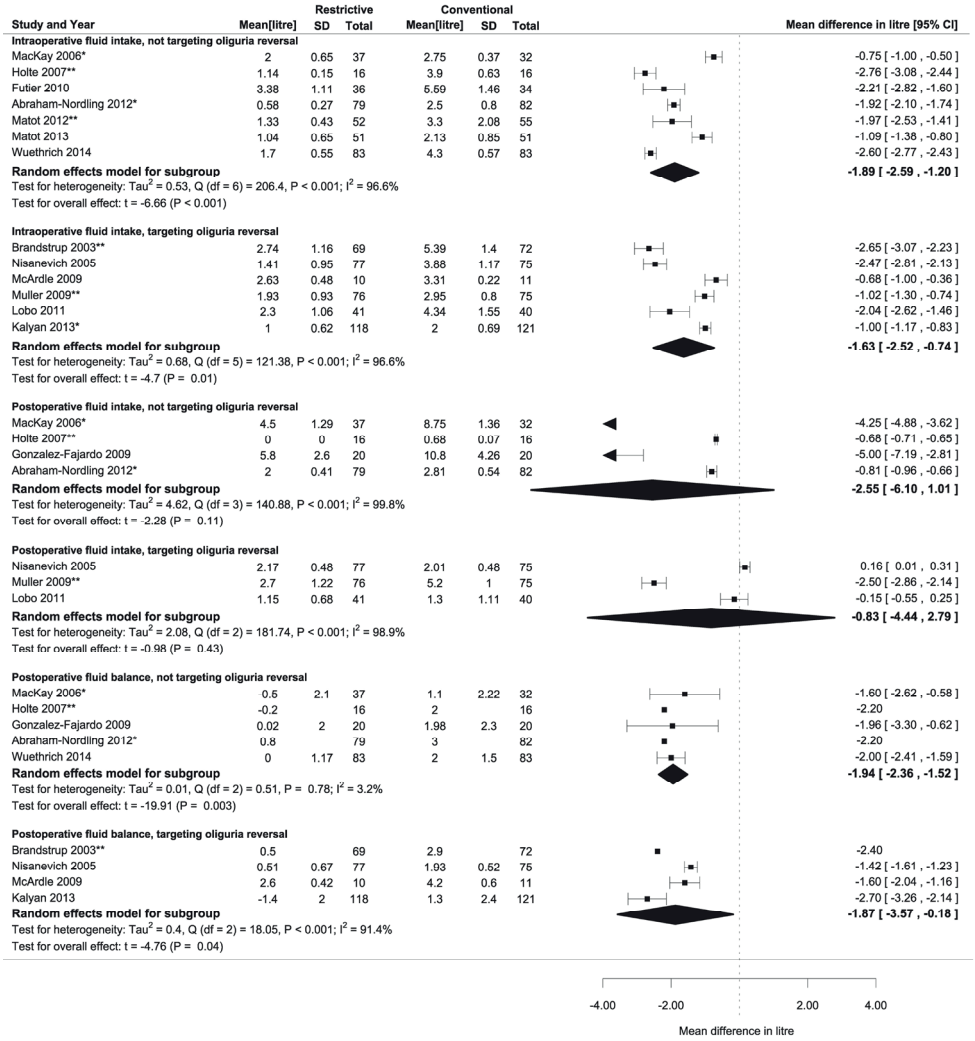

Figure 6.7 Forest plot of the mean difference in infused fluids in liters between restrictive and conventional fluid management during the intraoperative and postoperative period.

*: mean and standard deviation derived from median and interquartile range; **: mean and standard deviation derived from median and range. SD: standard deviation; IV: inverse variance; CI: confidence interval.

protocol. One study (26) reported that restrictive fluid management was associated with more additional fluid boluses, and one study (29) reported no difference in additional fluid boluses between protocols.

The mean difference in intraoperative fluid intake could be extracted and calculated for twelve studies (**Figure 6.7**). Less fluid was infused during the intraoperative period in those receiving restrictive fluid management than in those with conventional fluid management

irrespective of targeting oliguria. There was insufficient evidence to suggest that targeting oliguria reversal was associated with a smaller difference in fluid intake between restrictive and conventional fluid management (OR 1.32; 95% CI 0.47 to 3.77; P=0.56).

The mean difference in postoperative fluid intake could be extracted and calculated for seven studies (**Figure 6.7**). The studies without oliguria reversal as a target continued the use of the restrictive fluid management protocol into the postoperative period, while the studies with oliguria reversal as a target had the same postoperative fluid regime for both restrictive and conventional arms (**Table 6.1**). Postoperative fluid intake was lower in restrictive fluid management than in conventional fluid management in studies without oliguria reversal as a target and in studies with oliguria reversal as a target; however the differences were not statistically significant suggesting that factors other than postoperative fluid restriction affect fluid intake.

Nine studies (25-27,30-33,36,39) reported on postoperative fluid balance either in terms of volume or weight increase (**Figure 6.7**). Postoperative fluid balance was lower in those receiving restrictive fluid management than in those with conventional fluid management irrespective of targeting oliguria. There was insufficient evidence to suggest that targeting oliguria reversal was associated with a smaller difference in postoperative fluid balance between restrictive and conventional fluid management (OR 1.07; 95% CI 0.33 to 3.55; P=0.88). The heterogeneity in the fluid intake and fluid balance analyses were high.

Indirect comparison

Because there were no studies investigating targeting oliguria reversal with not targeting oliguria reversal, we performed an indirect comparison to analyze the effects of including targeting oliguria reversal or excluding targeting oliguria reversal on the occurrence of ARF (**Table 6.3**). Targeting oliguria reversal in a restrictive protocol does not appear to affect the occurrence of ARF, whereas targeting oliguria reversal in a conventional protocol may possibly even increase the occurrence of ARF.

Table 6.3 Indirect comparison of the effect of targeting oliguria reversal in restrictive and conventional fluid management.

	Targeting oliguria reversal					
	Yes		No			
Protocol	**ARF (%)**	**Total**	**ARF (%)**	**Total**	**OR (95% CI)**	**P value**
Restrictive	8 (2.0)	391	12 (2.97)	404	0.68 [0.24, 1.84]	0.50
Conventional	16 (4.1)	394	4 (0.98)	405	4.24 [1.35, 17.65]	0.006

For each analysis, the pooled data from all relevant studies targeting oliguria reversal was compared to the pooled data from studies not targeting oliguria reversal – separating data from restrictive fluid management protocols from conventional fluid management protocols. Odds ratio and 95% confidence intervals were then calculated and the P-value was calculated using the Fisher's exact test to test whether there was a difference in acute renal failure occurrence between targeting and not targeting oliguria reversal in each protocol.
ARF: acute renal failure; OR: odds ratio; CI: confidence interval.

DISCUSSION

In this meta-analysis, we found insufficient evidence to associate restrictive fluid management with an increase in oliguria and ARF occurrence. The difference in intraoperative fluid intake between conventional and restrictive fluid management was similar whether oliguria reversal was targeted or not. In line with our initial hypothesis, excluding targeting oliguria reversal in a restrictive fluid management protocol does not seem to be associated with an increase in ARF occurrence when compared with including oliguria reversal as a target.

Similar to the findings from the meta-analysis of major abdominal surgery by Boland et al. (12), we were unable to demonstrate an association between restrictive fluid management and an increase in the occurrence of postoperative ARF. Additionally, the FACCT trial in patients with acute lung injury was unable to demonstrate a difference in renal failure-free days between a restrictive and conventional fluid management strategy, though the restrictive fluid management strategy utilized diuretics when oliguria occurred (40). Even when looking at more specific ARF definitions, we found insufficient evidence that restrictive fluid management was associated with an increase in the need for renal replacement therapy or with a postoperative increase in serum creatinine concentrations. The latter, however, could be explained by a positive postoperative fluid balance diluting any increase to near preoperative levels.

We were unable to demonstrate an increase in the occurrence rate of oliguria due to the restrictive fluid management protocols, and targeting oliguria reversal did not seem to influence fluid intake. It is likely that patients given restrictive fluid management were already normovolemic during surgery since most postoperative fluid balances were near zero. This suggests that oliguria is the result of a physiological stress response during surgery to maintain an adequate intravascular volume through activity of several neurohormonal systems such as the renin-angiotensin-aldosterone axis and antidiuretic hormone (16,41). Hence, oliguria does not necessarily reflect absolute hypovolemia and additional fluid administration could increase urine output, but likely without any true benefit in terms of renal function.

Our findings suggest that excluding targeting oliguria reversal does not seem to increase ARF occurrence when using a restrictive fluid management protocol. However, since the postoperative fluid intake did not noticeably differ between restrictive and conventional fluid management in both studies targeting and not targeting oliguria reversal, we cannot exclude that the postoperative fluid protocols could have had an effect on the occurrence of ARF. It may be that protocols which restrict postoperative fluid intake do not compensate for patients being unable to manage their own fluid balance. Without an adequate postoperative fluid protocol to compensate for this fluid deficit, this may eventually lead to an increase in ARF occurrence by prolonged and recurrent episodes of hypovolemia.

Moreover, intravascular volume could change during the postoperative period, while the physiological stress response from surgery may continue and influence the activity of neurohormonal systems. It is therefore possible that to maintain an adequate intravascular volume during the postoperative period requires more fluids due to vasodilation-mediated volume redistribution.

Lastly, it is important to note that in the indirect comparison groups are treated as a cohort based on the cumulative ARF occurrence in each fluid management protocol with or without targeting oliguria reversal therefore lacking the benefit of randomization. This indirect comparison is the best available surrogate effect estimate, since there were no trials available which either directly compared targeting with not targeting oliguria reversal, or compared restrictive fluid management without against conventional fluid management with targeting oliguria reversal. As a result, we recommend future studies to prospectively investigate the effects of targeting oliguria reversal on the occurrence of ARF.

Limitations

This meta-analysis has several limitations. The low event rates in the selected studies can be a cause for bias and are most likely caused by excluding patients with preoperative chronic kidney disease, and by the inconsistent ARF definition among the included studies as reported in **Table 6.1**. The funnel plot for ARF occurrence suggested possible publication bias. This may be due to the lack of published studies with ARF as an investigated outcome leading to selection bias or perhaps due to language bias from excluding trials not published in English. Since most of the studies only included patients with normal preoperative serum creatinine and undergoing elective surgery, the a priori risk of ARF in these patients was lower than for patients with chronic kidney disease or undergoing emergency surgery (42,43). Nevertheless, the incidence of postoperative ARF in this meta-analysis is well within the margins reported in current literature (15,43,44). However, it must be noted that the incidence of ARF may be an underestimation. The latest diagnostic criteria for acute kidney injury – the consensus definition which incorporates the whole spectrum of renal dysfunction (18) - incorporated small increases in serum creatinine (45). These small increases have been associated with an increased mortality rate (46,47), however it remains unknown whether these small changes are merely a marker of underlying pathology which are the cause of the mortality increase or whether these changes in serum creatinine represent fluctuations in kidney function with clinical importance (45).

Second, the fluid administration protocols greatly differed between the included studies. As described by the I^2 in **Figure 6.7**, the heterogeneity in the fluid intake comparisons was very high. In addition, the adherence to the protocols during the study might have been poor. While only three studies actively reported deviations from protocol, it can be assumed that other studies had similar issues, which bias our findings. Nevertheless, restrictive fluid

management reduced intraoperative fluid intake irrespective of the use of oliguria reversal as a target.

It is also important to note that unlike earlier meta-analyses (9,10) we did not redefine restrictive and conventional fluid management, but rather used the study definitions. This may introduce some bias since some restrictive fluid management protocols were considered to be either too restrictive or not restrictive enough. However, most of the restrictive fluid management protocols infused roughly 2 liters during surgery, which in the meta-analysis by Varadhan et al (10) was defined as a state of fluid balance for the average patient without ongoing fluid deficits or losses. Additionally, most of the studies reporting postoperative fluid management had a neutral fluid balance with restrictive fluid management, suggesting that in these studies restrictive fluid management was closer to an optimal fluid strategy than the conventional fluid management.

CONCLUSION

In conclusion, even though event numbers are small, we found insufficient evidence to associate restrictive fluid management with an increased occurrence of oliguria and risk for ARF. Intraoperative fluid intake and postoperative fluid balances remained lower with restrictive fluid management. Similarly, adding targeting oliguria reversal in both protocols did not influence ARF occurrence, fluid intake or fluid balance. There was insufficient evidence to suggest that restrictive fluid management in combination with oliguria reversal as a target influences ARF occurrence in either direction. However, this may be due to postoperative rather than intraoperative fluid management when oliguria occurs. Future studies are needed to confirm the effects of targeting oliguria reversal, though restrictive fluid management seems to be a safe and viable perioperative fluid strategy for the kidney, considering the currently available evidence.

SUPPLEMENT

Table S6.1: Search strategy for MEDLINE database via PubMed

#1	restrictive	
#2	conservative	
#3	limited	
#4	(#1 OR #2 OR #3)	
#5	conventional	
#6	liberal	
#7	(#5 OR #6)	
#8	“Fluid Therapy/methods”[Mesh]	
#9	“Fluid Therapy”[Mesh]	
#10	“fluid therapy”	
#11	“fluid management”	
#12	“fluid resuscitation”	
#13	“maintenance fluid”	
#14	(#8 OR #9 OR #10 OR #11 OR #12 OR #13)	
#15	outcome	
#16	“acute renal failure”	
#17	“acute kidney injury”	
#18	“oliguria”	
#19	“urine output”	
#20	“urinary output”	
#21	“diuresis”	
#22	“creatinine”	
#23	(#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)	
#24	(#14 AND (#4 OR #7))	
#25	randomized	
#26	controlled	
#27	trial	
#28	“Randomized Controlled Trial” [Publication Type]	
#29	#28 OR (#27 AND (#25 OR #26))	
#30	(#23 AND #24 AND #29)	141

Table S6.2: Search strategy for EMBASE database

#1	restrictive	
#2	conservative	
#3	limited	
#4	#1 OR #2 OR #3	
#5	conventional	
#6	liberal	
#7	#5 OR #6	
#8	'fluid therapy'	
#9	'fluid therapy'/exp	
#10	'fluid management'	
#11	'fluid resuscitation'	
#12	'maintenance fluid'	
#13	#8 OR #9 OR #10 OR #11 OR #12	
#14	outcome	
#15	'acute renal failure'	
#16	'acute kidney injury'	
#17	'oliguria'	
#18	'urine output'	
#19	'urinary output'	
#20	'diuresis'	
#21	'creatinine'	
#22	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	
#23	#13 AND (#4 OR #7)	
#24	randomized	
#25	controlled	
#26	trial	
#27	#26 AND (#24 OR #25)	
#28	#22 AND #23 AND #27	334

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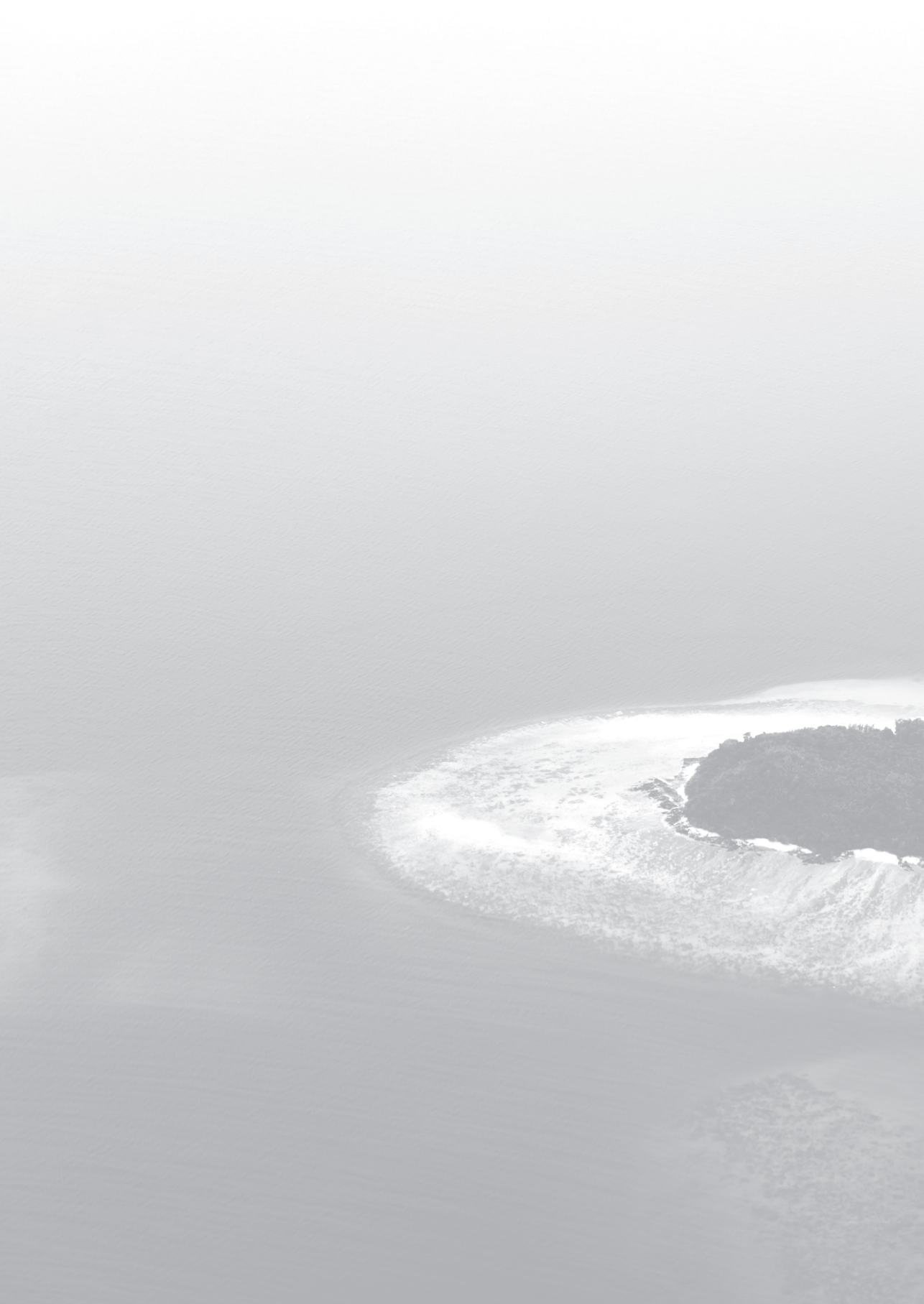
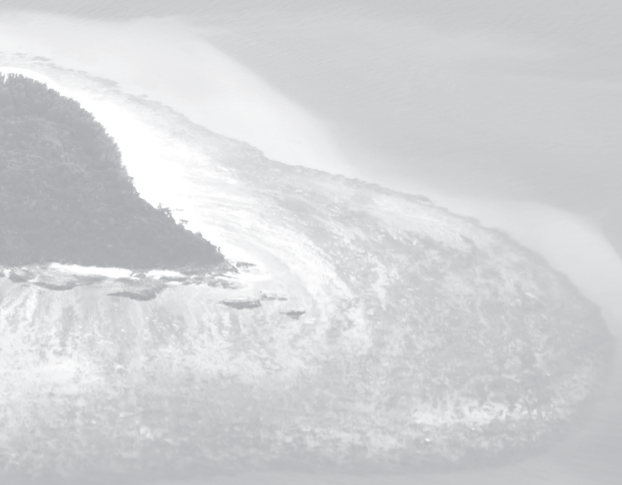


PART III

Fluid management in oliguria



CHAPTER 7

NGAL as a diagnostic marker for acute kidney injury in oliguric critically ill patients: a post-hoc analysis

ABSTRACT

BACKGROUND Oliguria occurs frequently in critically ill patients, challenging clinicians to distinguish functional adaptation from serum-creatinine-defined acute kidney injury (AKI_{sCr}). We investigated neutrophil gelatinase-associated lipocalin (NGAL)'s ability to differentiate between these two conditions.

METHODS This is a post-hoc analysis of a prospective cohort of adult critically ill patients. Patients without oliguria within the first six hours of admission were excluded. Plasma and urinary NGAL were measured at four hours after admission. AKI_{sCr} was defined using the AKIN criteria with pre-admission serum creatinine or lowest serum creatinine value during the admission as the baseline value. Hazard ratios (HR) for AKI_{sCr} occurrence within 72 hours were calculated using Cox regression and adjusted for risk factors such as sepsis, pre-admission serum creatinine, and urinary output. Positive (PPV) and negative predictive values (NPV) were calculated for the optimal cutoffs for NGAL.

RESULTS Oliguria occurred in 176 patients, and 61 (35%) patients developed AKI_{sCr}. NGAL was a predictor for AKI_{sCr} in univariate and multivariate analysis. When NGAL was added to a multivariate model including sepsis, pre-admission serum creatinine and lowest hourly urine output, it outperformed the latter model (plasma P=0.001; urinary P=0.048). Cutoff values for AKI_{sCr} were 280 ng/mL for plasma (PPV 80%; NPV 79%), and 250 ng/mL for urinary NGAL (PPV 58%; NPV 78%).

CONCLUSIONS NGAL can be used to distinguish oliguria due to functional adaptation from AKI_{sCr}, directing resources to patients more likely to develop AKI_{sCr}.

INTRODUCTION

Oliguria is defined as a drop in urine output to less than 0.5 mL/kg/h and frequently occurs in critically ill patients. Oliguria - in the absence of a serum creatinine increase – in a patient without invasive monitoring of cardiac output and fluid status is a challenge for the intensivist's decision to either continue fluid resuscitation in order to treat presumed hypovolemia and thereby prevent the onset of acute kidney injury (AKI) (1) or to limit fluid intake to avoid the adverse effects of fluid overload. Indeed, a decrease in urine output can be due to hypovolemia, transiently inadequate perfusion, or renal cell injury (2). Accordingly, oliguria by itself is at best a moderate predictor for acute kidney injury defined as a serum creatinine increase (AKI_{sCr}) (3,4).

Traditionally, urinary markers such as the fractional excretion of sodium or urea are used to differentiate between prerenal or renal causes of AKI. However, its utility in critically ill patients has been challenged due to confounders such as fluid resuscitation, diuretics and vasoactive drugs, and by a poor correlation with severity of AKI (5). Recently, the advent of renal biomarkers has seen many studies investigating their use as early predictors for AKI (6). Neutrophil gelatinase-associated lipocalin (NGAL), one of those biomarkers, is produced in the distal nephron and its concentration increases when tubular cellular injury is present (7-9). The increase in NGAL levels in case of cellular damage – i.e. acute tubular injury – precedes a rise in serum creatinine (9-11).

To address whether NGAL is able to identify those critically ill patients with early oliguria that will develop $AKI_{sCr,}$ we performed a post-hoc analysis in a previously described cohort (12). Our hypothesis was that low NGAL concentrations in oliguric critically patients are most likely due to hemodynamic or hormonal compensation mechanisms whereas a high NGAL concentration heralds AKI_{sCr}. Our objective was to investigate whether NGAL, measured after the occurrence of oliguria, can identify AKI_{sCr} within the first 72 hours in patients with oliguria occurring within six hours of intensive care unit (ICU) admission.

PATIENTS AND METHODS

Patient selection

We performed a post-hoc analysis on a prospectively gathered biomarker dataset from a previously published cohort (12,13). The institutional review board of Erasmus MC, University Medical Center Rotterdam, The Netherlands, approved the initial study. All consecutive admitted patients between September 2007 and April 2008 were eligible for enrollment. The original exclusion criteria were age under 18 years, refusal of consent, nephrectomy, chronic kidney disease (glomerular filtration rate using pre-admission serum creatinine < 60 mL/min/1.73m^2), end-stage renal disease, and renal transplantation. Deferred consent

was used, and written informed consent was obtained from all participants or their health care proxy (14). From this dataset, we excluded readmissions and all patients who did not develop oliguria within the first six hours of the ICU admission (**Figure 7.1**). All patients without a recorded weight or without sufficient urine output data within six hours of ICU admission – i.e. only one recorded measurement during the six-hour period - were excluded.

Data collection and definitions

Data was retrospectively collected from our electronic patient data monitoring system (Picis Clinical Solutions, Massachusetts, USA). Urine output was prospectively recorded by the attending nurses in irregular intervals, depending on the urine output, ranging from one hour up to three hours. We assumed a constant rate of urine flow within each interval, and calculated the hourly urine output by averaging the volume over each hour in that interval. Oliguria was defined as urine output less than 0.5 mL/kg/h. Mean urine output and lowest hourly urine output were calculated from the urine output available in the first six hours. Furosemide and bumetanide were pooled together when looking at diuretics use. Serum creatinine was measured at admission and at least once daily at 6:00 AM. Pre-admission serum creatinine was defined as the steady state level 4 weeks before admission (12). Patients who required renal replacement therapy were identified, which in our clinical setting is initiated for metabolic disorders due to AKI or diuretic-resistant fluid overload.

We collected the following variables from the clinical chart: gender; age; Acute Physiology and Chronic Health Evaluation (APACHE) and the Sequential Organ Failure Assessment (SOFA) score at day of admission; presence of the systemic inflammatory response syndrome (SIRS) criteria was scored during the first six hours of ICU admission; the presence of sepsis at admission defined according to American College of Chest Physicians/ Society of Critical Care Medicine consensus criteria (1) and the presumed or confirmed source. The primary admission diagnosis was collected for each patient and categorized to either respiratory failure, gastrointestinal hemorrhage, liver failure, esophagectomy, vascular surgery, gastrointestinal surgery, liver transplant, multi-trauma, subarachnoid hemorrhage, neuro-trauma and neurosurgery. Admission diagnoses were then pooled according to medical, surgical or neurological etiologies.

Plasma and urinary NGAL samples were collected and measured in the original study at admission and at 7 time points thereafter (4, 8, 24, 36, 48, 60 and 72 hours) using the Triage® point-of-care immunoassay (Biosite Inc., San Diego, USA), which measures the NGAL monomer (12). AKI_{sCr} was defined according to the acute kidney injury network (AKIN) serum creatinine criteria using the pre-admission serum creatinine as the baseline value (15). If pre-admission serum creatinine was not available, the lowest value during the admission was used as a surrogate (16). Patients who did not develop AKI_{sCr} in the first 72 hours of ICU admission were allocated to the noAKI_{sCr} group, and those who did

were allocated to the AKI_{sCr} group. If in AKI_{sCr} the lowest serum creatinine value during the admission was measured after the highest serum creatinine value within the first 72 hours, it was categorized as transient AKI_{sCr} (16).

Statistical analysis

Since most data were not normally distributed (Kolmogorov-Smirnov test P<0.05), data was reported as median with interquartile range (IQR). Missing plasma and urinary NGAL data were imputed using multiple imputations with the MICE package, using predictive mean matching of NGAL at admission, 4 hours and 8 hours after admission with 25 imputations across 50 iterations (17). Categorical variables were summarized by numbers and percentages. Differences between the two groups were compared using the Mann-Whitney U test for continuous variables, and the Fisher's exact test for categorical variables.

NGAL measured 4 hours after admission was used for all analyses due to being the closest measured value after most occurrences of oliguria. Cox's proportional hazard regression analysis was used to estimate the effect of NGAL, pre-admission serum creatinine, sepsis, mean urine output, lowest hourly urine output and duration of oliguria as predictors for AKIsCr. These variables were also inputted in a multivariate model, one for plasma NGAL and one for urinary NGAL and variables were subsequently eliminated using a stepwise backward selection method. A multivariate model without NGAL was created using a stepwise backward selection method to investigate the additive value of NGAL to the multivariate model. The continuous net reclassification improvement (NRI) and the integrated discrimination improvement (IDI) were calculated to quantify the improvement in AUROC after adding NGAL. The NRI statistic describes the proportion of patients based on the new model assigned a probability for AKI_{sCr} closer to 1 for those with AKI_{sCr} and closer to 0 for patients without AKI_{sCr}. The IDI statistic describes the mean change in probabilities (increases for events and decreases in non-events) between the new and old model.

To assess whether NGAL - either univariate or in a multivariate model – leads to an improvement in AKI_{sCr} prediction, we first compared the area under the receiver operating characteristics curves (AUROC) for the NGAL models against the AUROC of the multivariate model without NGAL at 24, 48 and 72 hours after admission. Optimal cutoff values at 24, 48 and 72 hours after admission were estimated for univariate plasma and urinary NGAL and admission serum creatinine using Youden's J-statistic (18).

All analyses were performed using R statistical software package (R Foundation for Statistical Computing; Vienna, Austria) (19) and the time-dependent AUROCs for the Cox's regression models were calculated and compared with the timeROC package (20). A P value < 0.05 was defined as significant, and exact P values were given unless P<0.001.

RESULTS

Of the 632 patients included in the original study and after excluding readmissions and records with insufficient urinary data from the original cohort (12), 439 patients remained with an AKI_{sCr} incidence of 25% (**Figure 7.1**). After excluding patients without oliguria within the first six hours of ICU admission, 176 patients remained. In ten patients (5.7%) pre-admission serum creatinine was not available. The general characteristics are reported in **Table 7.1**. Sixty-one patients (35%) developed AKI_{sCr} during the first 72 hours of ICU admission. AKI_{sCr} occurred relatively early in the ICU admission (87% within 24 hours), and 16 patients had transient AKI_{sCr} (**Table 7.2**). Plasma NGAL data was missing for 15 patients (AKI_{sCr} 6, $noAKI_{sCr}$ 9) and urinary NGAL data were missing 21 patients (AKI_{sCr} 7, $noAKI_{sCr}$ 14), for which imputed data was used. Admission serum creatinine was higher in the AKI_{sCr} group compared to the $noAKI_{sCr}$ group (P<0.001). Mean urine output and lowest hourly urine output during the first six hours were lower in AKI_{sCr} than in $noAKI_{sCr}$. Plasma and urinary NGAL were higher in AKI_{sCr} compared to those in the $noAKI_{sCr}$ group (plasma NGAL: P< 0.001; urinary NGAL: P<0.001).

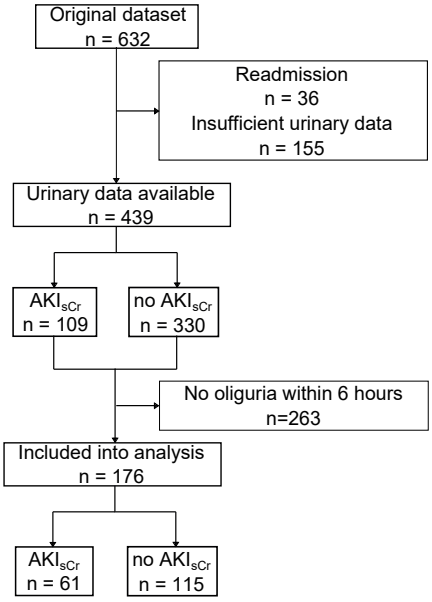


Figure 7.1 Inclusion flow chart

This figure shows the number of patients included in the original article (12), and the exclusion criteria and number of patients excluded from this post-hoc analysis. AKI_{sCr}: serum creatinine defined acute kidney injury.

Table 7.1 General characteristics

	AKI_{sCr}	no AKI_{sCr}	P
n	61	115	
Male	37 (61)	75 (65)	0.622
Age (year)	62 (47 - 72)	61 (49 - 71)	0.889
APACHE II score	22 (17 - 28)	16 (13 - 20)	<0.001
SOFA score on day of admission	8 (6 - 12)	4 (1.5 - 6)	<0.001
Pre-admission serum creatinine (μmol/L)	75 (60 - 90)	70 (60 - 80)	0.139
Admission serum creatinine (μmol/L)	115 (84 - 148)	68 (55.5 - 82)	<0.001
Lowest serum creatinine during admission (μmol/L)	73 (53 - 108)	56 (46 - 68)	<0.001
Admission type			
Medical	39 (64)	36 (31)	<0.001
Surgical	19 (31)	61 (53)	0.007
Neurological	3 (5)	18 (16)	0.049
Admission diagnosis			
Respiratory failure	14 (23)	10 (9)	0.011
Gastrointestinal hemorrhage	4 (7)	5 (4)	0.500
Liver failure	2 (3)	0 (0)	0.119
Esophagectomy	3 (5)	19 (17)	0.031
Vascular surgery	6 (10)	10 (9)	0.789
Gastrointestinal surgery	7 (11)	13 (11)	1.000
Liver transplant	2 (3)	1 (1)	0.276
Multitrauma	4 (7)	5 (4)	0.500
Subarachnoid hemorrhage	0 (0)	7 (6)	0.097
Neurotrauma	1 (2)	7 (6)	0.265
Neurosurgery (elective and emergency)	3 (5)	17 (15)	0.078
SIRS ≥ 2 criteria	52 (85)	81 (70)	0.042
Sepsis	23 (38)	12 (10)	<0.001
Pulmonary	10 (16)	6 (5)	0.025
Abdominal	11 (18)	6 (5)	0.013
Urogenital	1 (2)	0 (0)	0.347
Soft tissue	4 (7)	1 (1)	0.050
Central nervous system	0 (0)	2 (2)	0.544
Length of stay (hours)	205 (85 - 416)	64 (25 - 158)	<0.001
28 day mortality	17 (28)	12 (10)	0.005

Data is presented as median (interquartile range) or number (percentage) where appropriate.
AKI_{sCr}: acute kidney injury by serum creatinine definition; SIRS: Systemic inflammatory response syndrome; more than one location could be recorded as the diagnostic site of (suspected) sepsis.

Table 7.2 Renal data

Variable	AKI_{sCr}	no AKI_{sCr}	P
n	61	115	
Urine output during first 6 hours			
Time from admission to oliguria (hours)	2 (1 - 3)	1 (1 - 2)	0.080
Cumulative oliguria duration (hours)	4 (3 - 5)	3 (2 - 4)	0.003
Mean urine output (mL/kg/h)	0.48 (0.24 - 0.71)	0.66 (0.47 - 0.88)	0.001
Lowest hourly urine output (mL/kg)	0.25 (0.1 - 0.35)	0.33 (0.24 - 0.4)	0.002
Diuretics used during first 6 hours	0 (0)	3 (3)	0.552
AKI by serum creatinine criteria			
Time from admission to AKI_{sCr} (hours)	1 (0 - 14)		
Transient AKI_{sCr}	16 (26)		
AKI_{sCr} within 24 hours	53 (87)		
Highest AKI_{sCr} stage reached within 24 hours	43 (70)		
Highest AKI_{sCr} stage within 72 hours			
AKI_{sCr} stage 1	31 (51)		
AKI_{sCr} stage 2	20 (33)		
AKI_{sCr} stage 3	10 (16)		
Renal replacement therapy			
Need for renal replacement therapy	12 (20)	0 (0)	<0.001
NGAL 4 hours after admission			
Plasma NGAL (ng/mL)	349 (192 - 566)	150 (86 - 216)	<0.001
Urine NGAL (ng/mL)	754 (186 - 4124)	99 (52 - 228)	<0.001

Data is presented as median (interquartile range) or number (percentage) where appropriate.
Oliguria is defined as hourly urine output < 0.5 ml/kg. AKI_{sCr}: acute kidney injury by serum creatinine criteria; NGAL: neutrophil gelatinase-associated lipocalin.

Multivariate models

In order to assess how the predictive ability of NGAL was related to other risk factors for AKI_{sCr}, we performed univariate and multivariate Cox proportional hazards regression analyses. The univariate Cox analyses are reported in **Table 7.3**. In the multivariate model without NGAL – using stepwise backward elimination – pre-admission serum creatinine, sepsis and lowest hourly urine output were significant predictors for AKI_{sCr} (**Table 7.4**). The addition of NGAL to the multivariate model – and subsequent stepwise backward elimination – resulted in pre-admission serum creatinine becoming a nonsignificant predictor of AKI_{sCr}, and NGAL,

sepsis and lowest hourly urine output remained significant predictors. The AUROCs for the univariate NGAL and the multivariate models are shown in **Table 7.5**. NGAL as a univariate predictor was not inferior to the multivariate model without NGAL at all time points, whereas the addition of NGAL to the multivariate model slightly increased the AUROC of predicting AKI_{sCr} at 24 and 72 hours after admission. Specifically, the improvement in AUROC by adding NGAL to the multivariate models seems mainly to be due to better classification of patients without AKI_{sCr} within the first 24 hours (**Table 7.6**). While a similar effect is present in the multivariate urinary NGAL model for patients without AKI_{sCr} within the first 72 hours, the multivariate plasma NGAL does not improve the classification of patients with and without AKI_{sCr} within the first 72 hours.

Table 7.3 Univariate Cox regression analysis for AKI_{sCr} as the outcome

	Univariate		
Variable	**HR**	**95% CI**	**P**
Plasma NGAL (x 100 ng/mL)	1.278	1.196 - 1.365	<0.001
Urinary NGAL (x 100 ng/mL)	1.049	1.034 - 1.065	<0.001
Pre-admission serum creatinine (µmol/L)	1.010	0.998 - 1.022	0.103
Sepsis	3.259	1.938 - 5.482	<0.001
Mean urine output (mL/kg/h)	0.385	0.174 - 0.850	0.018
Lowest hourly urine output (mL/kg)	0.015	0.002 - 0.118	<0.001
Duration of oliguria (hours)	1.300	1.110 - 1.522	0.001
Admission serum creatinine (µmol/L)[a]	1.015	1.012 - 1.018	<0.001

[a]: Variable not included in the full multivariate model due to prediction bias. HR: hazard ratio; CI: confidence interval.

Table 7.4 Multivariate models for the occurrence of AKIsCr within the first 72 hours of intensive care admission

	Multivariate model			Multivariate + plasma NGAL			Multivariate + urinary NGAL		
Variable	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Plasma NGAL (x 100 ng/mL)		–		1.170	1.075 - 1.274	<0.001		–	
Urinary NGAL (x 100 ng/mL)		–			–		1.033	1.016 - 1.050	<0.001
Pre-admission serum creatinine (µmol/L)	1.013	1.001 - 1.026	0.035	1.010	0.997 - 1.023	0.131	1.011	0.998 - 1.025	0.088
Sepsis	3.980	2.310 - 6.858	<0.001	2.513	1.335 - 4.748	0.004	2.891	1.598 - 5.230	<0.001
Lowest hourly urine output (mL/kg)	0.026	0.003 - 0.201	0.001	0.123	0.012 - 1.231	0.075	0.054	0.006 - 0.477	0.009

The multivariate models initially included all variables in the univariate analysis (Supplemental Digital Content Table S1), and variables were eliminated using a stepwise backward selection method. If pre-admission serum creatinine was unavailable, lowest serum creatinine during the admission was used as a surrogate. HR: hazard ratio; CI: confidence interval.

Table 7.5 Comparison of area under the receiver operating characteristics curve of predictors for AKIsCr for different time points

	24 hours after admission			48 hours after admission			72 hours after admission		
Variable/Model	**AUC**	**95% CI**	**P**	**AUC**	**95% CI**	**P**	**AUC**	**95% CI**	**P**
Multivariate model (reference)	0.733	0.645 - 0.821	ref.	0.746	0.658 - 0.834	ref.	0.704	0.603 - 0.805	ref.
Plasma NGAL (univariate)	0.728	0.634 - 0.821	0.924	0.729	0.639 - 0.820	0.773	0.785	0.699 - 0.871	0.223
Urinary NGAL (univariate)	0.755	0.672 - 0.838	0.617	0.770	0.688 - 0.852	0.610	0.757	0.667 - 0.848	0.318
Plasma NGAL + multivariate model	0.779	0.696 - 0.861	0.028	0.783	0.699 - 0.867	0.072	0.779	0.689 - 0.868	0.001
Urinary NGAL + multivariate model	0.772	0.689 - 0.855	0.048	0.781	0.698 - 0.865	0.052	0.741	0.645 - 0.837	0.043

The multivariate model (pre-admission serum creatinine + sepsis + lowest hourly urine output) was used as the reference standard against which the NGAL models were compared, resulting in the reported P values.

Table 7.6 Net reclassification index and integrated discrimination improvement

Multivariate model vs.	Multivariate plasma NGAL			Multivariate urinary NGAL		
Outcome	**Estimate**	**95% CI**	**P**	**Estimate**	**95% CI**	**P**
AKI_{sCr} within 24 hours						
NRI_{event}	0.057	-0.212 - 0.325	0.680	-0.132	-0.399 - 0.135	0.332
$NRI_{nonevent}$	0.285	0.115 - 0.454	<0.001	0.789	0.680 - 0.897	<0.001
NRI	0.341	0.023 - 0.659	0.035	0.657	0.368 - 0.945	<0.001
IDI	0.051	0.011 - 0.090	0.012	0.075	0.029 - 0.121	0.001
AKI_{sCr} within 72 hours						
NRI_{event}	0.082	-0.168 - 0.332	0.521	-0.180	-0.427 - 0.067	0.152
$NRI_{nonevent}$	0.165	-0.015 - 0.345	0.072	0.722	0.595 - 0.848	<0.001
NRI	0.247	-0.061 - 0.555	0.116	0.541	0.264 - 0.818	<0.001
IDI	0.047	0.012 - 0.081	0.008	0.067	0.026 - 0.109	0.001

The NRI statistic describes the proportion of patients based on the new model assigned a probability for AKI_{sCr} closer to 1 for those with AKI_{sCr} and closer to 0 for patients without AKI_{sCr}. The IDI statistic describes the mean change in probabilities (increases for events and decreases in non-events) between the new and old model. AKI_{sCr}: acute kidney injury by serum creatinine criteria; NRI: net reclassification index; IDI: integrated discriminatory improvement.

Optimal cutoff and test characteristics

Because plasma and urinary NGAL as a univariate predictor for AKI_{sCr} was not inferior to the multivariate model, we calculated the test characteristics of the optimal cutoff values for NGAL as predictors of AKI_{sCr} occurrence within 24, 48 and 72 hours of ICU admission. The result of this analysis is shown in **Table 7.7**, and the 2x2 tables for the optimal cutoff values for NGAL are reported in **Tables 7.8-7.10**. The optimal cutoff for plasma NGAL across the different time points resulted in positive likelihood ratios ranging from 4.6 to 8.2, whereas the optimal cutoff values for urinary NGAL led to positive likelihood ratios ranging from 2.2 to 2.6. For AKI_{sCr} within 48 and 72 hours, plasma NGAL was able to correctly predict 80% of patients with and without AKI_{sCr} based on the optimal cutoff.

Table 7.7 Test characteristics for the prediction of AKI_{sCr} at different time points within the first 72 hours of intensive care admission

Variable	Cutoff (N >)	Sens	Spec	PPV	NPV	PLR	NLR	Post-positive test probability	Post-negative test probability	AUROC
24 hours										
Plasma NGAL (ng/mL)	340 (42)	55%	88%	67%	82%	4.66	0.51	0.67 (0.36 -> 1.0)	0.18 (0.14 - 0.24)	0.71 (0.64 - 0.79)
Urinary NGAL (ng/mL)	270 (67)	69%	72%	52%	84%	2.50	0.42	0.52 (0.36 - 0.77)	0.16 (0.11 - 0.23)	0.71 (0.63 - 0.79)
48 hours										
Plasma NGAL (ng/mL)	370 (37)	49%	94%	81%	78%	8.21	0.54	0.81 (0.40 -> 1.0)	0.22 (0.17 - 0.28)	0.72 (0.64 - 0.80)
Urinary NGAL (ng/mL)	230 (72)	75%	69%	56%	84%	2.38	0.37	0.56 (0.39 - 0.8)	0.16 (0.11 - 0.25)	0.72 (0.64 - 0.80)
72 hours										
Plasma NGAL (ng/mL)	280 (55)	59%	91%	80%	79%	6.40	0.45	0.80 (0.50 -> 1.0)	0.21 (0.16 - 0.29)	0.69 (0.60 - 0.78)
Urinary NGAL (ng/mL)	250 (68)	68%	70%	58%	78%	2.24	0.46	0.58 (0.40 - 0.84)	0.22 (0.15 - 0.32)	0.67 (0.58 - 0.77)

Acute kidney injury defined by serum creatinine criteria occurred in 53, 58 and 61 patients at 24, 48 and 72 hours after admission, respectively. 29, and 51 patients were lost to follow-up due to death or intensive care discharge after 24 and 48 hours, respectively; Pre-test probability (corrected for loss to follow-up) was 0.31, 0.35 and 0.38 for 24, 48 and 72 hours after admission, respectively. Test characteristics are adjusted for loss to follow-up. Sens: sensitivity; spec: specificity; PPV: positive predictive value; NPV: negative predictive value; PLR: positive likelihood ratio; NLR: negative likelihood ratio; AUROC: area under receiver operating characteristic curve.

Table 7.8 2x2 tables for distribution of patients based on the optimal cutoff values for NGAL at 24 hours after admission.

	AKI_{sCr}	**$noAKI_{sCr}$**
Plasma NGAL > 340 ng/mL	29	13
Plasma NGAL ≤ 340 ng/mL	24	110
Urinary NGAL > 270 ng/mL	37	30
Urinary NGAL ≤ 270 ng/mL	16	93

Table 7.9 2x2 tables for distribution of patients based on the optimal cutoff values for NGAL at 48 hours after admission.

	AKI_{sCr}	$noAKI_{sCr}$
Plasma NGAL > 370 ng/mL	29	8
Plasma NGAL ≤ 370 ng/mL	29	110
Urinary NGAL > 230 ng/mL	43	29
Urinary NGAL ≤ 230 ng/mL	15	89

Table 7.10 2x2 tables for distribution of patients based on the optimal cutoff values for NGAL at 72 hours after admission.

	AKI_{sCr}	$noAKI_{sCr}$
Plasma NGAL > 280 ng/mL	36	19
Plasma NGAL ≤ 280 ng/mL	25	96
Urinary NGAL > 250 ng/mL	42	26
Urinary NGAL ≤ 250 ng/mL	19	89

DISCUSSION

The main finding of this post-hoc analysis is that NGAL can be used in a clinical setting to discriminate between oliguric critically ill patients with AKI_{sCr} within the first 72 hours from oliguric patients with a functional reversible glomerular adaptation. In an oliguric patient with known risk factors, the addition of NGAL improves the ability to rule out AKI_{sCr}. Furthermore, univariate NGAL is not inferior to a multivariate model of known risk factors, and NGAL can be used to identify or exclude AKI_{sCr} in oliguric patients even when pre-admission serum creatinine value and other risk factors are unknown. Given these findings, clinicians can use NGAL to identify patients with oliguria due to functional adaptation during the early ICU admission. In other words, when oliguria occurs, low NGAL values may rule out structural cellular damage signifying AKI_{sCr}.

Our results partly agree with previous literature on oliguria and AKI in the critically ill. A recent study in critically ill patients with new-onset oliguria strongly suggests that not all episodes of oliguria carry the same risk for worsening renal function (21). In contrast to

our analysis, only patients with six consecutive hours of oliguria at some point during the ICU admission were included and worsening renal outcome was defined as both serum creatinine and urine output defined AKI. However, as the occurrence of oliguria takes place farther from the initial renal hit, biomarkers with a time course similar to NGAL may become less informative (11). In our study, this is illustrated by the decrease in NRI and IDI for plasma NGAL when predicting AKI_{sCr} within 72 hours when compared with the prediction of AKI_{sCr} within 24 hours after admission.

This study has several strengths: First, we showed that NGAL measurements in a patient group with a high pre-test probability, such as oliguric patients, are of additional value for the early diagnosis of AKI_{sCr} and can be done in a clinically practical manner. Limiting NGAL measurements to a high pre-test probability population improves the cost-effectiveness of biomarkers for AKI (22). Secondly, considering its time course, NGAL only improves the differentiation between functional oliguria and oliguria due to renal injury within a relative short time after the initial renal injury. Thus, NGAL is best suited for use early during the ICU admission or shortly after an event leading to the initial renal injury. Lastly, in oliguric patients NGAL can be used to identify those without AKI_{sCr} without having to wait for a second serum creatinine measurement or search for a pre-admission serum creatinine value. Given the lag time, the measurement frequency of serum creatinine, and the paucity of available pre-admission data, NGAL provides early information on renal outcome.

This study has several potential limitations: Firstly, because this study was a post-hoc analysis of a prior prospective dataset, future studies are needed to validate our findings. Secondly, the lack of an adequate gold standard to diagnose AKI_{sCr} distorts the performance of any biomarker (23). Therefore, injury biomarkers have potential in conjunction with functional markers such as serum creatinine and urine output. Furthermore, in our clinical practice serum creatinine is measured at admission and at least once daily at 6.00 AM thereafter. While serum creatinine may take up to 24 hours to increase after a reduction in glomerular filtration (24), measuring serum creatinine once daily could delay the recognition of AKI_{sCr}. Moreover, since we did not correct the measured serum creatinine concentration for the cumulative fluid balance in the first 72 hours of ICU admission (25), it is possible that some patients were incorrectly classified as not having AKI_{sCr}. Thirdly, to calculate hourly urine output from irregular collection intervals, we assumed that urine flow was constant during each interval, which ignores any effects of treatment or disease progression during a single period of variable length which could increase or decrease urine output. Additionally, collecting enough urine to measure urinary NGAL is difficult in patients with very low urine output, which may explain some of the missing values for urinary NGAL. The missing data rate for plasma and urinary NGAL measurements was 8.5% and 12% respectively, due to interventional procedures or transport at the time of collection. We used multiple imputations using predictive mean matching of NGAL at admission, 4 hours and 8 hours

after admission to gather valid data to use as a surrogate. Lastly, we did not normalize urinary NGAL concentrations for urinary creatinine concentration, since urinary creatinine data was not available, and doubts remain about the necessity for such a correction (26,27).

The main clinical application of our findings is that it provides early awareness which should trigger interventions to stop further renal injury in oliguric patients with NGAL above the cutoff value. Decision algorithms similar to the one proposed for cardiac-surgery-associated-AKI could be used to triage patients and resources (28). In this population with possible AKI_{sCr}, fluid resuscitation should be limited to the restoration of systemic hemodynamic variables, and nephrotoxic agents should be discontinued. In a research setting, NGAL is able to adjust the inclusion criteria to create early intervention studies similar to the STOP-AKI trial (29) currently including patients only after serum creatinine starts to increase, reducing the lag-time before interventions are started.

More importantly, measuring NGAL may lead to differentiation between structural renal injury and functional adaptation. Patients with higher NGAL but without an increase in serum creatinine should be classified as subclinical AKI_{sCr} (23). These patients have worse outcomes than those with a low NGAL value and no increase in serum creatinine most likely due to adequate renal reserves (30), suggesting that subclinical AKI_{sCr} should be considered similar to AKI_{sCr} with elevated NGAL levels. Conversely, patients with AKI_{sCr} may have relatively low NGAL levels due to glomerular impairment without tubular injury which is associated with worse outcomes than those with low NGAL and no serum creatinine increase (23,30). Whether these patients should be treated as AKI_{sCr} or as a third entity in the AKI spectrum remains to be determined.

CONCLUSION

In summary, NGAL is able to discriminate between critically ill patients with oliguria associated with AKI_{sCr} and those with oliguria due to functional adaptation. More specifically, NGAL as part of a multivariate model is able to exclude AKIsCr whereas NGAL as a single marker can identify oliguric patients at risk for AKI_{sCr}. Thus, NGAL could be used to aid clinical management in patients presenting with early oliguria. Guided by NGAL, clinicians can reduce further renal injury and identify patients with subclinical AKI_{sCr}. However, since serum creatinine is an imperfect diagnostic standard for factual renal cellular injury, further prospective studies are needed to confirm our findings.

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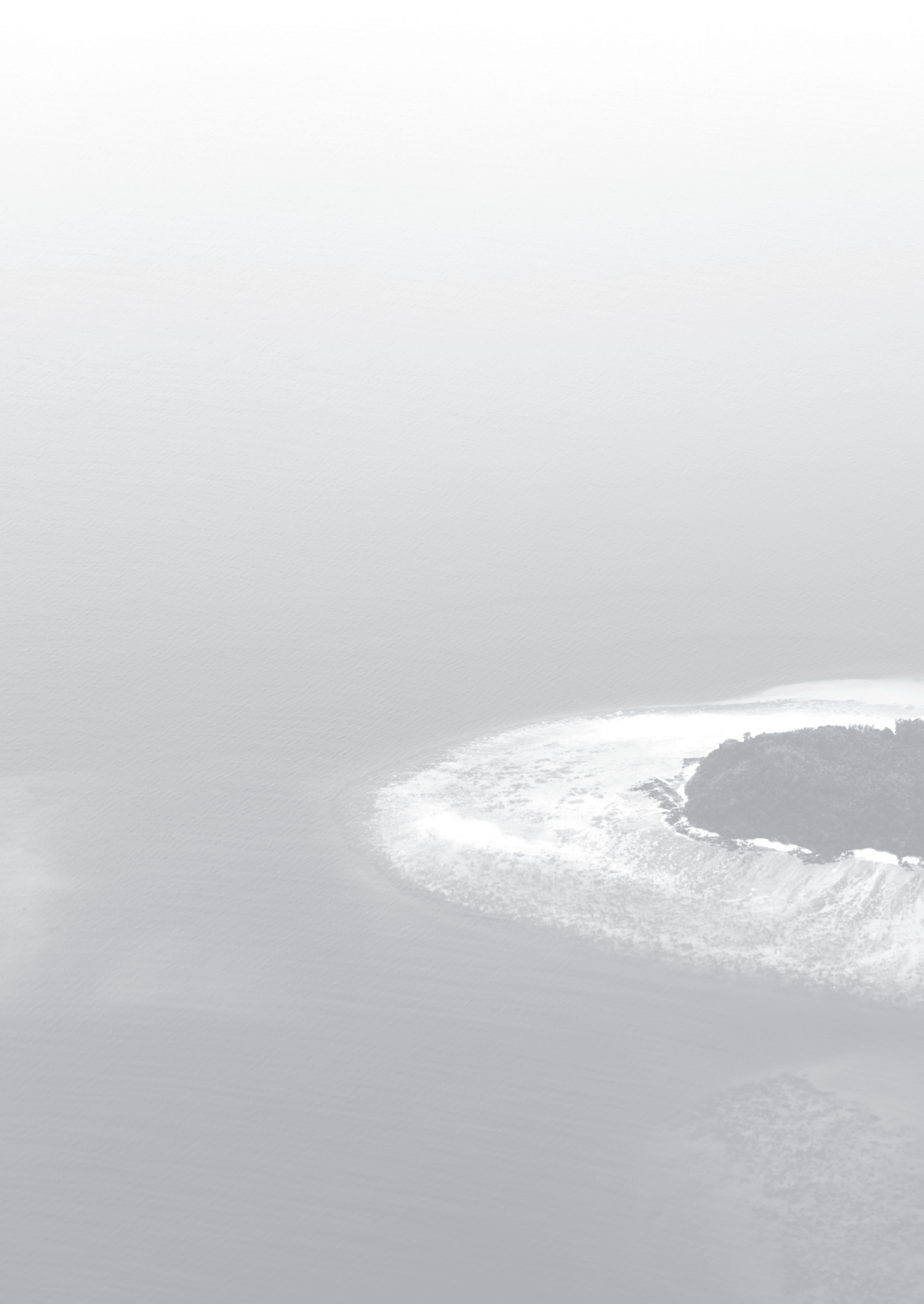
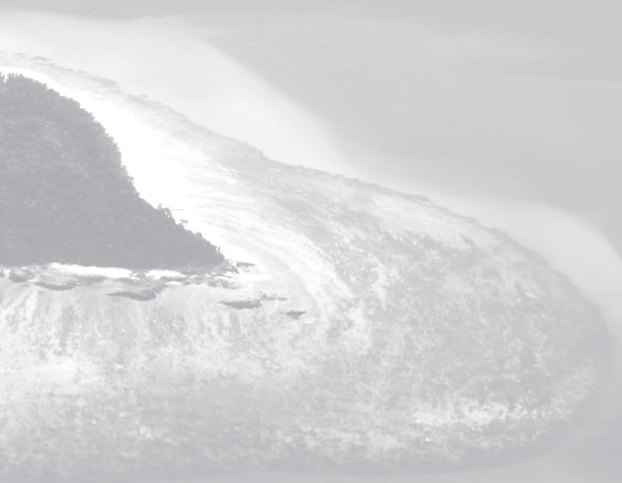
CHAPTER 8

Renal fluid responsiveness and acute kidney injury in oliguric critically ill patients: a prospective interventional single-center study



PART IV



CHAPTER 9

Summary and future Perspective

Consequences of fluid management

There appears to be a mismatch between intravenous fluid administration and fluid loss via urine output in the critically ill patient, which leads to fluid overload and related adverse events. Although commonly assumed, it has never been shown that patients who are still fluid responsive have a lower risk to develop tissue edema. Therefore, in **chapter 2**, we hypothesized that excessive fluid administration in the first days of intensive care admission is associated with higher extravascular lung water index (EVLWI), but not in fluid responsive patients. The main finding of this retrospective study was that a higher fluid balance was associated with an increase in EVLWI. However, increases in EVLWI were independent from the presence of fluid responsiveness, which may be due to fluid responsiveness not being a factor in fluid extravasation. More importantly, patients showed poorer oxygenation despite higher FiO2 when EVLWI increased. Preventing fluid overload may therefore lead to adequate oxygenation, less ventilatory support, and shorter length of stay. In **chapter 3**, we investigated whether high early fluid intake and fluid balances after admission were associated with the occurrence of delayed cerebral ischemia (DCI) in patients with aneurysmal subarachnoid hemorrhage (aSAH), and the feasibility of decreasing fluid input guided by cardiac output monitoring with transpulmonary thermodilution (TPT). In this retrospective study of two separate aSAH cohorts, early high daily fluid input was independently associated with DCI and poor outcome in one cohort, and fluid loading beyond normal preload occurred in the both cohorts. It was nevertheless feasible to significantly restrict fluid intake while maintaining adequate preload with TPT in selected high-risk patients with aSAH.

Taking both chapters together, these results corroborate the potential harm from fluid overload in patients and support further study on potential benefit of fluid restriction guided by cardiac output-based hemodynamic monitoring. While decreasing fluid intake may not necessarily directly improve outcome, it is likely that it will prevent adverse effects negatively impacting outcome.

Fluid management guided by targeting urine output

One of the main focuses of this thesis was to investigate whether additional fluid administration aimed at improving urine output had the desired effect of protecting against acute kidney injury (AKI) or other adverse outcomes. In **chapter 4 and 5**, both systematic reviews with meta-analyses, we focused on whether including urine output as a target in the protocols of studies comparing goal-directed therapy (GDT) with conventional fluid management (CFM) strategies in surgical and critically ill patients reduced the incidence of AKI and mortality, respectively. In **chapter 4**, while GDT was superior to CFM in preventing AKI, the addition of urine output as a target in either protocol appeared to increase the occurrence of AKI. In **chapter 5**, the principal finding was that while GDT might decrease 30-day mortality, including urine output as a target may increase 30-day mortality. However,

after adjusting for confounders, there was insufficient evidence to associate targeting urine output with an effect on 30-day mortality. Additionally, using the common urine output threshold of 0.5 ml/kg/h, there was insufficient evidence to suggest that targeting urine output affected 30-day mortality. In **chapter 6**, we investigated whether perioperative restrictive fluid management influenced the occurrence of oliguria, AKI, fluid intake and fluid balance. We also investigated whether targeting urine output influenced these parameters. In this meta-analysis, we found insufficient evidence to associate restrictive fluid management with an increase in oliguria and AKI occurrence. The difference in intraoperative fluid intake between conventional and restrictive fluid management was similar whether urine output was targeted or not, and excluding urine output as a target in a restrictive fluid management protocol did not seem to be associated with an increase in AKI occurrence.

Summarizing these three chapters, at best, targeting urine output does not influence AKI or mortality, and at worst, the addition of urine output as a target in a fluid management protocol increases the risk for AKI and mortality. The difficulty in interpreting the findings from these meta-analyses lies in the high variability between studies and the lack of any direct comparison between targeting and not targeting urine output. Nevertheless, there appears to be no clear benefit of incorporating urine output as a target in any fluid management strategy. Overall, the findings in these chapters support the removal of urine output as a target in any fluid management protocol due to the lack of the desired effect on AKI.

Fluid management in oliguria

Another aim of this thesis was to assess whether the urine output response after a fluid challenge can be predicted, and whether this effect impacts patients' outcome. We used neutrophil gelatinase associated lipocalin (NGAL) as a marker for renal damage and in **chapter 7**, we performed a post-hoc analysis in a cohort of critically ill patients with oliguria occurring within 6 h of intensive care unit (ICU) admission. Our hypothesis was that low NGAL concentrations in oliguric critically patients are most likely due to hemodynamic or hormonal compensation mechanisms, whereas a high NGAL concentration heralded AKI by a rise in serum creatinine within the first 72 hours. The main finding was that NGAL can be used in a clinical setting to discriminate between oliguric critically ill patients with AKI from oliguric patients with a functional, reversible adaptation. In an oliguric patient with known risk factors, the addition of NGAL improved the ability to rule out AKI. Furthermore, NGAL by itself was not inferior to a multivariate model of known risk factors, and NGAL can be used to identify or exclude AKI in oliguric patients even when pre-admission serum creatinine value and other risk factors are unknown.

The supposed protective effects of renal fluid responsiveness (RFR) against AKI and renal damage have not been proven. In **chapter 8**, we performed a prospective interventional

study in critically ill patients with isolated oliguria for at least 2 hours to test whether cardiac fluid responsiveness (CFR) is associated with RFR, whether RFR protects against AKI occurrence or renal damage as assessed by NGAL, and whether there are predictors for RFR and AKI in this population. We found that CFR in critically ill patients with isolated oliguria was not associated with RFR, and the development of AKI was not influenced by RFR, though urinary NGAL after the fluid challenge - as a sign of tubular injury - was lower in RFR+ patients than in RFR- patients. Nevertheless, there were no good, specific predictors for RFR or AKI.

Summarizing both chapters, clinicians can use NGAL to identify patients with oliguria due to functional adaptation during the early ICU admission. Additionally, oliguria is not a reliable indicator of inadequate cardiac output, and RFR is difficult to predict. Simply put, when oliguria occurs, low NGAL values may rule out structural cellular damage and no additional fluid boluses aimed at improving urine output should be given in the absence of other signs of hemodynamic instability. These chapters findings support the paradigm that urine output should never be a goal onto itself, but should be viewed as a sign of an underlying problem.

Future perspectives

In this thesis, we showed the adverse effects of inappropriate fluid loading on tissue edema and outcome, while hemodynamic monitoring using TPT may be able to safely reduce fluid intake without negatively impacting cardiac output. Additionally, contrary to current practice, targeting urine output and a subsequent improvement in urine output do not protect against AKI either due to the resolution of hypovolemia through other resuscitation targets or because the cause of oliguria does not respond to fluids. Nevertheless, several questions remain.

Though hemodynamic monitoring – either by TPT or other methods – has become commonplace in the ICU for certain populations, its use in the general ICU population is limited. While the need for and beneficial effects of hemodynamic monitoring in sepsis and high-risk surgical patients are well documented, guiding fluid intake by hemodynamic monitoring tools other than conventional measures remains to be explored. For example, the cost-effectiveness of using TPT in patients with respiratory insufficiency necessitating mechanical ventilation to prevent increases in extravascular volume is an interesting topic. Although conventional hemodynamic parameters may be adequate to hypovolemia, it is the ability of hemodynamic monitoring tools such as TPT to signal hypervolemia which is of interest even outside the traditional target groups.

While we advocate the use of permissive oliguria in this thesis due to the lack of effect when targeting urine output, its impact on patient outcome needs to be investigated further. This is of increased importance when considering the use of early renal replacement therapy

during the deresuscitation phase when urine output is unable to adequately clear the fluid excess cumulated during the resuscitation phase. It is not only important to investigate when to start renal replacement therapy, but also how to monitor its effect on renal recovery and when to discontinue it. While the interventional burden of renal replacement therapy on this new group of patients may seem disproportionate, the expected benefits from reducing the effects of fluid overload would most likely outweigh it.

Lastly, further investigation into the underlying etiology of oliguria is needed. In this thesis, we showed that not all oliguric patients with elevated NGAL as a sign of tubular damage had an increase in serum creatinine and vice versa. Similarly, NGAL was elevated in patients with persistent oliguria who were cardiac fluid responsive, but not in patients who did not have an increase in stroke volume after a fluid challenge. The former is assumed to be due to microcirculatory dysfunction with inflammatory stress, while the latter could be considered a form of functional adaptation with glomerular dysfunction. It would be interesting to see whether the underlying etiology further influences the clinical course and long-term outcome, as well as finding new avenues for early interventions.

CHAPTER 10

Samenvatting en toekomstperspectieven

Consequenties van intraveneus vochtbeleid

Er lijkt een dissociatie te zijn tussen het intraveneus toegediende vocht en het vochtverlies via de urineproductie in ernstig zieke patiënten, wat leidt tot overvulling en daaraan gerelateerde complicaties. Alhoewel het algemeen aangenomen wordt, is het nog niet bewezen dat patiënt die reageren op een intraveneuze vochtbolus een lagere kans hebben op het ontwikkelen van weefseloedeem. Daarom is onze hypothese in **hoofdstuk 2** dat te veel intraveneuze vochttoediening in de eerste dagen van de intensive care opname geassocieerd is met een hogere extravasculair longwater index (EVLWI), maar niet in vochtresponsieve patiënten. De voornaamste bevinding in deze retrospectieve studie was dat een hogere vochtbalans geassocieerd was met een stijging in EVLWI. Maar stijgingen in EVLWI waren onafhankelijk van vochtresponsiviteit, wat verklaard kan worden doordat vochtresponsiviteit niet een bepalende factor is in het ontstaan van vochtlekkage uit de bloedvaten. Belangrijker was de bevinding dat, wanneer EVLWI toenam, patiënten een lagere arteriële zuurstofconcentratie hadden ondanks meer zuurstofaanbod via de beademing. Het voorkomen van overvulling zou daardoor kunnen leiden tot betere zuurstofopname, lagere beademingsvoorwaarden en een kortere opnameduur.

In **hoofdstuk 3** onderzochten wij of hoge vochtintake en vochtbalansen kort na de opname geassocieerd zijn met cerebrale ischemie (DCI) in patiënten met een aneurysmatisch subarachnoïdale bloeding (aSAH) en of hemodynamische monitoring middels de transpulmonale thermodilutie techniek (TPT) kan leiden tot het veilig verlagen van de vochtintake. In deze retrospectieve studie van twee verschillende aSAH cohorten was hoge vochtintake onafhankelijk gerelateerd met DCI en slechte uitkomst in een cohort. Daarnaast was de vochtintake hoger dan normaal in beide cohorten. Desondanks was het mogelijk om de vochtintake significant te verlagen met behoud van adequate hemodynamiek middels TPT in geselecteerde hoog risicopatiënten met aSAH.

Als beide artikelen samengenomen worden, dan zijn deze resultaten in overeenstemming met de mogelijke schade van overvulling in patiënten die in eerder studies zijn gezien. Daarnaast ondersteunen beide studies de noodzaak van verder onderzoek naar het potentiele voordeel van vochtbeperking middels hemodynamische monitoring. Alhoewel het verlagen van de vochtintake wellicht niet direct leidt tot betere uitkomsten, is het waarschijnlijk dat het nadelige effecten voorkomt.

Urineproductie gestuurde vochtbeleid

Een van de kernpunten van dit proefschrift was om te onderzoeken of extra vochttoedieningen gericht op het verbeteren van de urineproductie het gewenste effect bereiken, beschermen tegen acute nierschade (AKI) of het voorkomen van ongewenste uitkomsten. In **hoofdstuk 4 en 5**, beiden systematische review artikelen met meta-analyses, focusten we op of het toevoegen van urineproductie als een doel in behandelprotocollen leidde tot een

respectievelijke verlaging in het voorkomen van AKI en sterfte in studies die *goal-directed therapy* (GDT) vergelijken met conventioneel vochtbeleid (CFM) in chirurgische en ernstig zieke patiënten. In **hoofdstuk 4** was GDT superieur ten opzichte van CFM in het beschermen tegen AKI, maar het toevoegen van urineproductie als een behandeldoel in beide protocollen lijkt te leiden tot een hoger risico op het krijgen van AKI. De voornaamste bevinding in **hoofdstuk 5** was dat het toevoegen van urineproductie als een behandeldoel 30-dagen sterfte leek te verhogen, ondanks een risico reductie in 30-dagen sterfte door GDT. Desondanks was er na correctie voor vertroebelende factoren onvoldoende aanwijzingen dat urineproductie-gestuurd vochtbeleid de 30-dagen sterfte beïnvloedde. Daarnaast was er gebruikmakend van de standaard afkapwaarde van 0,5 ml/kg/uur voor urineproductie eveneens onvoldoende aanwijzingen dat urineproductie-gestuurd vochtbeleid de 30-dagen sterfte beïnvloedde. In **hoofdstuk 6** onderzochten wij of restrictief vochtbeleid tijdens de perioperatieve fase invloed had op het krijgen van oligurie, het ontstaan van AKI, vochtintake en vochtbalans. We onderzochten ook of urineproductie-gestuurde vochtbeleid invloed had op deze waarden. In deze meta-analyse vonden we onvoldoende aanwijzingen om een terughoudend vochtbeleid te associëren met een toename in oligurie en AKI. Het verschil in intra-operatieve vochtintake tussen een conventionele en restrictieve vochtbeleid was hetzelfde ongeacht of urineproductie als een behandeldoel werd gebruikt. Het ontbreken van urineproductie als een behandeldoel in een restrictief vochtbeleid leek niet geassocieerd met een toename in AKI.

Samenvattend lijkt het gebruik van urineproductie als behandeldoel in het beste geval niet van invloed op het ontstaan van AKI of sterfte, maar in het slechtste geval verhoogt het juist de kans op AKI of sterfte. De moeilijkheid in het interpreteren van de bevindingen uit deze meta-analyses komt door de grote verschillen in de gebruikte studies om het effect uit de beschreven literatuur te analyseren en het gebrek aan studies die een directe vergelijking maken tussen het gebruiken en het niet gebruiken van urineproductie als een behandeldoel. Desalniettemin lijkt er geen duidelijk voordeel te zijn aan het gebruik van urineproductie als behandeldoel. Al met al ondersteunen deze hoofdstukken het laten vallen van urineproductie als een doel in elke vochtbeleidsprotocol gezien het gebrek van enig gewenst effect op AKI.

Vochtbeleid in oligurie

Een ander kernpunt van dit proefschrift was het vaststellen of een stijging in urineproductie na een vochtbolus te voorspelling is en of dit effect van invloed is op de uitkomst van een patiënt. We gebruikten neutrophil gelatinase associated lipocalin (NGAL) als een marker voor nierschade en in **hoofdstuk 7** lieten we een post-hoc analyse zien van een cohort van ernstig zieke patiënten met oligurie in de eerste zes uur van de intensive care opname. Onze hypothese was dat een lage NGAL-waarde in oligure, ernstig zieke patiënten meest

waarschijnlijk door hemodynamische of hormonale compensatiemechanismen komt, terwijl een hoge NGAL-waarde een teken is van het krijgen van AKI in de eerste 72 uur van de opname. De voornaamste bevinding was dat NGAL in een klinische setting gebruikt kan worden om AKI in oligure, ernstig zieke patiënten te onderscheiden van functionele adaptatie als oorzaak voor de oligurie. In een oligure patiënt verbeterde de toevoeging van NGAL aan een voorspellingsmodel op basis van bekende risicofactoren de capaciteit om AKI uit te sluiten. Daarnaast was het voorspellend vermogen van enkel NGAL niet inferieur aan die van een model met bekende risicofactoren. NGAL kan zelfs gebruikt worden om AKI aan te tonen of uit te sluiten in oligure patiënten als serum creatinine waarden voor opname of andere risicofactoren niet bekend zijn.

De veronderstelde beschermende effecten van renale vochtresponsiviteit (RFR) op AKI en nierschade zijn niet bewezen. In **hoofdstuk 8** voerden wij een prospectieve interventie studie uit in ernstig zieke patiënten met oligurie gedurende tenminste 2 uur om te testen of cardiale vochtresponsiviteit (CFR) geassocieerd is met RFR, of RFR beschermt tegen het ontstaan van AKI of nierschade uitgedrukt in NGAL-expressie, en of er voorspellende factoren zijn voor RFR en AKI in deze patiëntenpopulatie. We vonden dat CFR in ernstig zieke patiënten met oligurie niet geassocieerd was met RFR en dat het ontstaan van AKI niet beïnvloed werd door RFR. Daarnaast was urine NGAL, als teken voor nierschade, lager in de RFR+ groep na de vochtbolus dan in de RFR- patiënten, maar er waren geen goede, specifieke voorspellers voor RFR en AKI.

Samenvattend kunnen artsen NGAL gebruiken om aan te tonen dat oligurie in de vroege intensive care opname veroorzaakt wordt door functionele adaptatie. Daarnaast is oligurie geen goede indicator voor een inadequate hemodynamiek en RFR is moeilijk te voorspellen. Simpel gezegd, als oligurie zich voordoet, sluit een lage NGAL-waarde nierschade uit en hebben extra vochttoedieningen gericht op het verbeteren van de urineproductie geen zin als andere tekenen van hemodynamische instabiliteit afwezig zijn. Deze hoofdstukken ondersteunen de zienswijze dat urineproductie niet een doel op zich moet zijn, maar dat het gezien moet worden als een teken van een onderliggend probleem.

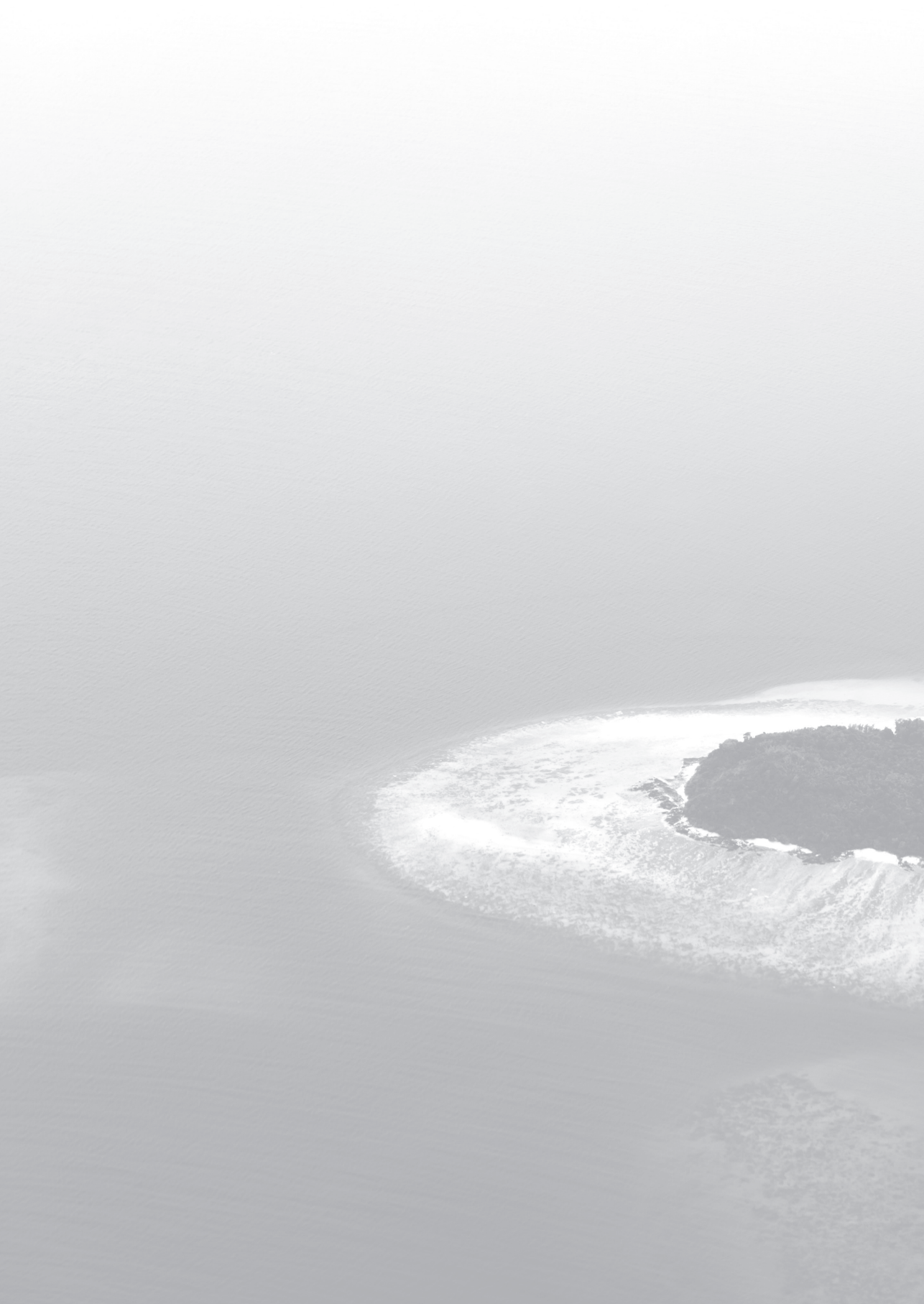
Toekomstperspectieven

In dit proefschrift toonden wij de effecten van ongepaste vochttoedieningen op weefseloedeem en uitkomst, terwijl hemodynamische monitoring middels TPT mogelijk kan leiden tot het veilig verlagen van de vochtintake. In tegenstelling tot wat in het algemeen gedacht werd, beschermen het gebruik van urineproductie als een behandeldoel en een stijging van de urineproductie na een vochtbolus niet tegen AKI. Dit is of vanwege het verbeteren van de ondervulling door andere behandeldoelen of doordat de oorzaak van de oligurie niet reageert op vulling. Desalniettemin blijven er vragen onbeantwoord.

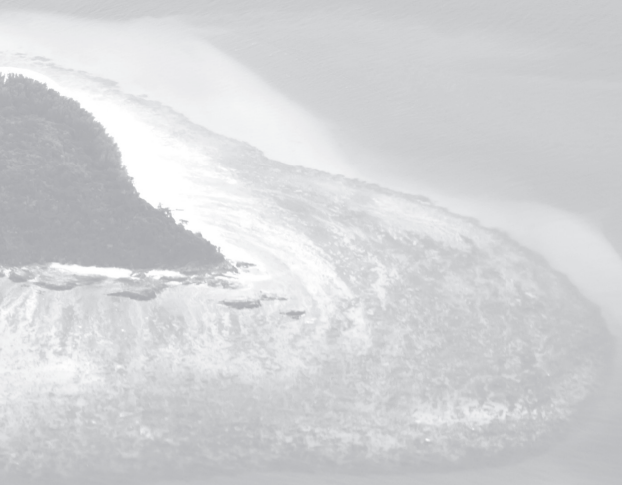
Alhoewel hemodynamische monitoring door middel van TPT of andere methoden ondertussen gemeengoed is geworden in bepaalde patiëntengroepen op de intensive care, is het gebruik ervan in de algemene intensive care populatie beperkt. De noodzaak voor en de voordelen van hemodynamische monitoring in sepsis en hoog-risico chirurgische patiënten zijn goed gedocumenteerd, maar het sturen van de vochtintake op geleide van hemodynamische monitoringstechnieken anders dan conventionele methoden moet nog uitgezocht worden. Een interessant onderwerp is bijvoorbeeld de kosteneffectiviteit van het gebruik van TPT ter voorkoming van stijging in EVLWI in patiënten met noodzaak tot mechanische beademing. Terwijl traditionele hemodynamische parameters adequaat genoeg zijn om ondervulling te beoordelen, is de toegevoegde waarde van technieken zoals TPT dat hiermee ook overvulling beoordeeld kan worden - ook buiten de gebruikelijk patiëntengroepen.

Alhoewel wij in dit proefschrift een voorstander zijn van het accepteren van oligurie gezien het gebrek aan effect als urineproductie als behandeldoel wordt gezien, moet de invloed van het accepteren van oligurie op uitkomstparameters verder onderzocht worden. Dit is vooral van belang vanwege het vroege gebruik van nierfunctie-vervangende therapie zoals tijdelijke dialyse tijdens de vroege deresuscitatie fase als de urineproductie niet in staat is om het ontstane vochtoverschot te kunnen verminderen. Het is niet alleen belangrijk om uit te zoeken wanneer er met nierfunctie-vervangende therapie gestart moet worden, maar ook het bijhouden van het effect op het herstel van de nierfunctie en wanneer er gestopt kan worden met nierfunctie vervangende therapie. De toename in het gebruik van nierfunctie vervangende therapie in deze nieuwe patiëntenpopulatie zou kunnen leiden tot een onevenredige behandelbelasting, maar de verwachte voordelen van het verminderen van de complicaties van overvulling zullen hier waarschijnlijk meer dan voldoende voor compenseren.

Als laatste is er verder onderzoek nodig naar de onderliggende ontstaanswijze van oligurie. In dit proefschrift toonden we dat niet alle oligure patiënten met een verhoogd NGAL-waarde als teken van nierschade een stijging van het serum creatinine doormaakte en omgekeerd. Daarnaast was NGAL hoger in patiënten met aanhoudende oligurie die wel cardiaal vocht responsief waren in tegenstelling tot patiënten die geen stijging van hun slagvolume lieten zien na een vochtbolus. Het eerste kan passen bij microcirculatoire dysfunctie met inflammatoire stress, terwijl het laatste gezien kan worden als een soort functionele adaptatie met glomerulaire dysfunctie. Het zou zeer interessant zijn om te onderzoeken of de onderliggende oorzaak ook invloed heeft op het klinische beloop en de uitkomst op lange termijn. Daarnaast zou verder onderzoek naar de onderliggende oorzaak ook nieuwe aanwijzingen kunnen geven voor vroege interventies.



PART V



CURRICULUM VITAE

Mohamud Egal was born on the 26th of June 1989 in Mogadishu, Somalia. After coming to the Netherlands as a refugee in the early 90s following the outbreak of a civil war, he graduated from secondary school (VWO, Veurs Lyceum, Leidschendam) in 2006. From 2006 till 2012, he studied Medicine at the faculty of Medicine (Erasmus MC) at the Erasmus University Rotterdam, The Netherlands. After graduation, he started as a junior doctor at the Intensive Care department of the Erasmus MC, Rotterdam in 2013 initially under supervision of prof. dr. J. Bakker and later prof. dr. D.A.M.P.J. Gommers. Simultaneously, he started as a PhD student under the supervision of prof. dr. A.B.J. Groeneveld and later prof. dr. D.A.M.P.J. Gommers, resulting in this thesis.

After three and a half years of working at the Intensive Care department of the Erasmus MC, he started working at the Internal Medicine department of the Elisabeth-Tweesteden Hospital (ETZ, location Elisabeth) in Tilburg in August 2016. He started his training in Internal Medicine in 2018 at the Elisabeth-Tweesteden Hospital (ETZ, location Elisabeth) under the supervision of dr. M.E.E. van Kasteren. He will continue his residency training at the Erasmus MC in a few years' time.

PUBLICATIONS

Publications related to this thesis

- **Egal M**, Erler NS, de Geus HR, van Bommel J, Groeneveld AB. 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. Anesthesia & Analgesia. 2016;122(1):173-85.
- **Egal M,** de Geus HR, van Bommel J, Groeneveld AB. Targeting oliguria reversal in perioperative restrictive fluid management does not influence the occurrence of renal dysfunction: A systematic review and meta-analysis. European Journal of Anaesthesiology. 2016;33(6):425-35.
- **Egal M**, de Geus HR, Groeneveld AB. Neutrophil gelatinase-associated lipocalin as a diagnostic marker for acute kidney injury in oliguric critically ill patients: a post-hoc analysis. Nephron. 2016;134(2):81-88
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- Vergouw LJM*, **Egal M***, Bergmans B, Dippel DWJ, Lingsma HF, Vergouwen MDI, Willems PWA, Oldenbeuving AW, Bakker J, van der Jagt M. High Early Fluid Input After Aneurysmal Subarachnoid Hemorrhage: Combined Report of Association With Delayed Cerebral Ischemia and Feasibility of Cardiac Output-Guided Fluid Restriction. J Intensive Care Med. 2017 [Epub ahead of print].

Publications unrelated to this thesis

- Bikker IG, Preis C, **Egal M**, Bakker J, Gommers D. Electrical impedance tomography measured at two thoracic levels can visualize the ventilation distribution changes at the bedside during a decremental positive end-expiratory lung pressure trial. Critical care. 2011;15(4):R193.
- Scohy TV, Golab HD, **Egal M**, Takkenberg JJ, Bogers AJ. Intraoperative glycemic control without insulin infusion during pediatric cardiac surgery for congenital heart disease. Paediatric anaesthesia. 2011;21(8):872-9.
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Abstract/Case reports/Other

- Bergmans B, **Egal M**, van Bommel J, Bakker J, Van der Jagt M. Effects of cardiac output-guided hemodynamic management on fluid administration after aneurysmal subarachnoid hemorrhage. Critical care. 2014;18(Suppl 1):P455.
- **Egal M**, Lima A, van Bommel J, Bakker J, Groeneveld ABJ. Association between maximum daily lactate levels and daily sequential organ failure assessment score: A retrospective, observational study. Intensive Care Medicine. 2014;40(1):S117-S8.
- Weigel JD, **Egal M**, Lima A, Koch B, Hunfeld NG, van Gelder T, et al. Vancomycin is underdosed in patients with high estimated glomerular filtration rate. Intensive Care Medicine. 2014;40(1):S252.
- Weigel JD, **Egal M**, Bakker J. Fatal calyceal-venous fistula. Intensive Care Med. 016 Nov;42(11):1805
- **Egal M**, de Geus HRH. Reducing Mortality in Acute Kidney Injury. Anesth Analg. 2017 [Epub ahead of print]

* denotes shared first authorship

PHD PORTFOLIO

Summary of PhD training and teaching activities

Name PhD student: M. Egal	**PhD period:** 2013 – 2018
Erasmus MC Department: Intensive Care Medicine	**Promotors:** prof. dr. ABJ Groeneveld† and prof. dr. DAMPJ Gommers
Research School: COEUR	**Supervisor:** dr. J. van Bommel and dr. H.R.H. de Geus

1. PhD training

	Year	Workload (ECTS)
General academic skills		
Basis regelgeving onderzoek (BROK)	2013	1.5
In-depth courses (e.g. Research school, Medical Training)		
FCCS	2013	1.5
Presentations		
ESICM 2014, Barcelona, Spain, poster presentation	2014	0.3
International conferences and symposia		
ESICM 2014, Barcelona, Spain	2014	0.9
Seminars and workshops		
Various Intensive Care (evening) symposia	2013-2015	2.0
Internal Medicine (evening) symposia	2016-2017	1.5
Didactic skills		
Teach the teacher II	2017	0.3
Other		
Intensive Care research meetings (weekly)	2013-2015	2.0
Journal Club Intensive Care (weekly)	2013-2016	2.0
Journal Club Internal Medicine (weekly)	2016-2017	0.8

2. Teaching activities

	Year	Workload (Hours/ECTS)
Supervision of students		
Temporary supervision of D. Wilschut	2016	0.1
Temporary supervision of O. Dedeoglu	2016	0.1
Temporary supervision of N. Matabadal	2016	0.1
Total		13.1