Pharmacological management of fluid overload

S. Goldstein1*, S. Bagshaw2, M. Cecconi3, M. Okusa4, H. Wang5, J. Kellum6, M. Mythen7 and A. D. Shaw8 for the ADQI XII Investigators Group

1 Center for Acute Care Nephrology, Nephrology and Hypertension, The Heart Institute, Cincinnati Children’s Hospital Medical Center, 3333 Burnet Avenue, MLC 7022, RILF2, Cincinnati, OH 45229, USA
2 University of Alberta, Edmonton, Canada
3 St George’s Hospital and Medical School, London, UK
4 University of Virginia Health System, Charlottesville, VA, USA
5 University of Alabama School of Medicine, Birmingham, AL, USA
6 University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
7 University College London, London, UK
8 Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, TN, USA

* Corresponding author. E-mail: stuart.goldstein@cchmc.org

Editor’s key points

- The authors investigate the management of fluid overload (FO) in critically ill patients.
- Based on a modified Delphi analysis in the Acute Dialysis Quality Initiative Working Group, they provide guidance for fluid management in the patient at-risk of FO.

Background. Standard treatment practice for the hypotensive patient with poor tissue perfusion is rapid volume resuscitation; in some scenarios, such as septic shock, this is performed with targeted goal-directed endpoints within 6 h of presentation. As a result, patients often develop significant positive fluid accumulation, which has been associated with poor outcomes above certain thresholds.

Methods. The aim of the current paper is to provide guidance for active pharmacological fluid management in the patient with, or at risk for, clinically significant positive fluid balance from either resuscitation for hypovolaemic shock or acute decompensated heart failure.

Results. We develop rationale for pharmacological fluid management targets (prevention of worsening fluid accumulation, achievement of slow vs rapid net negative fluid balance) in the context of phases of critical illness provided in the earlier Acute Dialysis Quality Initiative 12 papers.

Keywords: acute kidney injury; fluid overload; medications

Accepted for publication: 11 March 2014

Standard treatment practice for the hypotensive patient with poor tissue perfusion is rapid volume resuscitation; in some scenarios, such as septic shock, this is performed with targeted goal-directed endpoints within 6 h of presentation.1–3 Such critically ill patients often develop, or are at risk for, significant positive fluid accumulation as an adverse effect.4

Multiple observational studies demonstrate a strong, independent association with increasing fluid accumulation and poor outcome in children5–11 and adults,12–17 although it is important to note that no study has directly demonstrated that fluid overload (FO) causes poor outcome. Initially, this association was observed in critically ill children who received continuous renal replacement therapy (CRRT). Positive fluid accumulation or %FO has most often been normalized for patient body weight using the following formula:6

\[
\%FO = \left( \frac{\text{fluid intake (litre)} - \text{fluid output (litre)}}{\text{ICU admission weight (kg)}} \right) \times 100
\]

While this formula provides a feasible and easy assessment of relative FO, we caution that inherent limitations include lack of incorporation of insensible losses and wound losses, and also loss of visceral mass in a patient who has had an extended intensive care unit (ICU) stay. Nevertheless, the collective paediatric experience reveals that >10–20% FO at CRRT initiation confers a three- to eight-fold increased odds for mortality, after adjustment for illness severity, multi-organ failure (MOF), and age (from infants to young adults). The largest report, including 297 patients from the Prospective Paediatric CRRT Registry Group,7 showed >20% FO conferred greater odds ratio (OR) for mortality than the presence of MOF or oncological diagnosis at CRRT initiation. Interestingly, a recent study8 found that increasing %FO was associated with worsening oxygenation index in children who did not receive CRRT. Collectively, these paediatric data provide observational evidence to support prevention of >15–20% FO in the critically ill child.

Data from adult studies yield similar results. The multicentre Program to Improve Care for Acute Renal Disease experience showed the association between mortality and >10% fluid accumulation at RRT initiation.12 Observational data from 212 adult patients with sepsis showed increased survival in patients who received both adequate initial fluid resuscitation and late conservative fluid management (defined as even to negative fluid balance for two consecutive days).14 Although not reported by the authors, calculation of %FO
Pharmacological management of fluid overload

Methods

The 12th Scientific ADQI Meeting on Fluid Therapy assembled experts on this topic, including nephrologists, intensivists, paediatricians, emergency physicians, physiologists, and epidemiologists.

This report is the result of a modified Delphi analysis performed by the ADQI Working Group. The Delphi method is a structured and standardized process for collecting, summarizing, and disseminating knowledge from a group of experts focused on a specific problem or task. A detailed description of the ADQI methodology is available at: www.adqi.net.

Before the meeting, the working subgroup on the topic of Pharmacologic Fluid Management developed a list of preliminary questions and objectives, addressing three broad themes: when should pharmacological fluid management be initiated; what are the optimal mechanisms to monitor the trajectory of pharmacological fluid management; what are the ideal targets (endpoints) to discontinue pharmacological fluid removal. A literature search was conducted using the MEDLINE database (via the PubMed interface), using two broad search themes: (1) ‘fluid balance’, ‘fluid overload’, ‘fluid accumulation’ and (2) ‘resuscitation’, ‘shock’, ‘acute kidney injury’, and ‘heart failure’.

Findings

Indications to avoid active pharmacological fluid management

The clinical context will dictate when a trial of pharmacological management of fluid removal is appropriate or should be avoided/abandoned early and extracorporeal fluid removal with RRT organized.

While an initial trial of pharmacological management may serve as a temporizing measure, patients with symptomatic FO in addition to severe AKI characterized by concomitant conventional indications for RRT initiation (i.e. hyperkalaemia, uraemia, acidosis) or with life-threatening complications of FO and low probability of immediate response to pharmacological management should be referred urgently for RRT. Timely, RRT referral in critically ill patients with AKI likely represents an important source of bias in the association between diuretic therapy and outcome in prior studies. Mehta and colleagues reported that diuretic use was associated with an increased risk of death and non-recovery of kidney function in a cohort of 552 critically ill patients with AKI. However, poor outcome was predominantly evident among the subgroup of patients least responsive to diuretic therapy, defined as a ratio of daily furosemide dose equivalent to urine output (mg ml⁻¹ day⁻¹) ≥ 1.0, whereas diuretic responsive patients showed equivalent outcomes to patients not exposed to diuretics.

A trial of pharmacological management to determine the physiological response (e.g. urine output) should not delay definitive therapy with RRT. To better inform on the probability of an adequate response to a diuretic challenge, Chawla and colleagues recently described a functional bedside assessment of ‘diuretic responsiveness’ termed the furosemide stress test (FST). Patients with early stage AKI (KDIGO stage I or II) were administered a single dose of furosemide (1–1.5 mg kg⁻¹) to evaluate responsiveness as a surrogate for AKI severity and to predict worsening AKI (KDIGO stage III). Patients with urine output < 200 ml within 2 h after the furosemide challenge had a higher likelihood of worsening AKI (sensitivity 87%; specificity 84%; AuROC 0.87).

Indications to start pharmacological fluid management

After the initial phases of rescue and physiological optimization, ongoing assessment of daily fluid balance and tolerance of fluid accumulation should occur. A positive fluid balance and some accumulation may be expected to occur during this phase; however, as noted above, excessive fluid accumulation contributes to worse outcomes, across a range in clinical settings, particularly in AKI. Fluid balance is increasingly recognized as a complementary ‘vital sign’ or ‘biomarker’ of critical illness.

Studies from perioperative and critical care settings reinforce the concept of ‘ebb and flow’ in fluid management (i.e. loading, accumulation, and removal). These represent phases of resuscitation that exist on a continuum, whereby the observed between-patient variability in fluid balance is a dynamic process and will not necessarily follow a fixed temporal pattern or time scale. While this dynamism creates challenges for determining if and when pharmacological fluid management is indicated, in the absence of a life-threatening complication attributable to FO, pharmacological fluid removal is

from data in the report revealed 19.6% FO in non-survivors vs 10.1% in survivors.

These data argue for a fluid management strategy aimed to prevent fluid accumulation. The landmark Fluid And Catheter Treatment Trial (FACTT) compared a tightly prescribed comparison of a liberal vs conservative fluid management strategy, using fluid restriction and diuretics to maintain lower central venous pressure and PCWP in the conservative arm in adults with acute respiratory distress syndrome (ARDS). The conservative management strategy led to fewer ventilator days, and a post hoc analysis suggested diuretic-induced negative fluid balance may improve survival in patients with AKI. Thus, pharmacological fluid management may improve outcomes in the critically ill via mitigating excessive fluid accumulation.

The aim of the current paper is to provide guidance for active pharmacological fluid management in the patient with, or at risk for, clinically significant positive fluid balance from either resuscitation for hypovolaemic shock or acute decompensated heart failure (ADHF). We develop rationale for pharmacological fluid management targets (prevention of worsening fluid accumulation, achievement of slow vs rapid net negative fluid balance) in the context of phases of critical illness provided in the earlier Acute Dialysis Quality Initiative (ADQI) 12 papers. In all instances, active pharmacological fluid management should be linked to a patient-centred outcome.
indicated when fluid accumulation contributes or is likely to contribute to patient morbidity (e.g. delayed weaning from mechanical ventilation, disrupted wound healing, impaired organ recovery, suboptimal rehabilitation).

Thus, pharmacological fluid removal will be initiated, most often, in the stabilization or de-escalation phases after acute resuscitation. Importantly, in all patients at risk of or suffering from excessive fluid accumulation, judicious fluid management will begin by minimization of all non-essential fluid therapy concurrent with introduction of active pharmacological fluid removal. Active fluid removal is more likely to be tolerated in patients who have achieved haemodynamic stability (e.g. restoration of central haemodynamics, stable or decreasing vasoactive support) and individualized resuscitation endpoints (e.g. lactate clearance, normalized central venous oxygenation).

While these principles seem intuitive, few studies have evaluated strategies of post-resuscitation fluid management in critical illness, and no study has specifically evaluated the optimal timing or triggers for the introduction of pharmacological therapy to guide active fluid removal in critical illness for patients with AKI whose capacity to excrete fluid and solute is impaired. Indeed, with the exception of the FACTT trial and selected trials of conservative perioperative fluid regimens, the available evidence is predominantly post hoc, associative rather than causal. Studies have not prospectively evaluated the optimal clinical, physiological, biochemical, and/or organ-specific damage parameters to guide the initiation and discontinuation of active pharmacological fluid removal, or described the temporal relationships between active fluid removal and organ function, adverse events, and survival. These represent major knowledge gaps in our understanding of how to optimally manage fluid in the recovery phases of critical illness. Innovative clinical studies are beginning to integrate novel diagnostic and organ damage biomarkers to guide clinical decision-making and guide therapeutic strategies.

**Trajectory of active (pharmacological) fluid management**

For many years, one of the biggest questions in the care of critically ill patients has been ‘how to give fluids?’ The question of ‘how to remove fluids’ should be given at least the same importance. The critically ill patient presents a dynamic challenge for fluid management, since the answers to the above questions change not only depending on the reason for ICU admission (i.e. trauma, sepsis, surgery) but also according to the different phases of fluid management (i.e. rescue, stabilization, de-escalation). We propose that every patient should have an ‘ideal trajectory of fluid balance’ as part of the daily review.

We define the desired trajectory of fluid balance as the safe removal of fluid to achieve context-specific physiological endpoints, and suggest that these endpoints must be monitored.

Clinicians are accustomed to setting and monitoring goals and clinical endpoints in the rescue phase of fluid management for ICU patients. Goal-directed therapy has been studied during this phase in surgery and in sepsis. From a physiological point of view, there is no reason why principles applied during fluid resuscitation cannot be applied during the subsequent phases of fluid management. For instance, in a patient treated for ARDS, the physiological endpoint can be an improvement in oxygenation (e.g. $P_{aO_2}/FiO_2$ ratio). To achieve this endpoint, the clinician may decide that a negative fluid balance is needed over the next few days. The trajectory by which the clinician achieves this negative fluid balance may change depending on whether the patient is still on vasopressors or not, whether the kidney function and electrolytes have been stable or not over the previous days (Fig. 1).

Pharmacological fluid removal should be considered a temporary measure which should be stopped if the goal is achieved or failure occurs. Failure is not represented only by the inefficacy diuretics in producing negative fluid balance, but also by the occurrence of an adverse event (where pharmacological fluid removal is not safe anymore). Two examples (summarized in Table 1) may clarify this concept. In Example 1, a patient admitted with septic shock secondary to community-acquired pneumonia has received large-volume resuscitation during the rescue phase. On day 3, the patient is off vasopressors, is clinically overloaded, heavily dependent on the ventilator, and the clinician determines a negative fluid balance could improve oxygenation and facilitate ventilator weaning. A negative fluid balance of 1 litre in 24 h is set as a target, and

![Fig 1 Trajectories of fluid balance and management. A patient’s planned fluid balance trajectory correlates with the phases of resuscitation. A typical fluid balance pathway is depicted by scenario 1. Fluid balance may increase through initial salvage and optimization (A) until attainment of initial treatment goals. After a period of stabilization (B), de-escalation (C) may encompass fluid removal to return the patient to net euvoema. In select situations, the planned fluid balance trajectory may differ. For example, in ADHF, the patient may enter salvage and optimization with a relatively high fluid balance, but may require more rapid fluid removal during de-escalation (scenario 2, green line). In other situations, fluid removal efforts during de-escalation may fail, prompting escalation of fluid management interventions (scenario 3). Reproduced with permission from ADQI (www.ADQI.org).](image-url)
Examples of how to set and review clinical endpoints, fluid balance targets, and safety limits during pharmacological fluid removal

<table>
<thead>
<tr>
<th>Individualized endpoints/targets/safety limits</th>
<th>Evolution at 24 h</th>
<th>Comment</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 1 Summary: Patient day 4 in ICU, admitted with septic shock because of community-acquired pneumonia, inflammatory markers decreasing, now oedematous, on $F_{\text{IO2}}$, 0.45 PEEP 10 cm H$<em>2$O to maintain $S</em>{\text{O2}} &gt; 92%$. Problem: overloaded, oedematous, difficult to wean</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical endpoint</td>
<td>Oxygenation improvement</td>
<td>Not achieved yet</td>
<td>(1) There has been no achievement of clinical endpoint</td>
</tr>
<tr>
<td>Fluid balance target in 24 h</td>
<td>−1 litre (20%)</td>
<td>−0.5 litre</td>
<td>(2) The negative fluid balance is below target</td>
</tr>
<tr>
<td>Perfusion safety endpoints</td>
<td>Vasopressor/perfusion markers</td>
<td>No need for vasopressor no lactate increase</td>
<td>(3) The safety endpoints have not been reached</td>
</tr>
<tr>
<td>Renal function/electrolytes safety endpoints</td>
<td>Creatinine and BUN increase &lt; 25%</td>
<td>Creatinine BUN stable/increase &lt; 25%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No change &lt; 4 mmol litre$^{-1}$</td>
<td>Na change &lt; 4 mmol litre$^{-1}$</td>
<td></td>
</tr>
<tr>
<td>Example 2 Summary: Patient day 5 in ICU, admitted after emergency abdominal aortic aneurysm repair, then developed abdominal compartment syndrome on day 2 (emergency laparostomy) with impaired renal function. Now creatinine and BUN have recovered stable, the patient is oedematous with postop ileus. Problem: clinically significant oedema, probably contributing to ileus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical endpoint</td>
<td>Tissue oedema resolution</td>
<td>Not achieved yet</td>
<td>(1) There has been no achievement of clinical endpoint</td>
</tr>
<tr>
<td>Fluid balance target in 24 h</td>
<td>−1 litre (20%)</td>
<td>−1.2 litre</td>
<td>(2) The negative fluid balance is on target (upper limit)</td>
</tr>
<tr>
<td>Perfusion safety endpoints</td>
<td>Vasopressor/perfusion markers</td>
<td>No need for vasopressor/lactate stable</td>
<td>(3) There has been an increase in BUN and creatinine and Na change is above the safety limit</td>
</tr>
<tr>
<td>Renal function/electrolytes safety endpoints</td>
<td>Creatinine and BUN increase &lt; 25%</td>
<td>Creatinine increase &gt; 40%, BUN increase &gt; 20%, Na change 4 mmol litre$^{-1}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No change &lt; 6 mmol litre$^{-1}$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig 2 Fluid balance trajectory. Clinical care encompasses adherence to an intended fluid balance trajectory. Deviation from the trajectory (either above or below the intended pathway) should prompt adjustments in fluid management strategies. Reproduced with permission from ADQI (www.ADQI.org).

also safety endpoints. During the next 24 h, the goal negative fluid balance is not achieved, but safety endpoints are stable; therefore, the decision is to carry on/increase the diuretic.

In Example 2, a patient admitted post-emergency aortic aneurysm repair is now day 5 in ICU. On day 2, he developed abdominal compartment syndrome with associated kidney failure and need for an emergency laparotomy (with laparotomy). The patient never received RRT, and kidney function is now recovering. In the perioperative rescue phase of both emergency operations, the patient received large volumes of fluid and is now clinically overloaded; among the different features of FO, the clinician is also concerned about a non-resolving ileus. A negative fluid balance is set and achieved during the next 24 h, the oedema is not resolved, but the creatinine increase is above the safety endpoint; therefore, the decision is to stop the diuretic.

The rate of fluid balance change may also help to indicate the continuation, discontinuation, or failure of pharmacological therapy. As depicted in Figure 2, there is an acceptable ‘safe’ range of variation from the targeted fluid balance trajectory. An upward drift in fluid balance trajectory indicates that fluid removal is below therapeutic goals; adjustment of pharmacological therapy or initiation of extracorporeal therapy may be appropriate in these situations. Conversely, a downward drift in fluid balance trajectory may indicate overaggressive use of pharmacological therapy and the need for medication adjustment. Implicit in this concept is that the targeted fluid balance must be continually re-evaluated and adjusted.

The dosage and timing of pharmacological fluid measures may depend upon the relative level of FO, the targeted and actual rates of active fluid removal and underlying kidney function. For example, in a patient fully resuscitated from septic shock with intact kidney function, urine output may be adequate to allow early tapering or discontinuation of pharmacological measures. In contrast, in a patient with heart failure (HF) and evidence of azotemia, prolonged pharmacological assistance may be necessary to maintain urine output to reach...
targeted fluid balance. In the latter case, there may also be urgency in the rate of fluid removal, prompting clinicians to plan a more rapid fluid removal trajectory, perhaps with the use of extracorporeal therapy.

**Pharmacological measures to manage fluid**

In critically ill patients with sepsis, inflammation, and HF, oncotic pressure will often be low, which may have a variety of adverse effects related to transcapillary fluid movement favouring an increase in interstitial fluid volume in peripheral tissue and in lung and reduced plasma volume. Counter regulatory hormones (e.g. angiotensin II, sympathetic hormones, vasopressin) are increased, leading to sodium retention. These factors may reduce effectiveness of diuretics, despite the fact that these patients are significantly volume overloaded. Thus, maintenance of normal oncotic pressure is critical for normal fluid homeostasis and optimizing diuretic effectiveness. Plasma albumin contributes importantly to plasma oncotic pressure; hence, hypoalbuminaemia limits diuretic effectiveness. An albumin–furosemide complex given i.v. to humans with hypoalbuminaemia and diuretic resistance results in increased natriuresis.

**Loop diuretics**

The basis for loop diuretics in the treatment of AKI rests with experimental studies using furosemide to decrease oxygen consumption by blocking the NaK2Cl co-transporter in the thick ascending limb. In this region, there is a delicate balance between oxygen supply and demand and furosemide reduced not only morphological and biochemical damage to the thick ascending limb but also in the S3 segment of the proximal tubule. High-dose furosemide when administered to patients with established AKI requiring dialysis improved urine output but did not affect renal recovery, number of dialysis sessions, or mortality. Continuous infusion of furosemide similarly showed no impact on renal recovery, despite improvement in urine output. Other studies have shown similar result in improving urine output but without change in mortality or renal recovery. The largest studies have resulted in different conclusions. As noted above, diuretic use was associated with an increased risk of death or non-recovery of renal function (OR, 1.77; 95% confidence interval, 1.14–2.76). In contrast, Uchino and colleagues, in a prospective multi-centre study of 1743 patients from 54 centres and 23 countries, found that after adjustment for known differences between the groups, there was no association between diuretics and mortality. Most recently, in a secondary analysis of the FACTT trial, Grams and colleagues found that higher diuretic dose in AKI was associated with improved survival. This finding was mediated through achieving a negative fluid balance with diuretic therapy. These data suggest that diuretic therapy, in particular for those with AKI, can be safe when utilized in the right context. Given these discrepant results, the results of the SPARK Study, a phase II randomized masked controlled trial examining the role of furosemide in critically ill patients with early AKI will be of significant interest.

I.V. continuous vs intermittent bolus diuretic infusion

Furosemide can be given either as a bolus or as continuous infusion. Intermittent administration of furosemide may lead to intervals where drug concentrations may be subtherapeutic; continuous infusion eliminates periods of compensatory sodium retention. Studies in different clinical situations have yielded varying results. Results have also been inconsistent in patients with ADHF. Despite the theoretical advantages of continuous infusion, no major differences in improvement of symptoms, changes in kidney function, or urine output were observed between intermittent and continuous infusion administration in the Diuretic Optimization Strategies Evaluation trial. In a Cochrane review of eight clinical trials that included 254 patients with ADHF, patients receiving continuous-infusion diuretic administration had greater urine output compared with those receiving equivalent intermittent bolus administration.

**Combination loop and distal convoluted tubule diuretic therapy**

Chronic diuretic use may lead to compensatory changes that may limit its efficacy, including an increase in plasma renin activity, stimulation of the sympathetic nervous system, and adaptive changes in distal nephron structure and function because of diuretic-induced increases in distal sodium load. Diuretic strategies that rely on combinations of diuretics (loop + distal convoluted tubule diuretic) may prevent structural and functional adaptations to chronic furosemide infusions that lead to diuretic resistance. Clinical studies suggest that combination therapy maybe more effective than single-dose therapy. However, the use of diuretic combinations is associated with significant hypokalaemia and hyponatraemia.

**Renal perfusion**

**Dopamine and fenoldopam**

Pharmacological methods to enhance renal perfusion have relied principally on inotropic and vasoactive agents. Dopamine stimulates α-, β-adrenergic receptors, and dopaminergic receptors that increase splanchnic and renal perfusion. Although low-dose dopamine has been shown to worsen renal perfusion as assessed by renal resistant indices in critically ill patients with acute kidney injury, it may have beneficial effects in patients with cardiorenal syndrome. In the Dopamine in ADHF, 60 consecutive patients with HF (35%) were treated with low-dose furosemide or combination of low-dose furosemide and low-dose dopamine. The results demonstrated that both regimens were equally effective in length of stay, 60 day mortality, or re-hospitalization rates, but the combination therapy was associated with improved renal function and potassium homeostasis.

Fenoldopam is a selective dopamine A1 receptor agonist whose effects may have potential importance in critically ill patients. In patients receiving i.v. contrast, fenoldopam increased renal blood flow compared with baseline by 15.8%, whereas 0.45% saline reduced renal blood flow by 33.2%.
Although there was no effect on incidence of radiocontrast-induced nephropathy (RCIN),\textsuperscript{60} in a prospective, placebo-controlled, double-blind, multi-centre randomized trial in patients with renal insufficiency, fenoldopam had no affect to reduce the incidence of RCIN (33.6\% vs 30.1\%; \( P=\text{NS} \)).\textsuperscript{61} In the paediatric population, the use of high-dose fenoldopam was assessed in infants with congenital heart disease undergoing cardiopulmonary bypass. Although urinary NGAL and CysC were increased in both the fenoldopam and placebo groups, lower levels were observed in the fenoldopam group. AKI as assessed by pRIFLE classification was 50\% in the fenoldopam group and 73\% in the placebo group (\( P=0.08 \)). Interestingly, there was a significant reduction in furosemide administration in the fenoldopam group.\textsuperscript{62}

**Natriuretics and aquaretics**

**Natriuretics**

Nesiritide, a recombinant human B-type natriuretic peptide, produces vasodilatory effects and was approved for the treatment of symptomatic relief of ADHF. Because of natriuretic effects in normal humans,\textsuperscript{63,64} nesiritide was thought to increase urine output in patients with HF. While early studies demonstrated a favourable effect of nesiritide,\textsuperscript{65} two randomized trials, the FUSION II and Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure trial, showed no additional benefit of nesiritide over loop diuretics alone.\textsuperscript{66}

**Aquaretics**

Vasopressin levels are inappropriately elevated in HF patients and play a key role in mediating water retention through its action on collecting tubule V2 receptors. The discovery of small molecule antagonists has opened up additional therapeutic options for the treatment of HF. The EVEREST study (the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) was designed to determine the efficacy of vasopressin antagonism in hospitalized patients, although there was no effect on all-cause mortality.\textsuperscript{67}

**Research agenda**

As noted above, the recent fluid management literature comprises clinical trials in fluid management focusing on standardizing resuscitation goals and observational studies of the association between excessive fluid accumulation and poor outcomes. Pharmacological fluid removal has been used ubiquitously, but often with a ‘trial and error’ mind set, and with limited consistent efficacy.\textsuperscript{68} We propose that the trajectories of fluid management presented in this article can serve as a foundation to standardize prospective outcome studies of pharmacological fluid management. The specific research questions that need to be addressed are:

- Can kidney damage biomarkers predict diuretic failure?
- Can real-time physiological biomarkers be used to monitor microvascular tissue oxygenation as an index of optimal diuretic therapy?
- Can the ‘FST’ be used to determine diuretic responsiveness, guide an optimal diuretic strategy, or both?
- Is a continuous vs intermittent diuretic strategy superior for a late conservative fluid management strategy?
- Is there benefit to addition of thiazides to loop diuretics in a late conservative fluid management strategy?

**Authors’ contributions**

S.G: Co-chaired the Pharmacological Management of Fluid Overload Work Group, provided the initial draft for the Methods, Indications to Avoid and Indications to Start Pharmacological Fluid Management sections, and reviewed and contributed to the final draft for review by co-authors. M.C.: Participated in Pharmacological Management of Fluid Overload Work Group, provided the initial draft for the Trajectories of Active Pharmacological Fluid Management section, and edited and contributed to the final draft for review by co-authors. M.O.: Contributed to the Pharmacological Management of Fluid Overload Work Group, provided the initial draft for the Indications to Discontinue Pharmacological Fluid Management aspects, developed all figures, and edited and contributed to the final draft for review by co-authors. H.W.: Established the final draft for review by co-authors. S.B: Co-chaired the ADQI XII meeting and reviewed and edited the Pharmacological Management of Fluid Overload Work Group drafts and figures.

**Supplementary material**

Supplementary material is available at *British Journal of Anaesthesia* online.

**Declaration of interest**

None declared.

**References**

Pharmacological management of fluid overload