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Treatment of fluid overload in intensive care patients

Ph.D. Thesis

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Ph.D. Thesis: Treatment of fluid overload in intensive care patients

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Preface

This PhD thesis is based on four papers which are part of a larger research programme. The papers were written during my employment at the Department of Anaesthesiology, Copenhagen University Hospital, North Zealand Hospital from 2020 to 2023.

I want to express my gratitude to everyone who has contributed to my research, including colleagues, research staff, patients, and their relatives. I want to extend a special appreciation to Professor Morten Bestle, my principal supervisor, whose unwavering support and belief in me made this journey possible. Morten always took the time to listen to my thoughts, ideas, and concerns with an open mind. He has been the constant pillar of support, and his often-repeated words, "We find a way," have been the anchor throughout this PhD endeavour. I also want to acknowledge the contributions of my co-supervisors: Anders Perner, whose precise and insightful guidance and support enriched my work; Theis Itenov, for his expertise in statistics; and Rasmus Berthelsen, for his thoughtful feedback.

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I'm grateful for my family and friends' eternal support and encouragement, especially my son, Fredrik, who makes it all matter.

Sine Wichmann
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Original papers

This PhD thesis is based on the following papers:

Study I:

Paper I: **Wichmann S**, Barbateskovic M, Lindschou J, et al. Loop diuretics in adult intensive care patients with fluid overload: A protocol for a systematic review of randomised clinical trials with meta-analysis and Trial Sequential Analysis. Acta Anaesthesiologica Scandinavica 2020;64(9):1327–34.

Paper II: **Wichmann S**, Barbateskovic M, Liang N, et al. Loop diuretics in adult intensive care patients with fluid overload: a systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. Annals of Intensive Care 2022;12(1):52.

Study II:

Paper III. **Wichmann S**, Schønemann-Lund M, Perner A, et al. Goal-directed fluid removal with furosemide versus placebo in intensive care patients with fluid overload: A randomised, blinded trial (GODIF trial—First version). Acta Anaesthesiologica Scandinavica 2023;67(4):470–8.

Study III:

Paper IV. **Wichmann S**, Itenov TS, Berthelsen RE, et al. Goal directed fluid removal with furosemide versus placebo in intensive care patients with fluid overload: A trial protocol for a randomised, blinded trial (GODIF trial). Acta Anaesthesiologica Scandinavica 2022;66(9):1138–45.

Summary

Background
Fluid overload is a common condition in the Intensive Care Unit (ICU) and has been linked to organ dysfunction and mortality. Multiple factors, including critical illness and various treatments, contribute to fluid overload in ICU patients. Loop diuretics are the predominant treatment for fluid overload, but there are currently no established recommendations regarding timing, method, or rate of fluid removal. This PhD project aimed to investigate the benefit and harm of fluid removal with loop diuretics in adult ICU patients with fluid overload, and we hypothesised that loop diuretics would improve patient-important outcomes.

Methods
We assessed the existing evidence for the use of loop diuretics in adult ICU patients with fluid overload in a systematic review of randomised clinical trials (RCTs). We performed meta-analyses and trial sequential analyses (TSA) and evaluated the risk of bias and the quality of evidence. To obtain further knowledge we conducted a multi-centre RCT investigating fluid removal using furosemide compared with a placebo in adult ICU patients with at least 5% fluid overload (The GODIF trial - first version). Fluid overload was determined by calculating the cumulative fluid balance in litres as a percentage of the ideal body weight. Fluid removal continued until a neutral cumulative fluid balance was achieved. The trial was prematurely terminated due to challenges with trial design and the definition of fluid status. Consequently, the trial protocol was revised for the second version of the GODIF trial. The second version commenced enrolment in June 2021 aiming to enrol 1000 participants. The primary outcome for the GODIF trials was the number of days alive and out of hospital at day 90.

Results
The systematic review included ten RCTs. The main results were based on trials comparing loop diuretics with placebo or no interventions. We observed no statistically significant difference in mortality and only 11.5% of the required information size was met to draw firm conclusions. The number of serious adverse events or reactions was statistically lower in patients receiving loop diuretics compared with those receiving a placebo or no intervention, but this finding was contested by the TSA. Only 34.7% of the required information size was met. No data on health-related quality of life could be identified. All the trials had an overall high risk of bias, and the quality of evidence was very low.

The first version of the GODIF trial was terminated after enrolling 41 participants (4,1% of the sample size). In 32% of the participants, the clinical assessment of fluid status did not align with the cumulative fluid balance. This resulted in adjustments of the cumulative fluid balance as the stopping criteria for the intervention was a neutral cumulative fluid balance. Furthermore, protocol violations occurred in 29% of the participants. This affected the trial's conduct and data, and trial termination was deemed necessary. No significant differences between groups were found for any outcome.

A revised protocol for the second version of the GODIF trial was developed and published. The key modification involved redefining fluid status to a clinical assessment based on daily and cumulative fluid balances, changes in body weight, and clinical examination instead of using the cumulative fluid balance as the sole parameter for fluid status. Fluid removal should continue until the patient was assessed to have achieved a neutral fluid status. The second version of the GODIF trial is ongoing, with patients enrolling in six countries across 23 trial sites.

Conclusion

The quality of evidence regarding the use of loop diuretics in adult ICU patients with fluid overload remains uncertain and of very low quality. The first version of the GODIF trial highlighted the imprecision of relying solely on the cumulative fluid balance as the parameter for fluid status. For the second version of the GODIF trial, the assessment of fluid status was changed to include multiple parameters mirroring clinical practice. We expect this to be more accurate and provide high-quality data on the benefits and harm of loop diuretics compared with a placebo in adult ICU patients with at least 5% fluid overload on patient-important outcomes.

Danish Summary

Baggrund
Væskeophobning førende til overhydrering er en hyppig tilstand som udvikles hos kritisk syge patienter indlagt på intensivafdelinger. Overhydrering er associeret til organsvigt og øget dødelighed. Loop-diuretika er den mest anvendte behandling af overhydrering, men der er aktuelt ingen etablerede anbefalinger vedrørende metode, timing eller hastighed af behandlingen. Formålet med denne Ph.d. var at undersøge fordele og ulemper ved målstyret væskefjernelse med loop diuretika hos voksne intensivpatienter med overhydrering. Hypotesen var at målstyret væskefjernelse ville bedre patienternes prognose.

Metode
Vi lavede et systematisk litteraturstudie for at afdække den eksisterende evidens for behandling med loop-diuretika til voksne intensivpatienter med overhydrering baseret på randomiserede kliniske forsøg. Vi anvendte meta-analyser, trial sequential analyser samt vurderede risikoen for bias og kvaliteten af evidensen. For at opnå mere viden på området designede vi et blindet randomiseret multicenter studie, som undersøgte effekten af furosemid versus placebo hos voksne intensivpatienter med minimum 5% overhydrering – første version af GODIF-studiet. Overhydrering blev beregnet ud fra den kumulative væskebalance og idealkropsvægten. Interventionen skulle fortsætte ind til en neutral kumulativ væskebalance var opnået. Vi stoppede studiet tidligt pga. udfordringer med forsøgsdesign og definition af væskestatus ud fra den kumulative væskebalance. Dette resulterede i en revision af protokollen og anden version af GODIF-studiet blev initieret i juni 2021. Målet er 1000 deltagere, og det primære endepunkt er antallet af dage i live udenfor hospitalet efter 90 dage.

Resultater
Ti randomiserede forsøg indgik i det systematiske litteraturstudie, og de primære resultater var baseret på forsøg, der sammenlignede loop-diuretika med placebo eller ingen intervention. Der blev ikke fundet nogen statistisk signifikant forskel i dødelighed, men kun 11.5% af det nødvendige antal patienter var inkluderet i analysen for at sikre konklusioner kunne drages. Meta-analysen viste statistisk lavere forekomst af alvorlige bivirkninger hos patienter behandlet med loop-diuretika, men dette blev bestridt i trial sequential analysen, og kun 34.7% af det nødvendige antal patienter for solide resultater var opnået. Ingen data om helbredsrelateret livskvalitet var rapporteret. All forsøgene havde høj risiko for bias, og mængden og kvaliteten af evidensen var meget lav.

Første version af GODIF-studiet blev afsluttet tidligt efter 41 patienter var inkluderet (4.1% af det planlagte antal). Hos 32% af deltagerne afveg den kliniske vurdering af væskestatus så betydeligt fra den kumulative væskebalance, at de behandlende læger justerede den kumulative væskebalance, formentligt fordi interventionen var målsat til at opnå en neutral kumulativ væskebalance. Yderlige forekom der protokolbrud hos 29% af deltagerne. Sammenlagt påvirkede dette forsøgets praktiske gennemførelse og data uacceptabelt meget. Resultaterne for de 41 patienter viste ingen forskelle mellem grupperne for alle effektmål.

En revideret protokol for anden version af GODIF-studiet blev udviklet og publiceret. Den primære ændring var definitionen af væskestatus, som nu var ændret til en klinisk vurdering ud fra daglig og kumulativ væskebalance, ændringer i kropsvægt samt klinisk undersøgelse i stedet for den kumulative væskebalance alene. Interventionen skulle fortsætte indtil en klinisk neutral væskestatus var opnået. Anden version af GODIF-studiet inkluderer fortsat patienter på 23 intensivafdelinger i seks lande.

Konklusion

Kvaliteten af evidensen for loop-diuretika til voksne intensivpatienter med overhydrering er usikker og meget lav. Første version af GODIF-studiet fremhævede at den kumulative væskebalance er et unøjagtigt mål for overhydrering, når den bruges som eneste parameter i vurdering af væskestatus. I anden version af GODIF-studiet vil væskestatus blive vurderet ud fra flere parametre, som det gøres i vanlig klinisk praksis, hvilket forventes at være mere præcist og bidrage med valide data. Vi sigter mod at levere data af høj kvalitet for effektiviteten og sikkerheden af loop-diuretika sammenlignet med placebo hos voksne intensivpatienter med mindst 5% overhydrering.

Abbreviations

AE	Adverse Event
AFIB	Atrial Fibrillation
AR	Adverse Reaction
AKI	Acute Kidney Injury
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials Statement
COVID-19	Coronavirus Disease 2019
CVP	Central Venous Pressure
DARIS	Diversity Adjusted Required Information Size
DMC	Data Monitoring Committee
GIPS	Global Increased Permeability Syndrome
HRQoL	Health-Related Quality of Life
IBW	Ideal Body Weight
ICU	Intensive Care Unit
IQR	Inter Quartile Range
IV	Intravenous
KDIGO	Kidney Disease – Improving Global Outcomes
MAP	Mean Arterial Pressure
MD	Mean Difference
1. *NICE*	National Institute for Health and Care Excellence
POCUS	Point of Care Ultrasound
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
PROSPERO	International Prospective Register of Systematic Reviews
RCT	Randomised Clinical Trial
RIS	Required Information Size
RR	Relative Risk
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
TSA	Trial Sequential Analysis
WHO	World Health Organisation

Introduction

The development of intravenous (IV) fluid therapy began slowly in the early 1800s during the cholera epidemic in Europe, but it wasn't before the early 1900s that IV therapy became more used and further developed during World War I.[1] It was discovered that IV fluids could be used to treat dehydration, shock, and blood loss, and as a medium for delivering medications and nutrients into the bloodstream. In the 20th century, several types of IV fluids were developed and they are today an essential part of the treatment of critically ill patients in the ICU.

Fluid accumulation develops due to multiple reasons and some of the main reasons are IV fluid therapy, critical illness with capillary leakage of fluid into the tissues, and kidney failure with impaired fluid excretion. Many different remedies have been used to treat oedemas since the ancient Egyptians but it was not before the 1950s-60s that pharmaceutical diuretics were developed for clinical use.[2]

Fluid overload is associated with organ dysfunction and mortality.[3] This PhD project aimed to investigate the treatment effect of fluid removal with loop diuretics in adult ICU patients with fluid overload. The results of a systematic review, a randomised clinical trial (RCT), and protocol for an ongoing large international RCT will be presented in the following thesis.

Background

Definition of fluid overload

Fluid overload is a condition with excess fluid in the body, but the term is not well defined. Fluid overload has been defined as a condition with hypervolemia (excessive blood volume).[4] Hypervolemia results in increased systemic circulatory pressure which entails fluid leak into the interstitial space resulting in the formation of oedemas. However, the term fluid overload is also used for patients with fluid accumulation without the presence of hypervolemia. The term fluid overload is therefore discussed.[4,5] In this thesis, the terms fluid overload and fluid accumulation will be used to describe a condition with fluid accumulation in the body with or without hypervolemia.

In research papers, fluid overload is often defined as a percentage of 5% or 10% according to body weight. The calculation is based on an increase in cumulative fluid balance (litres) or body weight (kg) after admission to the ICU.[3,6] The incidence of fluid overload of 5% or higher has been reported in up to 51% of the patients in the ICU.[6] Fluid therapy is an important contributor to the development of fluid overload. Practices in fluid therapy are prone to change with new research and guidelines such as Surviving Sepsis Campaign,[7,8] which can impact the incidence of patients with fluid overload over time and regions.

Development of fluid overload

Fluid accumulation and oedema are formed when capillary filtration or leakage exceeds the lymphatic drainage in the interstitial space and/or due to kidney failure with reduced urinary excretion.[9] Low oncotic pressure in the blood or increased microvascular hydrostatic pressure as seen in liver failure or heart failure can also result in fluid filtration into the interstitial space.[9,10] When fluid leaks into the interstitial space intravascular hypovolemia might develop, and the perfusion of the kidneys and the glomerular filtration rate will decrease. The kidneys respond with increased sodium and water retention to maintain hemodynamic stability which can contribute to further fluid accumulation. This is mediated by a neurohormonal cascade involving the renin-angiotensin-aldosterone system and antidiuretic hormone.[11,12] Fluid accumulation in the interstitial space can also compromise lymphatic drainage due to increased pressure in the tissue. A longer list of drugs (corticosteroids, beta-blockers, calcium channel blockers, nonsteroidal anti-inflammatory agents, clonidine, methyldopa, hormones etc.) can cause oedema and several of them are frequently used in the ICU.[9]
The ICU patients are at specific risk of developing fluid overload due to critical illness with one or more organ failures and the need for intensified treatment including fluid therapy.

Capillary leakage

The luminal surface of blood vessels is covered by a protective layer known as the glycocalyx. The glycocalyx plays a vital role in maintaining normal vascular function by regulating the passage of substances across the blood vessel wall.[13–16]

Inflammation, infections, sepsis, hyperglycaemia, hypernatremia, trauma, major surgery, and hypervolemia are factors which can cause the degradation of the glycocalyx.[13,17–19] This degradation has significant consequences, leading to increased permeability of the blood vessels, uncontrolled vasodilation, formation of thrombosis in the small vessels, and altered adhesion of white blood cells. Important plasma proteins such as albumin and fluid leak into the interstitial space, leading to the accumulation of fluid when the lymphatic drainage is surpassed.[13–15]

Sodium

The water and sodium regulation in the body is complex and mainly regulated by the kidneys, hormones, and blood pressure.[20] It takes days for the kidneys to regulate sodium excretion to sudden changes in sodium intake,[21] and in patients with acute kidney injury (AKI) it will take longer. The kidneys can maximally concentrate sodium in the urine to double the plasma concentration.[22] A sudden increase in sodium intake can therefore result in salt retention and secondary water retention. Sodium load delivered by fluid therapy, medicine, and nutrition in the ICU often contribute to sodium and water accumulation.[23] Sodium probably plays an important role in the development of fluid overload in the ICU and should be considered.[21,23,24]

World Health Organization (WHO) recommends less than 5 g of salt (NaCl) daily for adults which is equivalent to 2g of sodium.[25] Just 1 litre of balanced crystalloids such as Ringer lactate, Ringer acetate, or Plasma-Lyte will deliver the recommended daily sodium intake. ICU patients receive a high sodium load through their treatment (IV fluids and medicine) and enteral/parental nutrition (full nutrition contains the recommended dose of sodium).[26] The prevalence of hypernatremia in the ICU is reported to be 4-27% and it is an independent risk factor for mortality and length of stay in the ICU.[27–33] Hypernatremia is common in patients with fluid overload and AKI and it is probably a consequence of the fluid and diuretic therapy given.[24]
A systematic review found that sodium restriction in maintenance fluids and/or in the fluids used as a diluent for medicine can reduce the daily sodium load by 117 mmol and the incidence of hyperchloremia.[23] The effect of sodium restriction on fluid overload and mortality is not clear and must be investigated further.

Fluid therapy

Fluid therapy is central in intensive care medicine. For septic shock patients, fluid therapy can be divided into four phases – resuscitation, optimisation, stabilisation, and evacuation.[34]
Surviving Sepsis Campaign recommends 30 ml/kg of crystalloids within the first 3 hours during the resuscitation phase.[7] Additional fluids should only be administered after individual evaluation - preferably guided by dynamic parameters.[7] The recommendations from the Surviving Sepsis Campaign are all weak recommendations based on very low-quality evidence but the guideline is widely implemented in the world. Systematic reviews assessing restrictive versus liberal fluid resuscitation in septic shock have so far not shown significant effects on mortality, but divagating effects on time in mechanical ventilation.[35–37] It is important to note that not all included trials in the systematic reviews achieved a separation in fluid volumes between the restrictive and liberal groups, which could have impacted the results of the reviews

not considering this. Unfortunately, the trials included in the reviews provide data on fluid balances and some only fluid input without considering output. They do not report the number of patients with fluid overload, which makes the results of these trials/systematic reviews difficult to interpret concerning fluid overload.

A randomised clinical trial from 2006 investigated liberal versus restrictive fluid therapy in patients with acute lung injury and they did not find any difference in 60-day mortality, but the time in mechanical ventilation and length of stay in the ICU were shorter in the restrictive group.[38] A systematic review supported these findings for patients with acute respiratory distress syndrome and sepsis.[39]

Most fluids administered in the ICU are administered to replace losses, maintain adequate perfusion of organs and tissues, electrolyte disturbances, and as a diluent for medicine. Nutrition and blood products also contribute to a significant daily fluid input. Fluid creep is a term defining fluids administered unintentionally as a vehicle for enteral, oral or IV medication, or flushing of IV lines.[40] In a large cohort of mixed ICU patients in Belgium the resuscitation fluids accounted for 6.5%, blood products 3.2%, maintenance and replacement fluids 24.7%, nutrition 33.0%, and fluid creep 32.6% of all fluid input.[40] In a Japanese study fluid creep was reported to be 25.2% of the total IV fluid input,[41] but in the two studies, the daily fluid creep aligned according to mL (645mL and 661 mL). In a study from Australia and New Zealand, 62% of the ICU patients received maintenance fluid which consisted of 35% of the total fluid input.[42] Maintenance fluid is recommended by the National Institute for Health and Care Excellence (NICE) guideline,[43] which is followed in many countries but not in the Nordic countries. Maintenance fluid delivers a significant fluid load and should be carefully considered in case of fluid overload.

Fluid therapy with balanced crystalloids versus isotonic saline according to mortality is widely researched and no significant difference in mortality has been found.[44] Data does suggest that balanced crystalloids might be the best choice,[44,45] except for patients with traumatic brain injury, which seems to benefit from isotonic saline.[46,47] Fluid boli have a small and short-lived effect on intravascular volume expansion. Only around 17% of infused Ringer's lactate will remain in the intravascular space after one hour in non-septic patients.[48] It can be argued that this percentage is much lower in septic shock patients with capillary leakage.

Colloids such as hydroxyethyl starch, gelatine, and dextran are not used in many countries any more due to safety concerns.[49–51] Albumin is recommended in the Surviving Sepsis Campaign for septic shock patients who received large volumes of crystalloids (weak recommendation with moderate quality of evidence).[7] Albumin might be superior to crystalloids in stabilising hemodynamic parameters during resuscitation with less volume,[52] and 20% albumin might improve mortality in septic shock patients.[53] The role of human albumin as a volume expander is still being investigated (ARISS trial NCT03869385).[54] A post hoc analysis of the ALBIOS trial found a reduced 90-day mortality for septic shock patients receiving albumin to maintain a

serum concentration of albumin of at least 30g/L compared with crystalloids alone.[55] This is now being prospectively investigated in the randomised clinical ALCAMIST trial (NCT05148286) and ALBIOSS-BALANCED trial (NCT03654001).

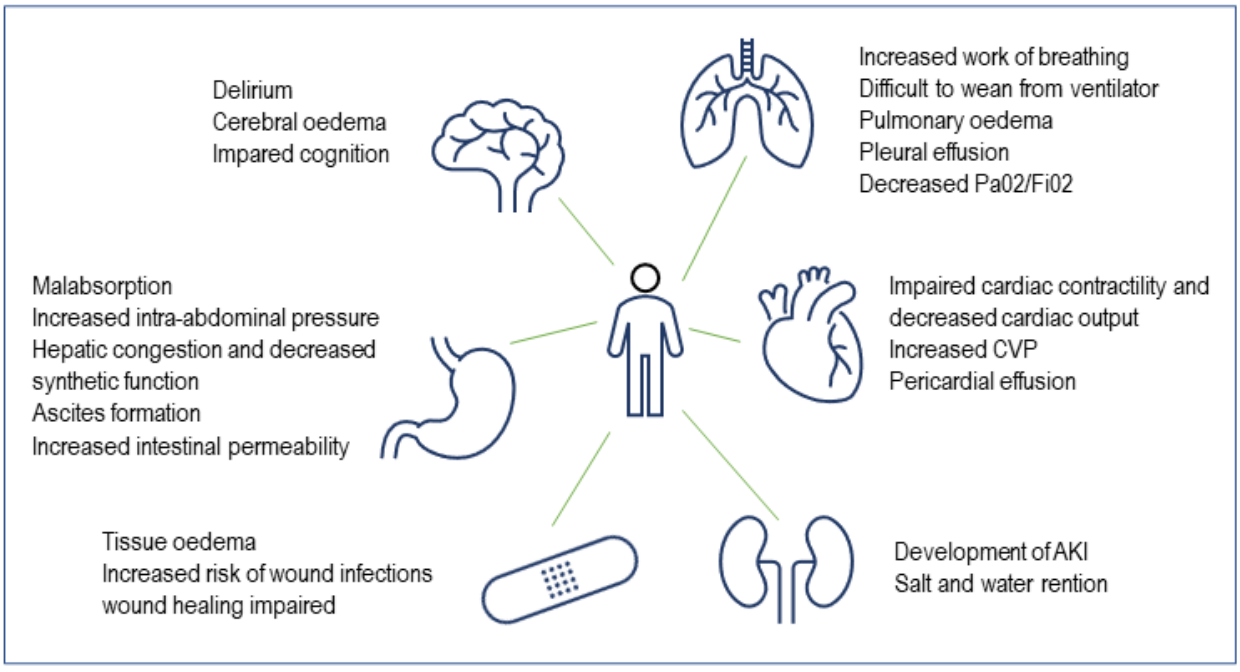
There is a general agreement that fluids must be considered as a drug and dosing must be individualised and adjusted according to regular assessment of the patient during the day to minimise adverse events.[34,56,57]

Risks of fluid overload

Fluid overload is associated with increased mortality in ICU patients with sepsis[58–62], respiratory failure[63], AKI[64–70], traumatic brain injury[71], surgical patients[72,73], and general ICU patients.[3,6,69] Fluid overload is probably not only a risk factor for worse outcomes but also a marker of severity of disease. The most severely ill patients often require fluid resuscitation, have capillary leakage, and longer ICU admissions.[74]

Oedema can impair microcirculation and tissue oxygenation, and lead to organ dysfunctions such as AKI,[75,76] intraabdominal hypertension,[77–79] cognitive impairment,[80] respiratory failure with prolonged mechanical ventilation,[38,39,70,81] and dysfunctions of other organs,[74] some of them are illustrated in Figure 1.

Figure 1. Fluid accumulation and organ function impairment



Assessment of fluid accumulation

No gold standard measuring method for fluid status in ICU patients exists. Several surrogate measures are being used to estimate fluid accumulation: body weight, fluid balance, lung ultrasound, clinical examination for peripheral oedema, estimation of lung water on cardiovascular monitoring, bioimpedance, point of care ultrasound (POCUS), radiology, oxygen requirements, etc.[82–86] None of them can quantify the exact fluid status in patients. Studies in the field often only use one surrogate parameter (fluid balance or body weight) as a marker of fluid status, and this is a challenge and bias for these studies. In clinical practice, the assessment of fluid status often incorporates several available parameters, including clinical examination.[87,88]

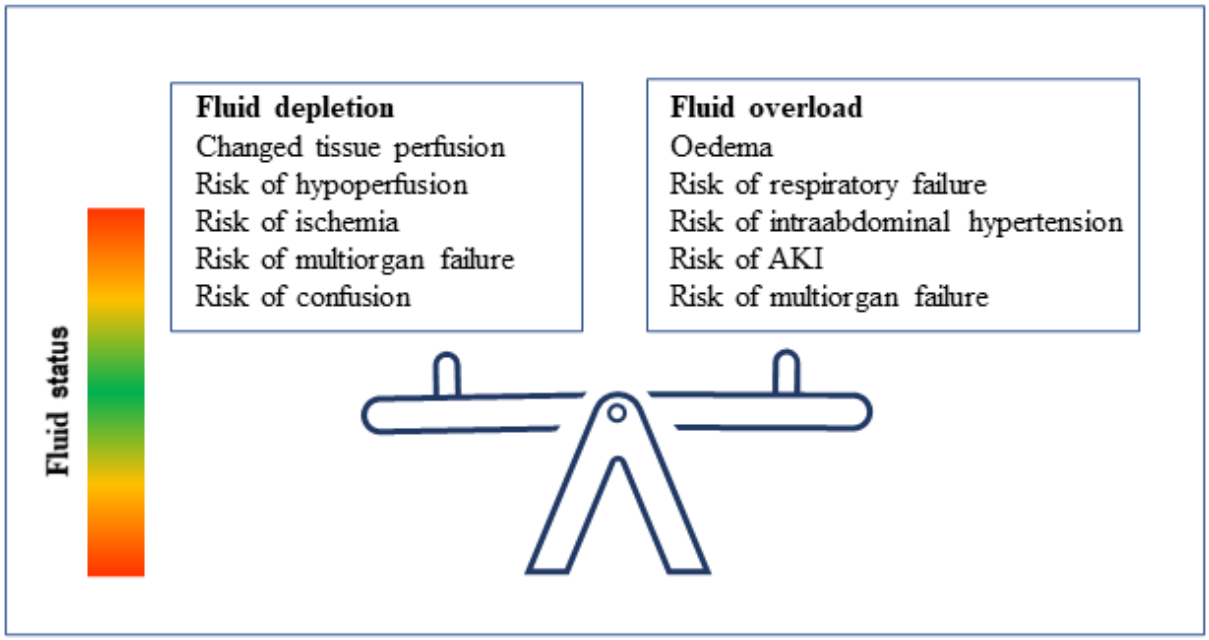
Treatment of fluid overload

Treatment modalities are fluid restriction, diuretics, or renal replacement therapy (RRT). Diuretics and fluid restriction are the preferred treatment modalities among ICU physicians and RRT is less often used.[87,89,90] The evidence for using diuretics to treat fluid overload in ICU patients is sparse and inconclusive and with very low-quality evidence.[91–93] The Kidney Disease – Improving Global Outcomes (KDIGO) guidelines recommend diuretics in patients with AKI and fluid overload (grade 2C – a very weak recommendation).[94]

The research in fluid therapy and fluid removal has so far not delivered solid evidence for interventions reducing mortality in patients with fluid overload.[35,92,95–97] Restrictive fluid therapy might reduce the number of patients developing fluid overload and the degree of fluid overload. Treatment of fluid overload is not based on solid evidence or supported by clinical guidelines, so today it is at the individual physician's discretion. The importance of sodium is unclear. It needs more attention and to be investigated further.

Treatment of fluid overload can be challenging. The best time to start fluid removal or the optimal rate of fluid removal has not yet been identified. It is important to minimise the risk of harm as both volume depletion and fluid overload come with side effects (Figure 2). Some patients spontaneously excrete the accumulated fluid when they are entering a recovering phase of critical illness, but other patients do not and enter a stage of global increased permeability syndrome (GIPS), where active fluid removal is needed.[74] Suggestions for how fluid removal should be performed and monitored have been proposed[5,57,98], but it need to be validated in randomised clinical trials.

Figure 2. The balance of fluid therapy and fluid removal



Renal replacement therapy

Research in RRT conducted in the ICU has predominantly focused on AKI patients. A systematic review investigating the timing of RRT in ICU patients with AKI found no survival advantage associated with early initiation of RRT compared to delayed initiation.[99] Moreover, early initiation of RRT was associated with an increased risk of RRT-related infections and episodes with hypotension.[99] It should be noted that while many AKI patients experience fluid overload, not all do. This limitation must be considered when evaluating the outcomes of renal replacement therapy (RRT) trials in the context of treating fluid overload. A pre-planned post hoc analysis of the large STandard versus Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury trial (STARRT-AKI) examined the impact of early RRT for patients with different ranges of fluid accumulation at baseline (fluid balance).[100] The analyses revealed that the timing of RRT did not have an impact on all-cause mortality in patients with different cumulative fluid balances at baseline.[100]

It is important to acknowledge that while RRT can effectively remove fluid, it is accompanied by various drawbacks, such as high cost, limited availability, immobilisation of the patient during treatment, and an invasive method leading to potential side effects such as infections and damage to the vessels.

Diuretics

Loop diuretics were developed and introduced to the market in the 1960s. Today six different loop diuretics are on the market – furosemide, bumetanide, etacrynic acid, piretanide, torsemide, and azosemide. Only furosemide and bumetanide are available in Denmark and furosemide is the primarily used drug. Loop diuretics block the sodium-potassium-chloride co-transporter in the

ascending loop of Henle in the nephrons and prevent the reabsorption of sodium, chloride, and potassium. Loop diuretics additionally inhibit the reabsorption of calcium and magnesium.[101] In the distal convoluted tubules, there is some reabsorption of sodium at the expense of the excretion of potassium and hydrogen into the filtrate. This results in increased excretion of sodium, chloride, potassium, calcium, magnesium, hydrogen, and subsequent water through osmosis.[101] Loop diuretics are the most potent diuretics available and they can increase sodium excretion by up to 20%.[101,102] Loop diuretics also have a vasodilating effect that occurs before the diuretic effect which is utilized in the treatment of pulmonary oedema.[101] Loop diuretics can be administered orally, as IV bolus injections, or as continuous infusion. In the ICU, loop diuretics are the most commonly used diuretics.[87,103–106] In case resistance towards loop diuretics is observed - an addition of a thiazide diuretic to a loop diuretic often results in increased urine output.[93] Furosemide has a 95% binding affinity to albumin in the blood, with the protein-bound fraction reaching its target site within the nephrons. In cases where blood albumin levels are low, concurrent administration of albumin and furosemide can potentially enhance urine output. This approach becomes pertinent when dealing with diuretic resistance in a patient with low albumin and fluid overload.[107]

The impact of loop diuretics on mortality, length of stay, time on mechanical ventilation, and AKI remains uncertain. Many studies are retrospective cohort studies, which are prone to confounding by indication. Additionally, the results of these studies are conflicting. For instance, one study in non-cardiac ICU patients with at least 5% fluid overload found no association between loop diuretics and mortality.[108] Conversely, other studies have reported an association between loop diuretics and lower mortality in ICU patients receiving vasopressor support[109] or acute lung injury/acute respiratory distress syndrome,[110,111] but the results regarding AKI are inconsistent.[108,112,113] To establish more conclusive evidence, further research using RCTs is necessary.

The GODIF research programme

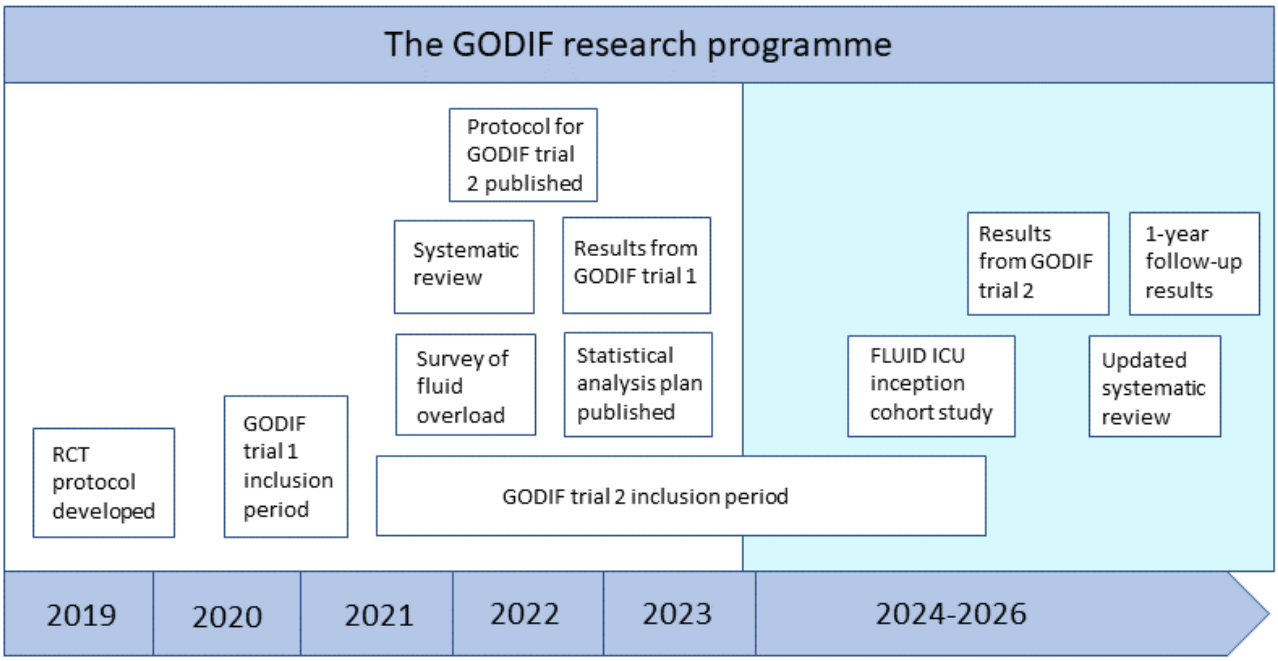
The research program is focused on GOal-DIrected Fluid removal (GODIF) in patients with fluid overload. The programme is expected to span eight years and encompasses various elements. These elements include published protocols, the randomised clinical trial (GODIF trial), supplementary studies connected to the GODIF trial, and systematic reviews.

The supplementary studies for the randomised clinical trial encompass the following works:

1) A systematic review evaluating the existing evidence for fluid removal with furosemide in adult ICU patients with fluid overload.
2) A survey describing the definitions, assessments, treatments, and attitudes of ICU physicians towards fluid overload in the ICU.
3) The first version of the GODIF trial, which can be considered an unplanned pilot trial.
4) A large comprehensive international prospective inception cohort study named FLUID-ICU is planned to investigate current practices in fluid administration, the incidence of fluid overload,

and the use of diuretics in the treatment. The study is expected to start enrolling patients in 2024.

Figure 3. The GODIF research programme



All protocol versions are available at https://www.cric.nu/godif-protocol/.
One-year follow-up refers to the GODIF trial second version.

This PhD is based on the first part of the GODIF research programme.

Overall aim and hypothesis

Fluid overload is a multifactorial condition where critical illness, systemic inflammation/infection, shock, capillary leakage, organ failures, sodium load, medicine, and fluid therapy all contribute to the development of fluid overload. There is a large knowledge gap in how fluid overload should be treated. No clinical guidelines exist for treating fluid overload in the general ICU population but loop diuretics are extensively used.[89,103–105,114] We hypothesise that fluid removal with loop diuretics will improve patient-important outcomes in adult ICU patients with at least 5% fluid overload.

This PhD project aimed to evaluate the existing knowledge of the treatment of fluid overload in the ICU using loop diuretics and to generate new, high-quality data on patient-important outcomes in this field of research.

The objectives were:

1. Assess and evaluate the existing evidence from RCTs on treatment fluid overload with loop diuretics in adult ICU patients in a systematic review with meta-analysis and trial sequential analysis (*Study I*).
2. Design and conduct of a large RCT assessing patient-important outcomes of fluid removal with furosemide versus placebo in stable adult ICU patients with at least 5% fluid overload (*Study II and III*).

The RCT (GODIF trial – first version) was launched in August 2020, but we chose to stop the trial after 6 months and 41 enrolled patients. We found that substantial protocol changes were needed to obtain the high-quality data we aimed for. *Study II* is a full report and analysis of data from the patients included in the first RCT (GODIF trial – first version). *Study III* is a protocol article describing the revised protocol for the RCT (GODIF trial – second version), which was launched in June 2021 and still enrols patients.

Study I: A systematic review with meta-analysis and trial sequential analysis

Aim

Exploring the existing data from RCTs investigating the treatment with loop diuretics in the adult ICU population with fluid overload calculating the combined effects on patient-important outcomes and assessing the quantity and quality of evidence.

Methods

Overview

Study I consist of a protocol article (paper I)[115] and the published systematic review (paper II).[91] The protocol was registered in the 'International Prospective Register of Systematic Reviews database (PROSPERO) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).[116,117] We followed the recommendations from The Cochrane Collaboration,[118] the steps suggested by Jakobsen et al,[119] and the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE).[120]

Eligibility criteria

RCTs assessing adult ICU patients with fluid overload randomised to a single loop diuretic versus one of the following control groups: 1) placebo/no intervention (standard of care or no diuretics); 2) other types of diuretics; 3) other pharmacological interventions; or 3) a different dose of a loop diuretic.

Outcome measures

Primary outcomes: 1) all-cause mortality; 2) quality of life; and 3) proportion of patients with one or more serious adverse events or reactions (SAE/SAR).
Secondary outcomes: 1) plasma concentration of creatinine: 2) proportion of patients without resolution of fluid overload; 3) Number of days in mechanical ventilation; 4) length of stay in the ICU; and 5) proportion of patients with adverse events or reactions (AE/AR) not considered serious.
Explorative outcomes: 1) single SAE/SAR; 2) single AE/AR; and 3) plasma concentration of sodium, potassium, and chloride.

Search strategy

We searched 11 databases from inception, four trial registries, Google Scholar, the US Food and Drug Administration, the European Medicines Agency, and clinical trial registries. No restriction on language applied.

Data extraction and risk of bias assessment
Study selection, data extraction, and assessment of risk of bias were performed independently by two or three persons. The second version of the Cochrane risk-of-bias tool for randomised trials (RoB2) was used on outcome level.[118,121]

Statistical analyses
Conventional meta-analyses were used to pool the estimates of the intervention effects. Relative risk (RR) with 95% confidence intervals (CI) for dichotomous outcomes and mean difference (MD) with 95% CI for continuous outcomes using both fixed effect and random effects models. The model presenting the most conservative result was reported. The threshold for significance was adjusted due to multiple outcomes. A significant p-value for the primary outcome was ≤ 0.025 and ≤ 0.017 for the secondary outcomes.

Trial sequential analysis (TSA) was employed to adjust for the risk of random errors stemming from sparse data and multiple testing of data for the primary and secondary outcomes. TSA also estimated the required information size for the meta-analyses to be conclusive based on predefined criteria.[122] The criteria included a 20% relative risk reduction or increase for dichotomous outcomes, and a difference of at least 0.5 times the observed standard deviation for continuous outcomes. A beta of 10% (90% power) with an adjusted alpha of 2.5% for the primary outcomes and 1.7% for the secondary outcomes, and the proportions of event rates in the control groups. *In the published systematic review, a mistake was made. The alpha was erroneously stated to be 0.025% and 0.017% on page 4.*

Heterogeneity was explored by subgroup analyses, Chi-squared (X^2) statistics, and inconsistency (I^2) statistics in the meta-analyses and the observed statistical diversity (D^2) was used in the TSA.[123] Sensitivity analyses were used to assess the impact of missing data.

Assessment of the quality of evidence
The quality of evidence is assessed according to GRADE.[120,124]

Results
Characteristics of the included trials
Ten trials enrolling 804 patients were included in the systematic review.[96,125–133] All trials had an overall high risk of bias. Six trials investigated loop diuretics versus placebo/no intervention,[96,125–128,133] two trials investigated loop diuretics (furosemide) versus another loop diuretic (piretanide, ethacrynic acid),[129,130] and two trials investigated loop diuretics versus another type of diuretics (acetazolamide, tolvaptan).[131,132] There was a large clinical heterogeneity between the trials, which all were relatively small (12 to 248 participants). The main results are based on the comparison loop diuretics versus placebo/no intervention. Results from the two other comparisons were sparse and without any significant differences between groups.

Results for the intervention loop diuretics versus placebo/no intervention

All-cause mortality

No survival benefit for the patients treated with loop diuretics versus placebo/no intervention was found (Table 1). TSA showed that the required sample size to reach a reliable result was far from reached, only 11.5% was accrued. The certainty of the evidence was very low.

Table 1. Results from meta-analyses and trial sequential analyses for the comparison of loop diuretics versus placebo/no intervention

Outcomes	No. of trials/par-ticipants	Loop diuretics events/total	Placebo/ no intervention events/total	Relative risk (95% CI)	TSA adjusted 95% CI
All-cause mortality	4/359	33/171	51/188	0.72 (0.49-1.06)	0.15-3.48
SAE/SAR*	6/476	87/230	116/246	0.81 (0.66-0.99)	0.55-1.20
Participants without resolution of fluid overload	2/92	4/41	24/51	0.22 (0.08-0.58)	0.00-11.80
AE/AR*	2/245	71/120	61/125	1.23 (0.98-1.55)	0.28-5.56
Single SAEs					
RRT	4/299	23/141	22/158	1.12 (0.67-1.88)	-
AKI	3/316	71/153	90/163	0.86 (0.63-2.18)	-
AFIB	3/264	14/126	23/138	0.71 (0.39-1.31)	-

Modified from paper II.[91] Abbreviation: AFIB = atrial fibrillation

*The analysis is made on the highest event rate of a single SAE or AE.

Health-related quality of life

No data was reported on this outcome.

Serious adverse events

The proportion of participants with one or more SAEs/SARs was not reported. Instead, we examined the SAE/SAR with the highest occurrence rate in each trial. The meta-analysis revealed a significant reduction in the number of SAEs/SARs in the loop diuretic group compared with the placebo/no intervention group, although the TSA analysis contested this finding. Only 34.7% of the required information size was accrued. The quality of evidence was very low.

Meta-analyses of three single SAEs (RRT, AFIB, and worsening of AKI) were possible and no significant differences were found between loop diuretics and placebo/no intervention.

Adverse events not considered serious

The proportion of participants with one or more AEs/ARs was not reported. We analysed the single AE/AR with the highest event rate in each trial. No statistical difference was found and only 6.7% of the required information size was accrued.

Plasma concentration of creatinine, sodium, potassium, and chloride
Three trials reported plasma concentrations of creatinine, two reported plasma concentrations of sodium and potassium and one reported chloride plasma concentrations. The data was not suitable for meta-analyses. No difference was found for creatinine, potassium, or chloride between groups, but one trial found higher sodium in the intervention group.

Participants without resolution of fluid overload
The meta-analysis indicated that the percentage of participants experiencing a resolution of fluid overload was higher in the group receiving loop diuretics. However, this finding was just not supported by the TSA analysis, and the accrued information size was only 6.2%.

The number of days on mechanical ventilation and length of stay in the ICU
It was reported in two trials, but no significant differences between loop diuretics and placebo/no intervention were observed. The data was not suitable for meta-analysis.

Subgroup analyses according to primary diagnosis, type of ICU, degree of fluid overload, and administration of loop diuretics in the control group could be performed for the primary outcomes and no differences between groups were found. Subgroup analyses assessing clinical heterogeneity and sensitivity analyses assessing incomplete outcome data did not seem to have a potential impact on the results in any of the outcomes. The certainty of evidence was low to very low for all outcomes.

Conclusion
The evidence is very uncertain about the effect of loop diuretics on patient-important outcomes, but it may reduce mortality and serious adverse events. This must be tested in large, randomised, placebo-controlled trials to be established.

Key information for study II and III

The following definitions are the same for studies II and III which are provided in the publications.[134,135]
Trial registrations EudraCT: 2019-004292-40; ClinicalTrials.gov: NCT04180397.

Trial design
It is an investigator-initiated, randomised, blinded, parallel-group, multi-centre trial. A central web-based randomisation with varying block sizes and stratification for three variables: trial site, AKI (yes/no), and Simplified Mortality Score for the Intensive Care Unit (SMS-ICU score)[136] (≥ 25 or < 25 points). The trial is conducted with blinding implemented for all involved parties including the statistician. The allocation is 1:1 to furosemide versus placebo.

Exclusion criteria
- Allergy to furosemide or sulphonamides
- Pre-hospitalisation advanced chronic kidney disease
- Ongoing renal replacement therapy
- Anuria for more than 6 hours
- Rhabdomyolysis with an indication of forced diuresis
- Ongoing life-threatening bleeding
- Acute burn injury of more than 10% of the body surface area
- Severe dysnatremia (plasma sodium < 120 mmol/L or > 155 mmol/L)
- Severe hepatic failure
- Patients undergoing compulsory treatment mandated by psychiatric legislation
- Pregnancy
- Consent not obtainable according to approved procedure.

Intervention
The trial drug must be administered with a starting bolus of 0.5-4.0 ml IV as determined by the treating physician. This should be followed by a continuous infusion at a rate of 2 ml/hour. The infusion rate must be adjusted as needed (0.0 – 4.0 ml/hour) to achieve a negative daily fluid balance of at least 1 ml/kg ideal body weight (IBW)/hour.

The treating physicians have the option to continue the administration of habitual diuretics prescribed to the patient before admittance to the hospital. In case hypernatremia develops, thiazides or aldosterone antagonists may be prescribed as a treatment modality. No other diuretics are allowed.

Escape procedures
Open-label furosemide can only be administered if at least one criterion is fulfilled:
- Hyperkalaemia (plasma potassium > 6.0 mmol/L)

- Respiratory failure (PaO2/FiO2-ratio < 26 kPa (200 mmHg)) where fluid overload or pulmonary oedema are assessed to contribute to or cause respiratory failure.

RRT can only be initiated if at least one criterion is fulfilled:
- Hyperkalaemia (plasma potassium > 6.0 mmol/L)
- Respiratory failure (PaO2/FiO2-ratio < 26 kPa (200 mmHg)) and fluid overload or pulmonary oedema are assessed to contribute to or cause respiratory failure.
- Severe metabolic acidosis caused by AKI (pH < 7.20 and standard base excess (< -10 mmol/L)
- Persistent AKI > 72 hours (oliguria/anuria or the plasma creatinine has not declined to 50% from the peak value).

Safety
If there are indications of hypoperfusion, such as lactate levels of 4.0 mmol/L or higher, a mean arterial pressure (MAP) below 50 mmHg that does not respond to vasopressors/inotropes, or mottling extending beyond the kneecaps,[137] fluid removal should be temporarily halted. A resuscitation algorithm should be initiated until the patient is stabilized without signs of hypoperfusion.

Days alive without life support
The number of days where the participant is alive without receiving any of the below life support remedies assessed 90 days after randomisation:
- Invasive mechanical ventilation
- Vasopressors or inotropes
- Renal replacement therapy of all kinds

Serious adverse events and reactions (SAE/SAR)
A list of predefined SAEs to fluid removal and SARs to furosemide are collected on all day forms within 90 days.

<u>Serious adverse events:</u>
- Cerebral ischemia
- Acute myocardial ischemia
- Intestinal ischemia
- Limb ischemia
- A new episode of AKI grade 3
- First onset atrial fibrillation

<u>Serious adverse reactions:</u>
- Anaphylactic reaction
- General tonic-clonic seizures due to furosemide-induced low calcium or magnesium

- Severe electrolyte disturbance of plasma potassium < 2.5 mmol/L or plasma sodium < 120 mmol/L or plasma chloride < 90 mmol/L
- Agranulocytosis
- Aplastic anaemia
- Pancreatitis
- Circulatory collapse leading to cardiac arrest
- Steven-Johnson syndrome
- Toxic epidermal necrolysis
- Hearing impairment

Sample size

A sample size of 1000 participants was determined to be necessary to detect an 8% improvement in the primary outcome, which is the number of days participants spent alive and outside the hospital at day 90 after enrolment. This calculation was based on a statistical power of 90% and a significance level of 5%.

Study II: A randomised clinical trial - the GODIF trial (first version)

Aim

Investigating the effects of furosemide versus placebo in adult ICU patients with moderate to severe fluid overload in a blinded randomised trial. We hypothesised that furosemide would improve patient-important outcomes.

Methods

Study design

A randomised clinical trial was conducted at three trial sites in Denmark. The participants were allocated to furosemide or placebo.

Eligibility criteria

All inclusion criteria must be met.

Inclusion criteria: age 18 years or above, acute admission to the ICU, clinical stability, and minimum 5% fluid overload calculated according to the cumulative fluid balance and ideal body weight (IBW).

Intervention

Daily protocolised fluid removal with trial drug. The intervention should continue until a neutral cumulative fluid balance was met (+/- 750 ml). A safety precaution allowed the clinicians to adjust the cumulative fluid balance if it did not correspond with the clinical assessment. This was permitted to avoid either severe dehydration or sustaining fluid overload, both of which could potentially pose a risk to the patient. The intervention continued during all ICU days within 90 days of enrolment.

Outcomes

Primary: days alive and out of hospital at day 90.

Secondary: 1) all-cause mortality at day 90; 2) days alive and without life support at day 90; and 3) number of patients with one or more SAE/SAR.

Statistical analysis

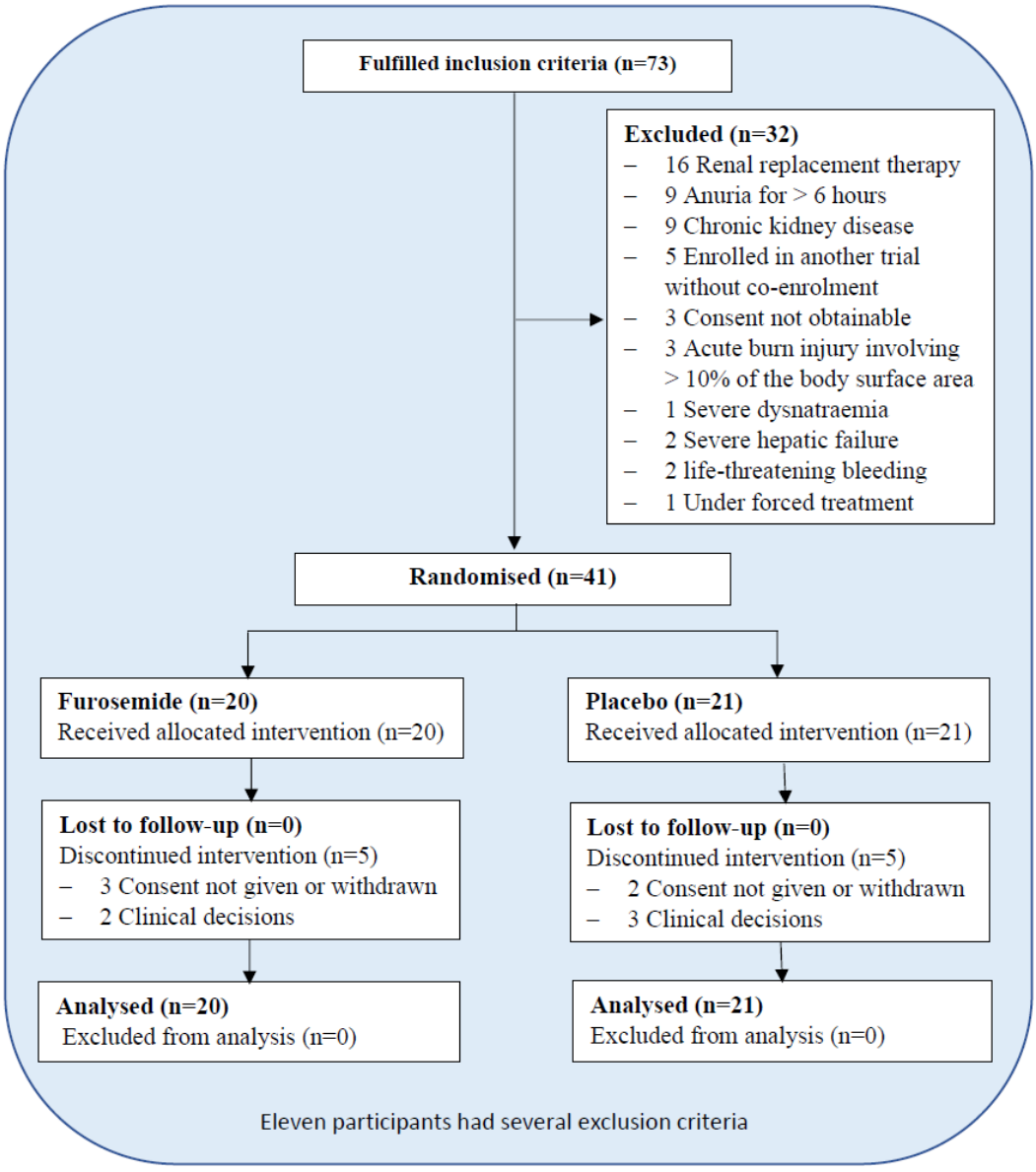
The trial was stopped after 41 (4.1%) of the participants were enrolled resulting in a modified pre-planned statistical analysis plan. The analyses were based on the intention-to-treat population. Unadjusted and adjusted linear regression and a Wilcoxon rank sum test were applied for the primary outcome and continuous secondary outcomes. Binary outcomes were analysed using unadjusted and adjusted logistic regression and Fischer's exact test. Kaplan-Meier plot illustrated 90-day mortality. The significance level for the primary outcome was a p-value < 0.05 and for secondary outcomes a p-value < 0.01. Analyses on the per-protocol

population were not performed due to the small number of participants. We decided not to perform 1-year follow-up.

Results

After enrolling 41 participants, the trial was stopped prematurely (Figure 4). Fluid balances are presented in Table 2. No differences were found between fluid removal with furosemide versus placebo for any outcomes (Table 3). Protocol violations were encountered in 29% of the participants (3 in the furosemide group, 9 in the placebo group). Unexpectedly the attending physicians adjusted the cumulative fluid balance during the trial in 32% of the participants (8 in the furosemide group, 5 in the placebo group) due to substantial discrepancies between the cumulative fluid balance and clinical assessment of fluid status.

Figure 4. Consolidated Standards of Reporting Trials Statement (CONSORT) diagram



Adapted from paper III[135]

Table 2. Development in the cumulative fluid balance

Cumulative fluid balance	Furosemide, N = 20	Placebo, N = 21
Cumulative fluid balance at baseline	6956 ml (5025 to 9890)	6036 ml (4100 to 7682)
Cumulative fluid balance at day 3	1927 ml (654 to 4146)	5139 ml (3198 to 9042)
Cumulative fluid balance at day 5	1551 ml (-247 to 3299)	4568 ml (2345 to 6277)
Cumulative fluid balance at day 90	868 ml (-678 to 3027)	3132 ml (690 to 5114)

Adapted from paper III.[135] All values are presented as medians with interquartile range (IQR). The cumulative fluid balance at day 90 represents the cumulative fluid balance on the last day of the ICU admittance within 90 days from enrolment.

Table 3. Primary and secondary outcomes in the intension-to-treat population

Outcomes	Absolute mean difference or relative risk	P-value
Primary outcome	95% CI	
Days alive and out of hospital at day 90	1 (-19 to 21)	0.94
Secondary outcomes	99% CI	
All-cause mortality day 90	1.40 (0.39 to 7.35)	0.44
Days alive and out of life support at day 90	-5 (-37 to 28)	0.72
Number of patients with one or more serious adverse reactions or events in ICU	1.38 (0.25 to 7.53)	0.40

Adapted from paper III.[135] Unadjusted results.

Termination of the trial

The decision to stop the trial prematurely was made based on the frequent protocol violations and adjustments of the cumulative fluid balance - which were unexpected and had repercussions on the intervention and data recording. The intervention targeted a neutral cumulative fluid balance instead of a clinically neutral fluid status, which likely led to numerous adjustments in the cumulative fluid balance. This highlighted the imprecision of using the cumulative fluid balance as the sole parameter for fluid status. We acknowledged that the trial design could be improved, and it was deemed necessary to obtain more accurate data of the high quality we aimed for. The decision to terminate the trial was made before breaking the allocation concealment.

Conclusion

The trial was terminated early with 41 included participants so no conclusions could be made on the intervention effect on patient-important outcomes. The results were used to revise the trial design for a second version of the GODIF trial.

Enhancing the trial design involved conducting interviews with clinicians to obtain in-depth insights into their approaches and viewpoints regarding fluid status assessment. Additionally, the management committee held meetings where discussions centred on the lessons learned from the initial GODIF trial and strategies for refining the trial design.

Study III: A protocol for a randomised clinical trial - the GODIF trial (second version)

Aim

Investigate the effects of furosemide versus placebo in adult ICU patients with fluid overload on patient-important outcomes based on a refined protocol with incorporated insights gained from the first version of the GODIF trial.

Methods

Study design

It is an international randomised blinded clinical trial investigating furosemide versus placebo.

Changes in trial design for the second version of the GODIF trial

1) The attending physicians must assess fluid status considering the cumulative fluid balance, daily fluid balances, changes in body weight, and clinical examination at enrolment and daily during the trial
2) The intervention must continue until the patient achieves a neutral fluid status assessed as above by the attending physician
3) The option to adjust the cumulative fluid balance is no longer relevant and disregarded
4) Minor adjustments in the resuscitation algorithm were made to improve feasibility.

Eligibility criteria

All inclusion criteria must be met.

Inclusion criteria: ≥ 18 years of age, acute admission to the ICU, clinically stable, and have fluid overload of at least 5% relative to their IBW as assessed by the physician.

Intervention

Fluid removal should continue until a neutral cumulative fluid balance is achieved, as assessed by the attending physician. The intervention continues during all ICU days within 90 days from randomisation. One year follow-up is a telephone interview.

Outcomes

Primary: days alive and out of hospital at day 90.

Secondary: 1) all-cause mortality at day 90; 2) days alive and without life support at day 90; 3) the number of patients with one or more SAE/SAR; 4) all-cause mortality at one year; 5) Health-related quality of life assessed by EQ-5D-5L questionnaire[138,139] at one year; 6) EQ visual analogue scale (EQ-VAS) score[138,139] at one year; 7) participants subjective assessment of their quality of life (unacceptable/neutral/acceptable) at one year; and 8) cognitive function as assessed by the Montreal Cognitive Assessment (MoCA) 5 min/telephone test[140] at one year.

Statistical analysis
The primary analyses will be performed in the intention-to-treat population. All analyses will be adjusted for the stratification variables. The results will be based on point estimates and CI. P-values will be reported but not used as a threshold for statistical inference. Sensitivity analysis of the primary outcome with further adjustment for five risk factors (ischaemic heart disease, septic shock, chronic obstructive pulmonary disease, diabetes, and stroke/neurodegenerative illness) will be performed. Secondary analyses within the per-protocol population will be carried out using identical adjustments.

The composite outcomes will be analysed with the method of Kryger Jensen and Lange which is specially designed for outcomes affected by mortality truncation.[141] The effect will be reported as the mean difference obtained by bootstrap with 95% CI for the primary outcome and with 99% CI for the secondary outcome.
Binary outcomes will be analysed with logistic regression. Risk ratios or risk differences with corresponding 99% CI will be calculated using G-computation based on the logistic regression. Survival outcomes will be supplemented with Kaplan-Meier plots. Continuous outcomes will be analysed using linear regression.

For the health-related quality of life and cognitive function outcomes, all dead will be assigned the lowest possible score or the value that corresponds to a health state equal to death. Sensitivity analyses on the survivors will be performed on these outcomes.

Heterogeneity of the treatment effect on the primary outcome will be explored in subgroup analyses on six baseline variables: SMS-ICU Score (< 25 versus ≥ 25), AKI (yes/no), coronavirus disease 2019 (COVID-19) (yes/no), septic shock before enrolment (yes/no), vasopressors (yes/no), and the degree of fluid overload ($< 10\%$ versus $\geq 10\%$).

Missing data
Multiple imputations will be performed in case of missing data of more than 5% in an outcome.

Interim analyses and monitoring
Two interim analyses were planned. The first was made after 100 enrolled participants and assessed process variables to evaluate the intervention effect according to mean cumulative fluid balance after 3 days in the two groups and the use of escape medicine. The second interim analysis will be conducted after 500 participants have been enrolled to assess the primary outcome and number of participants with one or more SAE/SAR. An international independent data monitoring committee (DMC) will make recommendations to the trial management committee on the conduction of the trial. DMC recommended continuing the trial unchanged in October 2022 after the first interim analysis.

Perspective

The GODIF trial second version is the largest RCT investigating fluid removal with a loop diuretic versus placebo in adult ICU patients. It has a strong methodology, and it will provide high-quality data. The results will be reported according to CONSORT.[142,143]

The trial uses a highly pragmatic approach to assess fluid status, a method that may face criticism. Given the current absence of a precise measurement of fluid status, we have adapted the trial to align with current clinical practices. By allowing all available tools for fluid status assessment, we believe the approach yields the most accurate estimates and offers the advantage of directly applicable results to daily clinical practice.

Status on the 27th of November 2023 is 384 enrolled patients in six participating countries and 23 trial sites. The enrolment is scheduled to end in December 2024, but it might extend into 2025. All trial documents are available online https://www.cric.nu/godif/.

Discussion

Principal findings

The systematic review (*Study I*) revealed limited data with an overall very low quantity and quality of evidence supporting loop diuretics for adult ICU patients with fluid overload. No significant reduction in mortality was found for loop diuretics versus placebo/no intervention. The CI indicated a 51% relative risk reduction to a 6% increase in mortality in the conventional meta-analysis. The number of SAEs was lower for patients treated with loop diuretics. The CI indicated a decrease between 44% to 1% in SAEs, but the significant result was contested in the TSA-adjusted CI. The results overall showed that treatment with loop diuretics for adult ICU patients with fluid overload might be beneficial. The TSA analyses and the GRADE assessment stated that more trials preferably with a low risk of bias are needed before firm conclusions on benefit and harm can be made.
The GODIF trial was planned to provide further high-quality data in this field of research.

The first version of the GODIF trial (*Study II*) was designed as a large, international, randomised, multi-centre trial investigating protocolised fluid removal with furosemide versus placebo in adult ICU patients with at least 5% fluid overload (based on the cumulative fluid balance). Early termination was deemed necessary due to the inaccuracy of the cumulative fluid balance as a sole measure of fluid status to obtain the high-quality data we aimed for. A very reduced sample size corresponding to 4.1% of the planned sample size resulted in inconclusive results.

Based on the lessons learned from the first version of the GODIF trial a revised protocol for the second version of the GODIF trial (*Study III*) was designed and published. The RCT was restarted with a more pragmatic protocol where fluid status was assessed according to several surrogate measurements reflecting current clinical practice. The trial is still ongoing, and enrolment is expected to be terminated at the end of 2024 but might continue into 2025. The trial will provide high-quality data with a low risk of bias.

Strengths and limitations and a discussion of the conduct of the systematic review (*Study I*)

The protocol for the systematic review was published before the review was conducted to increase transparency, avoid selection bias, and obtain the best possible quality of the review (*Paper I*), which is a strength of the study. This review is the first of its kind and has not been done before. We found consistency in the estimates in subgroups and sensitivity analyses which adds validity to the results even though the quality of evidence was very low. The review elucidates a lack of evidence for treatment with loop diuretics in patients with fluid overload according to patient-important outcomes. Diuretics are widely used and are prescribed to almost half of all ICU patients,[103–105,114] and loop diuretics are the predominant diuretic prescribed.[103,105] The results of the review are important and ratify that more research is needed to clarify the benefits and harms of the use of loop diuretics in patients with fluid overload in the ICU.

Meta-analyses
All the analyses were made with both fixed-effect and random-effect models. The method producing the most conservative result was used to ensure we did not overestimate the treatment effect. The random effect model assumes a degree of heterogeneity between the effect estimates which is not due to chance and normally produces wider CI compared to fixed effect models, which assume the same treatment effect of the included trials.[118] The difference in results between the two models was very small. For most of the analyses, the fixed effect model was applied.
We adjusted the significance level to 2.5% (primary outcomes) and 1.7% (secondary outcomes) due to the risk of multiple testing. These measures are a strength of the study.

Heterogeneity
Clinical heterogeneity was observed among the included trials. Not all trials had a definition for fluid overload. We included trials that tested a protocolized diuretic regime in patient populations associated with fluid overload such as AKI and acute heart failure. The degree of fluid overload in all the included trials cannot be quantified, which could potentially impact the results. The duration of the intervention also varied which is a limitation. Subgroup analyses were planned to test the clinical heterogeneity but only some of them could be performed due to lack of data, but the analyses performed did not reveal any significant heterogeneity which could impact the results. No trials with an overall low risk of bias were found which is a limitation.

The control groups in the RCTs in the review were heterogeneous. The main comparison was trials investigating loop diuretics versus placebo/no intervention (no intervention included no diuretics and standard of care). The decision to include standard of care in the control group can be discussed since diuretics are expected to be part of the standard of care. Rescue medication (diuretics) are often protocolized in trials with placebo/no diuretics due to safety, and protocol violations with diuretics are regularly reported. Therefore, we found it acceptable to pool these three types of control groups in one comparison. We conducted a post hoc subgroup analysis, comparing trials with control groups that reported administration of diuretics to trials with control groups that did not report diuretic administration. This was done for mortality and SAE/SAR outcomes. We found no difference in results for the two groups. This supported our choice of pooling the control groups in one comparison.

In general, the statistical heterogeneity was very small, assessed by the Chi-squared test and inconsistency (I^2) statistics which is a strength of the results.

Trial Sequential Analysis
Cochrane Collaboration does in general not recommend the use of TSA but accepts it as secondary pre-planned analyses to Cochrane reviews.[118] We used TSA to reduce the risk of type 1 and type 2 errors (false positive and false negative results) and to assess if firm conclusions could be made based on the data available and the effect size investigated.[123] The TSA-adjusted CI are wider than the CI from conventional meta-analysis until the required information size (RIS) is met. TSA creates boundaries for benefit, harm, and futility, and all three aspects can be declared before the

required information size is reached if the boundaries are crossed. If boundaries are not crossed the RIS is required to make a firm conclusion.[123]
The calculation of the RIS involved parameters, some of which were determined by the research team, which may be subject to criticism. Our calculations were based on the event proportion in the control group, diversity (D^2) statistics (estimate of heterogeneity), a relative risk reduction or increase of 20% (for dichotomous outcomes) or a minimum relevant difference of 0.5 times the observed standard deviation (for continuous outcomes). Additionally, it incorporated a beta level of 0.1 and an alpha level of 0.025 or 0.017 (according to the outcome). This calculation is also referred to as diversity adjusted required information size (DARIS). A risk reduction of 20% for mortality can be criticised since a lower risk reduction is relevant too. This must be considered when assessing the results of the TSA, and it is a limitation of the TSA analyses.

All the TSAs in our systematic review were inconclusive with no boundaries crossed and the DARIS was far from reached. This is useful information when scaling new trials. Our results emphasise a need for more RCTs and the GODIF trial can contribute substantially with new data in the future. When new trials are included in the meta-analyses the control event proportion used to calculate DARIS by TSA changes, and this might change the required number of patients. DARIS is therefore not a static parameter. By the time the second version of the GODIF trial is completed, there is a possibility that an updated systematic review will establish new boundaries for benefit, harm, or futility for certain outcomes and firm conclusions can be made.

Despite the limitation of an author-defined minimal relevant difference and alpha level used in the calculations by TSA, which might not reflect the views of other clinicians, patients, or other parties, we believe that TSA is a good tool to minimise the risk of random errors and protects against drawing firm conclusions on underpowered meta-analyses.

We unconventionally used the results of the DARIS in the evaluation of imprecision in the GRADE assessment for three outcomes. DARIS is not recommended for this purpose by the Cochrane Collaboration but it is being discussed.[118,144] The number of participants in all our outcomes was low so we found it appropriate to downregulate the evidence for all outcomes due to impression.

Strengths and limitations and a discussion of the conduct of a randomised clinical trial and protocol (*Study II and III*)
The GODIF trials were designed as conventional, blinded RCTs with parallel group intervention based on sample size calculations and monitored by interim analyses. The protocol (protocol version 2.4-2.5) for the first version of the GODIF trial is available online https://www.cric.nu/godif-protocol/. The second version of the GODIF trial is based on protocol version 2.7 (also available online) and it is published as a paper (S*tudy III*).[134] The detailed statistical analysis plan has been published in a separate paper.[145] Publication of protocol and statistical analysis plan was done to ensure transparency and reduce the risk of bias which is a strength of the trial.

The second version of the GODIF trial is an international multi-centre trial, which ensures high-quality data, and the results will apply to a broad population. Single-centre trials have been reported to overestimate effect estimates by up to 36% when compared to multicentre trials.[146,147] For that reason we expect the results from the second version of the GODIF trial to be valid.

Early termination of a trial

Research in fluid overload has proved to be a challenge, mainly due to the lack of a gold standard measuring method of fluid status and no generally accepted definition of fluid overload. The first version of the GODIF trial was designed with strong methodology as a large, randomised, stratified, blinded, parallel-group, multi-centre trial to achieve the best quality data possible. We chose to use the cumulative fluid balance as the parameter for fluid overload since it is the most used parameter in up to 88% of the literature.[3] The first version of the GODIF trial taught us that the cumulative fluid balance as the only parameter for fluid status would produce imprecise and flawed data to an extent we did not expect. In 32% of the participants (13 patients), the cumulative fluid balance did not align with the clinical assessment to a degree that the ICU physicians adjusted the cumulative fluid balance and continued the intervention according to this to achieve a neutral cumulative fluid balance. It was a challenge to the trial design that the goal for fluid removal was a neutral cumulative fluid balance (defined as +/- 750 ml). If we had allowed the intervention to continue until the patient was assessed in a clinical neutral fluid balance by the clinical team, we would not have encountered this problem. On the other side, it would not have drawn our attention to the extent of discrepancies between the cumulative fluid balance and the clinical assessment of fluid status. It is a major limitation that the cumulative fluid balance was different from the clinical assessment in one-third of the patients. In five patients (out of 13 patients) the adjustment was made more than once. It shows that estimation of fluid status can be difficult and/or that physicians do not agree on the assessment. Physicians assess fluid status in different ways in the absence of a guideline to support the assessment. Without a precise measurement method for fluid status, trials examining fluid status or fluid overload will face limitations.

The first version of the GODIF trial is important because it questions how fluid overload is described in large parts of the intensive care literature based on fluid balance. A positive cumulative fluid balance is not necessarily the same as fluid overload - but it cannot be dismissed as a parameter for fluid status. A large quantity of observational studies have shown that a positive fluid balance is associated with mortality.[60,66,69,72,74,75,148–154] Fluid balance may be an important tool in the assessment of fluid status, but it cannot stand alone. Efforts to develop a better bedside method to estimate fluid balance are urgently needed.

We did not statistically test if the intervention in the GODIF trial was effective according to predefined criteria. However, the fluid balances in the two groups in the first version of the GODIF trial suggested that the intervention was effective, why it wasn't changed for the second version of the GODIF trial.

The first GODIF trial could not provide any conclusive results due to the small sample size and point estimates with very wide confidence intervals. The point estimate indicated a risk of harm from the use of furosemide on 90-day mortality (RR 1.40, 95% CI 0.39 to 7.35) and the frequency of SAEs/SARs (RR 1.38, 95% CI 0.25 to 7.53). On the contrary, the days alive outside hospital at day 90 (MD 1.0 days, 95% CI -19 to21) and the days without life support at day 90 (MD -5.0 days, 95% CI -37 to 28) might indicate benefit from furosemide. Early stopping of RCTs is associated with overestimation of the treatment effect,[155] and with only 4.1% of the sample size included no conclusion can be made on any outcome.

The decision to stop the first GODIF trial was made before unblinding the trial data. After the discontinuation of the first GODIF trial, the results and the trial design were discussed with the management committee, and interviews were conducted with ICU physicians involved in the treatment of GODIF patients. The aim was to get additional insight into how physicians assessed, treated, and perceived fluid overload, as well as the challenges they met while treating GODIF patients. Their perspectives on how to improve the trial were elaborated upon. Very important lessons were learned, which were used to improve the protocol for the GODIF trial second version.

Assessment of fluid overload

Surveys and research publications on fluid overload reveal a diversity of methods to assess fluid status but the best method has not been proven.[87,88,90] Today fluid assessment is done according to the physicians' discretion. In clinical studies, the assessment of fluid status is often simplified and based on one or maybe two surrogate measurements. Fluid balance and body weight are the two most used surrogate measures of fluid overload in the literature[3] but the inaccuracy of the parameters is seldom discussed. It is not common practice to measure patients' body weight on admission to the hospital, so the reference body weight used in fluid assessments is often estimated or is the first body weight measured during the ICU admission. The first body weight measured can be several days after hospital admission and might not reflect a neutral fluid status. Furthermore, during critical illness and immobilisation, approximately 2% of muscle mass is lost daily,[156–158] which is a factor to consider when body weight is used for estimation of fluid status. Different scales and equipment in the patient bed (drains, tubes, wires, bedsheets, urine bags, clothes etc.) might vary from day to day adding to the impreciseness.

The cumulative fluid balance in litres is probably just as inaccurate. A detailed fluid chart is only performed in the ICU, so changes in fluid balance before the ICU admission might not be accounted for. Several parameters might be estimated in the fluid balance (stool, perspiration, metabolic water, aspirates (vomit)) and not all ICUs calculate perspiration and metabolic water. A correlation between body weight and fluid balance is poor,[84,85,90] and it is recommended to use both methods in the assessment of fluid status.[85] Lastly, it is worth questioning the assumption that body weight or fluid balance upon admission to the ICU reflects a neutral fluid status for a significant number of critically ill patients. This prompts the need to incorporate additional assessment modalities in the evaluation of fluid status.

In the first version of the GODIF trial the median body weight and cumulative fluid balance at day 90 was -4.0 kg and +868 ml in the furosemide group and -4.2 kg and +3132 ml in the placebo group. This supports the former finding that fluid balance and body weight do not correlate. We need more parameters in the fluid status assessment.

We conducted a survey across Nordic countries to explore how ICU physicians assess, define, and treat fluid overload after we stopped the first GODIF trial.[87] It revealed that ICU physicians primarily used the cumulative fluid balance, clinical examination of oedema, urinary output, body weight, and oxygen requirements in their assessment of fluid status, other modalities were not used as often.[87] This is consistent with survey results from the United Kingdom, Australia and New Zealand.[88]
This supported our choice of protocol changes for the second version of the GODIF trial, which introduced a new method for evaluating fluid status. ICU physicians were requested to assess fluid status using four parameters when possible: daily fluid balance, cumulative fluid balance, changes in body weight, and clinical examination (using their preferred tool which includes radiology, ultrasound etc.). These assessments were required upon enrolment and daily during the ICU admission for up to 90 days. The intervention had to be continued until a neutral fluid balance was achieved according to the attending physicians' assessment. We are aware that this is very pragmatic, and it can be criticised. We have no evidence supporting the superiority of physician assessments over the use of body weight or fluid balance alone in evaluating fluid status. However, individual differences will inevitably influence these assessments, reflecting the variability encountered in daily clinical practice. We believe using more surrogate parameters for the fluid status assessment will provide the best possible result and the method can easily be applied to clinical practice. With this new assessment strategy of fluid status, we minimise the risks of including patients with less than 5% fluid overload and it ensures a clinically neutral fluid status is the goal.

Definition of fluid overload
There is no general agreement on the definition of fluid overload, and surveys show a diversity in definitions among ICU physicians worldwide.[87,88] A way to define fluid overload is fluid accumulation as a percentage of body weight. The Nordic ICU physicians agreed that fluid overload can be defined by a minimum of a 5% increase in body weight.[87] In a survey of ICU physicians in the United Kingdom, Australia and New Zealand they agreed to a 10% increase in body weight or above,[88] but they were not asked about their attitude to 5% or above, so this remains unknown. Studies have shown that fluid overload of 5% is associated with increased mortality.[3,154,159] In clinical ICU trials, randomized treatment of fluid overload down to 3% has been conducted,[96] From that perspective, the choice of 5% used in the GODIF trial seems relevant.

We did take it a step further and calculated fluid overload according to ideal body weight, which is not common in the literature. It was done to minimize the inaccuracies with the use of admission weight (which is often estimated or might not reflect a neutral fluid status) and to compensate for extreme body weight (low as high). We regard this as a strength of the trial.

Blinding

The binding of all parties is important to achieve the best possible data and avoid performance bias, attrition bias, and detection bias and it is a strength of the GODIF trial. It can be argued that furosemide is not possible to blind due to the treatment effect of the drug. However, the blinding may be maintained in many participants, especially in patients with kidney failure and in patients with spontaneous polyurea. If escape furosemide is administered, there is a high risk of breaking the blinding to the clinical staff. Blinding is important, but blinding may not affect objective outcomes as mortality as much as subjective outcomes. A meta-analysis investigating blinding in RCTs in the ICU found that blinding did not affect mortality outcomes significantly.[160] Random sequence generation and allocation concealment seem to have a larger impact on effect estimates in RCTs.[160] We used a method with a low risk of bias - a computer computer-generated allocation sequence list with varying block sizes and only one person at the Copenhagen Trial Unit had access to the allocation list.

The CONSORT statement does not recommend testing the blinding in RCTs,[161] so we have abstained from that. We believe that blinding is important and the impact of possible compromised blinding for a part of the participants will probably not affect our outcomes – or we expect the effect to be minimal.

Fluid removal

The optimal rate of fluid removal has not been proven yet and the current research is primarily based on AKI patients on RRT. In the GODIF trials, the intended daily fluid removal was a minimum of 1 ml/kg IBW/hour. We based this decision on studies finding this feasible and with the best outcomes.[133,162,163] Fluid removal of <1 ml/kg/hour or >1.75 ml/kg/hour has been associated with higher mortality.[163] We adjust the fluid removal according to ideal body weight to consider extreme variations in body weight, ensuring that the daily fluid removal target remains achievable and safe for all patients. We defined a minimum criterion for daily fluid removal to ensure separation in fluid removal between the groups, which could be more challenging if the daily fluid removal were left to the discretion of the treating physician.

Outcomes

Composite outcomes are discussed because the interpretation can be complex, and the effect of each component can be unclear if not well-defined and reported.[164] This complexity is particularly pronounced when the outcomes of the individual components show conflicting trends such as both benefit and harm, resulting in a state of equipoise for the composite outcome. Composite outcomes are often used in RCTs since the composite outcome increases statistical power and reduces the sample size, which often enhances trial feasibility concerning the timeline for data gathering and costs.[165] Composite outcomes should only be used if the intervention effect is expected to go in the same direction for all components, and the importance of the components should be as equal as possible.

We have two composite outcomes for the GODIF trial: the primary outcome – days alive and out of hospital at day 90 and a secondary outcome - days alive without life support at day 90.

To enhance transparency and facilitate the interpretation of the primary outcome, we will report the results of both components, namely all-cause mortality at day 90 and the number of days spent outside the hospital within 90 days for the second version of the GODIF trial.[145] A limitation to our protocol and statistical plan is that we have not described if we will penalise for death in our analyses of composite outcomes. If the mortality rate is relatively high in a study population and the intervention has an impact on the mortality rate, then it might also impact the number of days admitted to the hospital. The survivors will probably have more days at the hospital compared to non-survivors due to their survival status. This was seen in the AID-ICU trial investigating treatment with haloperidol versus placebo in adult ICU patients with delirium.[166] The primary outcome was also days alive and out of hospital at day 90. The result of the primary outcome was insignificant. The 90-day mortality was significantly lower in the haloperidol group but the number of days at the hospital was longer compared with the placebo group resulting in equipoise for the primary outcome.[166] They did not penalise for dead and used the actual number of days alive irrespective of survival status at the end of the intervention period. This is a valid method, especially with the relatively long follow-up period of 90 days.[167] Most commonly death is penalised with 0 days or other value worse than the actual value.[167] It is important to be aware that the decision about using penalty for death or not might impact the results.[167] That is why it should be pre-specified in the statistical analysis plan.

While composite outcomes can be difficult to interpret, we believe they offer certain advantages. Our composite outcomes provide a more comprehensive picture than mere mortality; they also provide information regarding hospital length of stay, which can indirectly reflect disease severity, utilization of resources, readmissions within 90 days, and associated costs. We consider the combined outcomes to be valuable to both patients, clinical staff, and hospital administrations. We do not regard the composite primary outcome as a limitation.

Relatively few RCTs have been conducted on the pharmaceutical treatment of fluid overload in the ICU. Our choice of outcomes was based on what we considered the most patient-important and what was found feasible to investigate in one trial according to trial design, cost, timeline, and sample size. The statistical power of our secondary outcomes is low and a limitation which must be considered when interpreting the results. It can also be seen as a limitation that we do not have outcomes on hemodynamic monitoring during fluid removal as an extra safety outcome. Trials investigating different methods for assessing organ perfusion during fluid removal are desirable to guide the speed of fluid removal in the possible safest way. This very important topic must be investigated in separate trials.

Statistics

The GODIF trial is based on a power and sample size calculation detecting a 15% decrease in mortality and an overall improvement of 8% in days alive and out of hospital at day 90. This might seem optimistic with a risk of having an underpowered trial. Smaller effect sizes may be clinically important. Smaller effect size would require a larger sample size which comes with higher cost, use of more resources, and longer time. Large treatment effects are a challenge for many RCTs in

intensive care research.[168] We planned for the trial to be completed within two years and to achieve that, a pragmatic choice on estimation effect of sample size was made. It might be a limitation of the trial.

Conduction of the trial

Unfortunately, research seldom goes as planned. The start-up of the first version of the GODIF trial took place during the COVID-19 pandemic in 2020. It came with consequences as few departments and countries were allowed or able to apply their authorities for approval to start the GODIF trial, and many sites postponed their participation in the trial due to a lack of resources and nursing staff. During COVID-19 the patient categories in the ICUs changed with a declining number of patients with fluid overload. Fluid therapy changed as treatment guidelines for COVID-19 advocated restrictive fluid therapy[8] in line with recommendations for ARDS.[169–171] The experiences of the COVID-19 patients and the results from the CLASSIC trial[172] and CLOVER trial,[173] which found no harm from restrictive fluid therapy in septic shock patients might have had an impact on clinical practice. It probably increased the awareness of fluid overload as a risk factor for poor outcomes and that restrictive fluid therapy seemed safe. The inclusion rate for the GODIF trial has remained slow despite the growing number of active trial sites, which is now 23 sites in six countries (Denmark, Norway, Iceland, Finland, Switzerland, Netherlands) and more to come. We regard changes in fluid therapy and awareness of avoiding fluid overload as the main explanations for the low recruitment rate. The trial is still important as the best treatment for fluid overload has not been established yet. Unfortunately, the trial was not completed, and the results could not be a part of this thesis as planned.

Current evidence for fluid removal with loop diuretics

The evidence for the use of diuretics is sparse and with very low quality. Few trials are being conducted. Since the publication of our systematic review, the RADAR 2 trial has been published – a randomised feasibility trial investigating fluid removal with restrictive fluid therapy and diuretics versus standard of care in 180 participants.[97] The trial was powered to find a difference in fluid balance of 750 ml on the second day of the trial (24 hours) and was successful. The trial was not powered to conclude on mortality, but they found 30-day mortality of 21.6% in the intervention group versus 15.6% in usual care.[97] The POINCARE-2 stepped wedge cluster-randomised trial with 1361 participants investigated protocolized intervention versus standard of care to control fluid balance.[174] The intervention had multiple modalities (fluid restriction, furosemide, albumin infusion, ultrafiltration) applied according to a prespecified protocol. They used body weight as a measure of fluid accumulation. Unfortunately, they only found an MD of -1.1 kg with 95% CI -2.7 to 0.5 between groups after 7 days. The result of cumulative fluid balance between groups was insignificant too. The cumulative fluid balance increased daily for 14 days for both groups, and it increased more than the body weight. The primary outcome was 60 days mortality, and the sample size was based on an absolute decrease in mortality of 15%. They found a difference in mortality of 3%. This implies an underpowered trial. No significant differences were found for any outcomes except for a higher incidence of hypernatremia in the intervention group. This large trial illustrates how difficult research on fluid status can be. The lack of a precise measurement for fluid status, and

a non-blinded trial design where the Hawthorn effect might have affected the clinical practice in the standard-of-care group.
I have not found any other large ongoing or planned RCTs investigating the treatment of fluid overload with diuretics versus placebo in adult ICU patients.

Conclusions and perspectives to further research

Current research primarily focuses on approaches to avoid the development of a positive cumulative fluid balance in septic shock patients by fluid restriction and/or vasopressor use. So far there is no evidence that restrictive fluid therapy for septic shock patients will reduce mortality[35] but large trials are still ongoing (EVIS trial NCT05179499 and ARISE fluids NCT04569942). Unfortunately, trials investigating fluid therapy only report fluid balances and not the number of patients with clinical signs of fluid overload.

Three ongoing randomised feasibility trials are investigating fluid restriction and de-resuscitation in shock patients. They all have the same or similar short title. The REDUSE trial from Sweden is investigating restrictions on non-resuscitation fluids for septic shock patients.[175] The REDUCE trial from Thailand is investigating restrictive fluid management and early de-resuscitation in shock patients.[176] The REDUCE trial from Switzerland also investigates early fluid restriction and de-resuscitation in septic shock patients, but the latter will also report the number of patients with fluid overload of 5% according to cumulative fluid balance and body weight on admission.[177] These trials will contribute to more knowledge of the treatment effects of restrictive fluid therapy and fluid removal involving diuretics in septic shock patients.

Not only septic shock patients develop fluid overload in the ICU. Resuscitation fluids only contribute partly to the development of fluid overload. All fluids, medicine, blood products, and nutrition contribute to the fluid load given to the patients. A large retrospective study on a mixed ICU population from Belgium showed that resuscitation fluids on average contributed to 6% of all fluid inputs across all ICU admissions.[40] Broader research in optimal fluid therapy is warranted in the general ICU population with a focus on fluid accumulation and patient-important outcomes. Our research group is planning a large international inception cohort study in 2024 (FLUID ICU) to assess the incidence of fluid overload in adult ICU patients and to describe the types of fluids administered during admission to the ICU and treatment with diuretics. It will be a contemporary description of practices in the same period as the GODIF trial is enrolling patients, which can be relevant when evaluating the future results of the GODIF trial. The FLUID ICU study will contribute valuable knowledge for designing further trials in the fields of fluid therapy, fluid overload, and de-resuscitation. Especially, administration of non-resuscitation fluids (maintenance fluids and fluid creep) and salt load administered to ICU patients are easily modifiable factors we need to consider in preventing fluid overload, which should be investigated further in large trials.

Most likely, fluid overload cannot be avoided in all ICU patients. The most severely ill patients are probably more prone to develop fluid overload which can partly explain the association between fluid overload and mortality. It is still unclear if treatment of fluid overload can improve mortality. Loop diuretics have been used for almost 60 years, the side effects are well known, they are cheap, widely available, and a preferred choice by ICU physicians in the treatment of fluid overload. Furosemide is also on WHO's list of essential medicines,[178] which is a list of the most effective and

safe medicaments with a low cost-benefit ratio, which makes loop diuretics a good choice for investigating the treatment of fluid overload.

The second version of the GODIF trial is currently the largest RCT investigating the treatment of fluid overload with furosemide versus placebo. The trial has been enrolling patients since June 2021 (https://www.cric.nu/godif/) and it will provide high-quality data for treatment with loop diuretics in adult ICU patients with a minimum of 5% of fluid overload but it cannot stand alone. RCTs investigating different treatment regimens with diuretics are needed. Trials on timing and speed of fluid removal should be performed - preferably with safety measures for organ perfusion. A standardised definition of fluid overload should be established and new technologies or methods for assessing fluid status must be developed to ensure a safe and optimal fluid removal in the individual patient.

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The foundations have not played a role in the trial's design, conduct, data analysis, or publication of the results, and they will not have any claim to the data. No individuals have received any personal financial gain.

Sine Wichmann declares no conflict of interest.

Ethical and legal approvals

The GODIF trial was approved by the Danish Ethics Committee (H-19080597), Danish Medicines Agency (2019121067), EudraCT identifier: 2019-004292-40, and The Capital Region Knowledge Centre for Data Compliance. The GODIF trial has been approved by the relevant authorities in Norway, Finland, Iceland, Switzerland, and The Netherlands.

Illustrations

Frontpage: created by Sine Wichmann in Microsoft PowerPoint

Figure 1-3: created by Sine Wichmann in Microsoft PowerPoint

Figure 4 and Table 1-3: Adapted from figure and tables in *Goal-directed fluid removal with furosemide versus placebo in intensive care patients with fluid overload: A randomised, blinded trial (GODIF trial – First version).*[135] Created by Sine Wichmann in Microsoft PowerPoint or Word with permission from Wiley.

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Papers

Paper I: **Loop diuretics in adult intensive care patients with fluid overload: A protocol for a systematic review of randomised clinical trials with meta-analysis and Trial Sequential Analysis.** Wichmann S, Barbateskovic M, Lindschou J, Gluud C, Perner A, Bestle MH. Acta Anaesthesiologica Scandinavica 2020;64(9):1327–34.

Paper II: **Loop diuretics in adult intensive care patients with fluid overload: a systematic review of randomised clinical trials with meta-analysis and trial sequential analysis.** Wichmann S, Barbateskovic M, Liang N, Itenov TS, Berthelsen RE, Lindschou J, Perner A, Gluud C, Bestle MH. Annals of Intensive Care 2022;12(1):52.

Paper III: **Goal-directed fluid removal with furosemide versus placebo in intensive care patients with fluid overload: A randomised, blinded trial (GODIF trial—First version).** Wichmann S, Schønemann-Lund M, Perner A, Itenov TS, Lange T, Gluud C, Berthelsen RE, Brøcher AC, Wiis J, Bestle MH. Acta Anaesthesiologica Scandinavica 2023;67(4):470–8.

Paper IV: **Goal directed fluid removal with furosemide versus placebo in intensive care patients with fluid overload: A trial protocol for a randomised, blinded trial (GODIF trial).** Wichmann S, Itenov TS, Berthelsen RE, Lange T, Perner A, Gluud C, Lawson-Smith P, Nebrich L, Wiis J, Brøchner AC, Hildebrandt T, Behzadi MT, Strand K, Andersen FH, Strøm T, Järvisalo M, Damgaard KAJ, Vang ML, Wahlin RR, Sigurdsson MI, Thormar KM, Ostermann M, Keus F, Bestle MH. Acta Anaesthesiologica Scandinavica 2022;66(9):1138–45.

PAPER I

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REVIEW

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Loop diuretics in adult intensive care patients with fluid overload: A protocol for a systematic review of randomised clinical trials with meta-analysis and Trial Sequential Analysis

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Background: In the intensive care unit, fluid overload is frequent and a risk factor for organ dysfunction and increased mortality. Primarily, lung and kidney functions may be impaired by fluid overload resulting in acute respiratory failure and acute kidney injury. No clinical guidelines exist for treatment of fluid overload in intensive care patients. Loop diuretics, most often furosemide, appear to be the most frequently used pharmacological intervention. The aim of this protocol is to describe the methods of a systematic review assessing the evidence of treatment with loop diuretics in adult intensive care patients with fluid overload.

Methods: We will conduct a systematic review with meta-analysis and report it according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statements, use the recommendations of the Cochrane Handbook and assess the quality of the evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology. We will include randomised clinical trials identified through searches of major international databases and trial registers. Two authors will independently screen and select trials for inclusion, extract data and assess the methodological quality using the Cochrane risk of bias tool. Extracted data will be analysed using Review Manager and Trial Sequential Analysis. The protocol is registered at PROSPERO.

Discussion: We aim to provide reliable evidence on the use of loop diuretics in adult intensive care patients with fluid overload to guide clinicians, decision makers and trialists on clinical practice.

1 | BACKGROUND

Intensive care patients are often treated with substantial amounts of fluids and medicine leading to accumulation of fluid in the body. Excess fluid may result in oedema in tissues and organs which may affect their function. In this protocol we aim to describe the rationale and methods of a planned systematic review of randomised clinical trials assessing at the evidence of treating fluid overload with diuretics in adults admitted to the intensive care unit (ICU).

2 | DESCRIPTION OF THE CONDITION

Fluid overload can be defined as net positive fluid balance where fluid intake is larger than output. It is often presented as a percentage of the bodyweight. Fluid overload is common in ICU patients. It has become increasingly evident that fluid overload is a risk factor for organ dysfunction and increased mortality.[1-3] All organs get affected by fluid overload, but especially the lungs and kidneys are involved and frequently demands additional and prolonged treatment.

Excess fluid in the lungs may result in longer time on mechanical ventilation[4] and a restrictive fluid therapy is recommended for acute respiratory distress syndrome.[4-6] Fluid overload is also associated with development of acute kidney injury[7-10] which has an incidence of up to 57% in the ICU and is associated with increased mortality.[11] In one observational study of patients in ICU with acute kidney injury showed that 53% and 29% of the patients accumulated, respectively, 5% and 10% fluid overload after 5 days of admission.[12]

3 | DESCRIPTION OF THE INTERVENTION

Treatment of fluid overload can be done with fluid restriction, diuretics and dialysis. However, the optimal way to treat fluid overload is not established and it is unknown when and how fluid overload should be treated. Conservative fluid management and/or de-resuscitation with fluid removal may lead to reduced mortality.[13] In ICU patients, a reduction in fluid administration is often not enough to treat fluid overload and, in addition, the frequent development of acute kidney injury impairs the kidneys ability to excrete water. Diuretics is used in 49% of all ICU admissions and it is the predominant way to treat fluid overload.[14] Of these drugs, the loop diuretic furosemide is the predominant diuretic used in about 94%.[14] Other loop diuretics are torsemide, bumetanide, ethycrinic acid or azosemide, but they are sparsely used. Combinations of diuretics are uncommon in the ICU, and approximately 80% of the patients treated with diuretics receive only furosemide.[14]

Loop diuretics can be administered intravenous or orally. The diuretic effect is variable and adverse effects as electrolyte derangements are common. Other groups of diuretics such as thiazides/thiazide-type diuretics, mineralocorticoid receptor antagonists, carbonic anhydrase inhibitors and epithelial sodium channel blockers are also used in the ICU, but to a much lesser extent, and rarely as the only diuretic but often as adjunctive treatment.[14] Some diuretics are also used for other indications than fluid overload, eg hypernatraemia[15] and metabolic alkalosis.[16]

Acute respiratory distress syndrome is a condition with acute diffuse, inflammatory lung injury, leading to increased pulmonary vascular permeability, pulmonary oedema and loss of ventilated lung tissue.[6] Treatment with mechanical ventilation and positive end expiratory pressure help the oxygenation, recruitment of not ventilated lung areas and minimising the lung oedema. Restrictive fluid therapy or diuretics is a part of the treatment of the lung oedema in acute respiratory distress syndrome,[5,6] but is relevant to consider in all kinds of respiratory failure with wet lungs.

4 | HOW THE INTERVENTION MIGHT WORK

Furosemide is a weak acid where > 95% is bound to plasma proteins (almost exclusively to albumin). Only a very small fraction of furosemide is filtered through the glomerulus but the protein-bound furosemide is actively secreted into the lumen in the proximal tubule via organic acid transporter pathways.[17,18] In the tubules furosemide inhibits the sodium-potassium-chloride transporter in the thick ascending limb of the loop of Henle resulting in decreased reabsorption of water, sodium and chloride.[19] The renal action of furosemide peaks within 5 minutes after intravenous bolus and 1 hour after oral administration. Elimination half-life varies from 0.5 to 2 hours in healthy subjects, but in advanced chronic renal failure the mean plasma half-life of furosemide can be prolonged up to 24 hours and in case of liver failure up to 4.3 hours.[20]

The other loop diuretics (torasemide, bumetanide, etacrynic acid and azosemide) all primarily work as furosemide in the thick ascending limb of Henle.[21]

5 | WHY IT IS IMPORTANT TO DO THIS REVIEW

Fluid overload is a common condition associated with serious adverse effects and represents a detrimental outcome in intensive care patients. Guidelines for treating fluid overload do not exist, and the condition is often treated with loop diuretics on the physician's discretion.

We have not identified any systematic reviews investigating treatment of fluid overload in general intensive care patients, but we have found systematic reviews investigating furosemide in patients with acute decompensated heart failure,[22] co-administration of furosemide and albumin in patients with hypoalbuminemia[23] and furosemide's impact on mortality and requirement for renal replacement therapy in acute kidney injury.[24] Those reviews included only few randomised clinical trials among ICU patients.

6 | OBJECTIVES

We aim to assess the benefits and harms of loop diuretics in adult ICU patients with fluid overload based on results of randomised clinical trials.

7 | METHODS

This protocol has been reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols checklist (see Appendix 1).[25,26] We will follow the recommendations stated in The Cochrane Handbook of Interventions Reviews[27] and the eight-step assessment suggested by Jakobsen et al.[28]

The protocol is registered on the PROSPERO database.

8 | CRITERIA FOR CONSIDERING TRIALS FOR THIS REVIEW

8.1 | Types of trials

We will only include randomised clinical trials, irrespective of reported outcomes, publication date, publication language, publication type and

publication status. Unpublished trials will be included if methodological descriptions and trial data are provided from the trial investigators.

8.2 | Types of participants

We will include intensive care patients above 18 years of age. The patients must have fluid overload, as defined by the trialists. Definition of fluid overload varies among studies. In some studies, fluid overload is defined as a net positive fluid balance, whereas other trials present fluid accumulation in percentage adjusted for body weight (total intake (litres) – total output (litres)/baseline body weight).[7,8,12,29]

We will also include trials with adult ICU patients with acute kidney injury, acute decompensated heart failure or pulmonary oedema as these groups are considered to have fluid overload.

8.3 | Types of Interventions

Loop diuretics compared with placebo or no intervention.
Loop diuretics compared with other diuretics.
Loop diuretic compared with other pharmacological interventions.
Higher-dose loop diuretics compared with lower doses of loop diuretics.

We will accept any dose, formulation, timing and duration of intervention. In case the same loop diuretic is tested in two different doses, the highest dose will be considered the experimental group.

8.4 | Types of outcome measures

Primary outcomes.

1. All-cause mortality at longest follow-up.
2. Quality of life (any valid continuous quality of life scale will be accepted) at longest follow-up.
3. Proportion of participants with one or more serious adverse events at longest follow-up. We will use the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use – Good Clinical Practice (ICH-GCP) definition of a serious adverse event, which is any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolonging of existing hospitalisation and resulted in persistent or significant disability or jeopardised the participant.[30] If the trialists do not use the ICH-GCP definition, we will include the data if the trialists use the term "serious adverse event." If the trialists do not use the ICH-GCP definition nor use the term serious adverse event, then we will also include the data, if the event clearly fulfils the ICH-GCP definition for a serious adverse event.

Secondary outcomes.

1. Plasma concentration of creatinine at longest follow-up.
2. Proportion of participants without resolution of fluid overload, as defined by trialists, at longest follow-up.
3. Number of days in mechanical ventilation.
4. Length of stay in the ICU.
5. Proportion of participants with adverse events or reactions not considered serious at longest follow-up.

Explorative outcomes.

1. Single serious adverse events at longest follow-up.
2. Single adverse events not considered serious at longest follow-up.
3. Plasma concentration of sodium, potassium and chloride at longest follow-up.

9 | SEARCH METHODS FOR IDENTIFICATION OF STUDIES

9.1 | Electronic searches

Randomised clinical trials that fulfil the inclusion criteria will be identified through searching the literature with systematic search strategies designed to identify relevant trials without restrictions to language, publication year and journal.

The following databases will be searched from inception:

- Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, latest issue)
- Medline (OvidSP)
- PubMed
- EMBASE (OvidSP)
- Science Citation Index (web of science)
- Biosis Previews (web of science)
- Latin American Caribbean Health Sciences Literature (LILACS)
- China National Knowledge Infrastructure (CNKI)
- Wanfang Data
- VIP Chinese Science Journals Database
- Sinomed

For details on full search strategies, see Appendix 2.

9.2 | Searching other resources

Reference lists of relevant papers, reviews, randomised trials and non-randomised studies and editorials will be screened manually for potentially includable trials. Furthermore, authors of identified studies, experts for each area and pharmaceutical companies (if relevant) will be contacted and asked for knowledge on additional trials. Unpublished trials will be included if data and methodology on the trial can be assessed. A search in Google Scholar will also be performed.

On-going and unpublished trials will be searched on the following trial registers:

- ClincalTrials.gov
- WHO International Clinical Trials Registry Platform (ICTRP)
- EU Clinical Trial Register
- Australian New Zealand Clinical Trials Registry (ANZCTR)

Furthermore, we will search for unpublished trials, clinical study reports on the websites of:

- US Food and Drug Administration (FDA)
- European Medicines Agency (EMA)

10 | DATA COLLECTION AND ANALYSIS

The following methods on data collection and data analysis will be used.

10.1 | Selection of studies

Two authors (SW and MB) will independently screen all titles and abstracts of the trials identified by the searches. All relevant and potentially relevant articles will be screened in full text. Any disagreement will be resolved through consensus of a third reviewer (MHB, JL, AP or CG).

10.2 | Data extraction and management

A predefined data extraction form, developed by the review team, will be used when the two authors independently extract data from the included trials. In case of disagreement concerning the extracted data, consensus will be reached through discussion or through consultation with a third reviewer (MHB, JL, AP or CG). Whenever necessary, corresponding authors will be contacted to clarify issues related to data reporting or if further trial details are needed. We will extract the following data:

1. Trial: country, date of publication, duration, design (multi- or single-centre trial)
2. Participants: number of participants, number of analysed and lost to follow-up/withdrawn, type of participants, gender, age (median/mean), inclusion and exclusion criteria.
3. Interventions: type of intervention, comparator and concomitant medications.
4. Outcomes: primary and secondary outcomes specified, and time points reported.
5. Other: trial funding and notable conflicts of interest of the trial authors.

11 | ASSESSMENT OF RISK OF BIAS IN INCLUDED TRIALS

SW and MB will independently assess the methodological quality of each included trial, defined by the design of the trial and reporting. Any disagreement will be discussed between the two authors. We will assess the risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions[27] by using RoB2 tool.[31] Based on the risk of bias assessment, the included trials and each outcome result will be defined as overall low risk of bias if all bias domains are judged as low risk of bias.

12 | MEASURES OF TREATMENT EFFECT

For dichotomous outcomes risk ratio (RR) with confidence interval (CI) and Trial Sequential Analysis (TSA)-adjusted CI will be calculated. For continuous outcomes, both end scores and change scores will be included in the analyses. End scores will be used if both are reported. Mean difference (MD) and standardised mean difference (SMD) with CIs and TSA-adjusted CIs will be calculated for continuous outcomes.

13 | UNIT OF ANALYSIS ISSUES

Dealing with missing data.

We will contact trial investigators of the original papers for relevant missing data.

For both dichotomous and continuous outcomes, we will not be imputing missing data for any outcomes in the primary analysis and intention-to-treat data will not be used if the original report did not contain such data.

If standard deviations (SD) are not reported, the SDs will be calculated using data from the trial if possible.

In the sensitivity analysis, best-worst case scenario and worst-best case scenario for dichotomous and continuous outcomes, imputed data will be used, see 'Sensitivity analysis'.

14 | ASSESSMENT OF HETEROGENEITY

We will assess signs of heterogeneity by visual inspection of the forest plots. We will assess presence of statistical heterogeneity by Chi squared test with significance set at P 0 < .10 and by measuring the quantities of heterogeneity by I^2 static.[32] We will follow the recommendations for thresholds in The Cochrane Handbook for Systematic Reviews of Interventions[27]: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity.

We will explore potential clinical heterogeneity by conducting the pre-specified sub-group analyses, see 'Subgroup analysis and investigations of heterogeneity', which may explain the statistical heterogeneity.

15 | ASSESSMENT OF REPORTING BIASES

We will visually assess funnel plots for signs of asymmetry if 10 or more trials are included in an analysis.[27,28]

We will test asymmetry within dichotomous outcomes with the Harbord's test[33] and for continuous outcomes regression asymmetry test.[34]

16 | DATA SYNTHESIS

16.1 | Meta-analysis

We will conduct meta-analyses for outcomes with comparable effect measures if more than one trial is included. The statistical software Review Manager provided by The Cochrane Collaboration[35] and the TSA software[36] provided by the Copenhagen Trial Unit will be used. If clinical and statistical heterogeneity are large or unexpected, we will reconsider doing the meta-analysis. We will report the results narratively if a quantitative synthesis is not appropriate.

16.2 | Assessment of significance

We will assess our intervention effects with both random-effects model meta-analyses and fixed-effect model meta-analyses.[37,38] If the estimates from the two models are approximately equal, we will use the estimate with the widest CI. We will adjust our thresholds for statistical significance because of multiplicity problems due to multiple outcomes by dividing the pre-specified P-value threshold with the value halfway between 1 (no adjustment) and the number of primary or secondary outcome comparisons (Bonferroni adjustment).[28,39] We have defined three primary outcome and five secondary outcomes; thus, we will consider a P-value of 0.025 or less as significant for the primary outcomes and a P-value of 0.017 or less as significant for the secondary outcomes. We will report TSA-adjusted CIs which means that these CIs are adjusted for where the cumulative Z-curve of the TSA has reached in relation to the required information size. We will report 95% CIs as well. We will use the eight-step procedure to assess if the thresholds for significance are crossed.[28]

16.3 | Trial sequential analysis

Cumulative meta-analyses are at risk of producing random errors due to sparse data and multiple testing of accumulating data.[40-48] Therefore, TSA[36] can be applied to control this risk.[49] The required information size and the required number of trials[50] (the number of participants and trials needed in a meta-analysis to detect or reject an a priori pre-specified realistic intervention effect) can be calculated to minimise random errors.[51] The required information size is based on the event proportion in the control group, the assumption of a plausible relative risk reduction (RRR) or relative risk increase (RRI), and the heterogeneity variance[52] of the meta-analysis.[51] TSA enables testing for significance to be conducted each time a new trial is included in the meta-analysis. Based on the required information size and the required number of trials, trial sequential monitoring boundaries can be constructed. This enables one to determine the statistical inference concerning cumulative meta-analysis that has not yet reached the required information size.[43,44,46,48] We will analyse all primary and secondary outcomes with TSA. We will estimate the diversity-adjusted required information size[51] based on the proportion of patients with an outcome in the control group. In addition, we will use a family-wise error rate of 5%[28] leading to a statistical significance level of 2.5% for each of the primary outcomes, and 1.7% of the secondary outcomes a beta of 10% corresponding to a power of 90%, and the diversity (D^2) of the meta-analysis[51] suggested by the trials in the meta-analysis.[28] As anticipated intervention effects for dichotomous outcomes in the TSA, we will use realistic a priori RRR or RRI increases of 20%. For continuous outcomes, we will in the TSA use the observed SD, and a mean difference of the observed SD/2.

17 | SUBGROUP ANALYSIS AND INVESTIGATION OF HETEROGENEITY

We will try to determine if the benefits and harms of the treatment options are influenced by the following subgroup analyses:

- Trials at overall high risk of bias compared to trials at overall low or uncertain risk of bias.
- According to population:
  a. Type of ICU patients (medical compared to surgical as these likely have different responses and prognoses)
  b. Severity of fluid overload (up to 5% compared to 6% to 10% compared to over 10% as these groups may have different responses and prognoses)
  c. Diagnosis of acute kidney injury or decompensated heart failure or other diagnoses at randomisation as these groups may have different responses and prognoses

18 | SENSITIVITY ANALYSIS

To assess the potential impact of the missing data for dichotomous outcomes, we will perform the two following sensitivity analyses on both the primary and secondary dichotomous outcomes.

- 'Best-worst-case' scenario
- 'Worst-best-case' scenario

We will present results of both scenarios in our review. For a detailed explanation of analyses see Appendix 3.

Other post-hoc sensitivity analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results.[28]

19 | SUMMARY OF FINDINGS TABLES

We will use the GRADE system[53] to assess the certainty of the body of evidence associated with the outcomes by constructing Summary of Findings (SoF) per comparison using the GRADEpro software.[54] We will present the following seven outcomes in the SoF: all-cause mortality, quality of life, proportion of patients with one or more serious adverse events, concentration of plasma creatinine, proportion of participants with no resolution of fluid overload, number of days in mechanical ventilation and length of stay in the ICU. For each outcome, first we will present summary of findings in randomised clinical trials with overall low risk of bias and secondarily, results in all trials. The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality measure of a body of evidence considers within study risk of bias, the directness of the evidence, heterogeneity of the data, precision of effect estimates[34] and risk of publication bias. We will primarily base our conclusions on the analyses of trials with overall low risk of bias.

20 | DISCUSSION

This systematic review will present data from existing randomised clinical trials elucidating treatment modalities for fluid removal with diuretics in intensive care patients with fluid overload. Hopefully, the review will contribute with evidence for patient-important outcomes to diuretic treatment in intensive care patients with fluid overload.

This protocol has several strengths. It follows the PRISMA-P guideline and uses a methodology based on The Cochrane Handbook for Systematic Reviews of Interventions,[27] the eight-step assessment suggested by Jakobsen et al,[28] TSA[49] and GRADE assessment.[53] Hence, this protocol considers the risks of both random and systematic errors.

We are aware that by focusing only on randomised clinical trials we run the risk of focusing more on benefits than on harms. By not searching for observational studies, we will likely overlook observational studies reporting adverse events, especially late or rare adverse events. Therefore, if we demonstrate benefits of the loop diuretics, there will be a need to assess the occurrence of adverse events based on observational studies.

Our ambition with this systematic review is to provide reliable and powered evidence to better inform decision makers on clinical practice on the use of diuretics in intensive care patients with fluid overload.

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CONFLICT OF INTEREST

AP is the sponsor of a fluid restriction trial in patients with septic shock and receives grants from the Novo Nordisk Foundation. MHB is the sponsor of a fluid removal trial in ICU patients and has received a grant from the Novo Nordisk Foundation. SW, CG, MB and JL have no conflict of interest.

AUTHORS' CONTRIBUTIONS

SW drafted the manuscript and registered the protocol in PROSPERO. All authors contributed to the manuscript and read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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PAPER II

Annals of Intensive Care

REVIEW

Open Access

Loop diuretics in adult intensive care patients with fluid overload: a systematic review of randomised clinical trials with meta-analysis and trial sequential analysis

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Abstract

Background: Fluid overload is a risk factor for organ dysfunction and death in intensive care unit (ICU) patients, but no guidelines exist for its management. We systematically reviewed benefits and harms of a single loop diuretic, the predominant treatment used for fluid overload in these patients.

Methods: We conducted a systematic review with meta-analysis and Trial Sequential Analysis (TSA) of a single loop diuretic vs. other interventions reported in randomised clinical trials, adhering to our published protocol, the Cochrane Handbook, and PRISMA statement. We assessed the risks of bias with the ROB2-tool and certainty of evidence with GRADE. This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020184799).

Results: We included 10 trials (804 participants), all at overall high risk of bias. For loop diuretics vs. placebo/no intervention, we found no difference in all-cause mortality (relative risk (RR) 0.72, 95% confidence interval (CI) 0.49–1.06; 4 trials; 359 participants; $I^2 = 0\%$; TSA-adjusted CI 0.15–3.48; very low certainty of evidence). Fewer serious adverse events were registered in the group treated with loop diuretics (RR 0.81, 95% CI 0.66–0.99; 6 trials; 476 participants; $I^2 = 0\%$; very low certainty of evidence), though contested by TSA (TSA-adjusted CI 0.55–1.20).

Conclusions: The evidence is very uncertain about the effect of loop diuretics on mortality and serious adverse events in adult ICU patients with fluid overload. Loop diuretics may reduce the occurrence of these outcomes, but large randomised placebo-controlled trials at low risk of bias are needed.

Keywords: Critical care, Diuretics, Fluid accumulation, Fluid overload, Furosemide, Loop diuretics, Systematic review

Introduction

Intensive care patients receive substantial amounts of fluids during resuscitation, as maintenance fluid, with medicine, and nutrition. Large fluid input, capillary leak, and acute kidney injury (AKI) with accompanying oliguria often results in sodium chloride and water accumulation leading to fluid overload. Large iatrogenic sodium load is contributing to development of fluid overload. Sodium intake is mainly caused by isotonic maintenance fluid therapy and fluid creep from sodium containing fluids used as drug dissolvents [1]. The kidneys have a limited capacity to excrete sodium and adapts slowly (days) to substantial changes in sodium intake [1]. A high sodium

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intake will lead to subsequent water retention and contribute to fluid overload. Large volume fluid resuscitation and a positive fluid balance are associated with sepsis, severe burns, severe pancreatitis, and emergency surgery complicated with intraabdominal hypertension.

Fluid overload affects all organs and is an independent risk factor for intraabdominal hypertension [2–4] and the development of AKI [5–8]. AKI occurs in up to 57% of patients in the intensive care unit (ICU) [9]. Furthermore, fluid overload is associated with increased mortality in the general ICU population [10], including those with recent surgery [11, 12], sepsis [13–15], AKI [16–20], respiratory failure [21], and traumatic brain injury [22].

In an American study, diuretics were used in 49% of all patients admitted to the ICU. The loop diuretic furosemide was the predominant diuretic used in about 94% of diuretic-treated patients [23]. A multi-national study of ICU patients with AKI reported administration of diuretics in 61% of the patients and 98% of these patients received furosemide [24]. Only a minority of patients receive combinations of two or more types of diuretics [23–25].

No systematic reviews have assessed the benefits and harms of loop diuretics in the treatment of fluid overload in the ICU and no guidelines exist. With the present systematic review, our primary aim is to assess the existing evidence on all-cause mortality, quality of life, and serious adverse events from randomised clinical trials (RCT) on the treatment of fluid overload with loop diuretics in adult ICU patients [26].

Methods

This systematic review was conducted according to our published protocol and statistical analysis plan [26]. The protocol was registered in the International Register of Systematic Reviews Database PROSPERO (CRD42020184799). We adhered to the methodology recommended by The Cochrane Collaboration [27] and used an eight-step procedure to assess if the threshold for statistical and clinical significance were crossed [28]. The steps include: both fixed-effect and random-effects model meta-analyses, subgroup analyses, sensitivity analyses, adjusted thresholds for significance, calculated realistic diversity-adjusted required information sizes using Trial Sequential Analysis, Bayes factor, assessed the impact of bias including publication bias, and clinical significance [28]. In addition, we assessed the certainty of evidence with Grading of Recommendations, Assessments, Developments and Evaluations (GRADE) [29] system and reported the review as recommended by Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [30] (Additional file 1: S1).

Eligibility criteria

RCTs assessing adult ICU patients with fluid overload treated with the following four comparisons were included: (1) Single loop diuretic compared with placebo or no intervention (standard of care or no diuretics). (2) Single loop diuretic compared with other types of diuretics. (3) Single loop diuretic compared with other pharmacological interventions. (4) Higher-dose loop diuretic compared with lower dose loop diuretic. We accepted any dose, formulation, timing, and duration of intervention [26].

Outcomes

Primary outcomes

(1) All-cause mortality; (2) health-related quality of life; (3) proportion of participants with one or more serious adverse events (SAEs) according to either the definition from Good Clinical Practice Guideline of the International Conference on Harmonization (ICH-GCP) [31], the trialist's definition of 'serious adverse event', or available data that clearly fulfilled the ICH-GCP definitions for a SAE.

Secondary outcomes

(1) Plasma concentration of creatinine; (2) proportion of participants without resolution of fluid overload; (3) number of days on mechanical ventilation; (4) length of stay in days in the ICU; (5) proportion of participants with adverse events not considered serious (AE).

Explorative outcomes

(1) Single SAEs; (2) single AEs; (3) plasma concentration of sodium, potassium, and chloride.

All outcomes were assessed at longest follow-up.

Search methods for identification of trials

We searched the following databases: Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE (Ovid), Embase (Ovid), PubMed, Science Citation Index (Web of Science), Biosis Previews (Web of Science), Latin American Caribbean Health Sciences Literature (LILACS), China National Knowledge Infrastructure (CNKI), Wanfang Data, VIP Chinese Science Journals Database, and Sinomed. A search in Google Scholar was also performed.

Ongoing and unpublished trials were searched from databases of clinical trial registries and United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) [26].

We applied no restrictions according to language, publication status, or year. The literature searches were

last updated on April 13, 2021. Detailed search strategy in Additional file 1: S2.

Trial selection and data extraction

Three authors (SW, MB, NL) independently screened titles and abstracts for eligibility in Covidence.org [32]. Selected articles were evaluated in full text for inclusion in accordance with the inclusion criteria by at least two authors. Disagreements were resolved by consensus.

Two investigators (SW, MB) independently extracted data from the included trials in a predefined data collection form. The following data were collected: (1) Trial: country, date of publication, duration, design (multi- or single-centre trial). (2) Participants: number of patients randomised, analysed, and lost to follow-up/withdrawn, type of patients, sex, age, inclusion and exclusion criteria. (3) Interventions: type of intervention, comparator, and concomitant interventions. (4) Outcomes: specified primary, secondary, and explorative outcomes. (5) Trial funding and notable conflicts of interest [26].

Risk of bias

Two authors (SW, MB) independently assessed the risk of bias of all included trials and outcomes using The Cochrane Collaboration's risk of bias tool, RoB2, by answering all the signalling questions in the five domains [33]. Disagreements were resolved by consensus. All outcomes were judged at overall low risk of bias if all five domains were at low risk of bias. Outcomes were judged at overall high risk of bias when some concerns or high risk of bias was judged in one or more domains [26].

We planned to assess bias across trials by inspecting funnels plot for asymmetry when 10 or more trials were included in a meta-analysis and tested by Harbord's test [34] for dichotomous outcomes and with regression analysis [35] for continuous outcomes.

Data synthesis

Association measures

Risk ratios (RR) were calculated for dichotomous outcomes with 95% confidence interval (CI) and Trial Sequential Analysis (TSA)-adjusted CI. End-scores were used for continuous outcomes and mean difference (MD) with 95% CIs, and TSA-adjusted CIs were calculated.

Meta-analyses

The effect measures were analysed using Review Manager 5 [36]. The intervention effect was calculated using both fixed-effect model with the Mantel–Haenszel method and random-effects model with the DerSimonian and Laird method. We drew conclusions based on the most conservative estimates of the two [26, 28]. For the primary outcomes, we calculated the Bayes factor [28].

Dealing with missing data

Corresponding authors of the trials were contacted and asked for clarifications regarding methods, data, or missing data. We received raw data from one trial [37]. We conducted sensitivity analyses to assess the potential impact of missing data by calculating a best–worst case scenario and a worst-best case scenario [26, 28].

Assessment of heterogeneity

Visual inspection of forest plots, inconsistency (I^2) statistic, and diversity (D^2) statistic were used to assess statistical heterogeneity [38]. Subgroup analyses were performed to explore clinical and statistical heterogeneity by Chi-squared test with a significance level at $P < 0.1$ [26].

Subgroup analyses

We planned to perform the following subgroup analyses [26]: (1) Trials at overall high risk of bias compared to trials at overall low risk of bias. (2) Type of ICU (medical ICU compared to surgical ICU and to mixed ICU). (3) Severity of fluid overload (up to 5% compared to 6% to 10% and to above 10%). (4) Type of patients according to ICU diagnose (mixed diagnoses compared to AKI, to decompensated heart failure, and to acute lung injury (ALI)/acute respiratory distress syndrome (ARDS)). Due to few included trials and sparse data, we were only able to conduct subgroup analyses according to ICU diagnoses, type of ICU, and severity of fluid overload.

We conducted a post hoc subgroup analysis for the comparison of loop diuretics vs. placebo/no intervention. The control groups in this comparison consisted of placebo, no diuretics, and standard of care. Some trials with placebo or no diuretics as control group reported administration of loop diuretics as escape or protocol violations. In standard of care, diuretics are expected to be allowed. To investigate if administration of loop diuretics in the control group had an impact on the result, we made a post hoc subgroup analysis comparing trials that reported administration of loop diuretics in the control group to trials not reporting administration of loop diuretics in the control group. Further details in Additional file 1: S3.

Trial sequential analysis

TSA is used to control the risks of random errors and to test if the meta-analysis had reached the required number of randomised patients to reject or accept the a priory stipulated intervention effect [38–48]. If accrued information size is too small compared to the required information size, the TSA-adjusted CI becomes wider than the traditional 95% CI, and the threshold for statistical

significance will be further restricted. If the required information size is reached, the TSA-adjusted CI will be equal to the traditional naïve 95% CI for the tested intervention effect. We used a relative risk reduction (RRR) of 20% for dichotomous outcomes and minimal relevant difference of 0.5 of the observed standard deviation for continuous outcomes [28]. We used a familywise error rate of 5% [28], leading to an alpha of 0.025% for the three primary outcomes and 0.017% for the five secondary outcomes, and a beta of 10% resulting in a power of 90%.

Grading certainty of evidence

We used "The Grading of Recommendations Assessment, Development and Evaluation" (GRADE) approach to assess the certainty of the body of evidence associated with the predefined outcomes [49–51].

Results

Trial selection

We identified 8338 titles and assessed 109 full text papers for eligibility (Fig. 1). We included 10 RCTs with a total of 804 participants—one text in German and nine texts in English [37, 52–60]. One trial was only published as an abstract [57]. We also identified four ongoing or unpublished trials of relevance [61–64]. No data on unpublished trials were available for this review.

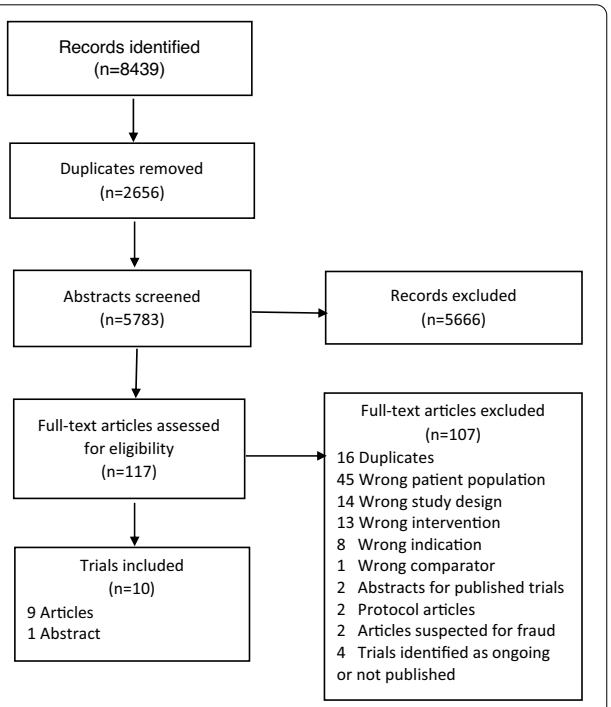

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart

Characteristics of the included trials

We were only able to include trials investigating loop diuretics vs. placebo/no intervention (six trials), loop diuretics vs. another loop diuretic (two trials), and loop diuretics vs. another type of diuretics (two trials). All trials were small ranging from 12 to 248 participants. As experimental intervention, nine trials used furosemide and one trial used torsemide. The control group interventions consisted of: no diuretics [54, 56, 57]; placebo [52]; standard of care [37, 55]; a different loop diuretic (piretanide, ethacrynic acid) [58, 59]; or a different group of diuretics (tolvaptan, acetazolamide) [53, 60]. Albumin is the carrier for furosemide and hypoalbuminemia might result in decreased effect of the drug. None of the trials presented data on albumin levels. Further details about the trials can be found in Table 1 and Additional file 1: S4.

Four trials primarily presented data as medians with interquartile range (IQR) because of skewed data [37, 53, 54, 60]. This format of data is not suitable for meta-analysis. The trials were small so it was not appropriate to apply the Wan method to approximate standard deviations [65]. We, therefore, described the data narratively.

Risk of bias

All outcomes in all trials were assessed to be at overall high risk of bias (Additional file 1: S5, S6a, S7a, S8a). With less than ten included trials in the meta-analyses, funnels plot and statistical analyses for asymmetry were not conducted. The trials were generally small. We could not assess publication bias.

Results for loop diuretics vs. placebo/no intervention

Six trials compared a loop diuretic (five trials with furosemide and one trial with torsemide) vs. placebo [52], no diuretics [54, 56, 57], or standard of care [37, 55].

All-cause mortality

Four trials reported on all-cause mortality with a follow-up of 28–90 days. The meta-analysis showed no difference between the group treated with loop diuretics vs. placebo/no intervention group (relative risk (RR) 0.72, 95% CI 0.49–1.06; $I^2 = 0\%$; 359 participants, 4 trials; TSA-adjusted CI 0.15–3.48) (Fig. 2). TSA showed that only 11.5% of diversity-adjusted required information size (DARIS) (3132 participants) was accrued and no monitoring boundaries for benefit, harm, or futility were crossed (Fig. 2). Bayes factor for a 20% relative risk reduction was 0.29. Tests for subgroup interaction showed no statistically significant differences (Additional file 1: S6c). The sensitivity

Table 1 Characteristics of included trials

Trial/year	Country	Sample size	Setting	Population	Experimental intervention	Comparator	Vasopressor treatment*	Duration of intervention	Primary outcome
Loop diuretics vs. placebo/no intervention									
Bagshaw 2017 [52]	Canada Australia	73	Mixed ICU	AKI	Furosemide bolus of 0.4 mg/kg followed by continuous infusion with starting dose of 0.05 mg/kg/hour. Goal directed titration. Max. 0.4 mg/kg/hour	In fusion of placebo (saline)	Yes (62.6%)	Max. 7 days	Worsening of AKI
Berthelsen 2018 [37]	Denmark	23	Mixed ICU	Moderate to severe AKI and > 10% of fluid overload	40 mg of furosemide iv followed by infusion of max. 40 mg/hour. If furosemide was not efficient enough according to protocol dialysis was initiated	Standard of care	Yes (100%)	5 days	Cumulative fluid balance 5 days after randomisation
Cardoso 2013 [55]	Brazil	72	Cardiac ICU	Decompensated heart failure	120 mg of furosemide followed by titration according to effect	Standard of care	Not reported[a]	10 days	Time to being free from congestion
Cinotti 2021 [54]	France	171	Mixed ICU	Mixed ICU patients	Furosemide 1–2 times a day. Max. 250 mg	No diuretics	Exclusion criterion	Until extubation or max. 28 days	Fluid balance. It was defined as weight variation from weight on randomisation to weight on successful extubation
Hamishehkar 2017 [56]	Iran	100	Surgical ICU	AKI	40–80 mg furosemide injection followed by infusion of 1–5 mg/hour	No diuretics	Yes (22%)	7 days	AKI
Sanchez 2003 [57]	Spain	40	Not described	AKI	Torsemide (dose not described)	Control not described	Yes[b]	Max. 7 days	Creatinine and need for RRT

Table 1 (continued)

Trial/year	Country	Sample size	Setting	Population	Experimental intervention	Comparator	Vasopressor treatment*	Duration of intervention	Primary outcome
Loop diuretics vs. other loop diuretics									
Han 2019 [59]	China	248	Cardiac ICU	Not described	Furosemide: 0.8 mg kg/hour	Ethacrynic acid: 0.5 mg/kg/hour	Not reported	Max. 3 days	Urine output
Wappler 1991 [58]	Germany	12	Surgical ICU	Post cardiac surgery with decompensated heart failure	Furosemide bolus of 40 mg followed by infusion of 20 mg/hour. Extra bolus of 40 mg of furosemide was allowed if the diuresis was too low	Piretanide bolus of 12 mg followed by infusion of 6 mg/hour. Extra bolus of 12 mg was allowed if the diuresis was too low	Yes (100%)	40 h	Fluid balance and electrolytes
Loop diuretics vs. other diuretics									
Ng 2020 [60]	USA	33	Cardiac ICU	Decompensated heart failure	Infusion of furosemide 5 mg/hour. Escalation possible after 24 h to a maximum of 20 mg/hour. Metolazone was allowed if the diuresis was less than protocolised on max. furosemide	Tablet tolvaptan 30 mg once a day. Escalation possible after 24 h to maximum 60 mg/day. Metolazone was allowed if the diuresis was less than protocolised on max. tolvaptan	Exclusion criterion	Max. 4 days	Urine output 24 h post randomisation
Brown 2019 [53]	Australia	25	Mixed ICU	Mixed ICU patients	40 mg furosemide injection	500 mg acetazolamide injection	Not reported	6 h	Urine output

ICU intensive care unit; *AKI* acute kidney injury, *RRT* renal replacement therapy

*Vasopressor treatment at baseline

[a] No vasopressor but 69.3% received dobutamine

[b] Unclear how many patients received vasopressor

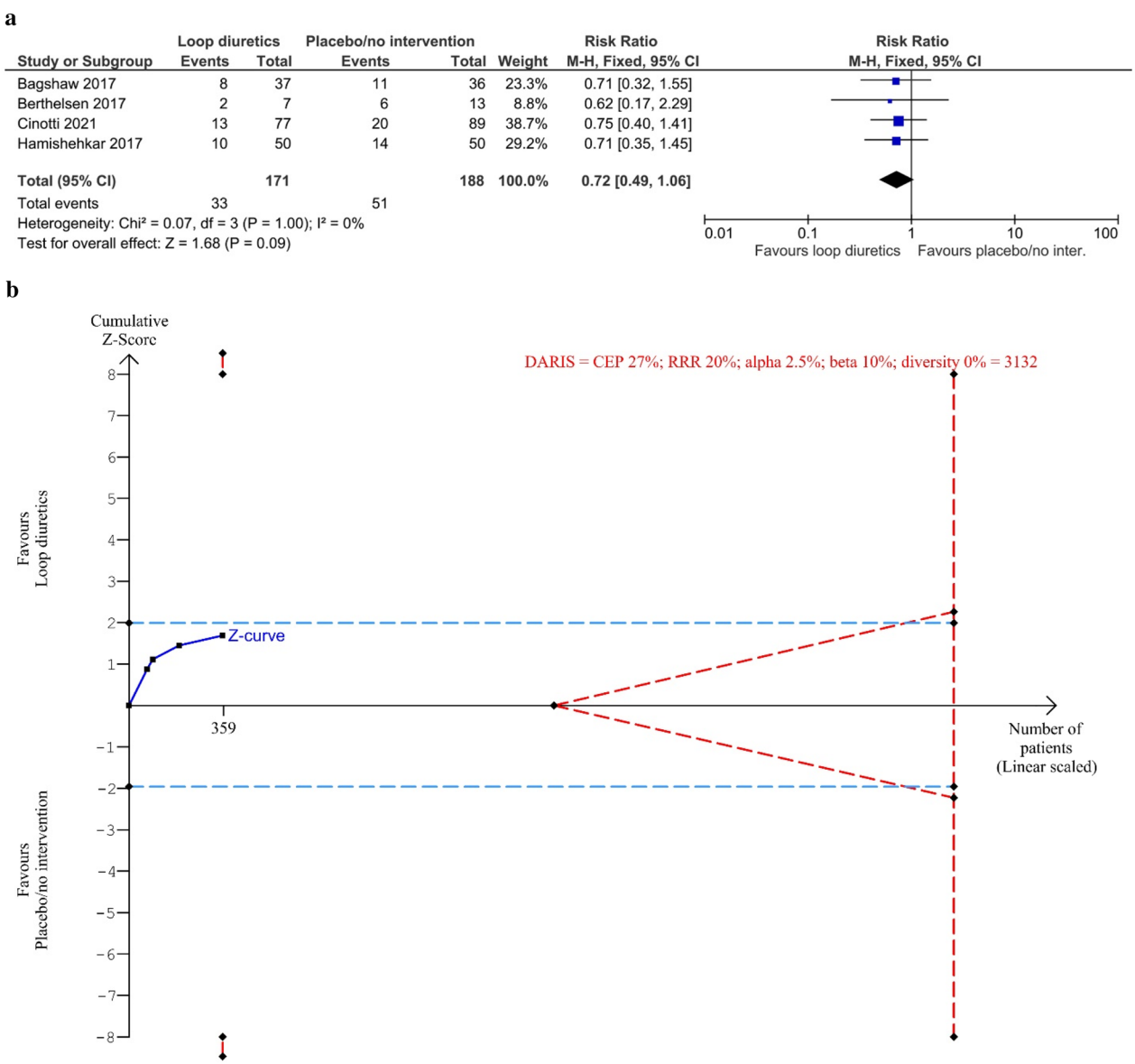

Fig. 2 Meta-analysis and TSA for all-cause mortality for loop diuretics vs. placebo/no intervention. **a** Meta-analysis. **b** TSA. The diversity adjusted required information size (DARIS) was calculated according to a mortality proportion in the control group (CEP) of 27%; risk ratio reduction (RRR) of 20% in the experimental intervention group; alpha of 1.7%; a beta of 10% (90% power); and diversity 0%. The DARIS was 3132 participants. The cumulative Z-curve (blue line) did not cross the trial sequential boundaries for benefit or harm or the inner-wedge futility line (red outward sloping red lines) nor the DARIS. The light blue dotted lines show naïve conventional boundaries (alpha 5%)

analyses assessing incomplete outcome data did not seem to have the potential to influence the result (Additional file 1: S6d). The certainty of evidence was very low (Table 2).

Health-related quality of life

None of the trials reported on health-related quality of life.

Serious adverse events

None of the trials reported on the proportion of participants with one or more SAEs. Six trials reported on events we categorised as SAEs [37, 52, 54–57]. We chose to analyse the single SAE with the highest event rate in each trial instead. The meta-analysis showed fewer SAEs in the group treated with loop diuretics vs. placebo/no intervention, but the TSA-adjusted result was not significant (RR 0.81, 95% CI 0.66–0.99; $I^2 = 0\%$; 476

Table 2 Summary of Findings with GRADE evaluation for loop diuretics vs. placebo/no intervention

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	**Study design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecission**	**Other considerations**	**Loop diuretics**	**Placebo/no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
All-cause mortality												
4	RCT	Serious[a]	Not serious	Serious[b]	Very serious[c]	None	33/171 (19.3%)	51/188 (27.1%)	RR 0.72 (0.49–1.06)	76 fewer per 1.000 (from 138 fewer to 16 more)	⊕◯◯◯ VERY LOW	CRITICAL
Quality of life—not reported												
–	–	–	–	–	–	–	–	–	–	–	–	CRITICAL
Serious adverse events (SAE)												
6	RCT	Serious[a]	Not serious	Serious[b]	Serious[d]	None	87/230 (37.8%)	116/246 (47.2%)	RR 0.81 (0.66–0.99)	90 fewer per 1.000 (from 160 to 5 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Plasma concentration of creatinine												
3[e]	RCT	Serious[a]	Not serious	Not serious	Serious[f]	None	0/0	0/0	The trials showed no significant difference in plasma creatinine at longest follow-up		⊕⊕◯◯ LOW	CRITICAL
Proportion of participants without resolution of fluid overload												
2	RCT	Serious[a]	Not serious	Very serious[g]	Very serious[h]	None	4/41 (9.8%)	24/51 (47.1%)	RR 0.22 (0.08–0.58)	367 fewer per 1.000 (from 433 to 198 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

Table 2 (continued)

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of Bias	Inconsistency	Indirectness	Imprecission	Other considerations	Loop diuretics	Placebo/no intervention	Relative (95% CI)	Absolute (95% CI)		
Days on mechanical ventilation												
2[i]	RCT	Serious[a]	Not serious	Serious[b]	Serious[j]	None	0/0	0/0	The trials showed no significant difference in days in mechanical ventilation		⊕◯◯◯ VERY LOW	IMPORTANT
Length of stay in ICU												
2[i]	RCT	Serious[a]	Not serious	Serious[k]	Serious[j]	None	0/0	0/0	The trials showed no significant difference in length of stay in the ICU		⊕◯◯◯ VERY LOW	IMPORTANT
Adverse event not considered serious (AE)												
2	RCT	Serious[a]	Not serious	Serious[l]	Serious[m]	None	71/120 (59.7%)	61/125 (48.8%)	RR 1.23 (0.98–1.55)	112 more per 1.000 (from 10 fewer to 268 more)	⊕◯◯◯ VERY LOW	NOT IMPORTANT

RCT randomised clinical trials, *CI* Confidence interval, *RR* Risk ratio

[a] All trials were at overall high risk of bias for this outcome

[b] Variations in experimental intervention and control groups

[c] TSA showed lack of data, because only 11.5% of optimal information size had been reached

[d] TSA showed lack of data, because only 34.7% of optimal information size had been reached

[e] Three trials reported on plasma creatinine. A meta-analysis could not be performed because of unsuitable data (medians and interquartile range or only graphical presentation of data)

[f] The total number of participants were only 193 in the included trials, which is concerning for imprecision

[g] Differences in ICU subpopulation (AKI vs. decompensated heart failure). Resolution of fluid overload is a surrogate outcome

[h] TSA showed lack of data. Only 6.2% of optimal information size had been reached

[i] Data was not suitable for meta-analysis. Both trials found no difference between groups

[j] The total number of participants were only 186 in the included trials, which is concerning for imprecision

[k] The two trials were dissimilar regarding ICU population, control group and length of stay in the ICU

[l] Differences in ICU subpopulation (AKI patients vs. mixed population)

[m] The total number of participants were only 244 in the included trials, which is concerning for imprecision

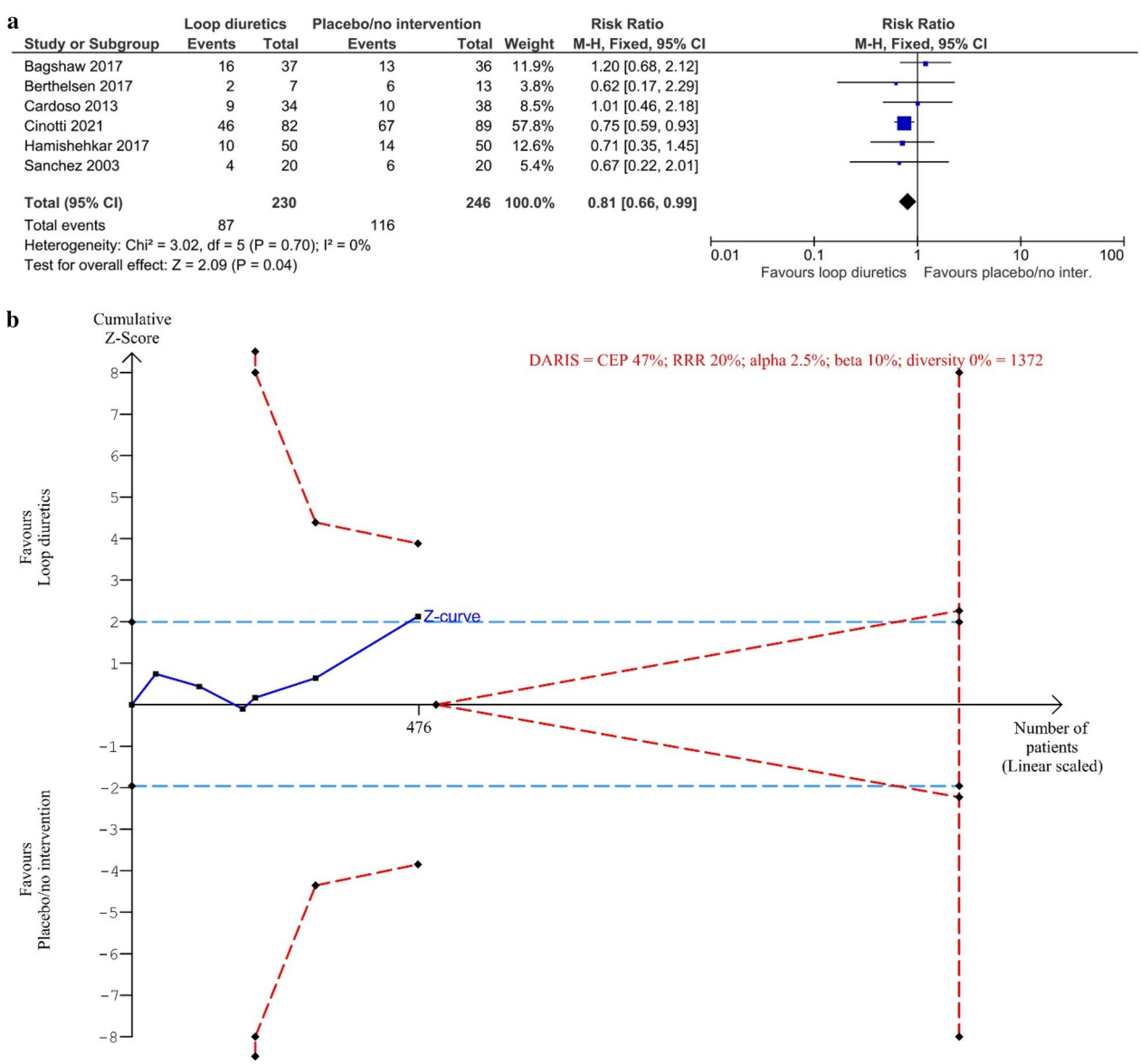

Fig. 3 Meta-analysis and TSA on highest event rate of SAEs for loop diuretics vs. placebo/no intervention. **a** Meta-analysis. **b** TSA. The diversity adjusted required information size (DARIS) was calculated according to the proportion of SAEs in the control group (CEP) of 47%; risk ratio reduction (RRR) of 20% in the experimental intervention group; alpha of 1.7%; a beta of 10% (90% power); and diversity 0%. The DARIS was 1372 participants. The cumulative Z-curve (blue line) did not cross the trial sequential boundaries for benefit or harm or the inner-wedge futility line (red outward sloping red lines) nor the DARIS. The light blue dotted lines show naïve conventional boundaries (alpha 5%)

participants; 6 trials; TSA-adjusted CI 0.55–1.20) (Fig. 3). TSA showed that only 34.7% of DARIS (1372 participants) was accrued and no monitoring boundaries for benefit, harm, or futility were crossed (Fig. 3). Bayes factor for a 20% relative risk reduction was = 0.15. Tests for subgroup interaction showed no statistically significant differences (Additional file 1: S6c). The sensitivity analyses assessing incomplete outcome data did not seem to have the potential to influence the result (Additional file 1: S6d). The certainty of evidence was very low (Table 2).

All individual single SAEs and analyses are described in the Supplementary. Meta-analyses were conducted on the following single SAEs: renal replacement therapy (RRT), worsening of AKI, and atrial fibrillation. Meta-analysis showed no difference between the groups treated with loop diuretics vs. placebo/no intervention on RRT (RR 1.12, 95% CI 0.67–1.88; $I^2 = 0\%$; 299 participants,

4 trials); worsening of AKI (RR 0.86, 95% CI 0.63–1.18; $I^2=29\%$; 316 participants, 3 trials); and atrial fibrillation (RR 0.71, 95% CI 0.39–1.31; $I^2=0\%$; 264 participants, 3 trials).

Adverse events not considered serious

None of the trials reported on the proportion of participants with one or more adverse events not considered serious. Two trials reported on individual AEs [52, 54]. The single AE with the highest event proportion in each trial was analysed instead. Meta-analysis showed no difference in occurrence of AEs in the group treated with loop diuretics vs. placebo/no intervention (RR 1.23, 95% CI 0.98–1.55; $I^2=43\%$; 245 participants; 2 trials; TSA-adjusted CI 0.28–5.56). TSA showed that only 6.7% of DARIS (3645 participants) was accrued and no monitoring boundaries for benefit, harm or futility were crossed (Additional file 1: S6b). Sensitivity analyses assessing incomplete outcome data did not seem to have the potential to influence the result (Additional file 1: S6d). Certainty of evidence was very low (Table 2).

All single AEs were only reported once, thus meta-analyses could not be conducted (Additional file 1: S6e).

Plasma concentration of creatinine

Three trials reported on creatinine using medians and IQR [37, 52, 56]. The individual trials showed no difference between the group treated with loop diuretics vs. placebo/no intervention. The data were not in a format suitable for meta-analysis. Certainty of evidence was low (Table 2).

Participants without resolution of fluid overload

Two trials [37, 55] reported on resolution of fluid overload. The meta-analysis showed that the proportion of participants without resolution of fluid overload was smaller in the group treated with loop diuretic vs. placebo/no intervention, but this was not confirmed with TSA (RR 0.22, 95% CI 0.08–0.58; $I^2=0\%$; 92 participants; 2 trials; TSA-adjusted CI 0.00–11.80). TSA showed that only 6.2% of DARIS (1487 participants) was accrued and no monitoring boundaries for benefit, harm, or futility were crossed (Additional file 1: S6b). Certainty of evidence was very low (Table 2).

Number of days on mechanical ventilation and length of stay in the ICU

Two trials [37, 54] reported on these two outcomes using medians and IQR and were not suitable for meta-analysis. Both trials found no difference between groups. Certainty of evidence was very low (Table 2).

Plasma concentration of serum sodium, potassium, and chloride concentrations

Two trials [37, 52] reported on sodium and potassium concentrations. The data was not suitable for meta-analysis. One trial [52] found no difference on potassium between the group treated with loop diuretics vs. placebo/no intervention but found that sodium was higher in the group treated with loop diuretics. No data on chloride was available. The other trial [37] found no difference in potassium, sodium, and chloride concentrations between the group treated with loop diuretics vs. placebo/no intervention.

Results for loop diuretics (furosemide) vs. another loop diuretic (piretanide or ethacrynic acid)

Two trials compared loop diuretic vs. another loop diuretic (260 participants) [58, 59]. Both trials included patients from cardiac ICUs. One trial with 12 participants tested furosemide vs. piretanide [58]. The other trial investigated furosemide vs. ethacrynic acid in 248 participants [59]. Two meta-analyses were possible for this comparison: plasma concentration of sodium (MD − 1.86 mmol/L; 95% CI − 6.27–2.54; $I^2=71\%$; 260 participants; 2 trials) and potassium (MD − 0.04 mmol/L; 95% CI − 0.16–0.08; $I^2=0\%$; 260 participants; 2 trials), showing no differences. The analyses and a detailed narrative description of the outcomes in the two trials is presented in the Additional file 1: S7b, S7c. S7d and S7e.

Results for loop diuretic (furosemide) vs. another type of diuretic (acetazolamide or tolvaptan)

Two trials compared loop diuretics vs. another type of diuretic (58 participants) [53, 60]. One trial included mixed ICU patients and investigated the effects of furosemide vs. acetazolamide over a study time of just 6 h [53]. The other trial included patients with decompensated hearth failure in a medical ICU investigating furosemide vs. tolvaptan for up to 96 h [60]. No meta-analyses could be performed on any outcomes. Detailed narrative description of the outcomes in the two trials is in the Additional file 1: S8b, S8c, and S8d.

Discussion

In this systematic review ten trials were included involving six types of diuretics. Six trials compared a loop diuretic (furosemide or torsemide) with placebo/no intervention. Our main results are based on this comparison in adult ICU patients with fluid overload.

Furosemide was tested against another loop diuretic (piretanide or ethacrynic acid) in two trials and against two different types of diuretics (acetazolamide

or tolvaptan) in two other trials. Primary and secondary outcomes of these trials could not be meta-analysed.

We found no difference in mortality when comparing loop diuretics vs. placebo/no intervention in ICU patients with fluid overload, but there seemed to be fewer SAEs in those treated with loop diuretics in the meta-analysis; however, the TSA-adjusted-CI crossed 1.0 (no effect) and the DARIS was far from reached. The proportion of participants without resolution of fluid overload was lower in the group treated with loop diuretic; again, the TSA did not confirm this. Effects on plasma concentrations of electrolytes and AEs were inconclusive. Health-related quality of life, length of stay in ICU, time on mechanical ventilation, and plasma concentrations of creatinine could not be analysed due to lack of data. All outcomes were adjudicated to be at low or very low certainty of evidence or no evidence at all.

Strengths and limitations

The strength of this systematic review of RCTs is the methodological quality, which included adhering to our pre-published protocol [26] and using the recommendations of the Cochrane Handbook on interventions [27]. We assessed risk of bias using the ROB2-tool [33] and followed the eight steps procedure by Jakobsen and co-workers [28]. We assessed the certainty of evidence with GRADE [29, 50] and reported the review as recommended by PRISMA [30].

Limitations

We only identified few and small trials, and all outcomes were at high risk of bias. Clinical heterogeneity between the trials was high; fluid overload was not defined in all trials and resolution of fluid overload was sparsely reported.

Fluid overload was defined as a percentage calculated from fluid balance and body weight on admission to the ICU or according to ideal body weight or by clinical signs of water retention (oedema, pulmonary crepitations, elevated jugular venous pressure, hepatomegaly). We also included RCTs with loop diuretics in ICU patients with AKI and acute heart failure even if fluid overload was not defined. These conditions are associated with fluid overload and we considered these groups of patients to have fluid overload when entering a trial of protocolised diuretic therapy [26]. We did that to assess all relevant RCTs in the field, but it is also a limitation due to an uncertainty of the degree of fluid overload.

Furthermore, the outcomes in the included trials were heterogenic making comparisons difficult. The experimental and the control regiments were insufficiently reported in several trials. The use of diuretics as escape or protocol violations in trials with placebo or no diuretics as control group hampers the interpretation further. Moreover, we only looked at a single loop diuretic as experimental intervention. Combinations of different loop diuretics need to be assessed in other systematic reviews.

Current results in relation to previous reviews

Fluid overload in ICU patients is common and a risk factor for death [66]. This review assessed the existing evidence of treating fluid overload with loop diuretics in ICU patients. No systematic reviews on treatment of fluid overload with loop diuretics vs. a control group in the ICU setting has been performed before. Two former systematic reviews focusing on liberal fluid therapy vs. conservative fluid therapy/de-resuscitation in ICU found diverging results. A review from 2014 [67], which pooled observational data together with data from RCTs, found that non survivors had a more positive fluid balance compared to survivors. Restrictive fluid management was associated with a lower mortality compared to liberal fluid management. Only some of the included trials involved diuretics. Another review from 2017 [68] focussed on conservative or de-resuscitative fluid strategies in adults and children with acute respiratory distress syndrome or sepsis in the post-resuscitation phase of critical illness. This meta-analysis of RCTs found no difference in mortality but a conservative or de-resuscitative strategy resulted in more ventilator-free days and shorter length of ICU stay compared with liberal fluid strategy or standard of care. Only few of the included trials involved diuretics. A systematic review from 2018 with pooled data from both observational studies and RCTs, assessed continuous infusion vs. intermittent bolus injection of furosemide in ICU patients [69]. This review found a larger diuretic effect for patients treated with continuous infusion compared to bolus injection. No differences in mortality or renal function were found.

Clinical implications and perspectives

Besides the fundamental lack of data, we identified numerous factors in the existing literature that hampers the interpretation of our results, for example the lack of a standardised definition of fluid overload and how to assess it. The trials investigating the effect of diuretics seldomly described or defined fluid overload and quantified it. The effect of diuretic therapy is likely influenced by the severity of fluid overload and the differing description makes it difficult to generalise and compare results. The trials often report urine output, fluid balance, or weight changes in a predefined timeframe but information about resolution of fluid overload was rarely reported. When assessing data on mortality it is important to know if fluid overload is removed or mitigated by the intervention/

treatment. This would make the assessment of mortality and other patient important outcomes more reliable.

The use of diuretics in the ICU patients appears safe due to fewer SAEs in the group treated with loop diuretics and no difference in single SAEs between groups. Timing of prescribing diuretics might have an impact on development of SAEs, which is not covered in this review.

Early prescription of diuretics, while the patient receives vasoactive therapy may reduce sodium chloride (NaCl) and water accumulation or minimise further accumulation which might reduce the adverse effects of fluid overload. It can be argued that later prescription of diuretics in the recovery phase is safer. The patient will be without vasoactive drugs and the risk of hypoperfusion is less. The evidence on this subject is sparce and conflicting [70–72]. The timing of prescribing diuretics in the ICU population with fluid overload would be relevant to investigate in a future RCT.

Patients with sepsis and septic shock have an increased risk of developing fluid overload following fluid resuscitation and about 40% receive diuretics during their ICU stay [73, 74]. This makes the debate of restrictive vs. liberal fluid therapy important. Focus on avoiding fluid administration when the perfusion is adequate, even if vasopressors are needed, and if the perfusion is inadequate, it is important to assess if fluid responsiveness is likely before fluid administration [75]. This could be an approach to minimise the risk of severe fluid overload.

It is important to keep in mind that the sodium administration to ICU patients often are much higher than normal dietary intake due to fluid therapy, nutrition, and isotonic sodium containing fluids used as drug dissolvents [1]. This is an important cofactor in development of fluid overload. Reducing sodium intake using hypotonic or low sodium solutions as maintenance fluid, dissolve medicine in dextrose 5% or glucose 5%, and convert to oral medication when possible, the sodium load can be minimised and the associated water retention [1]. Moreover, reduced sodium intake might reduce the risk of hypernatremia. Loop diuretics induces lager free water excretion compared to sodium excretion and can contribute to development of hypernatremia which is associated with increased mortality [76, 77].

Diuretic resistance can be a challenge in the ICU. Infusion of loop diuretic instead of bolus injections and combination therapy with loop diuretic and thiazides or carbon anhydrase inhibitors might increase the diuretic output but there is a risk of increased adverse effects [78].

It is still unclear if active de-resuscitation with loop diuretics in adult ICU patients with fluid overload will improve patient-important outcomes. A general accepted definition of fluid overload and resolution of fluid overload is missing. No gold standard method of measuring fluid status and no general accepted definition of fluid overload exist. We suggest defining fluid overload as > 5% increase in body water assessed according to fluid balances, changes in body weight, and clinical examination. Resolution of fluid overload should be assessed the same way. The surrogate outcomes are too imprecise when used alone. The weight on admission to the ICU might not represent the patient's habitual weight and during critical illness muscle mass is lost which makes body weight an imprecise measure. Fluid balances from the ICU will be imprecise, because the time in the hospital before referral to the ICU is not accounted for. Severely ill patients might have an affected fluid balance already on admission to the hospital, which are not reflected in the fluid charts. Clinical examination (oedema, lung ultrasound, radiologic findings, and other measures) is imprecise to assess the degree of fluid but it is needed to support, correct or to confirm the findings from development in body weight and fluid balance. A discussion of all the surrogate measurements for assessing fluid status is important but outside the scope of this review.

In the presence of insufficient evidence for the use of diuretics, it should be restricted to patients who may benefit the most based on physiological and observational data. Patients with sodium and water accumulation with associated respiratory insufficiency without other clear causes might benefit the most from diuretics. Retrospective data suggest that loop diuretics in patients with acute respiratory distress syndrome reduce mortality [79].

Large RCTs at low risk of bias are needed before definitive conclusions can be made on treatment of fluid overload with diuretics in adult ICU patients.

Conclusions

The evidence is very uncertain about the effect of loop diuretics on mortality and serious adverse events in adult ICU patients with fluid overload. Loop diuretics may reduce the occurrence of these outcomes, but large randomised placebo-controlled trials at low risk of bias are needed.

Abbreviations

ICU: Intensive care unit; TSA: Trial Sequential Analysis; PRISMA: Preferred reporting items for systematic reviews and meta-analysis; GRADE: Grading of recommendations, assessments, developments and evaluations; AKI: Acute kidney injury; RCT: Randomised clinical trials; SAE: Serious adverse event; ICH-GCP: Good Clinical Practice Guideline of the International Conference on Harmonization; AE: Adverse event; CNKI: China National Knowledge Infrastructure; FDA: Food and drug administration; EMA: European medicines agency; RR: Risk ratios; CI: Confidence interval; MD: Mean difference; ALI: Acute lung injury; ARDS: Acute respiratory distress syndrome; IQR: Interquartile range; DARIS: Diversity-adjusted required information size; RRT: Renal replacement therapy.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13613-022-01024-6.

Additional file 1. S1. PRISMA checklist. **S2.** Search strategy. **S3.** Post hoc subgroup analysis for the comparison of loop diuretics vs. placebo/no intervention. **S4.** Detailed characteristics of included trials. **S5.** Overall risk of bias for all included trials. **S6.** Comparison: loop diuretics vs. placebo/no intervention. **S6a.** Risk of bias of all outcomes. **S6b.** Meta-analyses and TSA. **S6c.** Subgroup analyses. **S6d.** Sensitivity analyses. **S6e.** Reported SAEs and AEs. **S7.** Comparison: loop diuretics vs. another loop diuretic. **S7a.** Risk of bias. **S7b.** Meta-analyses. **S7c.** Narrative description of the results. **S7d.** Reported SAEs and AEs. **S7e.** Summary of findings. **S8.** Comparison: loop diuretics vs. another type of diuretic. **S8a.** Risk of bias. **S8b.** Narrative description of the results. **S8c.** Reported SAEs and AEs. **S8d.** Summary of findings.

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Author contributions
SW, MB, and NL screened titles, abstracts, and full texts. SW and MB extracted all data, assessed risk of bias, and performed the statistical analyses. All authors contributed to interpretation of the results and revisions of the manuscript. The final manuscript was approved by all authors. SW is guarantor. All authors read and approved the final manuscript.

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Availability of data and materials
All data analysed in this study are included in the published article and in the Additional file material.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
SW, TSI, REB and MBH: The Dept. of Intensive Care, Copenhagen University Hospital, North Zealand receives support for research from the Novo Nordisk Foundation, Jacob Madsen's and wife Olga Madsen's Foundation, Svend Andersen's Foundation, Merchant Jakob Ehrenreich and wife Grete Ehrenreich's Foundation, and Health Insurance Denmark (Sygeforsikringen Danmark). MB, NL, JL and CG: None known. AP: The Dept. of Intensive Care, Rigshospitalet receives support for research from the Novo Nordisk Foundation, Health Insurance Denmark (Sygeforsikringen Danmark), Fresenius Kabi, Denmark, and Pfizer, Denmark.

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Publisher's Note

SUPPLEMENTARY MATERIAL

This supplementary material has been provided by the authors to give readers additional information about their work.

Supplement to:

Wichmann S, Barbateskovic M, Liang N, Itenov TS, Berthelsen RE, Lindschou J, Perner A, Gluud C, Bestle MH. Loop diuretics in adult intensive care patients with fluid overload: a systematic review of randomised clinical trials with meta-analysis and Trial Sequential Analysis.

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Electronic Supplement Material for

Loop diuretics in adult intensive care patients with fluid overload: a systematic review of randomised clinical trials with meta-analysis and Trial Sequential Analysis

Content

S1. PRISMA checklist

Table S1. Prisma checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6-7 + supplementary
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6-7 + supplementary
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6-7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6- 7

Section and Topic	Item #	Checklist item	Location where item is reported
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8-10
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8-10
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8-10
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	9
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	11
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	11 + Fig 1 + supplementary
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Fig. 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1 + supplementary
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	12 + supplementary
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	12-16 + supplementary
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Table 2 + supplementary
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	12-16 + Fig 2 + Fig 3 + supplementary
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	12-13 + supplementary
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	12-14 + supplementary
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	12 + supplementary

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	12-15 + Table 2 + supplementary
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	18-22
	23b	Discuss any limitations of the evidence included in the review.	17-18
	23c	Discuss any limitations of the review processes used.	17-18
	23d	Discuss implications of the results for practice, policy, and future research.	18-22
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	3 + 5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	10 + supplementary
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	23-24
Competing interests	26	Declare any competing interests of review authors.	24
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	supplementary*

* All analyses are presented in supplementary. A data collection form is available upon request from corresponding author.

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S2. Search strategy

Cochrane Central Register of Controlled Trials (CENTRAL)
Searched May 25th, 2020 Records identified: 2215
Updated search April 13th, 2021 Records identified: 2372

#1 MeSH descriptor: [Furosemide] explode all trees
#2 MeSH descriptor: [Torsemide] explode all trees
#3 MeSH descriptor: [Bumetanide] explode all trees
#4 MeSH descriptor: [Ethacrynic Acid] explode all trees
#5 MeSH descriptor: [Diuretics] explode all trees
#6 MeSH descriptor: [Fluid Therapy] explode all trees and with qualifier(s): [adverse effects - AE]
#7 MeSH descriptor: [Water-Electrolyte Balance] explode all trees
#8 MeSH descriptor: [Edema] explode all trees
#9 ((furosemide or torsemide or bumetanide or ethacrynic acid or azosemide or diuretic*)):ti,ab,kw
#10 (((fluid overload or hyperhydration or overhydration or positive fluid balance or hydration* or edema or water electrolyte imbalance) and (furosemide or torsemide or bumetanide or ethacrynic acid or azosemide or diuretic*))):ti,ab,kw
#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12 MeSH descriptor: [Critical Illness] explode all trees
#13 MeSH descriptor: [Critical Care] explode all trees
#14 MeSH descriptor: [Intensive Care Units] explode all trees
#15 ((critically ill or acutely ill or intensive care or critical care or ICU*)):ti,ab,kw
#16 MeSH descriptor: [Shock] explode all trees
#17 (shock):ti,ab,kw
#18 MeSH descriptor: [Acute Lung Injury] explode all trees
#19 ((acute lung injury or respiratory failure)):ti,ab,kw
#20 MeSH descriptor: [Respiratory Distress Syndrome, Adult] explode all trees
#21 MeSH descriptor: [Respiratory Insufficiency] explode all trees
#22 ((respiratory distress syndrome or ARDS or respiratory failure)):ti,ab,kw
#23 MeSH descriptor: [Multiple Trauma] explode all trees
#24 ((severe trauma or multiple trauma)):ti,ab,kw
#25 ((trauma and (ICU* or intensive care))):ti,ab,kw
#26 MeSH descriptor: [Sepsis] explode all trees
#27 MeSH descriptor: [Shock, Septic] explode all trees
#28 ((sepsis or septic shock)):ti,ab,kw
#29 MeSH descriptor: [Liver Failure, Acute] explode all trees
#30 ((acute hepatic failure or fulminating hepatic failure or renal failure or acute tubular necrosis)):ti,ab,kw
#31 MeSH descriptor: [Acute Kidney Injury] explode all trees
#32 ((acute kidney failure or acute renal injuries)):ti,ab,kw
#33 MeSH descriptor: [Pulmonary Edema] explode all trees

#34 (pulmonary edema):ti,ab,kw
#35 #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 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34
#36 #11 and #35

MEDLINE (OvidSP)
Searched May 25th, 2020 Records identified: 1076
Updated search April 13th, 2021 Records identified: 1126

1. exp Furosemide/
2. exp Torsemide/
3. exp Bumetanide/
4. exp Ethacrynic Acid/
5. exp Diuretics/
6. exp Fluid Therapy/ae [Adverse Effects]
7. exp Water-Electrolyte Balance/
8. exp Edema/
9. (furosemide or torsemide or bumetanide or ethacrynic acid or azosemide or diuretic*).tw.
10. ((fluid overload or hyperhydration or overhydration or positive fluid balance or hydration* or edema or water electrolyte imbalance) and (furosemide or torsemide or bumetanide or ethacrynic acid or azosemide or diuretic*)).tw.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp Critical Illness/
13. exp Critical Care/
14. exp Intensive Care Units/
15. (critically ill or acutely ill or intensive care or critical care or ICU*).tw.
16. exp Shock/
17. shock.tw.
18. exp Acute Lung Injury/
19. (acute lung injury or respiratory failure).tw.
20. exp Respiratory Distress Syndrome, Adult/
21. exp Respiratory Insufficiency/
22. (respiratory distress syndrome or ARDS or respiratory failure).tw.
23. exp Multiple Trauma/
24. (severe trauma or multiple trauma).tw.
25. (trauma and (ICU* or intensive care)).tw.
26. exp Sepsis/
27. exp Shock, Septic/
28. (sepsis or septic shock).tw.
29. exp Liver Failure, Acute/
30. (acute hepatic failure or fulminating hepatic failure or renal failure or acute tubular necrosis).tw.
31. exp Acute Kidney Injury/
32. (acute kidney failure or acute renal injuries).tw.
33. exp Pulmonary Edema/
34. pulmonary edema.tw.
35. 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 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. 11 and 35

37. randomized controlled trial.pt.
38. controlled clinical trial.pt.
39. randomized.ab.
40. placebo.ab.
41. clinical trial.sh.
42. randomly.ab.
43. trial.ti.
44. 37 or 38 or 39 or 40 or 41 or 42 or 43
45. exp animals/ not humans.sh.
46. 44 not 45
47. 36 and 46

PubMed

Searched May 25th, 2020 Records identified: 426
Updated search April 13th, 2021 Records identified: 452

((((((((((Furosemide[MeSH Terms]) OR (Torsemide[MeSH Terms])) OR (Bumetanide[MeSH Terms])) OR (Ethacrynic Acid[MeSH Terms])) OR (Diuretics[MeSH Terms])) OR (Water-Electrolyte Balance[MeSH Terms])) OR (Edema[MeSH Terms])) OR ((furosemide[Text Word] OR torsemide[Text Word] OR bumetanide[Text Word] OR ethacrynic acid[Text Word] OR azosemide[Text Word] OR diuretic*)[Text Word])) OR (((fluid overload[Text Word] OR hyperhydration[Text Word] OR overhydration[Text Word] OR positive fluid balance[Text Word] OR hydration*[Text Word] OR edema[Text Word] OR water electrolyte imbalance)[Text Word] AND (furosemide[Text Word] OR torsemide[Text Word] OR bumetanide[Text Word] OR ethacrynic acid[Text Word] OR azosemide[Text Word] OR diuretic*))[Text Word])) AND ((((((((((((((((((((Critical Illness[MeSH Terms]) OR (Critical Care[MeSH Terms])) OR (Intensive Care Units[MeSH Terms])) OR (Shock[MeSH Terms])) OR (Acute Lung Injury[MeSH Terms])) OR (Respiratory Distress Syndrome, Adult[MeSH Terms])) OR (Respiratory Insufficiency[MeSH Terms])) OR (Multiple Trauma[MeSH Terms])) OR (Sepsis[MeSH Terms])) OR (Shock, Septic[MeSH Terms])) OR (Liver Failure, Acute[MeSH Terms])) OR (Acute Kidney Injury[MeSH Terms])) OR (Pulmonary Edema[MeSH Terms])) OR ((critically ill[Text Word] OR acutely ill[Text Word] OR intensive care[Text Word] OR critical care[Text Word] OR ICU*)[Text Word])) OR (shock[Text Word])) OR ((acute lung injury[Text Word] OR respiratory failure)[Text Word])) OR ((severe trauma[Text Word] OR multiple trauma)[Text Word])) OR ((trauma[Text Word] AND (ICU*[Text Word] OR intensive care))[Text Word])) OR ((sepsis[Text Word] OR septic shock)[Text Word])) OR ((acute hepatic failure[Text Word] OR fulminating hepatic failure[Text Word] OR renal failure[Text Word] OR acute tubular necrosis)[Text Word])) OR ((acute kidney failure[Text Word] OR acute renal injuries)[Text Word])) OR (pulmonary edema[Text Word]))) AND ((((((((((randomized controlled trial[Publication Type]) OR controlled clinical trial[Publication Type]) OR randomized[Title/Abstract]) OR placebo[Title/Abstract]) OR clinical trials[MeSH Terms]) OR randomly[Title/Abstract]) OR trial[Title])) NOT ((animals[MeSH Terms]) NOT humans[MeSH Terms])))))

EMBASE (OvidSP)

Searched May 25th, 2020 Records identified: 1434
Updated search April 13th, 2021 Records identified: 1522

1. *furosemide/
2. *torasemide/
3. *bumetanide/
4. *etacrynic acid/
5. *diuretic agent/
6. *fluid therapy/ae [Adverse Drug Reaction]
7. *electrolyte balance/
8. *edema/
9. (furosemide or torsemide or bumetanide or ethacrynic acid or azosemide or diuretic*).tw.
10. ((fluid overload or hyperhydration or overhydration or positive fluid balance or hydration* or edema or water electrolyte imbalance) and (furosemide or torsemide or bumetanide or ethacrynic acid or azosemide or diuretic*)).tw.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp critical illness/
13. exp intensive care/
14. exp intensive care unit/
15. (critically ill or acutely ill or intensive care or critical care or ICU*).tw.
16. *shock/
17. shock.tw.
18. *acute lung injury/
19. (acute lung injury or respiratory failure).tw.
20. *adult respiratory distress syndrome/
21. *respiratory failure/
22. (respiratory distress syndrome or ARDS or respiratory failure).tw.
23. *multiple trauma/
24. (severe trauma or multiple trauma).tw.
25. (trauma and (ICU* or intensive care)).tw.
26. *sepsis/
27. *septic shock/
28. (sepsis or septic shock).tw.
29. *acute liver failure/
30. (acute hepatic failure or fulminating hepatic failure or renal failure or acute tubular necrosis).tw.
31. *acute kidney failure/
32. (acute kidney failure or acute renal injuries).tw.
33. *lung edema/
34. pulmonary edema.tw.
35. 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 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. 11 and 35
37. CROSSOVER PROCEDURE.sh.
38. DOUBLE-BLIND PROCEDURE.sh.
39. SINGLE-BLIND PROCEDURE.sh.
40. (crossover* or cross over*).ti,ab.
41. placebo*.ti,ab.
42. (doubl* adj blind*).ti,ab.

43. allocat*.ti,ab.
44. trial.ti.
45. RANDOMIZED CONTROLLED TRIAL.sh.
46. random*.ti,ab.
47. 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46
48. (exp animal/ or exp invertebrate/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans or man or men or wom?n).ti.)
49. 47 not 48
50. 36 and 49

Science Citation Index - Expanded (web of science) and Conference proceedings

Searched May 25th, 2020 Records identified: 998
Updated search April 13th, 2021 Records identified: 1050

#17 (#16 AND #15)
#16 TS=(random* OR control* OR RCT OR placebo OR group* OR trial*)
#15 (#14 AND #3)
#14 (#13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4)
#13 TS=(pulmonary edema)
#12 TS=(acute kidney failure or acute renal injuries)
#11 TS=(acute hepatic failure or fulminating hepatic failure or renal failure or acute tubular necrosis)
#10 TS=(sepsis or septic shock)
#9 TS=(trauma and (ICU* or intensive care))
#8 TS=(severe trauma or multiple trauma)
#7 TS=(respiratory distress syndrome or ARDS or respiratory failure)
#6 TS=(acute lung injury or respiratory failure)
#5 TS=(shock)
#4 TS=(critically ill or acutely ill or intensive care or critical care or ICU*)
#3 #2 OR #1

#2 TS=((fluid overload or hyperhydration or overhydration or positive fluid balance or hydration* or edema or water electrolyte imbalance) and (furosemide or torsemide or bumetanide or ethacrynic acid or azosemide or diuretic*))
#1 TI=(furosemide or torsemide or bumetanide or ethacrynic acid or azosemide or diuretic*)

BIOSIS Previews (web of science)
Searched May 25th, 2020 Records identified: 752
Updated search April 13th, 2021 Records identified: 790

#17 (#16 AND #15)
#16 TS=(random* OR control* OR RCT OR placebo OR group* OR trial*)
#15 (#14 AND #3)
#14 (#13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4)

#13 TS=(pulmonary edema)
#12 TS=(acute kidney failure or acute renal injuries)
#11 TS=(acute hepatic failure or fulminating hepatic failure or renal failure or acute tubular necrosis)
#10 TS=(sepsis or septic shock)
#9 TS=(trauma and (ICU* or intensive care))
#8 TS=(severe trauma or multiple trauma)
#7 TS=(respiratory distress syndrome or ARDS or respiratory failure)
#6 TS=(acute lung injury or respiratory failure)
#5 TS=(shock)
#4 TS=(critically ill or acutely ill or intensive care or critical care or ICU*)
#3 #2 OR #1
#2 TS=((fluid overload or hyperhydration or overhydration or positive fluid balance or hydration* or edema or water electrolyte imbalance) and (furosemide or torsemide or bumetanide or ethacrynic acid or azosemide or diuretic*))
#1 TI=(furosemide or torsemide or bumetanide or ethacrynic acid or azosemide or diuretic*)

Latin American Caribbean Health Sciences Literature (LILACS)

Searched May 25th, 2020 Records identified: 264
Updated search April 13th, 2021 Records identified: 284

(tw:((fluid overload OR hyperhydration OR overhydration OR positive fluid balance OR hydration OR water electrolyte imbalance OR furosemide OR torsemide OR bumetanide OR ethacrynic acid OR azosemide OR diuretic))) AND (tw:((critically ill OR acutely ill OR intensive care OR critical care OR icu))) AND (tw:((randomized OR randomised OR random OR randomly OR control OR controlled OR rct OR placebo OR group OR trial)))

Similar search strategy is applied to the following 4 Chinese databases:

China National Knowledge Infrastructure (CNKI)

Searched June 3rd, 2020 Records identified: 118
Updated search April 29th, 2021 Records identified: 130

Wanfang database

Searched June 3rd, 2020 Records identified: 203
Updated search April 29th, 2021 Records identified: 243

VIP Chinese Science Journals Database

Searched June 3rd, 2020 Records identified: 226
Updated search April 29th, 2021 Records identified: 244

Sinomed

Searched June 3rd, 2020	Records identified: 195
Updated search April 29th, 2021	Records identified: 226

Search through other resources:

ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (ICTRP), EU Clinical Trial Register, Australian New Zealand Clinical Trials Registry (ANZCTR), US Food and Drug Administration (FDA), European Medicines Agency (EMA), and Google scholar have been search without finding new relevant studies.

S3. Post hoc subgroup analysis for the comparison of loop diuretics vs placebo/no intervention

The comparison loop diuretics vs placebo/no intervention consists of six trials. The control group in this comparison is placebo, no diuretics, or standard of care. Four out of six trials reported use of diuretics in the control group. To assess if use of diuretics in the control group could influence the results, we made post hoc subgroup analyses for the comparison with the following two subgroups:

- Diuretics is reported administered in the control group [37, 52, 54-55]
- Diuretics is not reported administered in the control group [56-57]

Table S2. Administration of loop diuretics in the control group in the comparison loop diuretics vs placebo/no intervention

Loop diuretic vs placebo/no intervention		
Trial	**Intervention group**	**Control group**
Bagshaw [52]	Furosemide	**Placebo** The cumulative dose of furosemide for the intervention group was not reported. Protocol violations with supplementary diuretic therapy was reported as 76 events in 11 out of 36 patients in the placebo group. Det dose of supplemental diuretics were not reported.
Berthelsen [37]	Furosemide	**Standard of care** The cumulative furosemide dose was reported as mg/kg. Median dose in the group with loop diuretics: 9.0 (4.6 - 14.5) and median dose in standard of care: 2.0 (0.0 – 13.0).
Cardoso [55]	Furosemide	**Standard of care** The mean dose of furosemide in the intervention group was 78.3 (29.5) mg/day and 44.8 (23.6) mg/day in control group.
Cinotti [54]	Furosemide	**No diuretics** No diuretics was allowed in the control group but could be administered as rescue therapy in case of acute pulmonary oedema or de novo heart failure. The cumulative dose of furosemide in the intervention group was 160 mg (80-285) and in the control group 100 mg (40-160).
Hamishehkar [56]	Furosemide	**No diuretics** The cumulative dose of furosemide in the intervention group was not reported. No report of administration of diuretics in control group.
Sanchez [57]	Torsemide	**No diuretics** The cumulative dose of torsemide was not reported for the intervention group. No diuretics was reported in the control group.

S4. Detailed characteristics of included trials

Table S3. Detailed characteristics of the included trials

Bagshaw et al. 2017 [52]	
Methods	Multicentre, blinded, randomised clinical trial
Participants	**Sample size:** n=73 randomised (experimental: 37, control: 36) 72 analysed for outcomes. **Sex (M/F):** 57/16 **Age (mean):** 64 **Country:** Canada/Australia **Setting:** AKI patients in mixed ICUs. **Inclusion criteria:** 1) evidence of early AKI (RIFLE category – RISK); 2) peripheral or central intravenous catheter and urinary catheter; 3) ≥ 2 criteria for the systemic inflammatory response syndrome within 24 hours of screening and 4) achieved immediate resuscitation goals based on judgement of the treating physician and including one or more of the following: fluid resuscitation and/or vasoactive therapy to achieve mean arterial pressure ≥ 65 mmHg, central venous pressure ≥ 8 cm H_2O, central venous oxygen saturation ≥ 70% (if measured) and or cardiac index ≥ 2.5 L/min/1.73 m^2 (if measured) **Exclusion criteria:** 1) age < 18 years; 2) confirmed or suspected pregnancy; 3) suspected or confirmed obstructive ethology for AKI; 4) ≥ stage 4 chronic kidney disease, end stage kidney disease receiving maintenance dialysis or kidney transplantation; 5) recent RRT during ICU or index hospitalisation; 6) recovering AKI defined as a ≥ 25% or 44.2 μmol/L decline from peak increase in serum creatinine; 7) acute pulmonary oedema mandating urgent furosemide administration or RRT initiation or patient was already receiving a continuous furosemide infusion; 8) moribund status with expected death within 24 hours or significant limitations of medical therapy; 9) suspected or known allergy to furosemide; and 10) prior enrolment.
Interventions	**Experimental:** Furosemide bolus of 0.4mg/kg followed by a continuous infusion of furosemide with a starting dose of 0.05 mg/kg/h. Goal directed titration. Max. 0.4 mg/kg/h. **Control:** placebo (saline) **Co-intervention:** none **Duration:** minimum 24 hours; maximum 7 days
Outcomes	**Primary outcome:** worsening of AKI, defined as progression from RIFLE category – RISK to a more severe category of AKI (INJURY, FAILURE or receipt of RRT) in the 7 days following randomisation. **Secondary outcomes:** differences in cumulative fluid balance, serum electrolytes, acid-base status, rate of RRT initiation, rates of renal recovery, and hospital mortality between furosemide and placebo groups, respectively.
Notes	1 patient in the control group did not receive the intervention and was not included in the analysis.

	The trial was terminated early after 72 participants (216 planned participants) due to low recruitment, limited funding, influenza pandemic in 2009, and shortage of furosemide in North America in 2011. Author contacted in January 2021 and response received in February 2021 with clarifications to data. Adverse events and reactions were not divided in serious and not serious. Extra data on electrolytes were received. The data was not in a format that could be used in a meta-analysis.

Berthelsen et al. 2018 [37]

Methods	Multicentre, unblinded, randomised clinical trial
Participants	**Sample size:** 23 randomised (20 analysed) **Sex (M/F):** 12:8 **Age (mean):** 72 **Country:** Denmark **Setting:** AKI patients in two mixed ICUs. **Inclusion criteria:** 1) age 18 years or older; 2) AKI defined according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria; 3) renal recovery score (RS) ≤60%; 4) fluid overload defined as a positive fluid balance of at least 10% of ideal body weight; 5) able to undergo randomisation within 12 hours of fulfilling the other inclusion criteria. **Exclusion criteria:** 1) known allergy to furosemide or sulphonamides; 2) known prehospitalisation advanced chronic kidney disease (eGFR < 30 mL/min/1.73m^2 or chronic renal replacement therapy); 3) severe hypoxic respiratory failure (FiO_2 > 80% and positive end-expiratory pressure (PEEP) > 10 cm H_2O); 4) severe burn injury (≥ 10% total burned surface area); 5) severe dysnatraemia (plasma concentration < 120 or > 155 mmol/L); 6) hepatic coma; 7) mentally disabled undergoing forced treatment; 8) pregnancy/breastfeeding; 9) lack of commitment for ongoing life support including renal replacement therapy (RRT); and 10) lack of informed consent.
Interventions	**Experimental:** fluid removal to achieve a negative fluid balance of ≥ 1mL/kg/hour. First choice was furosemide infusion, and if it was insufficient according to goal assessed after 8 hours the patient was changed to continuous RRT to achieve the goal. **Control:** standard of care. **Co-intervention:** none **Duration:** 5 days
Outcomes	**Primary outcome:** cumulative fluid balance 5 days after randomisation. **Secondary outcomes:** 1) mean daily fluid balance during ICU stay; 2) cumulative fluid balance during the entire ICU stay; 3) time to neutral cumulative fluid balance; 4) number of patients with one or more major protocol violations; 5) accumulated SARs in each intervention arm during the ICU stay. **Exploratory outcomes:** 1) all-cause mortality at day 90; 2) Days alive and out of hospital within 90 days of follow-up; 3) days alive without mechanical ventilation within 90 days of follow-up; 4) Days alive without

	vasopressor/inotropic therapy within 90 days follow-up; 5) days alive without RRT within 90 days follow-up; 6) renal recovery at day 90.
Notes	The inclusion criteria were changes after inclusion of the first two participants. Three patients did not receive the allocated treatment and was not included in the analysis. The trial was terminated early due to futility. Less than half of the planned sample size was included. Author contacted in January 2021 and clarifying information and all raw data were provided. From raw data we could extract data not presented in the article for several of our outcomes (length of stay in ICU, creatinine, electrolytes, resolution of fluid overload, SAEs). The data of creatinine and electrolytes were screwed and not suitable for meta-analysis.

Brown et al. 2019 [53]

Methods	Single centre, randomised clinical trial
Participants	**Sample size:** 26 randomised (25 analysed) **Sex (M/F):** 15/10 **Age (median):** 55 **Country:** Australia **Setting:** Mixed ICU **Inclusion criteria:** 1) age above 18 years; 2) physician decision to administer an intravenous diuretic; 3) anticipated length of stay for more than 24 hours; 4) existing intra-arterial or central venous catheter and urinary catheter. **Exclusion criteria:** 1) allergy to furosemide or acetazolamide or other sulphonamides; 2) end-stage renal failure; 3) long-standing use of diuretics: 4) dose of any diuretic in the preceding 12 hours; 5) significant acid-base disturbance at the time of enrolment (pH < 7.3 or > 7.5); and 6) treatment with RRT.
Interventions	**Experimental:** single bolus of 40 mg furosemide **Control:** single bolus of 500 mg acetazolamide **Co-intervention:** none **Duration:** 6 hours
Outcomes	1) Change in cumulative fluid balance 6 hours after the intervention. 2) Change in the cumulative urine output and serum and urine biochemistry for 6 hours before and 6 hours after the intervention.
Notes	One patient withdrew consent and was not included in the analysis. Author contacted in February and response received.

Cardoso et al. 2013 [55]

Methods	Single centre, single blinded, randomised clinical trial
Participants	**Sample size**: n=72 (experimental: 34, control: 38 - randomised and analysed) **Sex (M/F):** 59/13 **Age (mean):** 58 **Country:** Brazil **Setting:** Patients with decompensated heart failure in Medical ICU

	Inclusion criteria: 1) ≥ 18 years of age; 2) NYHA class IV; 3) ejection fraction < 45%; 4) decompensated heart failure; 5) and presence of two or more signs of water retention. **Exclusion criteria:** 1) serum urea > 150 mg/dL; 2) serum creatinine level > 3 mg/dL; 3) peritoneal dialysis; 4) haemodialysis; 5) severe aortic stenosis; 6) and insulin dependent diabetes mellitus.
Interventions	**Experimental:** furosemide 120 mg/day as starting dose - titrated according to an algorithm. **Control:** standard of care **Co-intervention:** none described **Duration:** unclear. All patients were followed until free from congestion
Outcomes	**Primary outcome:** Time to being free from congestion **Secondary outcome:** worsening of renal function
Notes	Author contacted January and March 2021 without response

Cinotti et al. 2021 [54]

Methods	Multicentre, single blinded, randomised clinical trial.
Participants	**Sample size:** 171 randomised (166 analysed) **Sex (M/F):** 122/44 **Age (mean):** 66 **Country:** France **Setting:** Mixed ICU **Inclusion criteria:** 1) ≥ 18 years old; 2) admitted to an ICU and receiving invasive mechanical ventilation ($FiO_2 \leq 60\%$, and PEEP ≤ 10 cm H_2O on inclusion); 3) positive fluid balance defined as in-ICU weight increase ≥ 3%; 4) haemodynamic stable (no vasoactive drugs). **Exclusion criteria:** 1) pregnancy; 2) withdrawal of life-sustaining therapies in the 24 hours after admission; 3) allergy to furosemide; 4) admission for decompensated cirrhosis; central neurologic injury, and chronic kidney failure; 5) when treatment with diuretics are mandatory (acute pulmonary oedema, heart failure with a reduced ejection fraction ≤ 30%).
Interventions	**Experimental:** furosemide once or twice a day until successful extubation. Dose adjusted to every patient. **Control:** diuretic administration prohibited **Co-intervention:** diuretics is used as rescue therapy in case of pulmonary oedema or de novo heart failure. **Duration:** until successful extubation.
Outcomes	**Primary outcome:** fluid balance defined as weight variation from weight on randomisation to weight on successful extubation. **Secondary outcomes:** 1) rate of extubation failure; 2) duration of mechanical ventilation from randomisation to successful weaning; 3) number of ventilatory free days by day 28; 4) length of stay in ICU; 5) ICU mortality; 6) 60-day mortality post randomisation.
Notes	After inclusion of 36 patients the inclusion criteria were modified, which might have changed the study population to some degree. 5 patients were excluded in the intervention group because of violation of an inclusion criterion. Authors were contacted and response received.

Hamishehkar et al. 2017 [56]

Methods	Multicentre, randomised clinical trial
Participants	**Sample size:** n=106 randomised (analysed: experimental: 50, control: 50) **Sex (M/F):** 64/36 **Age (mean):** 63 **Country:** Iran **Setting:** patients with AKI in two surgical ICUs. **Inclusion criteria:** patients with increase in creatinine to more than 150% - 300% or urine output decreased to < 0.5 cc/kg/hour for 12 hours or more. **Exclusion criteria:** 1) previous history of AKI; 2) RRT; 3) renal transplantation; 4) urinary system obstruction; 5) previous history of diuretic use; 6) alkalosis, or 7) hypovolemia.
Interventions	**Experimental:** 40-80 mg of furosemide iv followed by infusion of 1-5 mg/hour according to urine output. **Control:** no diuretics **Co-intervention:** RRT was started in case of fluid overload resistant to medical therapy, severe acidosis resistant to medical treatment, severe electrolyte imbalance resistant to treatment, uremic signs or symptoms, and progressive azotaemia in the absence of uraemia. **Duration:** 7 days
Outcomes	Evaluate biomarkers (blood urea nitrogen, creatinine, plasma neutrophil gelatinase-associated lipocalin (NGAL), urine NGAL) in AKI patients.
Notes	106 patients were randomised but only 100 patients were analysed. It is unclear to which group the 6 excluded patients belonged. Reasons of exclusion: two patients died, three were ineligible after enrolment, and one declined to participate. The authors were contacted March and April 2021 without response.

Han 2019 [59]

Methods	Single centre, blinded, randomised clinical trial
Participants	**Sample size:** n=248 (experimental:124, control: 124) randomised and analysed **Sex (M/F):** 87:161 **Age (mean):** 45 **Country:** China **Setting:** Cardiac intensive care patients **Inclusion criteria:** 15-65 years of age with signs of fluid overload **Exclusion criteria:** 1) age below 15 or above 65 years; 2) cardiac issues (systolic blood pressure < 80 mmHg) and renal instability (serum creatinine > 3.99 mg dL^{-1}); 3) lack of informed consent; 4) pregnancy and breastfeeding; 5) patients who needed dialysis or ultrafiltration on the time of enrolment.
Interventions	**Experimental:** infusion of furosemide: 0.8 mg/kg/hour **Control:** infusion of ethacrynic acid 0.5 mg/kg/hour **Co-intervention:** none **Duration:** maximum 3 days

Outcomes	**Primary outcome:** increase urine output in young and adult patients with fluid overload. **Secondary outcome:** compare the efficacy and safety of furosemide with ethacrynic acid. The primary and secondary outcomes were different between protocol and article. These outcomes are from the article.
Notes	Author contacted February and March 2021 without response.

Ng et al. 2020 [60]

Methods	Single centre, open label, randomised clinical trial
Participants	**Sample size:** n=33 randomised and analysed (experimental: 15, control: 18) **Sex (M/F):** 25/8 **Age (mean):** 56 **Country:** USA **Setting:** Patients with acute heart failure admitted to an ICU. **Inclusion criteria:** 1) Acute heart failure with signs or symptoms of volume overload 2) Serum sodium < 135 mEq/L at time of or within first 48 hours of hospitalization 3) Informed consent. **Exclusion criteria: 1)** Severe symptomatic hyponatremia requiring acute treatment, 2) moderate to severe lever impairment, 3) Severe renal impairment upon admission (creatinine clearance < 20 mL/min), 4) Renal replacement therapy dependent or required upon admission, 5) Acute coronary syndrome on admission, 6) Evidence of cardiogenic shock or requiring intravenous vasopressors, 7) Pregnancy, 8) Concomitant use of strong CYP3A4 inhibitors (clarithromycin, ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, and telithromycin)
Interventions	**Experimental:** Furosemide infusion of 5 mg/hour with the option to titrate to a maximum of 20 mg/hour after the first 24 hours. **Control:** Tablet tolvaptan 30 mg daily with the option to titrate up to a maximum of 60 mg daily after the first 24 hours. **Co-intervention:** Baseline thiazide diuretics were discontinued during the trial. In case of maximum tolvaptan or furosemide administration metolazone could be added in both groups to achieve the desired urine output of 100 mL/hour. **Duration:** maximum 96 hours (4 days)
Outcomes	**Primary outcome:** 1) Mean urine output at 24 hours post randomisation 2) Mean change in serum creatinine at 24 hours post randomisation. **Secondary outcomes:** 1) Urine output and sodium change at 8, 48, 96 hours post-randomisation 2) Proportion of patients requiring escalation of study drug dose or the addition of metolazone 3) Change in self-rated dyspnoea (Likert Scale) at 24 and 96 hours 4) change in estimated glomerular filtration rate at 24, 48, and 96 h post randomisation 5) Incidence of acute increases in serum creatinine ≥26.5 μmol/L (0.3 mg/dL), 6) In-hospital mortality, 7) changes in biomarkers (plasma renin activity, copeptin, plasma N-terminal pro b-type natriuretic peptide, cystatin C, and Urinary neutrophil gelatinase-associated lipocalin.
Notes	Inclusion and exclusion criteria and outcomes in protocol and article differed. Data were only registered as long patients followed the protocol. The sample

	size was small, and many participants were discontinued from the study protocol after 48 hours because of clinical resolution or protocol violation according to diuretics (switch to bumetanide), so the results beyond 48 hours should be interpreted with caution. In-hospital mortality was not reported in article, but data can be found on Clincal.Trial.gov. No SAE/AE was reported on Clincal.Trial.gov. First sample size calculation was on 50 participants. Due to slow enrolment re-calculation of sample size was performed and sample size revised to 34-46 subjects. 33 participants included. Only per protocol analysis were performed. Authors were contacted in April 2021 and answer received.

Sanchez et al. 2003 [57]

Methods	Randomised clinical trial
Participants	**Sample size:** n=40 randomised and analysed (experimental: 20, control: 20) **Sex (M/F):** no info **Age (mean):** 68 **Country:** Spain **Setting:** patients with AKI in ICU. **Inclusion criteria:** 1) diuresis < 1 ml/kg/hour; 2) creatinine clearance < 60 ml/min; 3) hemodynamic resuscitation (mean arterial pressure ≥70 mmHg, CVP ≥12 mmHg). **Exclusion criteria:** not described.
Interventions	**Experimental:** torsemide – dose not described **Control:** no intervention **Co-intervention:** RRT on indication **Duration:** maximum 7 days
Outcomes	The effect of low dose dopamine and torsemide on creatinine clearance and the need for RRT in critically ill septic oliguric patients.
Notes	Only an abstract available. Participants were randomised to 4 groups: control, dopamine < 3mg/kg/min, torsemide iv bolus, and torsemide and dopamine. We only extracted data from the torsemide and control group. We interpreted the control group as no diuretics. No data on diuretics in the control group was reported. No contact information was found on the authors.

Wappler et al. 1991 [58]

Methods	Single centre, randomised clinical trial
Participants	**Sample size:** n=12 randomised and analysed (experimental: 6, control: 6) **Sex (M/F):** 5/7 **Age (mean):** 68 **Country:** Germany **Setting:** postoperative patients in a cardio surgical intensive care unit **Inclusion criteria:** not described **Exclusion criteria:** not described
Interventions	**Experimental:** bolus of 40 mg furosemide followed by infusion of 20 mg/hour. In case of decrease in diuresis bolus of 40 mg furosemide was allowed.

	Control: bolus of 12 mg piretanide followed by infusion of 6 mg/hour. In case of decrease in diuresis bolus of 12 mg piretanide was allowed. **Co-intervention:** all patients received 100 mg of spironolactone every 8 hours. Mannitol infusion was allowed. **Duration:** 40 hours
Outcomes	Comparison of the effect of furosemide and piretanide in patients in cardiosurgical intensive care unit.
Notes	No contact information on the authors were found.

S5. Overall risk of bias for all included trials

We used ROB2 tool in assessing the risk of bias. Trials or outcomes were judged at overall low risk of bias if all five domains had low risk of bias. Trials or outcomes were judged at overall high risk of bias when some concerns or high risk of bias was judged in one or more domains.

Table S4. Overall risk of bias assessment for all included trials

Study	Rando-misation	Deviations from intervention	Missing outcome data	Measure-ment of the outcome	Selection of the reported results	Overall risk of bias
Bagshaw	Low	Low	Low	Low	**Some concerns**[1]	**High**[2]
Berthelsen	Low	**High**[3]	**Some concerns**[4]	Low	Low	**High**[5]
Brown	Low	Low	Low	Low	**Some concerns**[6]	**High**
Cardoso	**Some concerns**[7]	**High**[8]	**High**[9]	**High**[10]	**Some concerns**[11]	**High**
Cinotti	Low	**Some concerns**[12]	Low	**Some concerns**[13]	**Some concerns**[14]	**High**
Hamishehkar	Low	**High**[15]	**High**[16]	Low	**Some concerns**[17]	**High**
Han	**Some concerns**[18]	Low	Low	Low	**Some concerns**[19]	**High**
Ng	**Some concerns**[20]	**High**[21]	Low	**High**[22]	**Some concerns**[23]	**High**
Sanchez	**Some concerns**[24]	**High**[25]	**High**[26]	**Some concerns**[27]	**Some concerns**[28]	**High**
Wappler	**Some concerns**[29]	**High**[30]	**Some concerns**[31]	Low	**Some concerns**[32]	**High**

1. Full trial protocol and statistical analysis plan were not available, but the trial was registered on ClincalTrials.gov. SAE/AE were not outcomes but reported.
2. The calculated sample size was 216 participants, but the trial was stopped after 73 included participants.
3. The trial was not blinded which might have affected the treatment in the standard of care group. Inclusion criteria were changed during the trial this might have changed the patient population to some degree.
4. Three participants (13%) were excluded out of 23 randomised participants. Data of the excluded participants were not used in the analyses. No sensitivity analyses could be performed due to small sample size.
5. The trial was stopped prematurely with less than half of the planned participants included.
6. No protocol or analysis plan is available, but the trial was registered at New Zealand Clinical Trials Registry. In the trial registry 15 secondary outcomes were listed, but only 8 outcomes were reported in the article.
7. Randomisation process was not described.

8. Only the participants were blinded for the intervention. The control group was standard of care. The knowledge of the allocation group might have affected the treatment in the standard of care group due to the Hawthorne effect. No information reported on exclusions, withdrawal and lost to follow-up.
9. No information about missing data. No CONSORT-diagram reported.
10. Outcome assessors were not blinded. The primary outcome "being free from congestion" were not defined. The lack of blinding has the potential to affect the assessment "being free from congestion" which is partly a subjective outcome. Objective outcomes are less or not affected by the lack of blinding.
11. No protocol, statistical analysis plan or trial registry available.
12. Change in inclusion criteria during the trial, which changed the randomised patient population to some degree. Five participants were excluded from the furosemide group due to inadequate inclusion criteria post randomisation. It is not reported if these five participants had received the intervention. They were excluded from the intention-to-treat analysis. Single-blinded trial.
13. The Primary outcome was fluid balance at the time of extubation. Knowledge of the intervention group might affect when the patients are judged ready to extubate. Other objective outcomes are less affected by the lack of blinding.
14. No protocol or statistical plan available, but the trial was registered on ClincalTrials.gov.
15. Discrepancies between trial registry and article. In the trial registry the trial was stated as double blinded, but blinding was not described in the article. The control group was reported to receive placebo in the trial registry, but in the article the control group was described as standard treatment with no diuretics. Six participants are excluded for the intention-to-treat analysis (two died during the trial, three were ineligible after enrolment and one declined to participate). Allocation groups not revealed for the excluded participants.
16. Two participants who died during the trial were excluded from the analysis and not included in the reported ICU mortality. The allocation group is unknow and might have an impact.
17. No published protocol or statistical analysis plan. The trial was registered at Iranian Registry of Clinical Trials.
18. Randomisation process not described.
19. Short protocol without statistical analysis plan was attached in the trial registry. One secondary outcome in the protocol was not reported in the article.
20. Allocation process not described.
21. No blinding. Only data on participants who remained on study protocol were registered. After the first 48 hours the trial intervention was stopped in a large percentage of participants - mainly in the tolvaptan group due to clinical decisions (clinical resolution or diuretic switch to bumetanide) and additional medicine as metolazone was used more in the tolvaptan group compared to the furosemide group. This especially affected the outcomes from 48 hours to 96 hours. Per protocol analyses were performed.
22. Due to no blinding the clinicians might be more prone to remove participants from the study protocol if they find other treatment options more advantageous. Only seven participants remained in protocol until 96 hours in the tolvaptan group and 11 patients in the furosemide group. The attrition from study protocol was due to clinical resolution or switch to bumetanide.
23. Three outcomes in the protocol were not reported in the article – some degree of selective reporting cannot be ruled out. SAE were only reported on ClincalTrials.gov – not in the article.
24. Randomisation and allocation process not reported.
25. Blinding and analysis methods were not described.
26. Unclear how many participants were randomised, and if all randomised participants were included in the analyses. No information on withdrawal, lost to follow-up and missing data.

27. Renal replacement therapy was stated to be initiated according to predefined criteria, but these criteria are not reported. No blinding.
28. Only published as an abstract. No protocol, statistical analysis plan or trial registry could be found.
29. Randomisation process not described.
30. No information about blinding or deviations for intended interventions.
31. Unclear how many participants were randomised and if all randomised participants were analysed.
32. No published protocol, statistical analysis plan or registration in a trial registry.

S6. Comparison: loop diuretics vs placebo/no intervention

S6a. Risk of bias of all outcomes

We used the ROB2 tool when assessing the risk of bias. Outcomes were judged at overall low risk of bias if all five domains had low risk of bias. Outcomes were judged at overall high risk of bias when some concerns or high risk of bias was judged in one or more domains.

Table S5. Risk of bias assessment on all-cause mortality for loop diuretics vs. placebo/no intervention

Study	Rando-misation	Deviations from intervention	Missing outcome data	Measure-ment of the outcome	Selection of the reported results	Overall risk of bias
Bagshaw	Low	Low	Low	Low	**Some concerns**[1]	**High**[2]
Berthelsen	Low	**High**[3]	**Some concerns**[4]	Low	Low	**High**[5]
Cinotti	Low	**Some concerns**[6]	Low	Low	**Some concerns**[7]	**High**
Hamishehkar	Low	**High**[8]	**High**[9]	Low	**Some concerns**[10]	**High**

1. Full trial protocol and statistical analysis plan were not available, but the trial was registered on ClincalTrials.gov.
2. The calculated sample size was 216 participants, but the trial was stopped after 73 included participants.
3. The trial was not blinded which might have affected the treatment in the standard of care group. Inclusion criteria were changed during the trial this might have changed the patient population to some degree.
4. Three participants (13%) were excluded out of 23 randomised participants. Data of the excluded participants were not used in the analyses. No sensitivity analyses could be performed due to small sample size.
5. The trial was stopped prematurely with less than half of the planned participants included.
6. Change in inclusion criteria during the trial, which changed the patient population to some degree. Five participants were excluded from the furosemide group due to inadequate inclusion criteria post randomisation. It is not reported if these five participants had received the intervention. They were excluded from the intention-to-treat analysis. Single-blinded trial.
7. No protocol or statistical plan available, but the trial was registered on ClincalTrials.gov.
8. Discrepancies between trial registry and article. In the trial registry the trial was stated as double blinded, but blinding was not described in the article. The control group was reported to receive placebo in the trial registry, but in the article the control group was described as standard treatment with no diuretics. Six participants are excluded for the intention-to-treat analysis (two died during the trial, three were ineligible after enrolment and one declined to participate). Allocation groups not revealed for the excluded participants.
9. Two participants who died during the trial were excluded from the analysis and not included in the reported ICU mortality. The allocation group is unknow and might have an impact.

10. No published protocol or statistical analysis plan. The trial was registered at Iranian Registry of Clinical Trials.

Table S6. Risk of bias assessment on serious adverse events for loop diuretics vs. placebo/no intervention

Study	Rando-misation	Deviations from intervention	Missing outcome data	Measure-ment of the outcome	Selection of the reported results	Overall risk of bias
Bagshaw	Low	Low	Low	Low	**Some concerns**[1]	**High**[2]
Berthelsen	Low	**High**[3]	**Some concerns**[4]	Low	Low	**High**[5]
Cardoso	**Some concerns**[6]	**High**[7]	**High**[8]	Low	**Some concerns**[9]	**High**
Cinotti	Low	**Some concerns**[10]	Low	Low	**Some concerns**[11]	**High**
Hamishehkar	Low	**High**[12]	**High**[13]	Low	**Some concerns**[14]	**High**
Sanchez	**Some concerns**[15]	**High**[16]	**High**[17]	**Some concerns**[18]	**Some concerns**[19]	**High**

1. Full trial protocol and statistical analysis plan were not available, but the trial was registered on ClincalTrials.gov. SAE/AE were not outcomes but reported.
2. The calculated sample size was 216 participants, and the trial was stopped after 73 included participants.
3. The trial was not blinded which might have affected the treatment in the standard of care group. Inclusion criteria were changed during the trial, this might have affected the patient population.
4. Three participants (13%) were excluded out of 23 randomised participants. Data of the excluded participants were not used in the analyses. No sensitivity analyses could be performed due to small sample size.
5. The trial was stopped prematurely with less than half of the planned participants included.
6. Randomisation process was not described.
7. Only the participants were blinded for the intervention. The control group was standard of care. The knowledge of the allocation group might have affected the treatment in the standard of care group due to the Hawthorne effect. No information reported on exclusions, withdrawal and lost to follow-up.
8. No information about missing data. No CONSORT-diagram reported.
9. No protocol, statistical analysis plan or trial registry available.
10. Change in inclusion criteria during the trial which changed the patient population to some degree. Five participants were excluded from the furosemide group due to inadequate inclusion criteria post randomisation. It is not reported if these five participants had received the intervention. They were excluded from the intention-to-treat analysis. Single-blinded trial.
11. No protocol or statistical plan available, but the trial was registered on ClincalTrials.gov.
12. Discrepancies between trial registry and article. In the trial registry the trial was stated as double blinded, but blinding was not described in the article. The control group was reported to receive placebo in the trial registry, but in the article the control group was described as standard

treatment with no diuretics. Six participants are excluded for the intention-to-treat analysis (two died during the trial, three were ineligible after enrolment and one declined to participate). Allocation groups not revealed for the excluded participants.

13. Six participants were excluded (5.7 %) from the intention-to-treat analysis (two died, one withdrew consent, and 3 were ineligible after enrolment). Allocation group not revealed. Missing data not mentioned in the trial.
14. No protocol or statistical plan available, but the trial was registered on Iranian Registry of Clinical Trials.
15. Randomisation and allocation process not reported.
16. Blinding not described.
17. Unclear how many participants were randomised, and if all randomised participants were included in the analyses. No information on lost to follow-up and missing data.
18. Renal replacement therapy was stated to be initiated according to predefined criteria, but these criteria are not reported. No blinding.
19. Only an abstract published. No protocol, statistical analysis plan or trial registry could be found.

Table S7. Risk of bias assessment on plasma creatinine for loop diuretics vs. placebo/no intervention

Study	Rando-misation	Deviations from intervention	Missing outcome data	Measure-ment of the outcome	Selection of the reported results	Overall risk of bias
Bagshaw	Low	Low	Low	Low	**Some concerns**[1]	**High**[2]
Berthelsen	Low	**High**[3]	**Some concerns**[4]	Low	**Some concerns**[5]	**High**[6]
Hamishehkar	Low	**High**[7]	**High**[8]	Low	**Some concerns**[9]	**High**

1. No protocol or statistical analysis plan available, but the trial was registered at ClinicalTrials.gov.
2. The calculated sample size was 216 participants, and the trial was stopped after 73 included participants.
3. The trial was not blinded which might have affected the treatment in the standard of care group. Inclusion criteria were changed during the trial.
4. Three participants (13%) were excluded out of 23 randomised participants. Data of the excluded participants were not used in the analyses. No sensitivity analyses could be performed due to small sample size.
5. Plasma creatinine was not an outcome in this trial, but it was calculated by the review group from raw data delivered by the authors.
6. The trial was stopped prematurely with less than half of the planned participants included.
7. Discrepancies between trial registry and article. In the trial registry the trial was stated as double blinded, but blinding was not described in the article. The control group was reported to receive placebo in the trial registry, but in the article the control group was described as standard treatment with no diuretics. Six participants are excluded for the intention-to-treat analysis (two

died during the trial, three were ineligible after enrolment and one declined to participate). Allocation groups not revealed for the excluded participants.
8. Six participants were excluded (5.7 %) from the intention-to-treat analysis (two died, one withdrew consent, and 3 were ineligible after enrolment). Allocation group not revealed. Missing data not mentioned in the trial.
9. No protocol or statistical plan available, but the trial was registered on Iranian Registry of Clinical Trials.

Table S8. Risk of bias assessment on proportion of participants without resolution of fluid overload for loop diuretics vs. placebo/no intervention

Study	Rando-misation	Deviations from intervention	Missing outcome data	Measure-ment of the outcome	Selection of the reported results	Overall risk of bias
Berthelsen	Low	**High**[1]	**Some concerns**[2]	Low	Low	**High**[3]
Cardoso	**Some concerns**[4]	**High**[5]	**High**[6]	**High**[7]	**Some concerns**[8]	**High**

1. The trial was not blinded which might have affected the treatment in the standard of care group. Inclusion criteria were changed during the trial and the trial.
2. Three participants (13%) were excluded out of 23 randomised participants. Data of the excluded participants were not used in the analyses. No sensitivity analyses could be performed due to small sample size.
3. The trial was stopped prematurely with less than half of the planned participants included.
4. Randomisation process was not described. Single blinded trial.
5. Only the participants were blinded for the intervention. The control group was standard of care. The knowledge of the allocation group might have affected the treatment in the standard of care group due to the Hawthorne effect. No information reported on exclusions, withdrawal and lost to follow-up.
6. No information about missing data. No CONSORT-diagram reported.
7. Outcome assessors were not blinded and the primary outcome “being free from congestion” (resolution of fluid overload) were not defined. The lack of blinding has the potential to affect the assessment of this outcome.
8. No protocol, statistical analysis plan or trial registry available.

Table S9. Risk of bias assessment on number of days on mechanical ventilation for loop diuretics vs. placebo/no intervention

Study	Rando-misation	Deviations from intervention	Missing outcome data	Measure-ment of the outcome	Selection of the reported results	Overall risk of bias
Berthelsen	Low	**High**[1]	**Some concerns**[2]	Low	Low	**High**[3]
Cinotti	Low	**Some concerns**[4]	Low	**High**[5]	**Some concerns**[6]	**High**

1. The trial was not blinded which might have affected the treatment in the standard of care group. Inclusion criteria were changed during the trial.
2. Three participants (13%) were excluded out of 23 randomised participants. Data of the excluded participants were not used in the analyses. No sensitivity analyses could be performed due to small sample size.
3. The trial was stopped prematurely with less than half of the planned participants included.
4. Change in inclusion criteria during the trial which changed the patient population to some degree. Five participants were excluded from the furosemide group due to inadequate inclusion criteria post randomisation. It is not reported if these five participants had received the intervention. They were excluded from the intention-to-treat analysis. Single-blinded trial.
5. The trial's primary outcome was fluid balance on extubation. Knowledge of the intervention might have affected when the participants were assessed ready to extubate - even they had a described weaning protocol from mechanical ventilation in the article.
6. No protocol or statistical plan available, but the trial was registered on ClincalTrials.gov.

Table S10. Risk of bias assessment on length of stay for loop diuretics vs. placebo/no intervention

Study	Rando-misation	Deviations from intervention	Missing outcome data	Measure-ment of the outcome	Selection of the reported results	Overall risk of bias
Berthelsen	Low	**High**[1]	**Some concerns**[2]	Low	**Some concerns**[3]	**High**[4]
Cinotti	Low	**Some concerns**[5]	Low	Low	**Some concerns**[6]	**High**

1. The trial was not blinded which might have affected the treatment in the standard of care group. Inclusion criteria were changed during the trial.
2. Three participants (13%) were excluded out of 23 randomised participants. Data of the excluded participants were not used in the analyses. No sensitivity analyses could be performed due to small sample size.
3. Length of stay was not an outcome in this trial, but it was calculated by the review group from raw data delivered by the authors.
4. The trial was stopped prematurely with less than half of the planned participants included.
5. Change in inclusion criteria during the trial which changed the patient population to some degree. Five participants were excluded from the furosemide group due to inadequate inclusion

criteria post randomisation. It is not reported if these five participants had received the intervention. They were excluded from the intention-to-treat analysis. Single-blinded trial.
6. No protocol or statistical plan available, but the trial was registered on ClincalTrials.gov.

Table S11. Risk of bias assessment on adverse events not considered serious for loop diuretics vs. placebo/no intervention

Study	Rando-misation	Deviations from intervention	Missing outcome data	Measure-ment of the outcome	Selection of the reported results	Overall risk of bias
Bagshaw	Low	Low	Low	Low	**Some concerns[1]**	**High[2]**
Cinotti	Low	**Some concerns[3]**	Low	Low	**Some concerns[4]**	**High**

1. No protocol or statistical analysis plan available, but the trial was registered at ClinicalTrials.gov.
2. The calculated sample size was 216 participants, and the trial was stopped after 73 included participants.
3. Change in inclusion criteria during the trial which changed the patient population to some degree.
4. No protocol or statistical plan available, but the trial was registered on ClincalTrials.gov.

Table S12. Risk of bias assessment on plasma sodium and potassium for loop diuretics vs. placebo/no intervention

Study	Rando-misation	Deviations from intervention	Missing outcome data	Measure-ment of the outcome	Selection of the reported results	Overall risk of bias
Bagshaw	Low	Low	Low	Low	**Some concerns[1]**	**High[2]**
Berthelsen	Low	**High[3]**	Low	Low	**Some concerns[4]**	**High[5]**

1. No protocol or statistical analysis plan available, but the trial was registered at ClinicalTrials.gov.
2. The calculated sample size was 216 participants, and the trial was stopped after 73 included participants.
3. The trial was not blinded which might have affected the treatment in the standard of care group. Inclusion criteria were changed during the trial.
4. Plasma electrolytes were not an outcome in this trial, but it was calculated by the review group from raw data delivered by the authors.
5. The trial was stopped prematurely with less than half of the planned participants included.

Table S13. Risk of bias assessment on plasma chloride for loop diuretics vs. placebo/no intervention

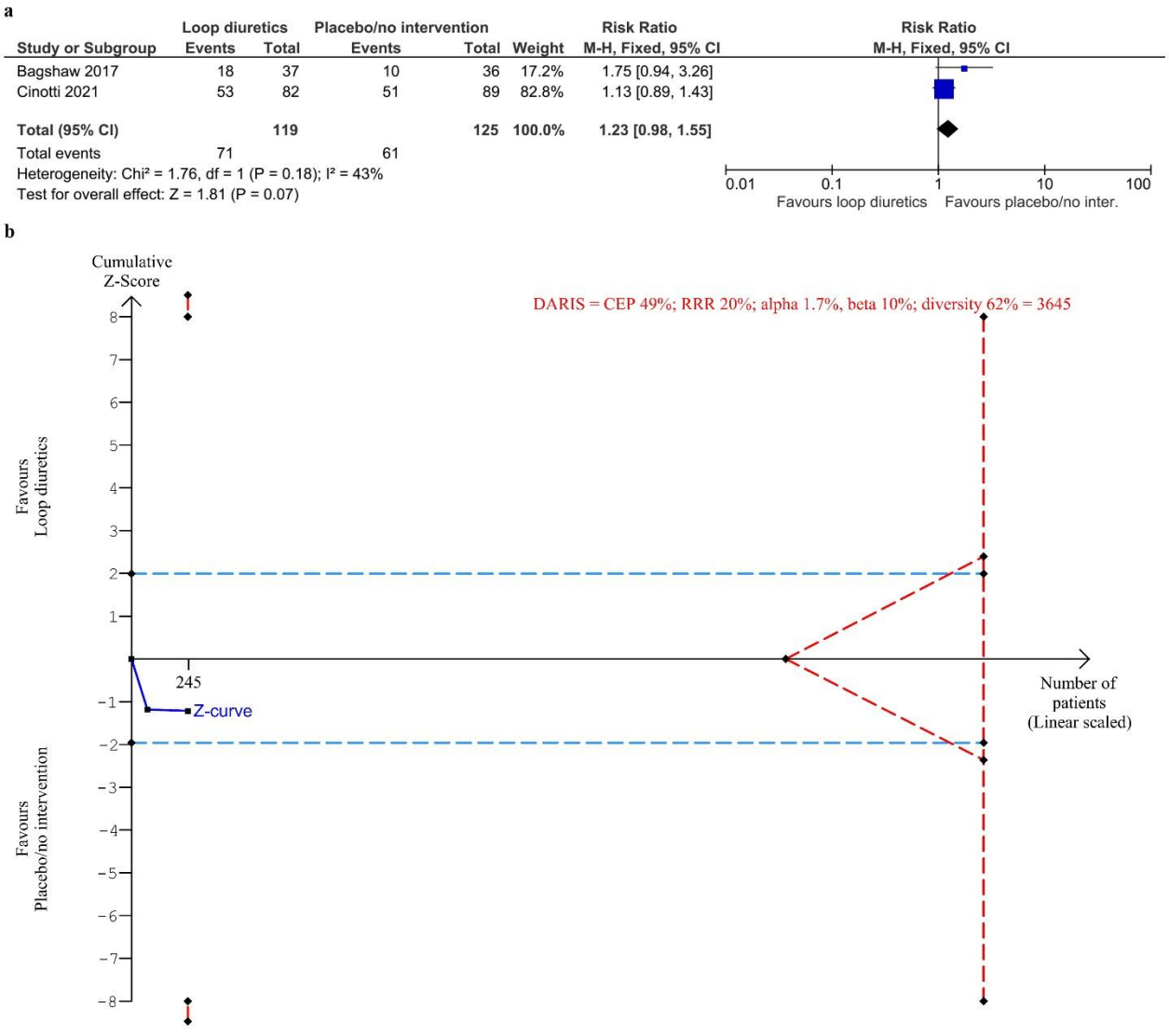
Study	Rando-misation	Deviations from intervention	Missing outcome data	Measure-ment of the outcome	Selection of the reported results	Overall risk of bias
Berthelsen	Low	**High**[1]	Low	Low	**Some concerns**[2]	**High**[3]

1. The trial was not blinded which might have affected the treatment in the standard of care group. Inclusion criteria were changed during the trial.
2. Plasma electrolytes were not an outcome in this trial, but it was calculated by the review group from raw data delivered by the authors.
3. The trial was stopped prematurely with less than half of the planned participants included.

S6b. Meta-analyses and TSA

TSA was conducted for primary and secondary outcomes with meta-analysis.

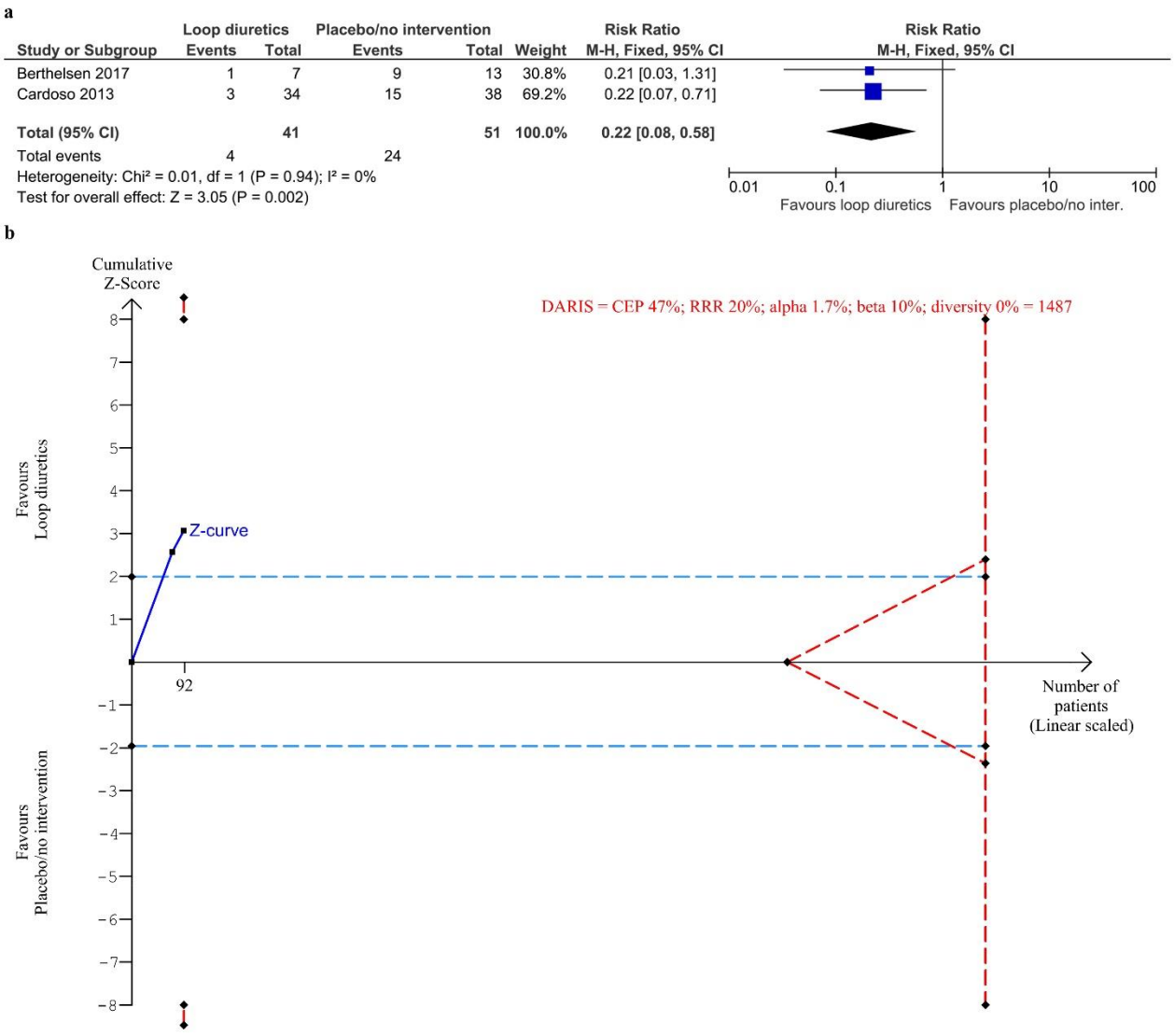
Fig. S1. Meta-analysis and TSA for adverse events not considered serious for loop diuretics vs. placebo/no intervention



a) Meta-analysis. b) TSA. The diversity adjusted required information size (DARIS) was calculated according to the proportion of AE/ARs in the control group (CEP) of 49%; risk ratio reduction (RRR) of 20% in the experimental intervention group; alpha of 1.7%; beta of 10% (90% power); and diversity 62%. The DARIS size was 3645 participants. The cumulative Z-curve (blue line) did not cross the trial sequential boundaries for benefit or harm nor the inner-wedge futility line (red

outward sloping red lines) nor the DARIS. The light blue dotted lines show conventional boundaries (alpha 5%).

Fig. S2. Meta-analysis and TSA for proportion of participants without resolution of fluid overload for loop diuretics vs. placebo/no intervention



a) Meta-analysis. b) TSA. The diversity adjusted required information size (DARIS) was calculated according to the proportion of participants without resolution of fluid overload in the control group (CEP) of 47%; risk ratio reduction (RRR) of 20% in the experimental intervention group; alpha of 1.7%; a beta of 10% (90% power); and diversity 0%. The DARIS was 1487 participants. The cumulative Z-curve (blue line) did not cross the trial sequential boundaries for benefit or harm or the inner-wedge futility line (red outward sloping red lines) nor the DARIS. The light blue dotted lines show naïve conventional boundaries (alpha 5%).

Fig. S3. Meta-analysis for single serious adverse event - renal replacement therapy, for loop diuretics vs. placebo/no intervention

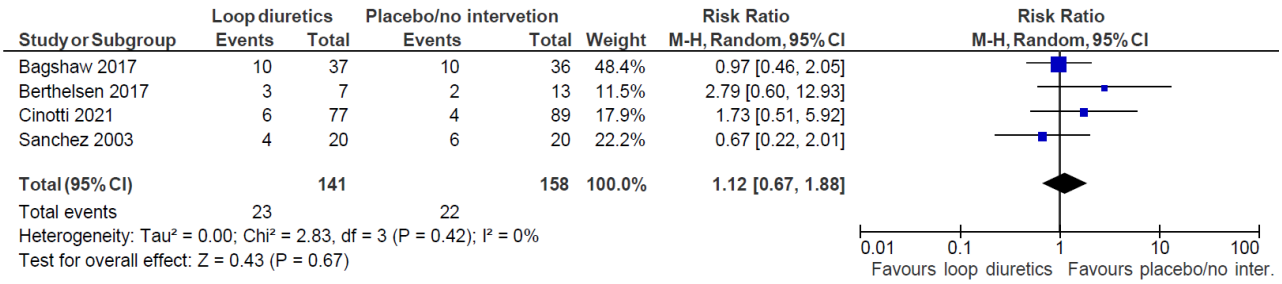


Fig. S4. Meta-analysis for single serious adverse event - worsening of acute kidney injury, for loop diuretics vs. placebo/no intervention

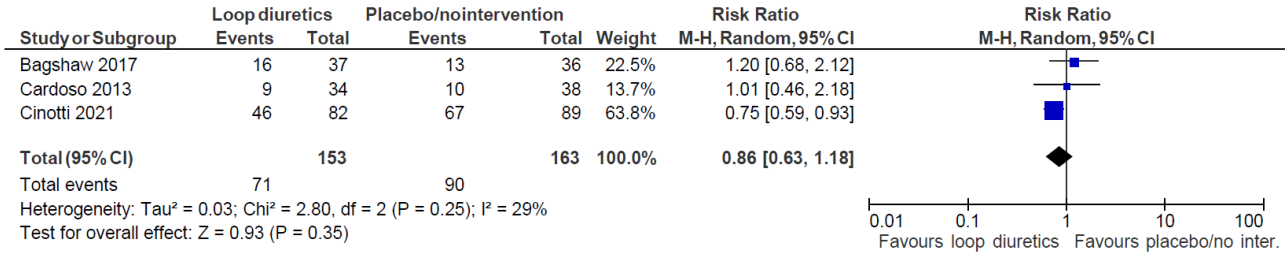
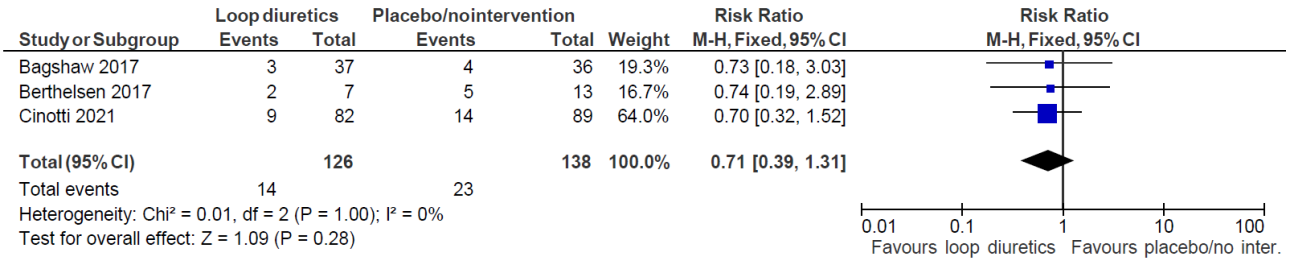


Fig. S5. Meta-analysis for single serious adverse event - atrial fibrillation, for loop diuretics vs. placebo/no intervention



S6c. Subgroup analyses

Fig. S6. Subgroup analysis of ICU diagnosis for all-cause mortality for loop diuretics vs. placebo/no intervention

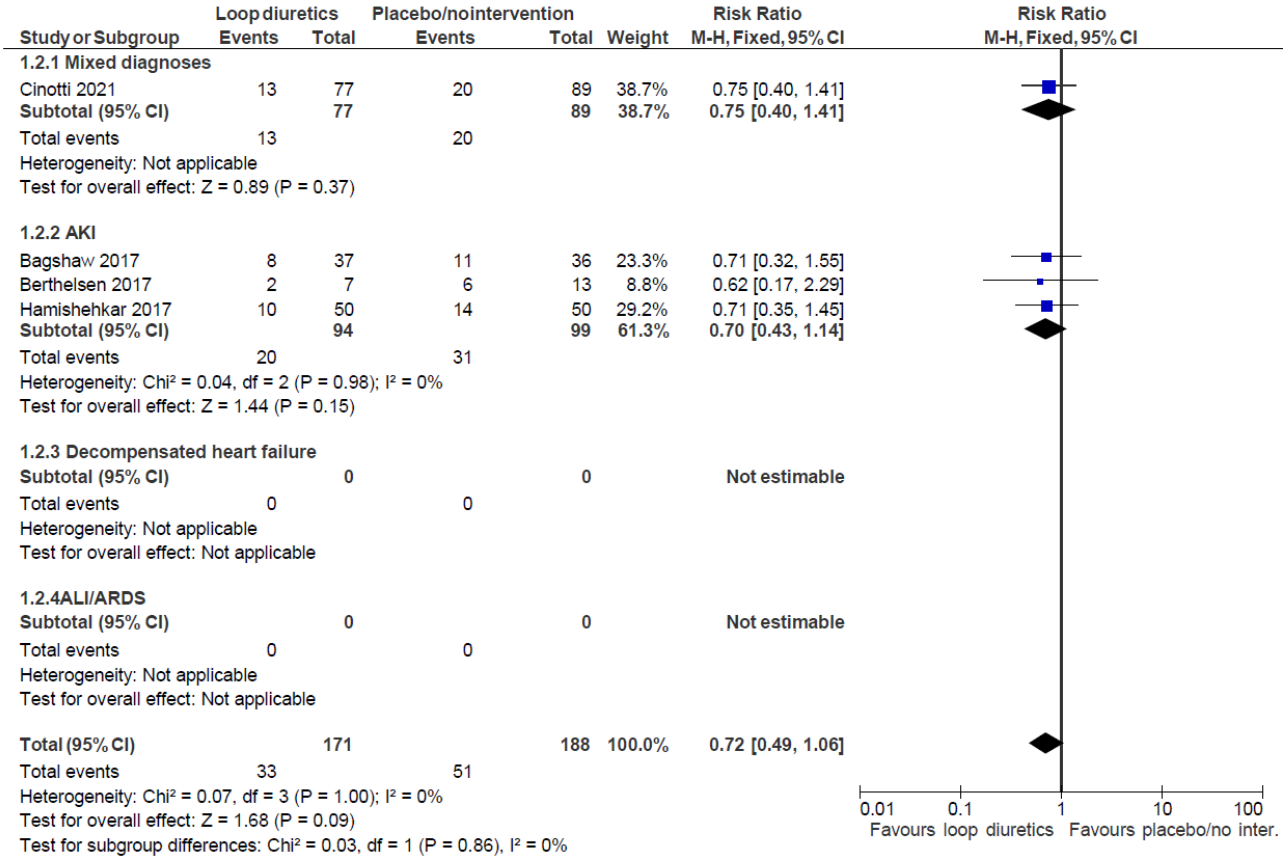


Fig. S7. Subgroup analysis of ICU population for all-cause mortality for loop diuretics vs. placebo/no intervention

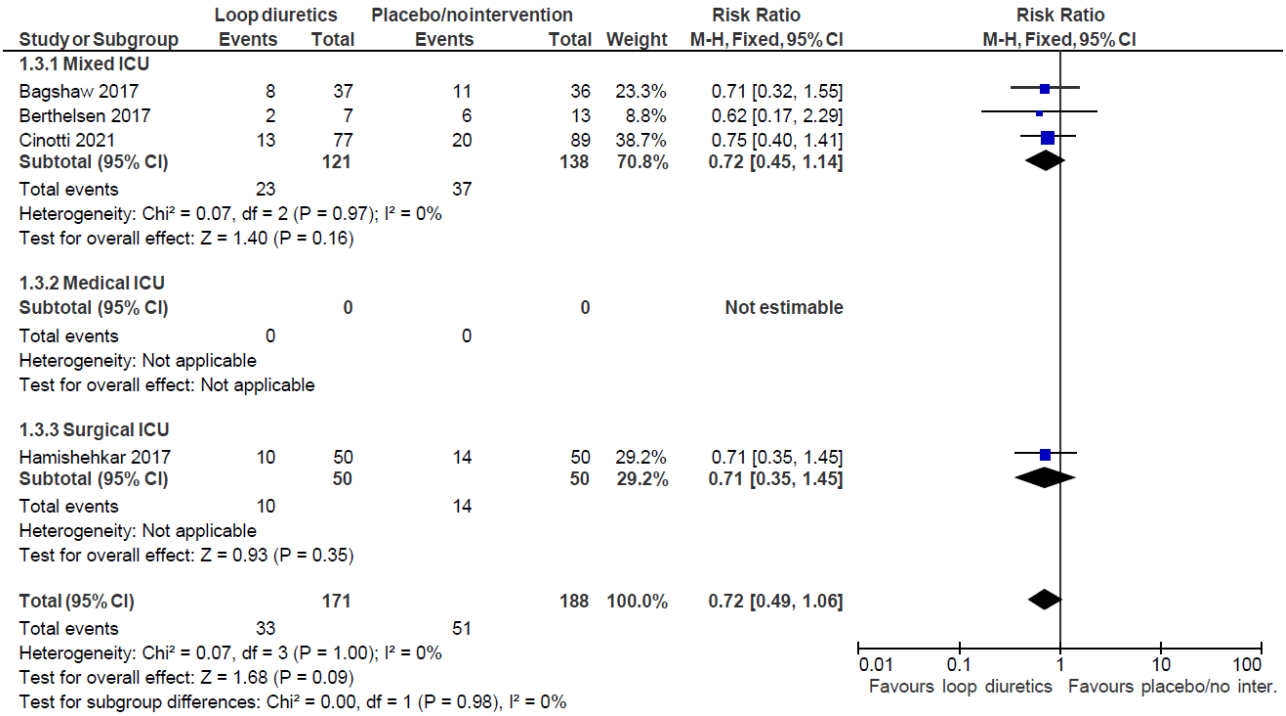


Fig. S8 Subgroup analysis of severity of fluid overload for all-cause mortality for loop diuretics vs. placebo/no intervention

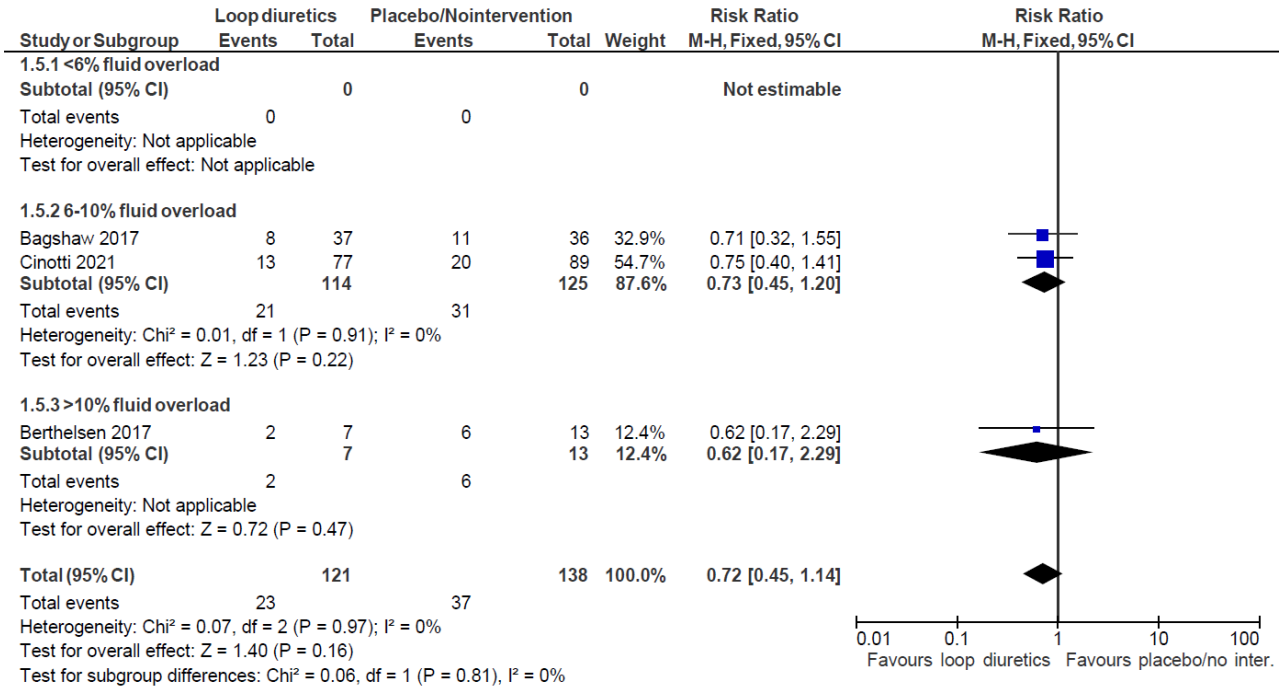


Fig. S9. Subgroup analysis of administration of diuretics in the control group for all-cause mortality for loop diuretics vs. placebo/no intervention

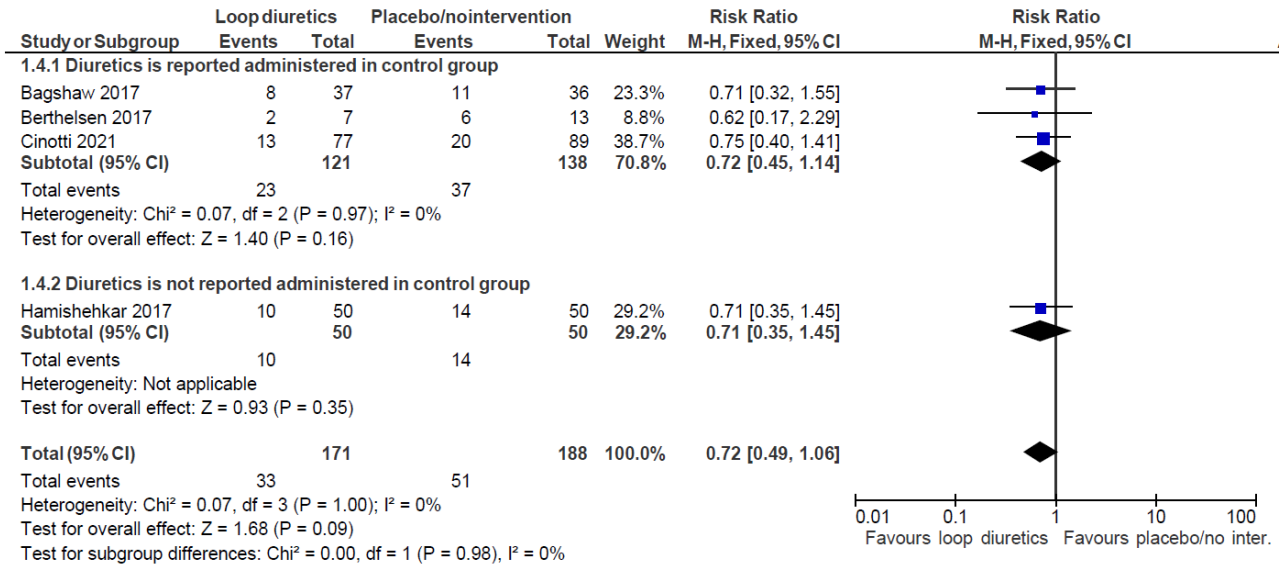


Fig. S10. Subgroup analysis of ICU diagnosis for serious adverse events for loop diuretics vs. placebo/no intervention

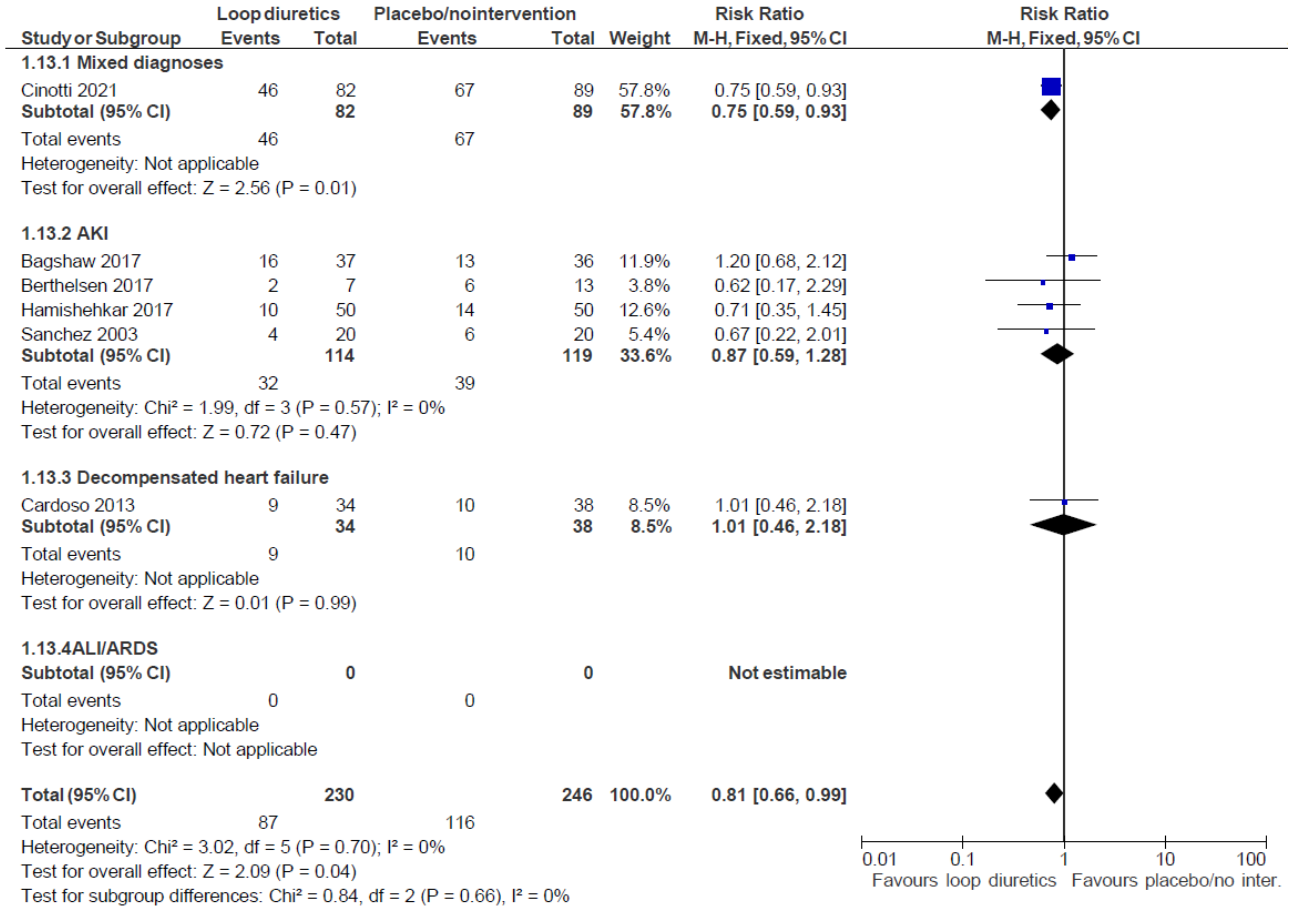


Fig. S11. Subgroup analysis of ICU population of serious adverse events for loop diuretics vs. placebo/no intervention

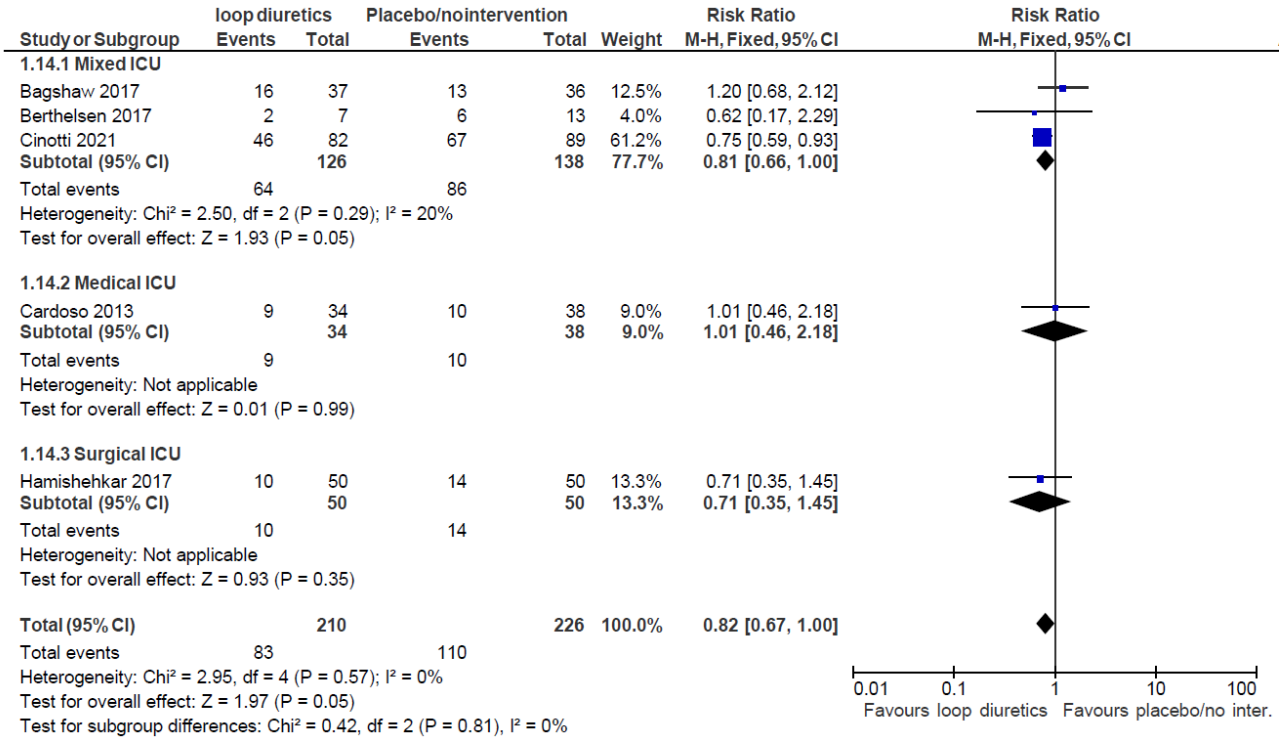


Fig. S12. Subgroup analysis of severity of fluid overload for serious adverse events for loop diuretics vs. placebo/no intervention

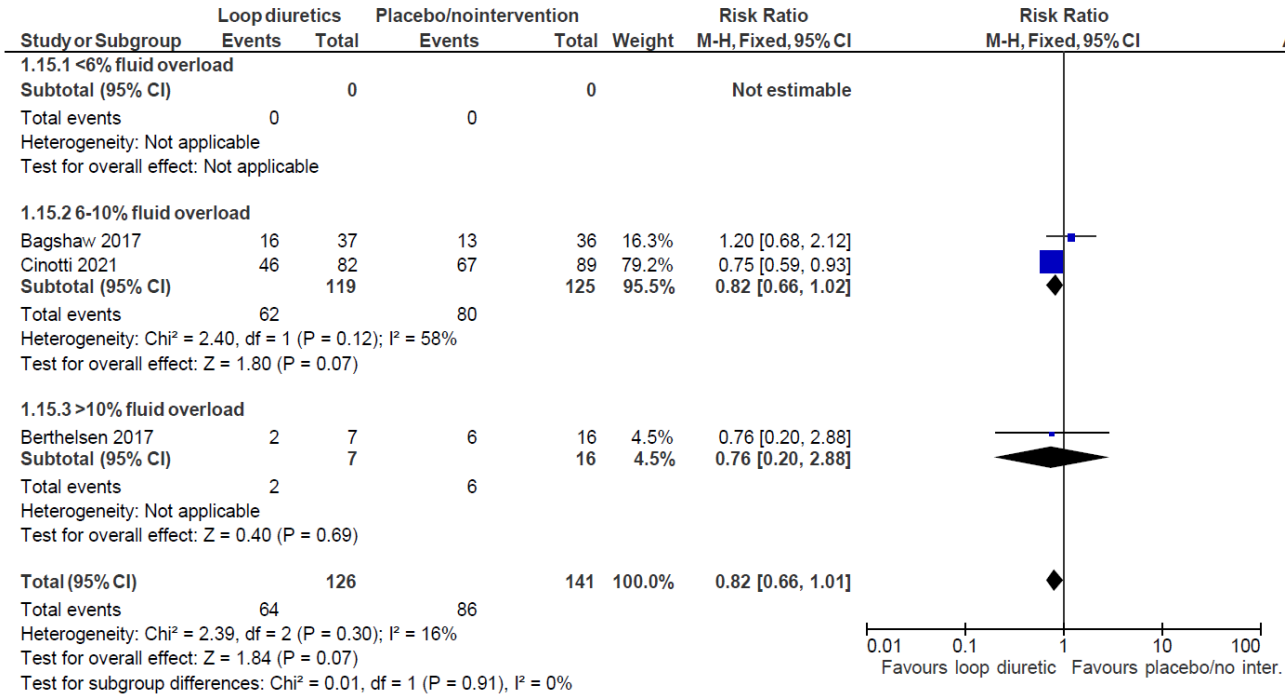
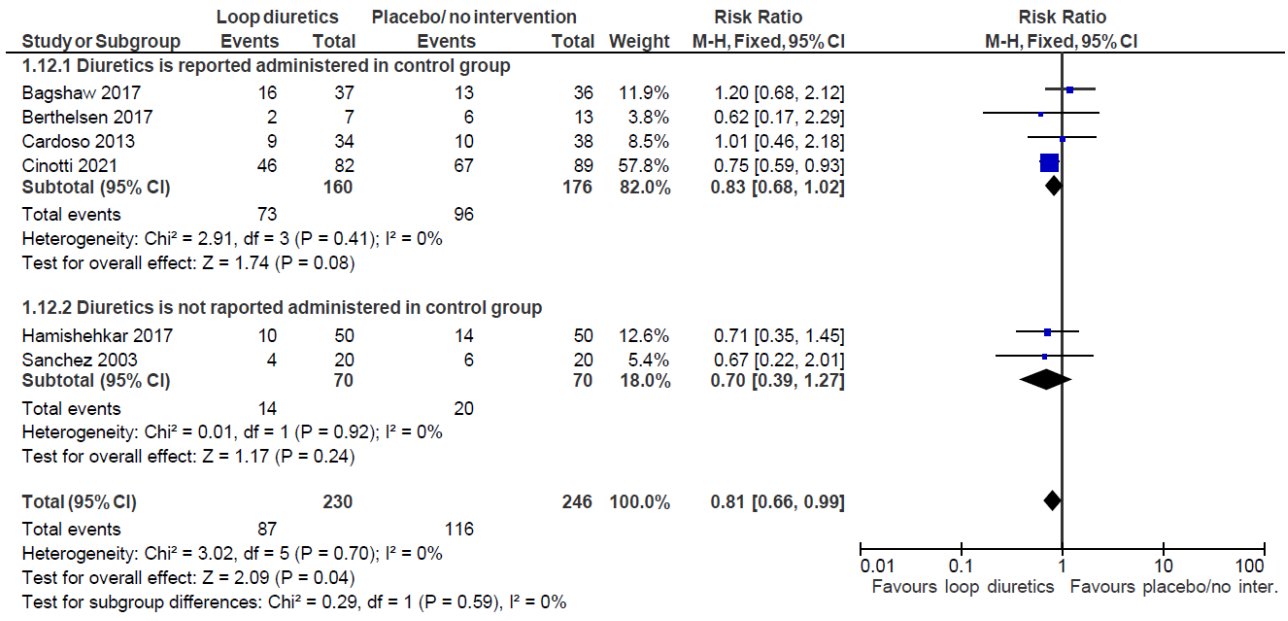


Fig. S13. Subgroup analysis of administration of diuretics in the control group for serious adverse events for loop diuretics vs. placebo/no intervention



S6d. Sensitivity analyses

Fig. S14. Sensitivity analysis, best – worst case scenario, of all-cause mortality for loop diuretics vs. placebo/no intervention

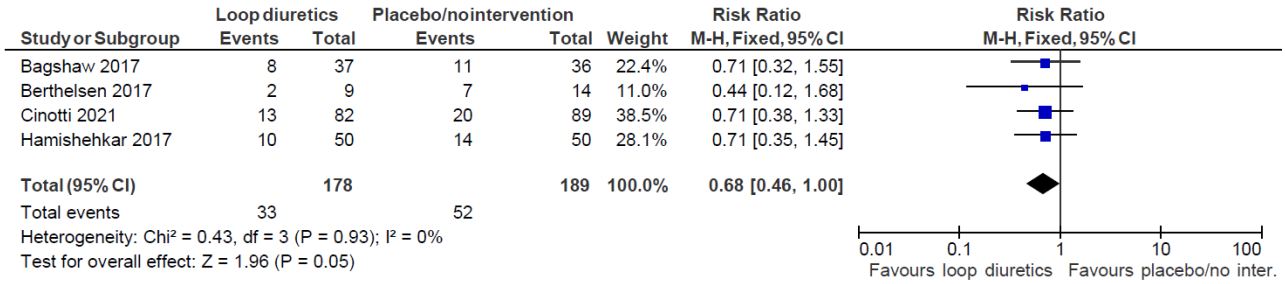


Fig. S15. Sensitivity analysis, worst – best case scenario, of all-cause mortality for loop diuretics vs. placebo/no intervention

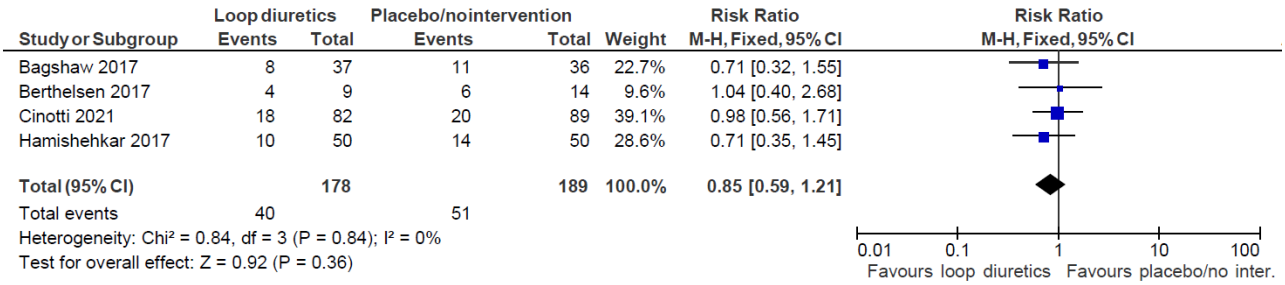


Fig. S16. Sensitivity analysis, best-worst case scenario, of serious adverse events for loop diuretics vs. placebo/no intervention

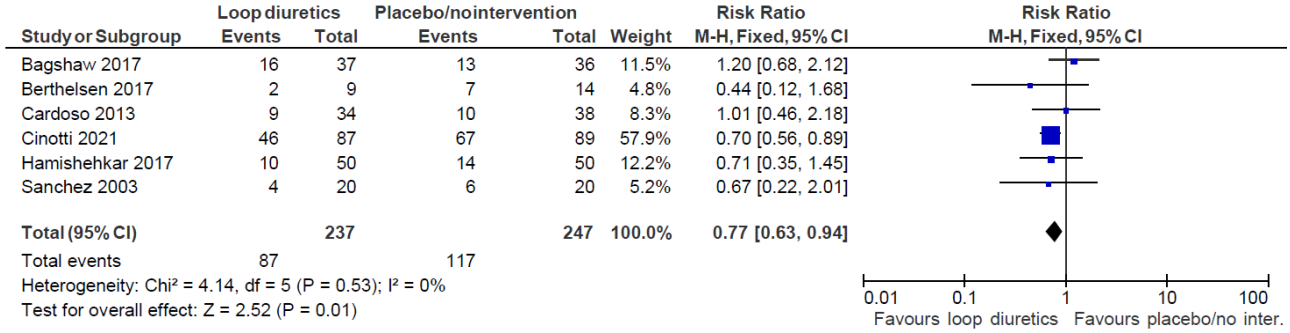


Fig. S17. Sensitivity analysis, worst - best case scenario, of serious adverse events for loop diuretics vs. placebo/no intervention

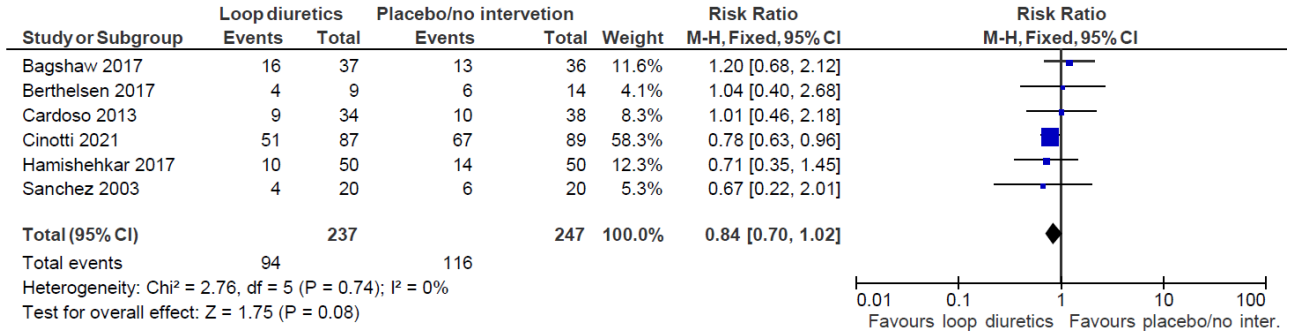


Fig. S18. Sensitivity analysis, best - worst scenario, of proportion of participants without resolution of fluid overload for loop diuretics vs. placebo/no intervention

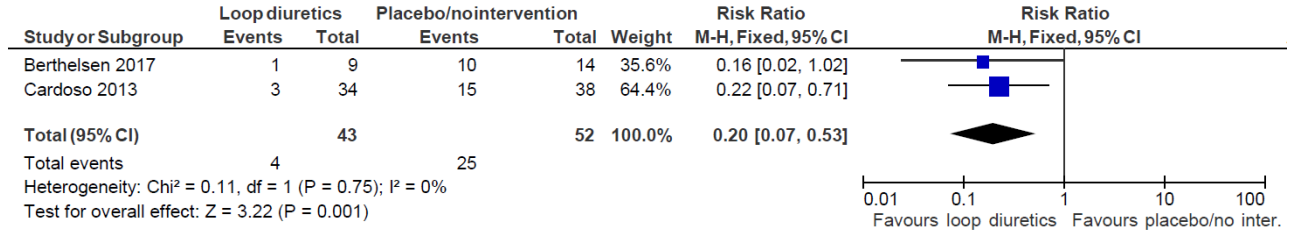


Fig. S19. Sensitivity analysis, worst - best scenario, of proportion of participants without resolution of fluid overload for loop diuretics vs. placebo/no intervention

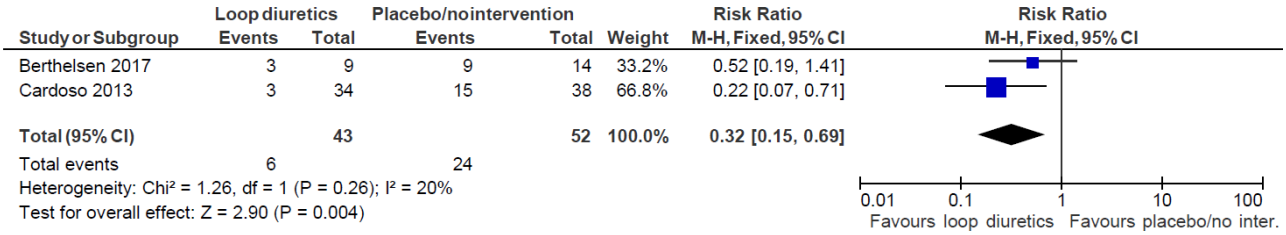


Fig. S20. Sensitivity analysis, best - worst scenario, of adverse events not considered serious for loop diuretics vs. placebo/no intervention

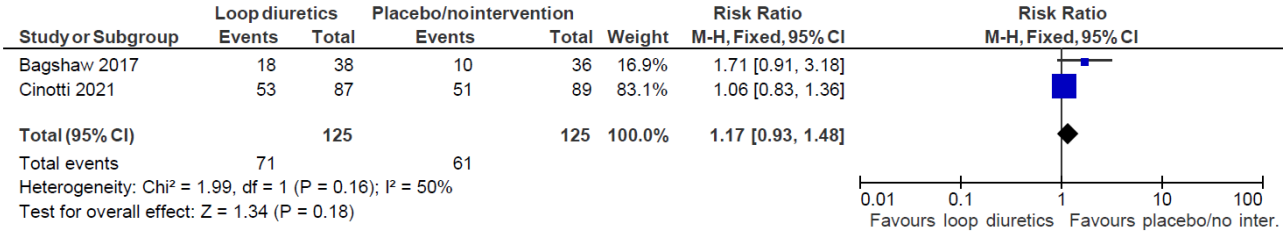
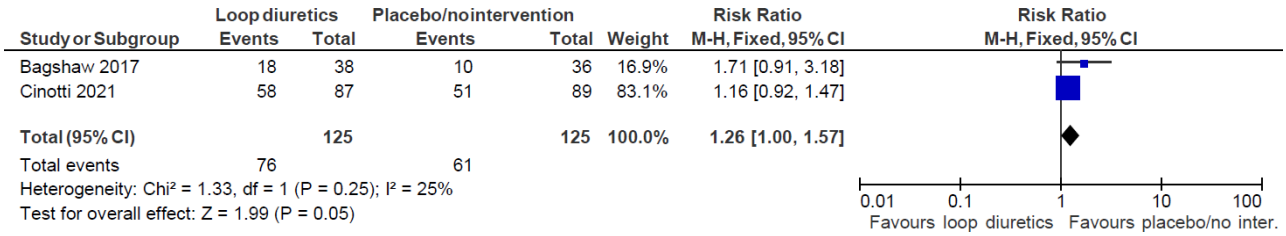


Fig. S21. Sensitivity analysis, worst - best scenario, of adverse events not considered serious for loop diuretics vs. placebo/no intervention



S6e. Reported SAEs and AEs

Serious adverse events and adverse events not considered serious, which includes reactions to trial drug (serious adverse reaction and adverse reaction) are often not reported or not reported according to the ICH-GCP guidelines. If adverse events are reported, they are seldom divided in serious and not serious. We extracted all SAE and AE from the trials according to ICH-GCP guideline – also events not categorised as adverse events by the authors.

Table S14. Single SAEs and AEs for loop diuretics vs placebo/no intervention

Loop diuretics vs placebo/no intervention			
Trials	**Single SAE**	**Intervention group**	**Control group**
Bagshaw [52]	RRT	10	10
	Worsening of AKI	16	13
	Ventricular Tachycardia/ventricular fibrillation	2	0
	Tinnitus	0	1
	Supraventricular tachycardia	3	4
	Mortality	8	11
Berthelsen [37]	RRT	3	2
	Atrial fibrillation	2	5
	Ischaemic event	1	1
	Anaemia requiring transfusion	2	3
	Hypokalaemia	2	0
	Thrombocytopenia < 50 x 10^9/L	2	2
	Pancreatitis	0	1
	Seizure	0	1
	Arrythmia	1	3
	Mortality	2	6
Cardoso [55]	Worsening AKI	9	10
Cinotti [54]	RRT	6	4
	Worsening of AKI	46	67
	Atrial fibrillation	9	14
	Torsade de pointes	1	0
	Ventricular fibrillation	1	2
	Ventricular tachycardia	2	2
	Mortality	13	20
Hamishehkar [56]	Mortality	10	14
Sanchez [57]	RRT	4	6
Trials	**Single AE**	**Intervention group**	**Control group**
Bagshaw [52]	Drug reaction	1	1
	Elevated lever enzymes	0	1
	Serum sodium ≥ 150 mmol/L	9	1

	Serum potassium < 3.0 mmol/L	4	2
	Serum magnesium < 0.7 mmol/L	2	4
	Serum bicarbonate ≥ 30 or pH ≥ 7.5	18	10
Berthelsen [37]	-	-	-
Cardoso [55]	-	-	-
Cinotti [54]	Serum sodium ≥ 145 mmol/L	40	40
	Serum sodium ≤135 mmol/L	33	42
	Serum potassium ≤ 3.5 mmol/L	53	51
Hamishehkar [56]	-	-	-
Sanchez [57]	-	-	-

Renal replacement therapy = RRT, Acute kidney injury = AKI

S7. Comparison: loop diuretics vs another loop diuretic

S7a. Risk of bias

Table S15. Risk of bias assessment on plasma creatinine for loop diuretics (furosemide) vs. another loop diuretic (piretanide or ethacrynic acid)

Study	Rando-misation	Deviations from intervention	Missing outcome data	Measure-ment of the outcome	Selection of the reported results	Overall risk of bias
Han	**Some concerns**[1]	Low	Low	Low	**Some concerns**[2]	**High**

1. Randomisation process not described.
2. Short protocol without statistical analysis plan was attached in the trial registry. One secondary outcome in the protocol was not reported in the article.

Table S16. Risk of bias assessment on plasma sodium and potassium for loop diuretics (furosemide) vs. another loop diuretic (piretanide or ethacrynic acid)

Study	Rando-misation	Deviations from intervention	Missing outcome data	Measure-ment of the outcome	Selection of the reported results	Overall risk of bias
Han	**Some concerns**[1]	Low	Low	Low	**Some concerns**[2]	**High**
Wappler	**Some concerns**[1]	**High**[3]	Low	Low	**Some concerns**[4]	**High**

1. Randomisation process not described.
2. Short protocol without statistical analysis plan was attached in the trial registry. One secondary outcome in the protocol was not reported in the article.
3. No information about blinding or deviations for intended interventions.
4. No published protocol, statistical analysis plan or registration in a trial registry.

Table S17. Risk of bias assessment on serious adverse events for loop diuretics (furosemide) vs. another loop diuretic (piretanide or ethacrynic acid)

Study	Rando-misation	Deviations from intervention	Missing outcome data	Measure-ment of the outcome	Selection of the reported results	Overall risk of bias
Han	**Some concerns**[1]	Low	Low	Low	**Some concerns**[2]	**High**

1. Randomisation process not described.
2. Short protocol without statistical analysis plan was attached in the trial registry. One secondary outcome in the protocol was not reported in the article.

Table S18. Risk of bias assessment on adverse events not considered serious for loop diuretics (furosemide) vs. another loop diuretic (piretanide or ethacrynic acid)

Study	Rando-misation	Deviations from intervention	Missing outcome data	Measure-ment of the outcome	Selection of the reported results	Overall risk of bias
Han	**Some concerns**[1]	Low	Low	Low	**Some concerns**[2]	**High**

1. Randomisation process not described.
2. Short protocol without statistical analysis plan was attached in the trial registry. One secondary outcome in the protocol was not reported in the article.

S7b. Meta-analyses

Fig. S22. Meta-analysis for plasma concentration of sodium for loop diuretics vs. another loop diuretic

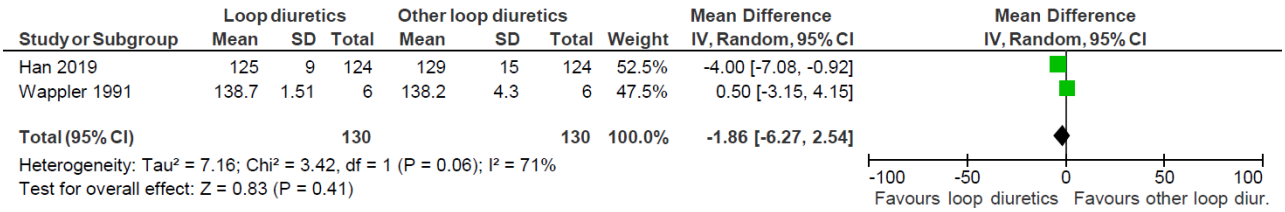
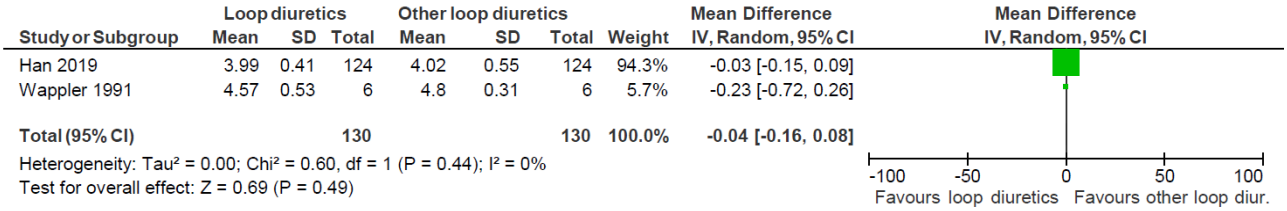


Fig. S23. Meta-analysis for plasma concentration of potassium for loop diuretics vs. another loop diuretic



S7c. Narrative description of the results

Results for loop diuretics (furosemide) vs. another loop diuretic (piretanide or ethacrynic acid)

Two trials compared loop diuretic vs another loop diuretic (260 participants) [58, 59]. Both trials represented patients from cardiac ICUs. One trial with 12 participants tested furosemide vs piretanide [58]. The other trial investigated furosemide vs ethacrynic acid in 248 participants [59]. The outcomes reported by the two trials were at overall high risk of bias. No data were reported on primary outcomes. Only two secondary outcomes (creatinine and AEs) were reported in one trial [59].

There was no difference in creatinine concentration between the group treated with loop diuretics vs another type of loop diuretic (ethacrynic acid).

One explorative outcome, concentration of sodium and potassium, were reported on in both trials. Meta-analysis showed no difference between the groups. No data was reported on serum chloride concentration.

S7d. Reported SAEs and AEs

Table S19. Reported SAEs and AEs for loop diuretics vs. another diuretic

Loop diuretics vs another loop diuretic			
Trials	**Single SAE**	**Intervention group**	**Control group**
Han [59]	Tinnitus and hearing loss	15	23
	Seizure	3	1
Wappler [58]	-	-	-
Trials	**Single AE**	**Intervention group**	**Control group**
Han [59]	Hypocalcaemia	8	0
	Hypomagnesemia	9	0
	Oral and gastric irritation	4	1
	Constipation	4	1
	Blurred vision	5	2
	Thrombophlebitis	15	16
	Hypotension	7	13
Wappler [58]	-	-	-

S7e. Summary of findings

Table S20. Summary of findings for loop diuretics vs. another loop diuretic

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of Bias	Inconsistency	Indirectness	Impreci-sion	Other considerations	Loop diuretics	Another loop diuretic	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of life – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Serious adverse events (SAE) – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Plasma concentration of creatinine												
1	RCT	Serious[a]	Not serious[b]	Serious[c]	Serious[d]	None	124	124	No statistically significant difference in creatinine after 3 days		⨁◯◯◯ VERY LOW	CRITICAL
Proportion of participants without resolution of fluid overload – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Days in mechanical ventilation – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Length of stay in ICU – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Adverse event not considered serious (AE)												
1	RCT	Serious[a]	Not serious[b]	Serious[c]	Serious[d]	None	15/124 (12.1%)	23/124 (18.5%)	-	-	⨁◯◯◯ VERY LOW	NOT IMPORTANT

RCT: randomised clinical trials; CI: Confidence interval; RR: Risk ratio

a. The outcome was judged at overall high risk of bias
b. Cannot be assessed with only one trial.
c. This trial only included patients in cardiac ICU who were able to sign an informed consent. This leaves out other ICU populations and more severely ill patients not able to consent before entering the trial.
d. The total number of participants were 248 participants, which is concerning for imprecision.

S8. Comparison: loop diuretics vs. another type of diuretic

S8a. Risk of bias

Table S21. Risk of bias assessment on mortality for loop diuretics (furosemide) vs. another type of diuretic (acetazolamide or tolvaptan)

Study	Rando-misation	Deviations from interventio n	Missing outcome data	Measure-ment of the outcome	Selection of the reported results	Overall risk of bias
Ng	**Some concerns[1]**	**High[2]**	**High[3]**	Low	**Some concerns[4]**	**High**

1. Allocation process not described
2. No blinding. Only data on participants who remained on study protocol were registered. After the first 48 hours trial intervention was stopped in a large percentage of participants - mainly in the tolvaptan group due to clinical decisions (clinical resolution or diuretic switch to bumetanide) and additional medicine as metolazone was used more in the tolvaptan group compared to the furosemide group. This affected the outcomes with data from 48 hours to 96 hours. Per protocol analyses were performed.
3. No data on withdrawal or missing data. Mortality was not reported in the article.
4. Mortality was listed as an outcome in the protocol and article but only reported on ClinicalTrials.gov.

Table S22. Risk of bias assessment on serious adverse events for loop diuretics (furosemide) vs. another type of diuretic (acetazolamide or tolvaptan)

Study	Rando-misation	Deviations from interventio n	Missing outcome data	Measure-ment of the outcome	Selection of the reported results	Overall risk of bias
Ng	**Some concerns[1]**	**High[2]**	Low	Low	**Some concerns[3]**	**High**

1. Allocation process not described
2. No blinding. Only data on participants who remained on study protocol were registered. After the first 48 hours trial intervention was stopped in a large percentage of participants - mainly in the tolvaptan group due to clinical decisions (clinical resolution or diuretic switch to bumetanide) and additional medicine as metolazone was used more in the tolvaptan group compared to the furosemide group. This affected the outcomes with data from 48 hours to 96 hours. In the protocol it is stated that the collection of data continued in case of patients were

taken out of the intervention due to safety. These data were not included in the analyses. Per protocol analyses were performed.
3. Three outcomes in the protocol were not reported in the article – some degree of selective reporting cannot be ruled out. SAE were only reported on ClincalTrials.gov – not in the article.

Table S23. Risk of bias assessment on plasma creatinine for loop diuretics (furosemide) vs. another type of diuretic (acetazolamide or tolvaptan)

Study	Rando-misation	Deviations from interventio n	Missing outcome data	Measure-ment of the outcome	Selection of the reported results	Overall risk of bias
Ng	**Some concerns [1]**	**High[2]**	Low	Low	Low	**High**

1. Allocation process not described
2. No blinding. Only data on participants who remained on study protocol were registered. After the first 48 hours trial intervention was stopped in a large percentage of participants - mainly in the tolvaptan group due to clinical decisions (clinical resolution or diuretic switch to bumetanide) and additional medicine as metolazone was used more in the tolvaptan group compared to the furosemide group. This affected the outcomes with data from 48 hours to 96 hours. Per protocol analyses were performed.

Table S24. Risk of bias assessment on adverse events not considered serious for loop diuretics (furosemide) vs. another type of diuretic (acetazolamide or tolvaptan)

Study	Rando-misation	Deviations from intervention	Missing outcome data	Measure-ment of the outcome	Selection of the reported results	Overall risk of bias
Ng	**Some concerns [1]**	**High[2]**	Low	Low	**Some concerns[3]**	**High**

1. Allocation process not described
2. No blinding. Only data on participants who remained on study protocol were registered. After the first 48 hours trial intervention was stopped in a large percentage of participants - mainly in the tolvaptan group due to clinical decisions (clinical resolution or diuretic switch to bumetanide) and additional medicine as metolazone was used more in the tolvaptan group compared to the furosemide group. This affected the outcome data from 48 hours to 96 hours. Per protocol analyses were performed.
3. Three outcomes in the protocol were not reported in the article – some degree of selective reporting cannot be ruled out. AEs were not reported in the article but on ClincalTrials.gov.

Table S25. Risk of bias assessment on plasma sodium and potassium for loop diuretics (furosemide) vs. another type of diuretic (acetazolamide or tolvaptan)

Study	Rando-misation	Deviations from intervention	Missing outcome data	Measure-ment of the outcome	Selection of the reported results	Overall risk of bias
Brown	Low	Low	Low	Low	**Some concerns[1]**	**High**
Ng	**Some concerns[2]**	**High[3]**	Low	Low	Low	**High**

1. No protocol or analysis plan is available, but the trial was registered at New Zealand Clinical Trials Registry. In the trial registry 15 secondary outcomes were listed but only 8 outcomes were reported in the article.
2. 1 Allocation process not described
3. No blinding. Only data on participants who remained on study protocol were registered. After the first 48 hours trial intervention was stopped in a large percentage of participants - mainly in the tolvaptan group due to clinical decisions (clinical resolution or diuretic switch to bumetanide) and additional medicine as metolazone was used more in the tolvaptan group compared to the furosemide group. This affected the outcome data from 48 hours to 96 hours. Per protocol analyses were performed.

Table S26. Risk of bias assessment on plasma chloride for loop diuretics (furosemide) vs. another type of diuretic (acetazolamide or tolvaptan)

Study	Rando-misation	Deviations from interventio n	Missing outcome data	Measure-ment of the outcome	Selection of the reported results	Overall risk of bias
Brown	Low	Low	Low	Low	**Some concerns[1]**	**High**

1. No protocol or analysis plan is available, but the trial was registered at New Zealand Clinical Trials Registry. In the trial registry 15 secondary outcomes were listed but only 8 outcomes were reported in the article.

S8b. Narrative description of the results

Results for loop diuretic (furosemide) vs. another type of diuretic (acetazolamide or tolvaptan)

Two trials compared loop diuretics with another type of diuretic (58 participants) [53, 60]. One trial included mixed ICU patients and investigated the effects of furosemide vs acetazolamide over a study time of just 6 hours [53]. The other trial included patients with decompensated hearth failure in a medical ICU investigating furosemide vs tolvaptan for up to 96 hours [60]. All outcomes for both trials were at overall high risk of bias. No meta-analyses could be performed on any outcomes.

The trial testing tolvaptan [60] found a mortality of 0% in both groups. No data reported on the remaining primary outcomes. The only secondary outcome reported was plasma concentration of creatinine and of explorative outcomes: plasma concentration of sodium, potassium and single AE. No difference between the group treated with furosemide vs tolvaptan was found for plasma concentration of creatinine and potassium, but plasma sodium concentration decreased statistically significant in the group treated with furosemide and increased in the tolvaptan group. One AE was reported. All outcomes were at overall high risk of bias.

The trial testing acetazolamide [53] did not report on any of our primary outcomes. They only reported on plasma creatinine, sodium, potassium, and chloride concentrations. The found no difference between the group treated with loop diuretics vs acetazolamide [53]. All outcomes were at overall high risk of bias.

S8c. Reported SAEs and AEs

Table S27. SAEs and AEs for loop diuretics vs. another type of diuretic

Loop diuretics vs another type of diuretic			
Trials	**Single SAE**	**Intervention group**	**Control group**
Brown [53]	-	-	-
Ng [60]	Mortality	0	0
Trials	**Single AE**	**Intervention group**	**Control group**
Brown [53]	-	-	-
Ng [60]	Plasma creatinine increase > 26.5 mmol/L	5	3

S8d. Summary of findings

Table S28. Summary of findings for loop diuretics vs another type of diuretic

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of Bias	Inconsistency	Indirect-ness	Imprecision	Other considera-tions	Loop diuretics	Another type of diuretic	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality – not reported												
1	RCT	Very serious[a]	Not serious[b]	Serious[c]	Very serious[d]	None	0/15 (0.0%)	0/18 (0.0%)	-	-	-	CRITICAL
Quality of life – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Serious adverse events (SAE) – not reported												
1[e]	RCT	Very serious[a]	Not serious[b]	Serious[c]	Very serious[d]	None	0/15 (0.0%)	0/18 (0.0%)	-	-	-	CRITICAL
Plasma concentration of creatinine												
2[f]	RCT	Serious[g]	Not serious	Serious[h]	Very serious[i]	None	-	-	The trials found no significant difference in plasma creatinine at longest follow up.		⊕◯◯◯ VERY LOW	CRITICAL
Proportion of participants without resolution of fluid overload – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Days in mechanical ventilation – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Length of stay in ICU – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Adverse event not considered serious (AE)												
1	RCT	Serious[j]	Not serious[b]	Serious[c]	Very serious[d]	None	5/15 (33.3%)	3/18 (16.7%)	The trial showed no significant difference in the highest event rate of a single AE between groups.		⊕◯◯◯ VERY LOW	NOT IMPORTANT

RCT: randomised clinical trials; CI: Confidence interval; RR: Risk ratio

a. The trial was at overall high risk of bias for this outcome. Mortality was listed as an outcome but not reported in the article only registered on ClinicalTrials.gov.
b. Cannot be assessed with only one trial

c. This trial consists of a subgroup of ICU patients with congestive heart failure able sign a consent form before enrollment. This is not representative for the ICU population in general.
d. The total number of participants were 33 participants, which is concerning for imprecision.
e. The review group registered mortality as an SAE. The mortality was reported as 0% in both groups on ClinicalTrials.gov.
f. A meta-analysis could not be performed because of unsuitable data.
g. All trials were at overall high risk of bias for this outcome
h. One trial lasted 6 hours and the other trial up to 96 hours. The time frame and different exposure to diuretics in dose and type is the reason for our judgment as serious inconsistency.
i. The total number of participants were 58 participants, which is concerning for impression.
j. The trial was at overall high risk of bias for this outcome

PAPER III

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RESEARCH ARTICLE

acta Anaesthesiologica Scandinavica

Goal-directed fluid removal with furosemide versus placebo in intensive care patients with fluid overload: A randomised, blinded trial (GODIF trial—First version)

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Abstract

Background: Salt and water accumulation leading to fluid overload is associated with increased mortality in intensive care unit (ICU) patients, but diuretics' effects on patient outcomes are uncertain. In this first version of the GODIF trial, we aimed to assess the effects of goal-directed fluid removal with furosemide versus placebo in adult ICU patients with fluid overload.

Methods: We conducted a multicentre, randomised, stratified, parallel-group, blinded, placebo-controlled trial in clinically stable, adult ICU patients with at least 5% fluid overload. Participants were randomised to furosemide versus placebo infusion aiming at achieving neutral cumulative fluid balance as soon as possible. The primary outcome was the number of days alive and out of the hospital at 90 days.

Results: The trial was terminated after the enrolment of 41 of 1000 participants because clinicians had difficulties using cumulative fluid balance as the only estimate of fluid status (32% of participants had their initially registered cumulative fluid balance adjusted and 29% experienced one or more protocol violations). The baseline cumulative fluid balance was 6956 ml in the furosemide group and 6036 ml in the placebo group; on day three, the cumulative fluid balances were 1927 ml and 5139 ml. The median number of days alive and out of hospital at day 90 was 50 days in the furosemide group versus 45 days in the placebo group (mean difference 1 day, 95% CI -19 to 21, *p*-value .94).

Conclusions: The use of cumulative fluid balance as the only estimate of fluid status appeared too difficult to use in clinical practice. We were unable to provide precise estimates for any outcomes as only 4.1% of the planned sample size was randomised.

KEYWORDS
diuretics, fluid accumulation, fluid overload, fluid therapy, furosemide, intensive care

Editorial Comment

The authors report the findings of the first version of the GODIF trial, comparing protocolised de-resuscitation with furosemide versus placebo for stable patients with fluid overload in the ICU. It was observed that clinicians frequently identified a discrepancy between listed cumulative balance and clinical examination and opted to readjust the cumulative fluid balance, rendering this measurement unreliable as the sole parameter for fluid balance. This led to the early termination of the study and a subsequent relaunch of a second version of the study using a more thorough fluid assessment tool.

1 | INTRODUCTION

Patients with critical illness admitted to intensive care units (ICU) are often treated with life-supportive interventions, administration of multiple medicines, intravenous fluid, and nutrition. This often leads to the accumulation of salt and water to the extent that many patients develop fluid overload of 5% or more. Fluid overload is a well-known risk factor for mortality in critically ill patients.[1] Fluid overload in this population is often treated with loop diuretics,[2–5] but the evidence for this clinical practice is sparse.[6,7] Clinical guidelines in this field are lacking.

We, therefore, designed the first version of the GODIF trial to assess the effects of fluid removal with furosemide versus placebo and hypothesised that furosemide would increase the number of days alive and out of the hospital after 90 days in adult ICU patients with fluid overload.

2 | METHODS

2.1 | Trial design

The GODIF trial was an investigator-initiated, randomised, stratified, parallel-group, blinded clinical trial investigating furosemide versus placebo in adult ICU patients with fluid overload.

The trial was initiated on 17 August 2020 and paused on 12 February 2021. We planned to randomise 1000 patients, but due to difficulties with trial design, we paused inclusion after 41 participants had been enrolled at three Danish ICUs. The trial was terminated on 10 May 2021 after the 90-day follow-up was completed for the 41 participants; 1-year follow-up was not performed.

We learned that the use of cumulative fluid balance as the sole parameter to assess fluid overload and neutral fluid balance was not ideal. Clinicians had the option to adjust the cumulated fluid balance on the fluid chart, but this appeared to be imprecise and impractical in daily clinical practice. Substantial protocol changes were therefore needed, which resulted in the early termination of this first version of the trial.

In this paper, we present why the trial was terminated and the full trial report of the 41 enrolled participants from the first version of the GODIF trial.

2.2 | Trial conduct

The GODIF trial was conducted following the Helsinki Declaration,[8] the International Council on Harmonisation on Good-Clinical-Practice (GCP) guideline,[9] and Danish laws including the General Data Protection Regulation. The results were reported following the Consolidated Standards of Reporting Trials (CONSORT) (Data S1).[10] The trial was approved by the Committees of Health Research Ethics in the Capital Region of Denmark: H-19080597, the Danish Medicine Agency: 2019121067, and The Capital Region Knowledge Centre for Data Compliance: P-2020-170. It was registered on ClinicalTrials.gov (NCT04180397) and EudraCT: 2019–004292-40. This first version of the GODIF trial was based on protocol version 2.4 and 2.5 which can be accessed at http://www.cric.nu/godif-protocol/. The trial was externally monitored.

2.3 | Randomisation, allocation concealment, and blinding

The Copenhagen Trial Unit conducted central web-based randomisation with a computer-generated allocation sequence stratified by acute kidney injury (AKI),[11] simplified mortality score for the intensive care unit (SMS-ICU),[12] and trial site with varying block sizes unknown to the investigators. The patients were randomised in a 1:1 ratio to furosemide versus placebo. The allocation list was exclusively known by the data manager.

Clinical staff, patients, investigators, outcome assessors, and statisticians were all blinded to the allocation group. The trial drug was furosemide 10 mg/mL or placebo (0.9% saline) produced by the Capital Region Pharmacy (Herlev, Denmark) in identical 50 ml vials.

2.4 | Inclusion and exclusion criteria

We screened patients for inclusion who (1) were acutely admitted to the ICU; (2) were aged 18 years or above; (3) had fluid overload defined as a positive cumulative fluid balance corresponding to minimum of 5% of ideal body weight; and (4) were clinical stable as assessed by the treating clinician. The criteria for clinical stability were mean arterial pressure above 50 mmHg and maximum infusion noradrenaline of 0.20 μ/kg/min and lactate below 4.0 mmol/L.

Exclusion criteria are described in Data S2.

2.5 | Trial interventions

Initially, an intravenous bolus of 0.5–4.0 ml (equal to 5–40 mg furosemide) of the trial drug was administered according to the treating physician's discretion followed by continuous intravenous infusion of the trial drug starting at 2 ml/h (equal to 20 mg/h). The trial drug was titrated to effect and to achieve the goal for the daily negative fluid balance defined as a minimum of 1 ml/kg ideal body weight/h. The allowed infusion rate was 0.0–4.0 ml/h. The intervention continued until a neutral fluid balance was met (defined as ±750 ml in cumulative fluid balance). A neutral cumulative fluid balance should be maintained for the rest of the ICU stay to a maximum of 90 days. If the patient was readmitted to the ICU within 90 days, the trial intervention continued if the participant still had fluid overload according to the cumulative fluid balance.

Escape use of open-label furosemide could be administered in case of hyperkalaemia (plasma potassium >6.0 mmol/L), pulmonary oedema, or respiratory failure (PaO_2/FiO_2 < 26 kPa (200 mmHg)) due to fluid overload as assessed by the treating physician.

Renal replacement therapy could be commenced if one of the above-mentioned escape criteria were present or in case of AKI leading to severe metabolic acidosis (pH below 7.2 and standard base excess less than −10 mmol/L) or persistent AKI for more than 72 h (defined as oliguria/anuria or serum creatinine not declined to 50% from peak value).

If patients were treated with diuretics before admission to hospital the treatment was allowed to be continued at the physician's discretion. In case of development of hypernatremia thiazides or aldosterone antagonists could be added as treatment for the high sodium level.

In case of signs of hypoperfusion with lactate ≥4.0 or mean arterial pressure below 50 mmHg resistant to vasopressor/inotropes or mottling beyond the edge of the kneecaps, the trial drug had to be paused and careful resuscitation with judicious fluid boluses could be performed. The trial drug should be resumed in a 25% reduced dose when all four criteria had been resolved for a minimum of 1 h.

If a patient had clinical signs of fluid overload despite a neutral cumulative fluid balance or was clinically dehydrated before achieving a neutral cumulative fluid balance, the clinicians could estimate a more precise cumulative fluid balance and continue the trial intervention with this adjusted cumulative fluid balance. This adjustment was allowed for safety reasons.

2.6 | Outcomes

2.6.1 | Primary outcome

Days alive and out of hospital at day 90 after randomisation.

2.6.2 | Secondary outcomes

All-cause mortality at day 90 after randomisation; days alive without life support (vasopressors/inotropes, mechanical ventilation, or renal replacement therapy) at day 90; the number of patients with one or more serious adverse events (SAE) and serious adverse reactions (SAR) to furosemide.

2.7 | Statistical analyses

We estimated that 1000 participants were needed to detect an improvement of 8% in the number of days alive and out of hospital with a power of 90% at an alpha level of 5%. Due to the early termination of the trial, we were not able to achieve the desired sample size and power. The accrued sample size of only 41 participants necessitated changes from our statistical analysis plan described in our protocol (http://www.cric.nu/godif-protocol/).

Baseline data were reported as medians with interquartile ranges (IQRs) for continuous variables and numbers and percentages for categorical variables.

The primary analyses were based on the intention-to-treat population, defined as all randomised patients with consent to use their data. Due to the small sample size, we did not perform secondary analyses based on the per-protocol population.

An unadjusted linear regression was used for the primary outcome–days alive and out of the hospital at day 90. A linear regression adjusted for the stratification variables (AKI, SMS-ICU score, site) was also performed and supplemented with a Wilcoxon rank sum test. A confidence interval (CI) not including 0.0 or a *p*-value of less than .05 were considered statistically significant for the primary outcome.

Binary secondary outcomes were analysed using an unadjusted generalised linear model with log link and binominal error distribution and with the same adjustment strategy as the primary outcome and supplemented with Fischer's exact test. Continuous secondary outcomes were analysed using an unadjusted linear regression supplemented with the same adjustment strategy as the primary outcome and a Wilcoxon rank sum test. A CI interval not including 1.0 [for relative risk ratio (RR)] or 0.0 [for mean difference (MD)] or *p*-values less than .01 were considered statistically significant for the secondary outcomes.

An unadjusted Kaplan–Meier plot was used to illustrate all course mortality at day 90 according to time.

Subgroup analyses were not performed due to the small sample size but the primary outcome according to subgroups is presented. We had no missing outcome data but missing data on body weight; imputation was not performed.

3 | RESULTS

A total of 41 participants were included: 20 randomised to furosemide versus 21 to placebo. The intervention was discontinued in

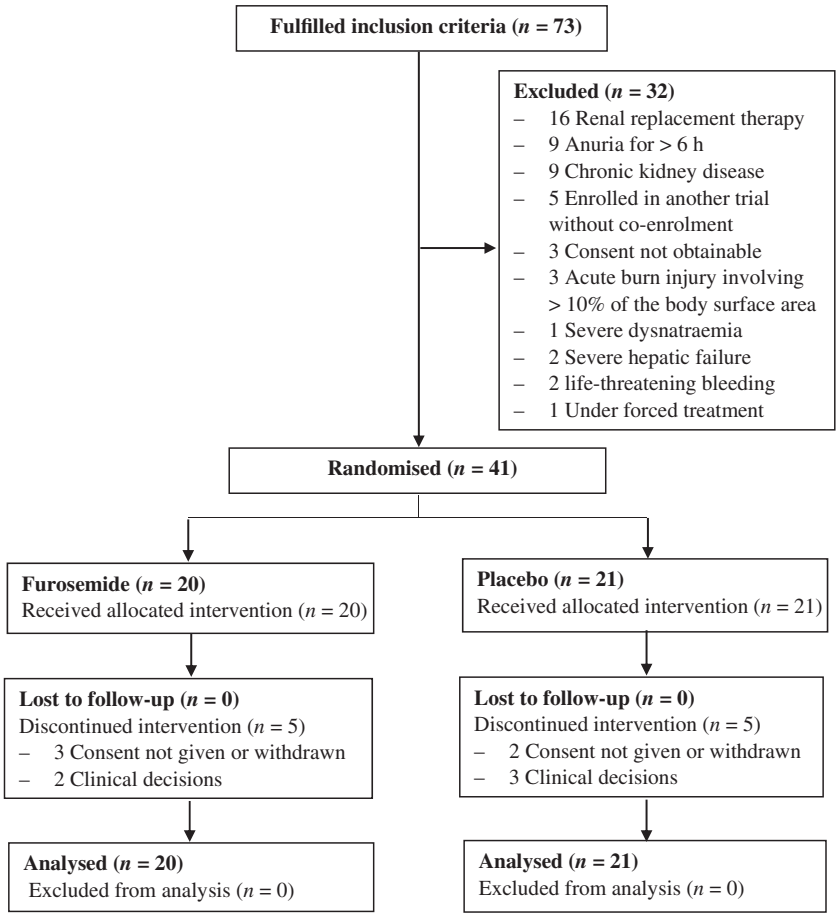

FIGURE 1 Screening, randomisation, and follow-up in the first version of the GODIF trial. Eleven patients had more than one exclusion criteria

five participants in both groups, but data registration was continued for all participants. Follow-up at day 90 was completed for all participants (Figure 1). Baseline characteristics are described in Table 1.

The median fluid removal on days 3, 5, and 90 was 5029 ml, 5405 ml, and 6087 ml for the furosemide group versus 897 ml, 1468 ml, and 2904 ml for the placebo group. A neutral cumulative fluid balance during ICU stay was achieved by 9 (45%) of participants in the furosemide group versus 7 (33%) in the placebo group. Escape use of open-label furosemide was administered in 3 (15%) and 11 (52%) of the participants, respectively.

Clinicians frequently experienced a discrepancy between the listed cumulative fluid balance and the clinical examination to a degree that they used the option to adjust the cumulative fluid balance in the fluid chart in 8 (40%) participants in the furosemide group versus 5 (24%) participants in the placebo group. For some of these participants, an adjustment of the cumulative fluid balance was made more than once. This made it difficult to register the cumulative fluid balance in a meaningful manner. All the reported fluid balances are the original fluid balances, and the manual adjustments of the cumulative fluid balance are only reported as events in Table 2.

Detailed results for cumulative fluid balance, trial drug administration, and protocol violations are presented in Table 2 and in Data S3.

3.1 | Outcomes

At 90 days, the median number of days alive and out of the hospital in the furosemide group was 50 days in the furosemide group versus 45 days in the placebo group, MD 1 day, 95% CI -19 to 21, *p*-value .94 (Tables 3 and 4). Mortality at 90 days in the furosemide group was 8 participants (40%) in the furosemide group versus six participants (29%) in the placebo group (Table 3 and Figure 2). Median days alive without life support at day 90 after randomisation were 72 days in the furosemide group versus 76 days in the placebo group (Table 3). The number of patients with one or more SAR or events in the furosemide group was 5 (25%) versus 3 (14%) in the placebo group (Table 3). Detailed reports of SAE and reactions are presented in Data S4.

4 | DISCUSSION

We are unable to provide any exact estimates on the benefits or harms of furosemide versus placebo in adult ICU patients with fluid overload for any of the outcomes because only 4.1% of the planned sample size was enrolled at the time of termination of this first version of the GODIF trial. We used the cumulative fluid balance as the only parameter to define both fluid overload and neutral fluid

TABLE 1 Baseline characteristics of the first version of the GODIF trial

Characteristic	Furosemide $N = 20$	Placebo $N = 21$
Age in years – median (IQR)	74 (67–77)	70 (62–75)
Sex—*n* (%)		
Female	12 (60%)	11 (52%)
Male	8 (40%)	10 (48%)
Type of admission—*n* (%)		
Medical	9 (45%)	10 (48%)
Surgical	11 (55%)	11 (52%)
Ischaemic heart disease or heart failure—*n* (%)	4 (20%)	1 (4.8%)
Chronic obstructive pulmonary disease—*n* (%)	4 (20%)	3 (14%)
Diabetes mellitus—*n* (%)	4 (20%)	2 (9.5%)
Stroke or neurodegenerative illness—*n* (%)	5 (25%)	1 (4.8%)
Treatment with diuretics before hospital admittance—*n* (%)	3 (15%)	7 (33%)
Admitted to the ICU from the following locations—*n* (%)		
Emergency department	9 (45%)	2 (9.5%)
Hospital ward	4 (20%)	10 (48%)
Operating room	7 (35%)	8 (38%)
Another ICU	0 (0%)	1 (4.8%)
Septic shock prior to enrolment—*n* (%)	8 (40%)	9 (43%)
SARS-CoV-2 infection—*n* (%)	0 (0%)	2 (9.5%)
Height in cm—median (IQR)	170 (162–181)	170 (161–178)
Weight in kg—median (IQR)	72 (61–83)	77 (66–89)
Ideal body weight in kg—median (IQR)	63 (58–72)	64 (57–70)
Cumulative fluid balance in ml—median (IQR)	6956 (5025–9890)	6036 (4100–7682)
Fluid overload in percentage of ideal body weight—median (IQR)	11.2 (7.4–13.0)	8.1 (6.5–13.6)
Respiratory support—*n* (%)	16 (80%)	17 (81%)
Vasopressors/inotropes—*n* (%)	12 (60%)	16 (76%)
Diuresis the last 24 h—median (IQR)	2145 (1415–2425)	2120 (1675–2540)
Creatinine in µmol/L—median (IQR)[a]	78 (53–168)	92 (65–144)
Acute kidney injury—*n* (%)	7 (35%)	5 (24%)
Grade AKI according to KDIGO—*n* (%)[b]		
0	13 (65%)	16 (76%)
1	1 (5.0%)	1 (4.8%)
2	4 (20%)	2 (9.5%)
3	2 (10%)	2 (9.5%)
Predicted 90-day mortality in %—median (IQR)[c]	30 (20–43)	40 (25–47)

[a]The highest measured plasma creatinine within the 24 h before enrolment.
[b]Grade of acute kidney injury defined by kidney disease: Improving Global Outcomes (KDIGO).[11]
[c]The predicted mortality was calculated from the simplified mortality score for the ICU and represents the risk of death at day 90 in percentage.[12]

balance. This was often perceived to be unacceptably imprecise by the treating physicians who frequently used the protocolised possibility to adjust the cumulative fluid balance according to their best clinical judgements. Fluid charts are prone to registration errors and particularly during longer stays in the ICU there is a widening gap between charted fluid balance and body weight.[13] Furthermore, fluid status prior to hospitalisation and/or admittance to the ICU is inherently difficult to assess. The frequent adjustments in the cumulative fluid balance were a huge challenge for the trial, and it made meaningful data registration difficult or impossible. These problems probably also affected the dosing of the trial drug. Protocol violations were common in the placebo group (43% of the participants) which might reflect that the standard of care for this group of patients often includes diuretics.

This first version of the GODIF trial became a very small trial and results cannot be generalised, but the 90-day mortality rates were

TABLE 2 Cumulative fluid balances, trial drug administration, and protocol violations in the first version of the GODIF trial

	Furosemide *N* = 20	Placebo *N* = 21
Urine output in mL per day in ICU—median (IQR)	2698 (2322–3161)	1758 (1315–2172)
Cumulative fluid balance at day 3—median (IQR)	1927 (654–4146)	5139 (3198–9042)
Cumulative fluid balance at day 5—median (IQR)	1551 (−247 to 3299)	4568 (2345–6277)
Cumulative fluid balance at day 90—median (IQR)[a]	868 (−678 to 3027)	3132 (690–5114)
Achievement of neutral fluid balance within 90 days—*n* (%)[b]	9 (45%)	7 (33%)
Days until neutral fluid balance—median (IQR)[c]	3.0 (2.0–4.0)	5.0 (4.0–10.5)
Patients with at least one adjustment of the cumulative fluid balance—*n* (%)[d]	8 (40%)	5 (24%)
Trial drug in mL in ICU within 90 days—median (IQR)	45 (25–90)	342 (151–666)
Number of patients who received escape open-label furosemide—*n* (%)	3 (15%)	11 (52%)
Dose of escape open-label furosemide in mg—median (IQR)	40 (30–55)	280 (100–375)
Escape use of RRT—*n* (%)	0 (0%)	1 (4.8%)
Change in body weight from baseline to ICU discharge in kg—median (IQR)[e]	−4.0 (−5.9 to 1.3)	−4.2 (−5.4 to −0.5)
Missing—*n*	12	10
Total number of protocol violations—*n*	16	69
Number of participants with one or more protocol violations—*n* (%)[f]	3 (15%)	9 (43%)

[a]The latest registered cumulative fluid balance from the ICU within 90 days.
[b]Neutral fluid balance is defined as ±750 ml on the cumulative fluid balance.
[c]Calculated for participants achieving neutral fluid balance in the ICU within 90 days.
[d]If a clinician found that the cumulative fluid balance was significantly different from the fluid status assessed by clinical examination, the clinician could choose to adjust the cumulative fluid balance in the patient record to match the clinical findings and continue the intervention from this new assessment. This was due to safety and the aim of obtaining a true neutral fluid balance.
[e]Calculated based on the body weight from the last day of the latest ICU discharge within 90 days.
[f]Detailed description of protocol violations in Supplementary Information.

TABLE 3 Primary and secondary outcomes of the first version of the GODIF trial

	Furosemide *N* = 20	Placebo *N* = 21	Absolute mean difference or relative risk	*p*-value
Primary outcome			(95% CI)	
Days alive and out of hospital at day 90, median (IQR)	50 (0–66)	45 (0–62)	1 (−19 to 21)	0.94[a]
Secondary outcomes			(99% CI)	
90-day mortality, *n* (%)	8 (40%)	6 (29%)	1.40 (0.39–7.35)	0.44[b]
Days alive without life support at day 90, median (IQR)	72 (0–87)	76 (0–83)	−5 (−37 to 28)	0.72[c]
Number of patients with one or more serious adverse reactions or events in ICU—*n* (%)	5 (25%)	3 (14%)	1.38 (0.25–7.53)	0.40[d]

Abbreviations: CI, confidence interval, IQR, interquartile range.
[a]Analysed using unadjusted linear regression. Supplemented by a linear regression adjusted for site, acute kidney injury, and SMS-ICU score >25 ($p = .75$), and by Wilcoxon rank sum test ($p = .90$).
[b]Analysed using an unadjusted generalised linear model with log link and binomial error distribution. Supplemented by a generalised linear model with log link and binomial error distribution adjusted for site, acute kidney injury and SMS-ICU score >25 ($p = .23$), and by Fisher's exact test ($p = .52$).
[c]Analysed using unadjusted linear regression. Supplemented by a linear regression adjusted for site, acute kidney injury, and SMS-ICU score >25 ($p = .72$), and by Wilcoxon rank sum test ($p = .69$).
[d]Analysed using an unadjusted generalised linear model with log link and binomial error distribution. Supplemented by a generalised linear model with log link and binomial error distribution adjusted for site, acute kidney injury and SMS-ICU score >25 ($p = .30$), and Fisher's exact test ($p = .45$).

relatively high as in septic shock trials[14–16] and might be explained by the GODIF participants' advanced age and severe disease.

In our limited data, the development in fluid balance was not in line with the development in body weight. At day 90, the body weight had declined 4.0 kg in the furosemide group versus 4.2 kg in the placebo group compared to a decline in cumulative fluid balance of 6087 ml versus 2904 ml. In theory, the body weight is expected to decline more than the cumulative fluid balance due to the loss of muscle mass caused by immobilisation in the ICU.[17,18] This was only evident for the placebo group. Explanations could

TABLE 4 The primary outcome in subgroups of participants in the first version of the GODIF trial

Subgroups	Furosemide		Placebo	
Acute kidney injury[a]	KDIGO 0-1 *N* = 14	KDIGO 2-3 *N* = 6	KDIGO 0-1 *N* = 17	KDIGO 2-3 *N* = 4
Days alive and out of hospital—median (IQR)	50 (0–65)	26 (0–64)	45 (0–59)	31 (0–67)
SMS-ICU score[b]	SMS-ICU ≤ 25 *N* = 17	SMS-ICU > 25 *N* = 3	SMS-ICU ≤ 25 *N* = 18	SMS-ICU > 25 *N* = 3
Days alive and out of hospital—median (IQR)	48 (0–66)	60 (30–64)	45 (0–66)	41 (20–50)
COVID-19	No, *N* = 20	Yes, *N* = 0	No, *N* = 19	Yes, *N* = 2
Days alive and out of hospital—median (IQR)	50 (0–66)	NA (NA–NA)	46 (0–65)	0 (0–0)
Septic shock prior to enrolment	No, *N* = 12	Yes, *N* = 8	No, *N* = 12	Yes, *N* = 9
Days alive and out of hospital—median (IQR)	50 (0–67)	26 (0–62)	49 (24–61)	0 (0–62)

Abbreviation: IQR, interquartile range.

[a]Acute kidney injury is presented according to KDIGO stages.[11]

[b]Simplified mortality score for the ICU. The score range is 0–42 and corresponds to predicted 90-day mortality of 3.3%–91%.[12]

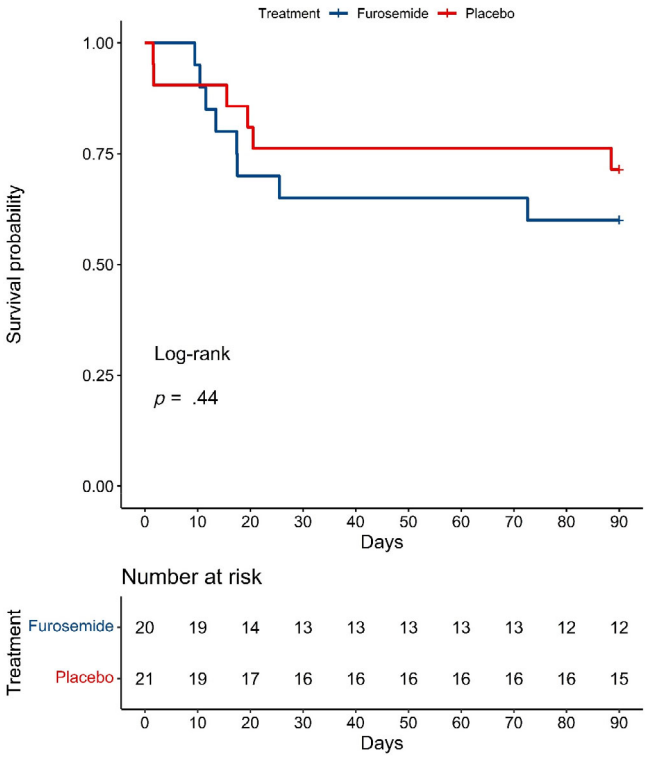

FIGURE 2 Survival curve at day 90 of the first version of the GODIF trial

partly be missing data on body weight, but impreciseness of fluid balances cannot be ruled out. A systematic review found the correlation between fluid balance and body weight to be poor—suggesting that the two parameters combined should be used in estimating fluid balance.[13]

At present there is no gold standard for measuring fluid status. In clinical practice of ICU physicians, parameters such as fluid balance, body weight, and clinical examination are most frequently used as surrogate measures of fluid status.[3,5,19] A combination of the three parameters might be more precise compared to one parameter alone. We therefore updated the GODIF protocol accordingly and now recruit into the second version of the GODIF trial.[20] Until 22 November 2022, 182 participants have been included at 15 active trial sites in Denmark, Norway, and Finland.

4.1 | Strengths

The first version of the GODIF trial was a randomised blinded, placebo-controlled, multicentre clinical trial. It was planned according to the SPIRIT statement for trials,[21] monitored by external staff, and reported in accordance with the CONSORT statement.[10] The experimental intervention with furosemide appeared to result in separation in cumulative fluid balance between the two intervention groups.

4.2 | Limitations

Early termination after only 4.1% of the planned participants were enrolled resulted in very uncertain results upon which we can make no conclusions. We decided to terminate the trial as 32% of the participants had one or several adjustments of the cumulative fluid balance during the trial. We experienced a high number of protocol violations and found cumulative fluid balance as a single measurement of fluid status too imprecise. We wanted to ensure that only participants with a minimum of 5% of fluid overload were included and that the intervention continued until a clinical neutral fluid balance was met. This required substantial changes in the protocol why the trial was terminated. Due to the reduced sample size, we made some post hoc adjustments to our statistical analysis plan.

4.3 | Perspectives

The protocol for the GODIF trial was revised and on 1 June 2021 the second version of the GODIF trial was launched according to our

adjusted protocol.[20] For this protocol, we developed a more pragmatic way of assessing fluid overload and neutral fluid balance. The clinicians must assess the fluid status of the participants according to the triad of fluid balances, changes in body weight, and clinical examination of signs of fluid accumulation. Fluid removal will continue until the participants are assessed to be in a neutral fluid balance by the same parameters. The changes are expected to provide more valid data and to better reflect current clinical practice. The intervention with the trial drug is, however, unchanged. We expect that the changes also will diminish the number of protocol violations.

5 | CONCLUSIONS

We were unable to provide precise estimates of the benefits and harms of furosemide versus placebo in adult ICU patients with fluid overload because only 4.1% of the planned sample size was enrolled due to our early termination of the trial. We learned very important lessons which have resulted in changes in trial design, so the GODIF trial is now enrolling under an updated, second version of the protocol.[20]

AUTHOR CONTRIBUTIONS

The article was drafted by Sine Wichmann and the statistical analyses were performed by Martin Schønemann-Lund. All authors contributed to the design and/or conduct of the trial and all critically revised the manuscript. Morten H Bestle was the sponsor of the trial.

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DATA AVAILABILITY STATEMENT

Data will be shared on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Supplementary Material

This supplementary material has been provided by the authors to give readers additional information about their work.

Supplement to:

Wichmann S, Schønemann-Lund M, Perner A, Lange T, Gluud C, Itenov TS, Berthelsen RE, Wiis J, Brøchner AC, Bestle MH. Goal-directed fluid removal with furosemide versus placebo in intensive care patients with fluid overload: a randomised, blinded trial (GODIF trial – first version)

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Content

S1. Consort checklist

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4, 6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	8

	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5-6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5-6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5-6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6
	11b	If relevant, description of the similarity of interventions	6
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9-10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10, Fig. 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Fig. 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	4
	14b	Why the trial ended or was stopped	4
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Fig. 1, Table 2, 3, and 4, Fig. 2

Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	11, Table 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	11, Table 3
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Table 3, Table 4
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	11, Table 3, Supplementary
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	11-13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-13
Other information			
Registration	23	Registration number and name of trial registry	5
Protocol	24	Where the full trial protocol can be accessed, if available	5
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	15

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

S2. Exclusion criteria

If one or more of the following exclusion criteria was met the patient was excluded:

1. Known allergy to furosemide or sulphonamides
2. Known pre-hospitalisation advanced chronic kidney disease (eGFR < 30 mL/minute/1.73 m^2 or chronic renal replacement therapy)
3. Ongoing renal replacement therapy
4. Anuria for more than 6 hours
5. Rhabdomyolysis with an indication for forced diuresis
6. Ongoing life-threatening bleeding
7. Acute burn injury of more than 10% of the body surface area
8. Severe dysnatremia (p-Na < 120 or > 155 mmol/L)
9. Severe hepatic failure as per the clinical team
10. Patients undergoing forced treatment
11. Pregnancy
12. Consent is not obtainable as per the model approved for the specific trial site.

S3. Protocol violations

Table S1. Protocol violations

Type of protocol violation	Total No. of violations/No. of patients with violations **Furosemide**	Total No. of violations/No. of patients with violations **Placebo**
The trial drug had been stopped/paused for > 48 hours before a neutral cumulative fluid balance has been achieved	1/1	4/2
Extra furosemide was administered without the presence of escape indications	1/1	48/8
Administration of other diuretics outside the trial protocol	0/0	15/2
The initiation or continued use of renal replacement therapy without the presence of escape indications	0/0	1/1
The trial drug had been administered/continued for > 48 hours after the patient reached a neutral cumulative fluid balance resulting in a negative cumulative fluid balance larger than -750 mL	14/2	1/1

S4. Serious adverse events and reactions

In critically ill patients admitted to the ICU, serious adverse events (SAE) and reactions (SAR) are frequently observed. To ensure a good report of the events, we pre-defined a list of SAEs for fluid removal and SARs for furosemide. The SARs were defined according to the Danish Summary of Product Characteristics for furosemide. During the trial, a daily registration if one or more of the listed SARs/SAEs had been present was done. Clinicians were not asked to assess if an event was caused by the trial drug. Only in case of a suspected unexpected serious adverse reaction (SUSAR), the clinicians had to assess the relation to the trial drug and report it in a dedicated form. No SUSARs were reported in this trial.

The predefined SAEs for fluid removal:

- Ischemic events are defined as cerebral ischemia, acute myocardial ischemia, intestinal ischemia, and limb ischemia
- A new episode of severe acute kidney injury is defined as modified KDIGO stage 3.
- New-onset atrial fibrillation in a participant who never had been diagnosed with atrial fibrillation.

The predefined SARs to furosemide:

- Severe electrolyte disturbance in plasma ($K < 2.5$ mmol/L or $Na < 120$ mmol/L or $Cl < 90$ mmol/L)
- Aplastic anaemia
- Agranulocytosis
- Pancreatitis
- Circulatory collapse leading to cardiac arrest
- Seizures due to furosemide-induced low calcium or magnesium
- Steven Johnsons syndrome
- Toxic epidermal necrolysis
- Hearing impairment/loss
- Anaphylaxis

Table S2. Reported SAEs and SARs

	Total No. of SAE/SAR /No. of patients affected **Furosemide**	Total No. of SAE/SAR /No. of patients affected **Placebo**
Serious adverse reactions to furosemide		
Circulatory collapse leading to cardiac arrest	1/1	0/0
Severe electrolyte disturbances[a]	4/2	3/1
Serious adverse events to fluid removal		
Atrial fibrillation (first onset)	3/3	0/0
Myocardial ischemia	0/0	1/1
New episode of stage 3 AKI	1/1	1/1

Some participants experienced the same SAR several times and some have experienced more than one SAE/SAR. The total number of participants with one or more SAE/SAR is reported in table 3 in the main manuscript.

[a] Plasma potassium < 2,5 mmol/L; or plasma natrium < 120 mmol/L; or plasma chloride < 90 mmol/L. Three participants experienced low plasma chloride and one low potassium

PAPER IV

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RESEARCH ARTICLE

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Goal directed fluid removal with furosemide versus placebo in intensive care patients with fluid overload: A trial protocol for a randomised, blinded trial (GODIF trial)

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Abstract

Background: Fluid overload is a risk factor for mortality in intensive care unit (ICU) patients. Administration of loop diuretics is the predominant treatment of fluid overload, but evidence for its benefit is very uncertain when assessed in a systematic review of randomised clinical trials. The GODIF trial will assess the benefits and harms of goal directed fluid removal with furosemide versus placebo in ICU patients with fluid overload.

Methods: An investigator-initiated, international, randomised, stratified, blinded, parallel-group trial allocating 1000 adult ICU patients with fluid overload to infusion of furosemide versus placebo. The goal is to achieve a neutral fluid balance. The primary outcome is days alive and out of hospital 90 days after randomisation. Secondary outcomes are all-cause mortality at day 90 and 1-year after randomisation; days alive at day 90 without life support; number of participants with one or more serious adverse events or reactions; health-related quality of life and cognitive function at 1-year follow-up. A sample size of 1000 participants is required to detect an improvement of 8% in days alive and out of hospital 90 days after randomisation with a power of 90% and a risk of type 1 error of 5%. The conclusion of the trial will be based on the point estimate and 95% confidence interval; dichotomisation will not be used. ClinicalTrials.gov identifier: NCT04180397.

Perspective: The GODIF trial will provide important evidence of possible benefits and harms of fluid removal with furosemide in adult ICU patients with fluid overload.

KEYWORDS
critical care, de-resuscitation, diuretics, fluid accumulation, fluid overload, fluid removal, furosemide, intensive care, loop diuretics, protocol, randomised clinical trial

1 | INTRODUCTION

Fluid therapy and fluid status are central to clinical practice in ICUs. Substantial amounts of fluids are used in ICU patients for resuscitation, correction of fluid deficits, and administration of medicines and nutrition.[1] Combined with common retention of salt and water in critical illness this often results in fluid overload which may lead to acute kidney injury (AKI)[2–5] (PMID: 26263435) and dysfunction of other organs.[6,7]

Observational studies show that fluid overload is a risk factor for death,[6–18] but sparse evidence exists on how and when to start removing fluid. Studies investigating strategies of restrictive fluid therapy and/or diuretics in ICU patients with fluid overload have found conflicting results with regards to mortality.[19–21] A systematic review of randomised clinical trials (RCT) in ICU patients with fluid overload found inconclusive evidence on the effects of loop diuretics versus placebo/no intervention on mortality.[22]

Up to 50% of ICU patients are treated with diuretics during their ICU stay, and the predominant diuretic is furosemide, used in more than 94% of the patients receiving diuretics.[23,24] Despite the awareness of the detrimental effects of fluid overload and frequent practice of prescribing diuretics, solid evidence and guidelines on timing, choice and rate of removal are lacking.

The aim of this RCT is to investigate the benefits and harms of goal directed fluid removal with furosemide versus placebo in adult ICU patients with fluid overload. We hypothesise that treatment with furosemide, as compared with placebo, will increase the number of days alive and out of hospital at day 90 post-randomisation.

2 | METHODS

2.1 | Trial design

The GODIF trial is an investigator-initiated, international, randomised, blinded, parallel-group, clinical trial investigating furosemide versus placebo in adult ICU patients with fluid overload. The results of the trial will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) Statement.[25]

2.2 | Trial conduct

The protocol was written in accordance with the Standard Protocol Items: Recommendation for Interventional Trials

(SPIRIT) 2013 statement (Supplementary S1).[26] The trial will be conducted in compliance with the Helsinki Declaration,[27] the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines,[28] and national laws in the participating countries.

2.3 | Randomisation

A central web-based randomisation system administered by the Copenhagen Trial Unit allocates participants in a 1:1 ratio to furosemide or placebo using a computer-generated allocation sequence stratified by AKI, Simplified Mortality Score for the Intensive Care Unit (SMS-ICU),[29] and trial site with varying block sizes.

2.4 | Allocation concealment and blinding

The allocation sequence list is exclusively known by the data manager at Copenhagen Trial Unit. Investigators, outcome assessors, clinical staff, patients, and statisticians are blinded. After the last participant has been followed for 90 days and the 90-day outcomes have been analysed, the management committee will write two versions of the abstract before the blinding will be demasked. The patients, researchers, and the staff doing the 1-year follow-up will remain blinded until the 1-year outcomes have been analysed.

Unblinding of the intervention for a participant may be done if deemed necessary by the clinician or investigator for safety reasons. Unblinding will be performed by data manager on request form the coordinating investigator.

The trial drug is furosemide 10 mg/ml or placebo (0.9% saline) and contained in identical vials containing 50 ml. The solution of furosemide is colourless and cannot be visually distinguished from saline. Each vial will be marked with an identification number which is used in a web-based program to allocate trial drugs to the participants.

2.5 | Inclusion and exclusion criteria

Inclusion and exclusion criteria are presented in Table 1.

A detailed description of the criteria is presented in Supplementary S2.

2.6 | Trial interventions

The aim is to achieve neutral fluid balance as fast as possible by daily goal directed fluid removal according to Table 2 and details in Supplementary S3.

Fluid balance is assessed daily by the treating clinicians based on one or more of the following: cumulative fluid balance, daily fluid balance, change in body weight and clinical examination. When a neutral fluid balance is obtained, the trial drug administration is paused or decreased to maintain a neutral fluid balance throughout the remaining time in ICU up to a maximum of 90 days. If the participant is discharged and readmitted to an ICU participating in GODIF trial during the 90-day period, the allocated intervention continues.

TABLE 1 Inclusion and exclusion criteria

Inclusion criteria All must be met	Exclusion criteria None must be met
• Acute admission to the ICU • Age 18 years or older • Clinically stable (minimum criteria: mean arterial blood pressure > 50 mmHg and maximum infusion of 0.20 μg/kg/min of noradrenaline and lactate < 4.0 mmol/L) • Fluid accumulation according to table below (>5% of ideal body weight)	• Allergy to furosemide or sulphonamides • Pre-hospitalisation advanced chronic kidney disease (eGFR < 30 ml/min/1.73 m^2 or chronic renal replacement therapy) • Ongoing renal replacement therapy • Anuria for ≥6 h • Rhabdomyolysis with indication for forced diuresis • Ongoing life-threatening bleeding • Acute burn injury of more than 10% of the body surface area • Severe dysnatraemia (plasma sodium <120 mmol/L or >155 mmol/L) • Severe hepatic failure • Patients undergoing forced treatment • Pregnancy • Consent not obtainable as per the model approved for the specific trial site

Minimum fluid accumulation on inclusion		
Height in cm	**Men**	**Women**
≤159 cm	+3000 ml	+2500 ml
160–169 cm	+3500 ml	+3000 ml
170–179 cm	+4000 ml	+3500 ml
180–189 cm	+4500 ml	+4000 ml
≥190 cm	+5000 ml	+4500 ml

Abbreviations: eGFR, estimated glomerular filtration rate; ICU, intensive care unit.

TABLE 2 Goal of daily negative fluid balance until resolution of fluid overload

Height in cm	Men	Women
≤159 cm	−1300 ml/24 h	−1200 ml/24 h
160–169 cm	−1500 ml/24 h	−1400 ml/24 h
170–179 cm	−1700 ml/24 h	−1600 ml/24 h
180–189 cm	−1900 ml/24 h	−1800 ml/24 h
≥190 cm	−2000 ml/24 h	−1900 ml/24 h

Open-label furosemide can only be used in the case of:

- Hyperkalaemia (plasma-potassium > 6.0 mmol/L)
- Respiratory failure (PaO_2/FiO_2-ratio < 26 kPa (200 mmHg)) and the treating physician suspects the respiratory failure or deterioration is due to fluid overload or pulmonary oedema.

Renal replacement therapy (RRT) may only be started in the case of:

- Hyperkalaemia (plasma-potassium > 6.0 mmol/L)
- Respiratory failure (PaO_2/FiO_2-ratio < 26 kPa (200 mmHg)) and the treating physician suspects the respiratory failure or deterioration is due to fluid overload or pulmonary oedema
- Severe metabolic acidosis attributable to AKI (pH < 7.20 and standard base excess (SBE) < -10 mmol/L)
- Persistent AKI > 72 hours (defined as oliguria/anuria or plasma creatinine that has not declined to 50% from the peak value).

FIGURE 1 Escape procedures

2.7 | Trial drug

Dosing of trial drug follows the same algorithm in both intervention groups: an IV bolus of 0.5–4.0 ml (5–40 mg of furosemide or matching placebo) at the treating clinician's discretion followed by a continuous IV infusion starting at 2 ml/h. The infusion must be titrated according to effect and daily target fluid balance. Allowed infusion rates are 0–4 ml/h. If the trial drug is infused at a maximum rate and the target fluid balance is not reached, no further interventions should be administered.

2.8 | Escape procedures

Escape procedures are presented in Figure 1.

The infusion of trial drug must continue in case of indication of escape open-label furosemide. The maximum recommended dose of furosemide is 1500 mg per day, which should not be exceeded.

If RRT is initiated, the trial drug must be paused. When the indication for RRT has subsided, RRT should be stopped, and the trial drug be restarted if the participant still has fluid overload.

2.8.1 | Resuscitation algorithm

In case of severe hypoperfusion defined as lactate ≥ 4.0 mmol/L or mean arterial blood pressure < 50 mmHg (resistant to vasopressor/inotropes) or mottling beyond the kneecaps (mottling score >2),[30] the trial drug should be paused. A bolus of isotonic crystalloid solution of 250–500 ml IV may be given followed by a re-evaluation of circulatory status. Trial drug and fluid removal should be restarted when the participant does not have any signs of hypoperfusion and is assessed as sufficiently stable to tolerate fluid removal.

2.8.2 | Co-interventions

Fluid therapy is administered at the clinicians' discretion. Habitual diuretics may be continued. Thiazides may be administered to treat hypernatremia. All other diuretics must not be administered. The use of vasopressors and inotropes is permitted.

TABLE 3 Outcomes for the GODIF trial

Primary outcome
Days alive and out of hospital at 90 days
Secondary outcomes
1. All-cause mortality at 90 days
2. Days alive without life support (vasopressor/inotropic support, invasive mechanical ventilation, or renal replacement therapy) at 90 days
3. All-cause mortality at 1-year
4. Number of participants with one or more serious adverse events (SAE) or serious adverse reactions (SAR).
5. Health-related quality of life as EuroQoL 5 dimensions, five-level questionnaire (EQ-5D-5L) index value at 1-year[31,32]
6. EQ visual analogue scale (EQ VAS) score at 1-year[31,32]
7. Participants subjective assessment of their quality of life (unacceptable/neutral/acceptable) at 1-year
8. Cognitive function as assessed by the Montreal Cognitive Assessment (MoCA) 5 min/telephone test at 1-year[33]

2.9 | Outcomes

All outcomes are presented in Table 3.

2.10 | Registered variables

Variables are registered on enrolment, daily during the trial period in the ICU, and at 90-days and 1-year follow-up. Detailed description of all variables is in Supplementary S4. All data will be entered on web-based electronic case-report forms (OpenClinica). Further information on data management, confidentiality, and responsibility in Supplementary S5.

2.11 | Serious adverse reactions and events

SAEs likely due to fluid removal and SARs likely due to furosemide will be registered daily in the database as detailed in Supplementary S6.

2.12 | Statistics

A detailed statistical analysis plan will be published before enrolment of the last participant.

Our primary analyses will be performed in the intention-to-treat population, defined as all randomised participants who have consented to the use of their data. Secondary analyses of the primary outcome will be performed in a per protocol population defined as all participants in the intention-to-treat population except those with a major protocol violation during the intervention period, defined as:

- Participants receiving other types of diuretics than allowed per trial protocol.
- Participants receiving open-label furosemide without fulfilling escape criteria.
- Initiation of RRT, without an indication as listed above.

The primary analyses will be adjusted for stratification variables (site, AKI, SMS-ICU score). As a sensitivity analysis, the primary outcome will also be adjusted for the following risk factors: ischaemic heart disease, septic shock, chronic obstructive pulmonary disease, diabetes, and stroke/neurodegenerative illness.

The primary publication of the GODIF trial will include the outcomes for day 90. The outcomes for 1-year follow-up will be published separately.

2.12.1 | Missing data

Complete case analysis will be performed if missing data is less than 5% for an outcome. If missing data are more than 5% multiple imputation will be performed.

2.12.2 | Primary outcome

The primary outcome will be compared between the treatment groups using a likelihood ratio test[34] building on a logistic model for mortality and a linear regression for days alive outside hospital within 90 days for patients discharged alive within 90 days. This is done to obtain maximal statistical power. The treatment effect will be quantified using raw means with 95% confidence intervals in the two groups and the mean difference obtained by bootstrap. The inference of the results will be based on the 95% CIs, but the *p*-value will also be reported. As the primary outcome is a composite outcome, results from each component will also be presented.

2.12.3 | Secondary outcomes

Binary secondary outcomes will be analysed with a logistic regression with the same adjustment strategy as the primary outcome. Using G-computation based on the logistic regression, we will compute risk ratios and risk differences and corresponding confidence intervals. Survival outcomes will also be analysed with Kaplan–Meier plots to illustrate time dynamics. Continuous secondary outcomes will be analysed using linear regression with the same adjustment strategy as the primary outcome. As the sample size is large non-normality is not deemed problematic.

Health-related quality of life at 1-year will be assessed with EuroQoL EQ-5D-5L index score based on the country value set and EQ-VAS scores[31,32] (the Danish value set will be used for those without a country-specific one). Participants who have died at 1-year will be assigned the value zero (EQ-5D-5L index score), which corresponds to a health state as bad as being dead and the worst possible value for EQ-VAS. Participants' subjective assessment of their quality of life will be presented in three categories (unacceptable/neutral/acceptable). Non-survivors will be assigned the value 'unacceptable'.

Cognitive function 1-year after randomisation will be assessed using the Montreal Cognitive Assessment (MoCA 5 min/telephone) score.[33] Non-survivors will be given the worst possible score.

Sensitivity analyses on health-related quality of life and cognitive function will be performed on the survivors.

2.12.4 | Sample size estimation

Sample size estimation for the primary outcome

A Wilcoxon rank sum test was used for the calculations as observational data were not normally distributed.[35] With the assumption of (1) lowering in-hospital mortality by 15% in the intervention group and (2) shifting the distribution of 'days alive out of hospital at day 90' to the right for the remaining population with a combined effect on the mean as an improvement of 8%, we will have 90% power ($\beta = .1$) to detect the described improvement at the 5% alpha level with 500 participants in each intervention group.

Power estimations for the secondary outcomes

1. Assuming a risk of 30% for all-cause mortality at day 90 after randomisation in the control group[35,36] we have about 37% power to detect a relative risk reduction of 15% at the 1% alpha level.
2. Assuming the same in-hospital mortality as in the primary outcome[35] and a 10% increase in days alive at day 90 without life support (vasopressor/inotropic support, invasive mechanical ventilation, or RRT) in the intervention group, then we have about 59% power at the 1% alpha level.
3. Assuming a risk of 37% for all-cause mortality at 1-year after randomisation in the control group,[37] we have about 52% power to detect a relative risk reduction of 15% at the 1% alpha level.

4. Assuming a control group proportion of participants with one or more SAEs and/or SARs of 30%,[36] we have about 37% power to detect a relative reduction of 15% at the 1% alpha level.

Because of a lack of sufficient knowledge, no meaningful power estimation could be performed for the outcomes health-related quality of life and cognitive function.

2.12.5 | Pre-planned subgroup analyses

We will compare the primary outcome in the following pre-specified subgroups:

1. Participants with SMS-score < 25 compared to ≥25
2. Participants with AKI compared to those without
3. Participants with SARS-CoV-2 infection compared to those without
4. Participants with septic shock prior to randomisation compared to those without
5. Participants on vasopressors compared to those without
6. Fluid overload ≥10% compared to <10%.

2.12.6 | Statistical inference

The conclusion of the trial will be based on the point estimate of the primary analysis of the primary outcome including a description of the uncertainty based on the 95% confidence interval. The *p* value will also be reported, but we will not dichotomise the results based on a specific *p* value cut-off. The term 'statistical significance' will not be used. For the secondary outcomes point estimates with 99% confidence intervals will be reported. *p* values will also be reported in the same way as for the primary outcome.

2.13 | Data Monitoring Committee (DMC)

An independent DMC will monitor the trial. The DMC consists of an independent clinician, a biostatistician, and a trialist with experience in conducting, monitoring, and analysis of randomised clinical trials. Charter for the DMC is available in Supplementary S7.

2.14 | Interim analysis for process variables

We will conduct an interim analysis when 100 participants (10%) have completed 90-day follow-up on the process variables: mean cumulative fluid balance after 3 days with censoring at discharge, and number of days with escape medicine. This is to ensure possible separation between the intervention groups. The DMC will make recommendations to the Management Committee regarding continuing, pausing, or stopping the trial after a qualitative assessment of the results.

2.15 | Interim analysis for clinical outcomes

The first interim analysis of clinical outcomes will be conducted after 500 participants (50%) have completed 90-day follow-up. The DMC will assess group-difference in the primary outcome and number of patients with one or more SAEs/SARs with statistical significance levels adjusted according to the Lan-DeMets group sequential monitoring boundaries based on O'Brien Fleming α spending function.[38] The DMC will make recommendations to the Management Committee regarding continuing, pausing, or stopping the trial.

2.16 | Monitoring during the study

The study will be monitored according to Good Clinical Practise (GCP)[28] and a pre-specified monitoring plan. The trial will also be monitored by the coordinating centre through the electronic case report form to ensure protocol adherence.

3 | DISCUSSION

Fluid accumulation in ICU patients is common and considered a risk factor for morbidity and mortality. Furosemide is the most frequently used agent in the treatment.[23,39] No guidelines for treating fluid accumulation in the general adult intensive care population exist and the evidence for using loop diuretics is sparce.[22] We want to investigate goal directed fluid removal in adult ICU patients with moderate to severe fluid overload with furosemide versus placebo and assess benefits and harms.

3.1 | Strengths

The GODIF trial is an international, randomised, blinded, placebo-controlled trial with high methodological standards designed to provide evidence of efficacy and safety of fast de-resuscitation with furosemide in adult ICU patients with fluid overload. The trial is conducted following the international guidelines for clinical trials and GCP. We will report patient-important outcomes. The trial is monitored according to GCP and an independent DMC.

3.2 | Limitations

Assessment of fluid overload is difficult with no available gold standard method. Cumulative fluid balance, daily fluid balance, changes in body weight, and clinical signs are all surrogate measures and thus inaccurate. During critical illness, patients quickly lose muscle mass[40] and weight loss which is not representing fluid shifts is expected. Clinical assessment is only a rough assessment of fluid overload by estimation of oedema, ascites, pleural effusions, and chest congestion using chest X-rays, CT-scans, echocardiography, ultrasound, and other diagnostic tools. The same is

true for the assessment of neutral fluid balance. This is a challenge for the trial and for future guidelines on the treatment of fluid overload.

4 | PERSPECTIVE

The assessment of fluid overload and neutral fluid balance in this trial is pragmatic. In the light of no available precise reference tool or method to assess fluid balance we believe that this approach provides the best assessments. It is in alignment with daily clinical practice and the method is easy to implement.

4.1 | Ethical considerations

The trial was registered at ClinicalTrials.gov and at the European Union Drug Regulation Authorities Clinical Trials Database. In Denmark, Norway, and Finland, the trial has been approved by national ethics committees and medicine agencies. All required approvals were obtained before the start of enrolment in the participating countries. Participants are enrolled after consent has been obtained according to national regulations.

4.2 | Dissemination

The trial results will be published in international peer-reviewed medical journals regardless of the results. We will adhere to the CONSORT statement in our reporting of results.[25] All documents inclusive protocol amendments will be available on www.cric.nu/godif/. Changes are communicated to relevant parties by newsletters. De-identified data will be made publicly available after ended trial.

4.3 | Trial status

The trial was launched on August 17, 2020 but paused on February 15, 2021 after randomisation of 41 participants. Protocol changes were made, and the trial was restarted on June 1, 2021 aiming to include 1000 participants more. The trial is expected to complete enrolment in December 2024. The first 41 participants will not be included in the primary analyses for the GODIF trial due to protocol changes but reported in a separate paper. The trial has currently 13 active trial sites in Denmark, Norway, and Finland. More European countries are currently applying to their authorities for approval to participate in the GODIF trial.

TRIAL SPONSOR

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APPLICABLE PROTOCOL REGISTRATION NUMBERS

Current protocol version 2.7 dated February 10, 2022. ClinicalTrials.gov identifier: NCT04180397; EudraCT: 2019-004292-40; Committees on Health Research Ethics in the Capital Region of Denmark: H-19080597; The Danish Medicines Agency: 2019121067; The Capital Region Knowledge Centre for Data Compliance: P-2020-170; The Finnish Medicines Agency: KLnro 19/2021; Finnish Ethics Committee, Hospital District of Southwest Finland: Dnro 17/1800/2021; Health Research Ethics Committee of Western Norway: 213330; The Norwegian Medicines Agency: 21/02350-9.

AUTHOR CONTRIBUTIONS

Sine Wichmann and Morten H. Bestle drafted this protocol, which was critically revised by all authors. All authors contributed substantially to development of this protocol, and all authors have read and approved the final manuscript.

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CONFLICT OF INTEREST

SW has received a grant from Merchant Jakob Ehrenreich and wife Grete Ehrenreich's Foundation to production of trial drug for the GODIF trial. AP has received research funding from the Novo Nordisk Foundation, Health Insurance Denmark (Sygeforsikringen Danmark), Fresenius Kabi, Denmark, and Pfizer, Denmark. MO has received research funding from Fresenius Medical Care, Baxter and Biomerieux. MHB has received research funding for the GODIF trial from Novo Nordisk Foundation, Jakob Madsen's and wife Olga Madsen's Foundation, Svend Andersen's Foundation, and Health Insurance Denmark (Sygeforsikringen Danmark). No authors received any financial gain. All other authors declared no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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SUPPLEMENTARY MATERIAL

This supplementary material has been provided by the authors to give readers additional information about their work.

Supplement to:

Wichmann S, Itenov TS, Berthelsen RE, Lange T, Perner A, Gluud C, Lawson-Smith P, Nebrich L, Wiis J, Brøchner AC, Hildebrandt T, Behzadi MT, Strand K, Andersen FH, Strøm T, Järvisalo M, Damgaard KAJ, Vang ML, Wahlin RR, Sigurdsson MI, Thormar KM, Ostermann M, Keus F, and Bestle MH. Goal directed fluid removal with furosemide versus placebo in intensive care patients with fluid overload: a trial protocol for a randomised, blinded trial (GODIF Trial)

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Content

S1. Sprit checklist

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	19
	2b	All items from the World Health Organization Trial Registration Data Set	-
Protocol version	3	Date and version identifier	19
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-4 + 20
	5b	Name and contact information for the trial sponsor	19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Supplementary S5

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Supplementary S5 + 15 + Supplementary S7
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7+18
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 1 + Supplementary S2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9 + Table 2 + Supplementary S3
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9-10

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Table 3 11 and Supplementary S4
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8+18
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13-14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	18
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7-8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7-8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11 + Supplementary S4
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11-12
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11 + Supplementary 5
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-13

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11-12 +14-15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11-12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15 + Supplementary S7
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15-16 + Supplementary S7
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11 + Supplementary S6
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18-19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Supplementary S5
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Supplementary S5 + 19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Can be provided on request

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

S2. Detailed description of inclusion and exclusion criteria

Inclusion criteria

All criteria below must be met**:**

- Acute admission to the ICU. We will only recruit sites that have the status as an ICU.
- Age 18 years of age or above. The age of the participant in whole years at the time of randomisation.
- Clinical stable assessed by the clinicians. Minimum criteria are mean arterial pressure > 50 mm Hg, maximum infusion of 0.20 microgram/kg/minute of noradrenaline and lactate < 4.0 mmol/L.
- Fluid accumulation in the body must be estimated according to the cumulative fluid balance, daily fluid charts, changes in body weight, and clinical examination (oedemas, congestion on x-ray, ultrasound etc.). If possible, cumulative fluid balance from before admission to the ICU are to be included in the calculation of cumulative fluid balance during the ICU admission. The minimum fluid accumulation on inclusion is 5% of ideal body weight. The following calculation of minimum fluid accumulation according to height should be used:

Height in cm	Men	Women
≤ 159 cm	+ 3000 mL	+ 2500 mL
160 to 169 cm	+ 3500 mL	+ 3000 mL
170 to 179 cm	+ 4000 mL	+ 3500 mL
180 to 189 cm	+ 4500 mL	+ 4000 mL
≥ 190 cm	+ 5000 mL	+ 4500 mL

Exclusion criteria

None of exclusion criteria must be met:

- Know allergy to furosemide or sulphonamides.
- Known pre-hospitalisation advanced chronic kidney disease with eGFR < 30 mL/minute/1.73 m^2 or chronic RRT as furosemide might not have the expected effect in this patient group.
- Acute renal replacement therapy or anuria for ≥ 6 hours. Administration of furosemide will often be a relative contraindication in these situations.

- Rhabdomyolysis with indication for forced diuresis.
- Ongoing life-threatening bleeding as these patients need specific fluid/blood product strategies.
- Acute burn injury of more than 10 % of the body surface area: burn injury leading to the present ICU admission as these patients need a specific fluid strategy. Patients with burn injury who are re-admitted to the ICU or were initially cared for in a general ward and admitted to the ICU for infection may be screened to enrolment. The latest documented estimate of the burn area will be used as these may be downgraded after the initial assessments.
- Severe dysnatraemia (plasma-Na < 120 mmol/L or > 155 mmol/L) as these patients may need a specific fluid or diuretic therapy.
- Severe hepatic failure (liver coma grade 3 and 4).
- Patients undergoing forced treatment.
- Pregnancy. Non-pregnancy must be confirmed by a negative urine- or plasma hCG for women below 50 years of age. Women of 50 years or beyond are considered being postmenopausal or at the investigator's discretion e.c.t women who have had a hysterectomy or other known conditions where pregnancy isn't possible. The hCG test must be documented in the patient file.
- Consent not obtainable according to national regulations: patients where the clinician or investigator is unable to obtain the necessary consent before inclusion of the patient according to the national regulations.

S3. Description of goal directed fluid removal

The therapeutic goal of the intervention is a negative fluid balance ≥ 1 ml/kg/h.
The ideal body weight (IBW) is used in the calculation of the desired negative fluid balance. This is especially relevant in obese patients where the goal for fluid removal can be unrealistic high if actual body weight is used. A simple formula for calculation of IBW is height in cm – 100 for men, and height in cm – 105 for women. This formula was used when the chart below was designed. This chart must be used for setting the goal for minimum daily fluid removal.

Height in cm	Men	Women
≤ 159 cm	-1300 mL/24 h	-1200 mL/24 h
160 to 169 cm	-1500 mL/24 h	-1400 mL/24 h
170 to 179 cm	-1700 mL/24 h	-1600 mL/24 h
180 to 189 cm	-1900 mL/24 h	-1800 mL/24 h
≥ 190 cm	-2000 mL/24 h	-1900 mL/24 h

The efficacy of fluid removal is evaluated and adjusted according to the therapeutic goal at least every eight hours or more often, while the safety variables are evaluated continuously.

S4. Registered variables for the GODIF trial

Table S4 A. Baseline registrations

Registration	Definition
Age	Calculated from birth year
Gender	Genotypic
Height	If not possible to obtain a measured height it can be estimated.
Body weight	If not possible to obtain a measured weight it can be estimated.
Hospital admission	Date
ICU admission	Date and time. If transferred from another ICU, the primary ICU admission time is registered.
From where the patient is admitted	Which department (emergency department, hospital ward, operating or recovery room, another ICU)
Elective surgery (y/n)	During the current hospitalisation prior to randomisation
Acute surgery (y/n)	During the current hospitalisation prior to randomisation
Septic shock (y/n)	During current hospital admission according to Sepsis-3 criteria: suspected/confirmed site of infection or positive blood culture *and* infusion of vasopressor/inotropic agent to maintain a mean arterial blood pressure of 65 mmHg or above *and* lactate of 2 mmol/L or above.
Fluid overload: - Cumulative fluid balance - Daily fluid balance - Weight - Clinical examination	Estimated fluid overload according to the four parameters: cumulative fluid balance, daily fluid balance, weight and clinical examination. The parameters used for the assessment is registered. All four parameters might not be available or used.
Lowest systolic blood pressure	Within 24 hours prior to randomisation. In case of cardiac arrest within 24 hours. Register 0.
Use of vasopressor or inotropes (y/n)	Within 24 hours prior to randomisation. (Noradrenaline, adrenaline, phenylephrine, vasopressin analogues, dopamine, dobutamine, milrinone or levosemindan)
Respiratory support (y/n)	Invasive or non-invasive mechanical ventilation including continuous mask CPAP or CPAP via tracheostomy within the last 24 hours prior to randomisation. Intermittent CPAP is not considered as respiratory support.
Urinary output	Within 24 hours prior to randomisation
Co-morbidities	
Ischemic heart disease or heart failure (y/n)	Previous myocardial infarction, invasive intervention for coronary artery disease, stable or unstable angina, NYHA class 3 or 4 or measured LVEF < 40%.

Chronic obstructive pulmonary disease (y/n)	
Diabetes (y/n)	
Stroke or neurodegenerative illness (y/n)	
Habitual treatment with diuretics (y/n)	If yes; the type of diuretics must be registered
Metastatic cancer or haematological malignancy (y/n)	Metastatic cancer (proven metastasis by surgery, CT scan or any other method). Haematological malignancy: leukaemia, lymphomas, multiple myeloma/plasma cell myeloma and myelodysplastic syndrome
Blood samples and tests	
Highest plasma creatinine	Within 24 hours prior to randomisation
Habitual plasma creatinine	Prior to current admission and maximum 6 months old value. If unobtainable it will be back calculated with the MDRD equation, and race will be registered.
Plasma sodium, potassium and chloride on inclusion	The value must maximum be 24 hours old
COVID-19 positive on admission (y/n)	A positive test leading to admission or positive test during admission. If a test is not made. The answer is no.
SMS-ICU score and if the patient has AKI according to the KDIGO guidelines[1] it will be calculated from the above parameters and used for stratification.	

CPAP: continuous positive airway pressure
NYHA: New York Heart Association
LVEF: Left ventricular ejection fraction
MDRD: Modification of Diet in Renal Disease equation
AKI: acute kidney injury
SMS-ICU score: Simplified Mortality Score for the Intensive Care Unit
KDIGO: Kidney Disease: Improving Global Outcomes

Table S4 B. Daily registrations during ICU admission

Registration	Definition
Fluid and drugs	
Daily fluid balance in mL	On this day (24 hours)
Urinary output	On this day (24 hours - the first and last day may be shorter)
Weight	Measured
Administered trial drug (mL)	On this day (24 hours - the first and last day may be shorter)
Achievement of neutral fluid balance (y/n)	Assessed according to the four parameters (if available): cumulative fluid balance, daily fluid balance, weight and clinical examination. If yes; registration of the parameters used in the assessment
Blood samples	
Highest plasma creatinine	On this day (24 hours) on any plasma sample, including point-of-care testing.

Highest plasma sodium	On this day (24 hours) on any plasma sample, including point-of-care testing.
Lowest plasma potassium	On this day (24 hours) on any plasma sample, including point-of-care testing.
Lowest plasma chloride	On this day (24 hours) on any plasma sample, including point-of-care testing.
Major protocol violations	
Administration of extra furosemide without presence of escape criteria (y/n)	We register dose of not protocolised furosemide administered
Administration of other diuretics (y/n)	Diuretics not allowed according to protocol. We register which types of diuretics (other loop diuretics than furosemide, thiazides, potassium sparing diuretics, carbon anhydrase inhibitors)
Initiation of RRT without presence of escape indications (y/n)	
Co-interventions	
Vasopressor or inotropes (y/n)	Noradrenaline, adrenaline, phenylephrine, vasopressin analogues, dopamine, dobutamine, milrinone or levosemindan
Mechanical ventilation (y/n)	Invasive or non-invasive mechanical ventilation with the use of positive pressure ventilation using a ventilator. CPAP alone is not regarded as mechanical ventilation.
Escape RRT (y/n)	RRT must only be started in case of hyperkalemia (plasma potassium > 6.0 mmol/L) *or* respiratory failure (PaO_2/FiO_2-ratio < 26 kPa (200 mm)) due to fluid overload or pulmonary oedema *or* severe metabolic acidosis attributable to AKI (pH < 7.20 and SBE < -10 mmol/L) *or* persistent AKI > 72 hours (defined as: oliguria/anuria or plasma creatinine has not declined to 50% from peak value).
Escape furosemide (y/n)	Open label furosemide can only be used in case of hyperkalaemia (plasma potassium > 6.0 mmol/L) or respiratory failure (PaO_2/FiO_2-ratio < 25 kPa (200 mmHg)) due to fluid overload or pulmonary oedema. If yes, the dose must be registered.
Use of resuscitation algorithm (y/n)	Resuscitation algorithm can be use in case of severe hypotension or severe circulatory impairment: lactate > 4.0 or MAP < 50 mmHg (+/- vasopressor/inotrope) or mottling beyond edge of kneecap (mottling score > 2).
Serious adverse events	
Cerebral ischemia (y/n)	Any form of cerebral ischemia on a CT-or MRI scan on this day
Acute myocardial ischemia (y/n)	Acute myocardial infarction (ST-elevation or non-ST elevation myocardial infarction) or unstable angina pectoris according to the criteria in the clinical setting in question (e.g. elevated biomarkers, ischemic signs on ECG and clinical presentation) AND the participant received treatment as a

	consequence of this (reperfusion strategies (PCI/thrombolysis) OR initiation/increased antithrombotic treatment.
Intestinal ischemia (y/n)	Ischemia verified by endoscopy OR open surgery on this day.
Limb ischemia (y/n)	Clinical signs AND need of open/percutaneous vascular intervention, amputation OR initiation/increased antithrombotic treatment on this day.
Development of a new episode of AKI stage 3 (y/n)	AKI modified KDIGO stage 3: three times increase in baseline plasma creatinine or increase in plasma creatinine to ≥ 354 μmol/L on this day.
First onset atrial fibrillation (y/n)	New onset atrial fibrillation. The patient must never have had atrial fibrillation before.
Serious adverse reactions	
Anaphylactic reaction	Urticaria AND at least one of the following: worsened circulation (> 20% decrease in blood pressure or > 20% increase in vasopressor dose), increased airway resistance (> 20% increase in the peak pressure on the ventilation), clinical stridor or bronchospasm, subsequent treatment with bronchodilators.
General tonic-clonic seizures due to furosemide induced low calcium or magnesium	
Electrolyte disturbance of plasma potassium 2.5 mml/L, plasma sodium < 120 mmol/L or plasma chloride < 90 mmol/L	On any plasma sample, including point-of-care testing.
Agranulocytosis	A new drop in granulocytes to < 0.5 x 10^9 L
Aplastic anaemia	A syndrome of bone marrow failure characterised by peripheral pancytopenia and morrow hypoplasia. Drop in haemoglobin < 5.0 mmol/L, neutrophil leucocytes < 0.5 x 10^9/L, thrombocytes < 20 x 10^9/L, reticulocytes < 1%.
Pancreatitis	Diagnosed after randomisation and start of trial drug
Circulatory collapse leading to cardiac arrest	
Steven Johnson's syndrome	
Toxic epidermal necrolysis	
Hearing impairment/loss	The patient complaining of hearing impairment (not former known)

RRT: renal replacement therapy
CPAP: continuous positive airway pressure
AKI: acute kidney injury
SBE: standard base excess
MAP: mean arterial pressure
MRI: magnetic resonance imaging
ECG: electrocardiogram
PCI: percutaneous coronary intervention
KDIGO: Kidney Disease: Improving Global Outcomes

Table S4 C. Registration at follow-up at day 90 and 1-year

Registration	Definition
90-day follow-up	
Dead (y/n)	Death by any cause within 90 days from randomisation
Date of death	Only registered if 'yes' to dead
Discharged from hospital (y/n)	If yes, date of hospital discharge of index admission.
Readmissions to hospital (y/n)	Within 90 days from randomisation
Days in hospital during readmissions	The number of calendar days, on which the patient was readmitted to the hospital within 90 days from randomisation in all types of hospitals. (Not including the primary admission)
1-year follow-up	**Telephone interview**
Dead (y/n)	Death by any course within 1 year from randomisation
Date of death	Only registered if 'yes' to dead
MoCA mini test performed (y/n)	If the answer is 'no' the reason must be reported
Registration of MoCA mini scores	
Euro-Qol 5 dimensions 5 level questionnaire and EQ visual analogue scale scores performed (y/n)	If the answer is 'no' the reason must be reported
Registration of EQ- 5D-5L and EQ-VAS scores	
Euro-Qol obtained by proxy (y/n)	'Yes' if EuroQol data are obtained by proxy through relative or caregiver (by proxy obtainment is only allowed if the patients are incapable answering themselves)
The patient's current assessment of their health-related quality of life: - Unacceptable - Neutral - Acceptable - Answer not obtainable	Only one answer can be registered

MoCA: Montreal Cognitive Assessment
EQ-5D-5L: Euro-Qol 5 - dimensions 5 level questionnaires about health-related quality of life
EQ-VAS scores: self-rated overall health on a visual analogue scale from the Euro-Qol group

Other registered variables

On discharge we register if the patient has been infected with COVID-19, co-enrollments, and the type of department the participant is discharged to.

In case of withdrawal we register the reason for withdrawal.

S5. Data management, confidentiality, funding, and responsibility

Data management

The data manager at Copenhagen Trial Unit (CTU) or his/her delegate will construct and oversee the electronic case-report forms (eCRF). He/she will, as the only person, have access to the randomisation list during the trial. The eCRF and the trial database will be hosted at the server of CTU with appropriate back-up and security as per the GCP regulative.

All original records (incl. consent forms, eCRFs, and relevant correspondences) will be archived for 15 years. We will ensure that long-term storage of data and source documentation will be made at each site.

Confidentiality

Each participant will receive a unique trial identification number. Trial investigators will receive a personal username and password to access the randomisation system and the eCRF. Each site will only have access to site specific participant data. Data will be handled according to national laws and regulations.

Collection, handling, storage of human biological material

No additional sampling of human material will be done in the trial as data entry will rely on routine testing done in the clinical setting.

Trial funding

The GODIF trial has received research grants from the following contributors:

Novo Nordisk Foundation, Merchant Jakob Ehrenreich and wife Grete Ehrenreich's Foundation, Jakob Madsen's and wife Olga Madsen's Foundation, Svend Andersen's Foundation, and Health Insurance Denmark (Sygeforsikringen Danmark).

None of the funding organisations have been or will be involved in the trial design, conduct, analyses, or reporting of the trial. Ownership of the data belongs to the sponsor.

Responsibilities of the coordinating centre and Management Committee

The coordinating centre, Department of Anaesthesiology, Copenhagen University Hospital - North Zealand, Hilleroed, Denmark is responsible for the overall management and coordination of the GODIF trial, which will be supervised by a Management Committee. National investigators are responsible for obtaining the national approvals and function as a coordinator for the GODIF trial in country in question. Principal investigators are responsible for maintenance of trial documents and data collections at their site. Site investigators' responsibility is to run the trial at their trial site according to the protocol.

The GODIF trial is part of the Collaboration of Research in Intensive Care (CRIC).

S6. Daily registration of serious adverse events (SAEs) and reactions (SARs)

We are considering the following conditions as SAEs to fluid removal, and they will be registered daily in the database:

- Ischaemic events defined as either
    - Cerebral ischaemia defined as any form of cerebral ischemia on a CT- OR MRI scan
    - Acute myocardial ischaemia defined as participant with acute myocardial infarction (ST-elevation myocardial infarction OR non-ST elevation myocardial infarction) OR unstable angina pectoris according to the criteria in the clinical setting in question (e.g. elevated biomarkers, ischemic signs on ECG and clinical presentation) AND the participant received treatment as a consequence of this (reperfusion strategies (PCI/thrombolysis) OR initiation/increased antithrombotic treatment).
    - Intestinal ischaemia defined as ischaemia verified by endoscopy OR open surgery OR CT-angiography.
    - Limb ischemia defined as clinical signs AND need of open/percutaneous vascular intervention, amputation OR initiation/increased antithrombotic treatment.
- A new episode of severe acute kidney injury defined as modified KDIGO 3[1] defined by three times increase in baseline p-creatinine or increase in p-creatinine to ≥ 354 μmol/L or use of renal replacement therapy (any form).
- New onset atrial fibrillation after randomisation in a participant who never have been diagnosed with atrial fibrillation before.

A SAR is defined as any adverse reaction that results in death, is life threatening, requires hospitalisation or prolongation for existing hospitalisation, or results in persistent or significant disability or incapacity[2]. Adverse reactions are specified in the Danish Summary of Product Characteristics for furosemide. We consider the following conditions to be SARs to furosemide, and they will be registered daily in the database.

- Severe electrolyte disturbance (plasma potassium < 2.5 mmol/L, plasma sodium < 120 mmol/L, or plasma chloride < 90 mmol/L)

- Aplastic anaemia (peripheral pancytopenia and marrow hypoplasia. Drop in hemoglobin < 5.0 mmol/l, neutrophil leucocytes < 0.5 x 10^9/l, thrombocytes < 20 x 10^9/L, reticulocytes < 1 %)
- Agranulocytosis (new drop in granulocytes to < 0.5 x 10^9/L)
- Pancreatitis
- Circulatory collapse leading to cardiac arrest
- Seizures because of furosemide induced low calcium or magnesium
- Steven Johnson's syndrome
- Toxic epidermal necrolysis
- Hearing impairment/loss
- Anaphylactic reaction defined as urticarial skin reaction AND at least one of the following observed in the ICU after randomisation:
    - Worsened circulation (> 20% decrease in blood pressure or > 20% increase in vasopressor dose)
    - Increased airway resistance (> 20% increase in the peak pressure on the ventilation)
    - Clinical stridor or bronchospasm
    - Subsequent treatment with bronchodilators.

S7. Charter for Data Monitoring Committee (DMC)

Introduction

This charter will define the minimum of obligations and responsibilities of the DMC as perceived by the GODIF Management Committee. The charter will outline the procedures for ensuring confidentiality, proper communication, implementation of the statistical monitoring guidelines, and describe the content of open and closed reports which will be provided to the DMC.

Primary responsibilities of the DMC

The DMC will be responsible for monitoring the overall conduct of the trial, safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial. DMC may provide recommendations relating to the recruitment/selection/retention of participants, about management of the participants, improving adherence to protocol, and procedures for data management and quality control. The DMC will provide recommendations about stopping or continuing the trial to the Management Committee of the GODIF trial.

The DMC will be advisory to the GODIF Management Committee, which will be responsible for reviewing the DMC recommendations promptly, to decide whether to continue or stop the trial, and to assess if amendments to the protocol or changes in trial conduct are required.

The DMC plan their own monitoring meetings to evaluate the planned interim analyses of the GODIF trial or other aspects of safety for trial participants. The interim analyses will be performed by an independent statistician. The sponsor will report the overall number of SARs annually to the DMC. The DMC can, at any time during the trial, request information about distribution of the events, outcome measures, and serious adverse reactions (SARs) according to intervention group. The DMC may also request unblinding of the intervention (see section on ‘closed sessions’) if deemed necessary by the data. The recommendations regarding stopping, continuing, or changing the design of the trial should be communicated without delay to the Management Committee of the GODIF trial. Within 48 hours the Management Committee has the responsibility to inform all investigators and sites participating in the trial, about the recommendation from the DMC and the Management Committee’s decision hereof.

Members of the DMC

The DMC is an independent group consisting of two clinicians and a biostatistician. They have experience in the management of ICU patients and in the conduct, monitoring, and analysis of randomised clinical trials.

DMC Clinician

Jonathan Silversides, MD, consultant, Queen's University Belfast, UK

DMC Trialist

Paul Young, MD, MD, specialist, medical Research Institute of New Zealand

DMC Biostatistician

Andreas Kryger Jensen, ass. professor, Department of Biostatistics, University of Copenhagen, Denmark.

Conflicts of interest

DMC members will sign a declaration of conflicts of interests and the members must be without any conflicts of interest. The conflicts may be financial, scientific, or regulatory in nature. Trial investigators or individuals employed by the sponsor, or individuals with regulatory responsibilities for the trial products cannot be members of the DMC. The DMC members do not own stocks in companies having products investigated by the GODIF trial.

The DMC members will disclose any consulting agreements or financial interests they have with the sponsor of the GODIF trial, with the contract research organisation (CRO) for the trial (if any), or with other sponsors having products that are being evaluated or having products that are competitive with those being evaluated in the GODIF trial. The DMC is responsible for deciding whether these consulting agreements or financial interests impact their objectivity in relation to the GODIF trial.

The DMC members must advice fellow members of any changes in these consulting agreements and financial interests that occur during the trial. If a DMC member develops significant conflicts of interest during the trial, the member should resign from the DMC.

DMC membership is for the duration of the clinical trial. If any members leave the DMC during the trial, the Management Committee will appoint the replacement.

Formal interim analysis meetings

Two formal interim analysis meetings will be held to review data relating to protocol adherence, treatment efficacy, and safety of the participants. The three members of the DMC will meet when 90-day follow-up data of 100 participants (10% of sample size) and 500 participants (50% of sample size) have been obtained.

Proper communication

Procedures will be implemented to ensure the DMC has sole access to evolving information from the clinical trial regarding comparative results of efficacy and safety data, aggregated by treatment group. An exception will be made to permit access to an independent statistician who will be responsible for serving as a link between the database and the DMC.

Open and closed sessions will be held to provide a forum for exchange of information among the parties who share the responsibility for successful conduct of the trial. The intent is to enable the DMC to preserve confidentiality of the comparative efficacy results and provide an opportunity for interaction between the DMC and others who have valuable insights into trial-related issues.

Closed sessions

Sessions involving only DMC members who generate the closed reports (called closed sessions) will be held to allow discussion of confidential data from the clinical trial, including information about the protocol adherence, and the relative safety and efficacy of interventions. To ensure that the DMC's primary mission of safeguarding the interest of participants, the DMC will be blinded in its assessment of safety and efficacy data. However, the DMC can request unblinding from the Management Committee.

Closed reports will contain analysis of the primary outcome measure. These closed reports will be prepared by an independent biostatistician (a member of the DMC), with assistance from the trial data manager, in a way that allow them to remain blinded. The closed reports should provide information that is precise, with follow-up on mortality that is completed within two months from the date of the DMC meeting.

Open reports

On the DMC meetings, open reports will be available to all who attend the meeting. The reports will include data on recruitment and baseline characteristics, data on eligibility violations, completeness of follow-up, and compliance. The independent statistician (member of the DMC) will prepare these open reports in co-operation with the trial data manager.

Minutes of the DMC Meetings

The DMC will write minutes of their meetings with description of the proceedings from all sessions, including the listing of recommendations by the committee. The minutes will be closed because they might contain unblinded information and must not reach individuals outside DMC.

Recommendations to the Management Committee

The planned interim analyses will be conducted after participant no. 100 and no. 500 has been followed for 90 days. The first interim analysis after 100 participants will only be on the process variables to ensure separation between the groups. The second interim analysis after 500 participants will be on primary outcome and SAE/SAR.

After the interim analysis meetings, the DMC will make a recommendation to the MC to continue, hold or terminate the trial.

The DMC will conduct a qualitative assessment of the results from the interim analysis of process variables to make recommendations for the trial. For the interim analysis after 500 participants of primary outcome measure and SAR/SAR - the DMC will recommend pausing or stopping the trial if group-difference is found with statistical significance levels adjusted according to the Lan DeMets group sequential monitoring boundaries based on O'Brien Fleming alfa-spending function[3].

If the recommendation is to stop the trial, the DMC will discuss whether the final decision to stop the trial will be made after the analysis of all participants included at the time (including participants randomised after this interim analysis) or whether the trial should be set on hold during these extra analyses. If further analyses are recommended after the interim analysis the rules for finally recommending stopping of the trial should obey the Lan DeMets stopping boundary[3]. Furthermore, the DMC can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises participant safety. However, stopping for futility to show an intervention

effect of 15% RRR (or RRI) for in-hospital mortality and improvement of 8% for ‘days alive outside hospital at day 90’ will not be an option. An intervention effect less than these may be clinically relevant as well.

The recommendation will be based primarily on safety and efficacy considerations and will be guided by statistical monitoring guidelines defined in trial protocol and this charter.

The Management Committee and the DMC are responsible for safeguarding the interests of participants and for the conduct of the trial. Recommendations to amend the protocol or on conduct of the trial made by the DMC will be considered and decided upon by the Management Committee. The Management Committee will be responsible for deciding whether to continue, hold or stop the trial based on the DMC recommendations. The DMC will be notified of all changes to the trial protocol or conduct.

Statistical monitoring guidelines

The outcome parameters are defined in the GODIF trial protocol. The DMC will evaluate data on:

Interim analysis of process variables after 100 participants have completed 90-days follow-up

Process variables:

- Mean cumulative fluid balance in mL after 3 days or censoring at discharge for participants in the two groups
- Number of days with escape medicine per participant

Interim analysis of process variables after 500 participants have completed 90-days follow-up

Primary outcome and SAE/SAR:

The primary outcome measure: Days alive and out of hospital day 90 after randomisation.
Number of participants with one or more SAEs/SARs at day 90.

The DMC will be provided with these data from the coordinating centre as:

- Number of participants randomised
- Number of participants randomised per intervention group
- Number of participants stratified per stratification variable per intervention group

- Number of events, according to the outcomes, in the two groups

Based on evaluations of these outcomes, the DMC will decide if they want further data from the coordinating centre for analysis and when to do the analyses. The data will be provided in one file as described below.

The DMC can be asked to ensure that procedures are properly implemented, to adjust trial sample size or duration of follow-up to restore power, if protocol specified event rates are inaccurate. If so, the algorithm for this should be clearly described.

Conditions for transfer of data from the Coordinating Centre to the DMC

The DMC will be provided with a CSV file containing the data defined as follows:

- Row 1 contains the names of the variables (to be defined below).
- Row 2 to N (where N-1 is the number of participants in the trial) each contains the data of one participant.
- Column 1 to p (where p is the number of variables to be defined below) each contains in row 1 the name of a variable and in the next N rows the values of this variable.

The values of the following variables should be included in the database for the first interim analysis:

1. screening_id: a number that uniquely identifies the participant
2. rand_code: The randomisation code (group 0 or 1). The DMSC will be blinded for group-intervention.
3.Mean cumulative fluid balance for the first 3 days or censoring at discharge.
4.Number of days with escape medicine per participant

The values of the following variables should be included in the database for the second interim analysis:

1. screening_id: a number that uniquely identifies the participant
2. rand_code: The randomisation code (group 0 or 1). The DMSC will be blinded for group-intervention.
3. days alive outside hospital during the 90 days observation period for each patient.

4. day_90_indic: 90 day-mortality indicators (2 = censored, 1 = dead, 0 = alive at day 90)
5. SAE/SAR_indic: SAE/SAR indicator (1 = one or more SAES/SARs, 0 = no SAE/SAR)

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3. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983:659–63.