Urinary Composition During Decongestive Treatment in Heart Failure With Reduced Ejection Fraction

Frederik H. Verbrugge, MD; Petra Nijst, MD; Matthias Dupont, MD; Joris Penders, MD, PhD; W.H. Wilson Tang, MD; Wilfried Mullens, MD, PhD

Background—The urinary composition, including sodium (Na⁺) and chloride (Cl⁻) concentrations, might provide useful information in addition to urine output during decongestive treatment in heart failure.

Methods and Results—Consecutive patients with heart failure (n=61), ejection fraction ≤45%, worsening symptoms, and scheduled treatment with intravenous loop diuretics were included. Patients received protocol-driven therapy until complete decongestion, assessed clinically and by echocardiography. Three consecutive 24-hour urinary collections were performed. With 2 mg (1–4 mg), 1 mg (0–2 mg), and 1 mg (0–1 mg) bumetanide administered in bolus during consecutive 24-hour intervals, in addition to combinational diuretic therapy in ≈70% and both oral spironolactone and vasodilators in ≈90%, euvolemia was reached, often within 24 hours. Urine output was higher during the first when compared with the second or third 24-hour interval (2700 versus 1550 or 1375 mL, respectively; P<0.001), but this was no longer significant after correction for diuretic dose (P=0.263), indicating preserved diuretic efficiency during the study. In contrast, urinary Na⁺ and Cl⁻ excretion both decreased significantly, even after correction for diuretic dose (P=0.040 and 0.004, respectively), leading to decreasing urinary concentrations with progressive decongestion. After reaching euvolemia, lower urinary Na⁺/Cr and Cl⁻/Cr ratios were both associated with urine output ≤1500 mL (area under the curve, 0.830 and 0.826, respectively; P<0.001 for both), in contrast to plasma N-terminal pro–B-type natriuretic peptide levels that were not (area under the curve, 0.515; P=0.735)

Conclusions—The urinary composition during progressive decongestion in heart failure with reduced ejection fraction is characterized by a drop in urinary Na⁺ and Cl⁻ concentrations. The urinary Na⁺/Cr or Cl⁻/Cr ratio might provide insightful information to titrate diuretic therapy.

Key Words: sodium ■ systolic heart failure ■ urea ■ urine

Signs and symptoms of congestion are the predominant cause of hospitalizations in patients with heart failure (HF).¹ Decongestive treatment in such cases may comprise different strategies, but diuretics remain by far the most frequently applied therapy.² Importantly, effective and complete decongestion in case of clear volume overload is associated with better survival and less frequent readmissions.³ ⁵ Yet, it is less clear when and whether diuretic therapy can safely be downtitrated once euvolemia is reached, still maintaining a neutral fluid balance. This is a relevant question as it remains concerning that a higher dose of maintenance diuretics is associated with increased mortality in HF.³ Yet, confounding by indication partly clouds this relationship because more advanced disease usually requires the use of higher diuretic doses. Nevertheless, it is prudent—and recommended by the guidelines—to use the lowest dose of diuretics, effective to achieve persistent decongestion.⁷–¹⁰ From a pathophysiological perspective, volume status is in fact governed by renal sodium (Na⁺) homeostasis, which might be substantially altered in HF.¹¹ Yet, surprisingly few studies have actually assessed urinary composition, including Na⁺ and chloride (Cl⁻) concentrations, in addition to urine output during decongestive treatment. We hypothesized that such qualitative analysis of diuresis might offer additional information in support to quantitative measurements of urine volume that are classically performed. Specifically, we sought for patterns associated with decongestion that might serve to provide insightful information to titrate diuretic therapy in HF.

Methods

Study Design

The first and last authors designed the study, which was performed in the HF intensive care unit of a single tertiary care center (Ziekenhuis
Oost-Limburg, Genk, Belgium). The study was conducted in accordance with the Declaration of Helsinki. The institutional review committee approved the study protocol, and written informed consent was obtained from every patient. All authors had full access to the data and contributed to the writing of the article. Together, they take responsibility for the integrity of the data and agree to the report as written.

Study Population
Patients were eligible for the study if they were aged ≥18 years and able to give informed consent. Additional inclusion criteria were (1) worsening symptoms because of HF, according to the treating cardiologist; (2) left ventricular ejection fraction ≤45% on screening echocardiography; (3) scheduled treatment with intravenous loop diuretics because of clinical signs of volume overload. Exclusion criteria were (1) treatment with intravenous loop diuretics during the index hospitalization before study inclusion; (2) concurrent diagnosis of an acute coronary syndrome; (3) inotropic or vasopressor support; (4) renal replacement therapy; or (5) ventricular assist devices, including the use of an intra-aortic balloon pump, at any time point during the study period.

Laboratory and Echocardiography Measurements
A baseline venous blood sample was obtained at baseline, before initiation of decongestive treatment, with repeated samples acquired in the morning of the next 3 days. Comprehensive 2-dimensional echocardiography examinations were performed at baseline and after reaching euvolemia within 3 days, by experienced cardiac sonographers with a commercially available system (Philips Healthcare, iE33). Images were acquired in the left lateral decubitus position, triggered to QRS complex, and digitally stored in cine loops in DICOM format. For study purposes, a single investigator (P.N.) analyzed the images offline. All reported measurements were averaged from 3 consecutive cycles and assessed as recommended by the American Society of Echocardiography.12 Finally, urine was collected during 3 consecutive 24-hour intervals; the first collection started together with the first administration of intravenous loop diuretics.

Study Protocol
For logistic reasons, patients who agreed to participate in the study were admitted at the HF intensive care unit, where they received a diet low in salt (<3 g) and were instructed to limit total daily fluid intake to 1.5 L. During the 72-hour study period, loop diuretics were administered under a standard protocol as intravenous boluses of bumetanide. The initial dose administered at baseline was equal to the double of the patient’s daily dose of oral loop diuretics. In loop diuretic naïve patients, a dose of 1 mg was used. On morning rounds of the next 3 days, patients were independently evaluated by 2 dedicated HF specialists involved in the study (M.D. and W.M.). On the basis of bedside information, they decided together whether the patient was still volume overloaded and in need of diuretics. Patients with a jugular venous pressure <8 mm Hg, no orthopnea and no edema was considered to have reached a euvolemic state, after which they were switched to oral therapy. To limit the occurrence of loop diuretic resistance, there was a strong emphasis on combinational diuretic therapy in the study protocol. Oral chlorothalidone, a thiazide-type diuretic, was preferentially added through once daily administration at a dose of 50 mg in patients with an estimated glomerular filtration rate <40 mL/min per 1.73 m². In addition, it was recommended that patients with a serum urea/Cr ratio of ≥50 received oral acetazolamide, a carbonic anhydrase inhibitor, at a daily dose of 250 mg. Finally, as combination therapy with potassium-wasting diuretics increases the risk of hypokalemia, all patients received once daily oral spironolactone at a dose of 25 mg, unless serum potassium levels were >5.0 mmol/L.

Statistical Analysis
Continuous variables were expressed as means±SD, if normally distributed, or otherwise as median (interquartile range). Normality was assessed by the Shapiro–Wilk statistic. Repeated measures ANOVA was used to assess intrapatient changes in diuresis and ion excretion, with adjustments for diuretic dose made by including loop diuretic dose as a covariate. The independent-samples Student t-test or Mann–Whitney U test were used as indicated for comparing between groups. Statistical significance was always set at a 2-tailed probability level of <0.05. Categorical data were expressed as percentages. Receiver operating characteristic curve analysis with nonparametric distribution assumption was used to calculate the area under the curve and 95% confidence interval for predictors of a neutral fluid balance (ie, urine output ≤1500 mL). All statistics were performed using IBM SPSS (version 22.0 for Windows).

Results

Study Population and Urinary Samples
Sixty-one consecutive patients were included in the study. Their baseline characteristics are presented in Table 1. Seven patients were discharged early from hospital after 48 hours and only had 2 urinary collections available, all others completed the study and had 3. Patients with an early discharge had a significantly higher left ventricular ejection fraction (33±8% vs 30±5%).
versus 23±9%; P=0.012) and lower New York Heart Association functional class (II/III/IV, 43/43/14% versus 11/56/33%; P=0.018). Other baseline characteristics were comparable with the rest of the population. From the total of 176 urinary collections, 1 (0.6%) was accidentally discarded and could not be analyzed.

**Decongestive Treatment**

Echocardiographic results were congruent with significantly improved diastolic function after decongestive treatment, illustrated by a significantly longer deceleration time, higher E/A ratio, and lower right ventricular systolic pressure after 3 days when compared with baseline (Table 2). The median (interquartile range) dose of bumetanide administered was 2 mg (1–4 mg) during the first, 1 mg (0–2 mg) during the second, and 1 mg (0–1 mg) during the third 24-hour interval, respectively. The percentage of patients receiving oral spironolactone was 95, 98, and 91 during the same 24-hour intervals, respectively. Forty-two patients (69%) received combinational diuretic therapy. Chlorthalidone without acetazolamide was used in 15%, 10%, and 11%; acetazolamide without chlorthalidone in 31%, 16%, and 9%; and both agents together in 16%, 10%, and 12%, during the first, second, and third 24-hour intervals, respectively. In addition, intravenous vasodilator therapy was used in most patients (89%) if they were normo- or hypertensive, whereas treatment with renin–angiotensin system blockers and β-blockers was continued unchanged.

**Quantitative Versus Qualitative Urinary Analysis**

Urine output was substantially higher during the first (2700 mL [1900–3450 mL]) when compared with that during the second (1550 mL [1006–2075 mL]) or third (1375 mL [1200–2200 mL]) 24-hour intervals (Figure 1A). After correction for loop diuretic dose, urine output remained stable during the entire study period at 1150 mL (718–1838 mL) per mg bumetanide (Figure 1B). Total 24-hour urinary Cr excretion was 1066±477 mg on average and stable overall in individual patients during the 72-hour study period (P=0.099). Similarly, total 24-hour urea excretion was 17.4±7.7 g on average and comparable between all 3 urinary collections within the same patient (P=0.816). In contrast, total 24-hour urinary Na+ and Cl− excretion decreased significantly after the first 24-hour interval (P<0.001 for both), remaining flat afterward (P=0.579 and 0.399, respectively; Figure 2A). This pattern was preserved after correction for loop diuretic dose, with urinary Na+ and Cl− excretion both decreasing significantly after 24 hours (P=0.001 for both), but remaining stable afterwards (P=0.201 and 0.959, respectively; Figure 2B).

**Urinary Patterns Associated With Decongestion**

During progressive decongestive treatment in the population as a whole, the urinary Na+ and Cl− concentrations decreased, whereas the urinary urea concentration increased (Figure 3). The urinary Na+/Cr and Cl−/Cr ratios were both particularly strong predictors of a urine output lower than the total fluid intake (<1500 mL), with a similar predictive value of the urinary urea concentration (Table 3). Alternatively, the fractional excretion of Na+ and Cl− was also significantly associated with low urine output, yet the area under the receiver operating characteristic curve was lower when compared with the urinary Na+/Cr and Cl−/Cr ratios, respectively (Table I in the Data Supplement). In contrast,
plasma N-terminal pro-B-type natriuretic peptide levels did not predict a neutral fluid balance. At a cutoff of 700 mg/dL, the urinary urea concentration demonstrated 94%/45% sensitivity/specificity to predict a urine output lower than the total fluid intake (≤1500 mL). Urinary Na+/Cr (cutoff, 85 mmol/g) and Cl−/Cr (cutoff, 55 mmol/g) had a lower sensitivity (54% and 55%, respectively) but higher specificity (91% for both). When urinary collections were stratified according to concomitant use of either acetazolamide or chlorothalidone, results were congruent with the overall results of the study (Tables II and III; Figures I and II in the Data Supplement).

**Urinary Analysis in Patients With Worsening Renal Function**

Sixteen patients (26%) developed a >0.3 mg/dL increase in serum Cr concentration when compared with baseline. When this occurred, urine output was lower when compared with patients without worsening renal function (1175 mL [818–1488 mL] versus 1900 mL [1300–2700 mL]; P<0.001). In addition, total 24-hour urinary Na+ (73 mmol [37–115 mmol] versus 155 mmol [100–263 mmol]; P<0.001), Cl− (51 mmol [17–99 mmol] versus 125 mmol [67–230 mmol]; P<0.001), Cr (788±334 versus 1102±481 mg; P=0.005), and urea excretion (11.5±5.8 versus 18.1±7.6 g; P<0.001), were all significantly lower in patients with versus without worsening renal function.

**Discussion**

The key message of this study in patients with HF with reduced ejection fraction and volume overload is that the urinary composition during decongestive treatment is characterized by a progressive decrease in urinary Na+ and

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### Table 3. Receiver Operating Characteristic Curve Analysis to Predict Low Urine Output

<table>
<thead>
<tr>
<th>Predictor</th>
<th>AUC (95% CI)</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Urinary sodium concentration, mmol/L</td>
<td>0.698 (0.619–0.778)</td>
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<td>Urinary chloride concentration, mmol/L</td>
<td>0.727 (0.649–0.806)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary chloride/creatinine ratio, mmol/g</td>
<td>0.826 (0.766–0.887)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary urea concentration, mg/dL*</td>
<td>0.831 (0.768–0.893)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary urea/creatinine ratio</td>
<td>0.652 (0.568–0.736)</td>
<td>0.001</td>
</tr>
<tr>
<td>Plasma NT-proBNP, ng/L</td>
<td>0.515 (0.428–0.602)</td>
<td>0.735</td>
</tr>
</tbody>
</table>

AUC indicates area under the curve; Cl, confidence interval; and NT-proBNP, N-terminal of pro-B-type natriuretic peptide.

* AUC under the reversed receiver operating characteristic curve.
Cl− excretion, even after correction for diuretic dose. In contrast, urine output corrected for diuretic dose (ie, diuretic efficiency), remained stable during the entire study period. As the urinary Na+ and Cl− excretion decreased disproportionately more than urinary output, a decrease in their urinary concentration was found with progressive decongestion. The urinary Na+/Cr and Cl−/Cr ratios in particular were strongly predictors of a neutral fluid balance once euvolemia was reached, in contrast to plasma N-terminal pro–B-type natriuretic peptide levels, which did not predict low urine output. Our results suggest that a qualitative analysis of the urinary composition might provide additional information to generally performed quantitative measurements of urinary output during decongestive treatment in HF.

Our study offers new, insightful information on urinary Na+, Cl−, and urea excretion during decongestive treatment in HF with reduced ejection fraction. First, we show that total 24-hour Cr and urea excretion remains relatively stable during decongestive treatment, which is expected if no major insult on the glomerular filtration rate occurs. In contrast, with progressive decongestion and correction of the underlying total body Na+ excess, 24-hour urinary Na+ and Cl− excretion drops, even after correction for diuretic dose. Importantly, after reaching euvolemia, we demonstrate that 24-hour urinary Na+ and Cl− excretion decreased disproportionately more than urinary output, resulting in a drop in their urinary concentrations. In addition, the result of a stable urinary urea excretion and lower urine output with progressive decongestion is a rise in the urinary urea concentration. This changing pattern of the urinary composition might provide better insight when euvolemia is reached. Moreover, it might help titrating diuretic therapy as in patients who achieve euvolemic and demonstrate low urinary Na+ and Cl− concentrations, the dose of diuretics can probably be safely reduced. In contrast, in patients who continue to excrete a substantial amount of Na+ and Cl−, the current dose has to be continued as maintenance therapy to prevent ongoing fluid accumulation. We feel that the Na+/Cr and Cl−/Cr ratios are particularly interesting parameters in this respect. The reason why the values corrected for urinary Cr performed better when compared with the absolute ion concentrations is probably that they account better for changes in underlying glomerular filtration rate, which are expected during decongestion. Indeed, in patients with worsening renal function, total 24-hour urinary Cr excretion did not remain stable but was significantly decreased.

Loop diuretics are a cornerstone in the decongestive treatment of HF because of their strong natriuretic effect. In the Acute Decompensated Heart Failure National Registry, 88% of patients were receiving intravenous loop diuretics, with monotherapy used in 63%. Importantly, loop diuretics are fast-onset diuretics with a short half-life (≈1–3 hours for both furosemide and bumetanide). Therefore, it is well known that in between dose administrations, after the diuretic effect has worn off, a period of increased Na+ retention occurs. If salt intake is high during that period, the net result may well be a neutral or even positive Na+ balance. Importantly, all patients in this study received a low salt diet to minimize postdiuretic Na+ retention. In addition, decreased urinary Na+ and Cl− excretion with repeated dosing of loop diuretics has been described, called the braking phenomenon. This phenomenon is not influenced by administration of renin–angiotensin system or ß-blockers, suggesting that it is (partly) independent of neurohumoral activation. One explanation is that intrinsic renal adaptations occur in the distal nephron, which compensate for decreased Na+ reabsorption in Henle’s loop because of prolonged loop diuretic therapy. Indeed, already after a few days of loop diuretic therapy, hypertrophy of distal tubular cells is evident, causing increased local Na+ uptake and aldosterone secretion. Alternatively, impaired delivery of loop diuretics to their place of action in the thick ascending limb of Henle’s loop might explain diminished natriuretic efficiency. However, such a change is only to be expected if there is an important drop in glomerular filtration rate. Finally, increased proximal Na+ reabsorption because of poor renal perfusion and intravascular underfilling might contribute to the braking phenomenon. Alternatively, if effective decongestion is achieved and, therefore, diuretic resistance is unlikely, a drop in urinary Na+ and Cl− concentrations after diuretic administration might indicate electrolyte depletion.

Clinical Implications
A remarkable 70% of patients in the Acute Decompensated Heart Failure National Registry receives maintenance diuretic therapy although many are probably not persistently volume overloaded. This might be somewhat disturbing as a higher dose of loop diuretics has been linked to worse clinical outcome in HF. Moreover, they may further stimulate ongoing neurohumoral activation and hamper up titration of neurohumoral blockers. Of course, this link is confounded by indication bias to some extent, which makes it difficult to interpret. Yet, as diuretics have not been shown to reduce either mortality or readmissions in HF, it is prudent to limit their use to the lowest dose effective to achieve a neutral fluid balance. Although signs and symptoms of congestion are an obvious reason to increase the diuretic dose, and many studies on biomarkers and new techniques evaluating possibilities to detect subclinical congestion better, the more difficult and unanswered question is when the dose of diuretics can safely be decreased. In this respect, our results offer some proof of concept that by assessing the urinary composition in addition to urinary output, one might be able to predict the need for diuretics better, making titration more convenient.

Limitations
Our results should be interpreted in the light of some study limitations. First, this was a single-center study with limited sample size and, therefore, results should be considered hypothesis generating. Second, our treatment strategy to achieve decongestion might have influenced the results. As is common practice at our center, there was a strong emphasis on combinational therapy with diuretics, spironolactone, and vasodilators, with an increase in loop diuretic dose only.
reserved for nonresponding patients. Although results on echocardiography clearly suggest successful decongestion in our population, it remains a possibility that the urinary composition could be different with loop diuretic monotherapy as is common practice in many centers. In such context, the external validity of our results remains unproven.

In addition, because of the inclusion of both patients with newly diagnosed HF and patients with a relative contraindication to renin–angiotensin system blockers because of poor renal function, baseline use of this medication class was rather low. However, the use of renin–angiotensin system blockers increased from 46% to 64% at discharge from hospital. Importantly, when urinary collections were stratified according to concomitant use of renin–angiotensin system blockers, study results remained unaffected (Table IV; Figure III in the Data Supplement). Third, we rigorously performed 24-hour urinary collections, which is impractical in daily clinical routine. However, as the urinary Na+/Cr and Cl−/Cr ratios, as well as the urinary urea concentration, can be assessed on spot samples taken shortly after the administration of diuretics, it would be interesting to see whether our results are confirmed in such a context. Fourth, we did not measure urine osmolality and, therefore, could not calculate free water excretion, which might have been interesting to explain the relatively preserved diuretic efficiency of diuretics, which represents the amount of diuretic agent reaching the renal tubules. Instead, we corrected for loop diuretic dose administered, which is more convenient but less accurate.

Conclusions

With progressive decongestion in patients with HF on a low salt diet, urinary Na+ and Cl− concentrations fall, whereas urea concentration increases. Either the urinary Na+/Cr or Cl−/Cr ratio (high specificity) in combination with the urinary urea concentration (high sensitivity) might provide useful information for titrating diuretic therapy.

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Disclosures

None.

References


**CLINICAL PERSPECTIVE**

This prospective study included 61 patients who presented with worsening symptoms because of heart failure with reduced ejection fraction. Patients received protocol-driven diuretic therapy until decongestion, assessed clinically and by echocardiography. Three consecutive 24-hour urinary collections were performed to assess changes in urinary sodium (Na⁺), chloride (Cl⁻), and urea excretion. Urea, such as creatinine (Cr) excretion, remained relatively stable with progressive decongestion, unless a major drop in glomerular filtration was observed. In contrast, urine output, Na⁺ and Cl⁻ excretion all decreased with progressive decongestion. Notably, after correction for loop diuretic dose, urine output remained relatively stable, whereas Na⁺ and Cl⁻ excretion significantly decreased during decongestion, most likely reflecting electrolyte depletion. The urinary Na⁺/Cr and Cl⁻/Cr ratios, in particular, were strong indicators of a neutral fluid balance once euvolemia was reached. Our results suggest that a qualitative analysis of the urinary composition might provide additional information to generally performed quantitative measurements of urine output during decongestive treatment in heart failure with reduced ejection fraction. More specifically, it might help downtitrating diuretic therapy, as in patients who achieve euvolemia and demonstrate low urinary Na⁺ and Cl⁻ concentrations, the dose of diuretics can probably safely be reduced. In contrast, in patients who continue to excrete a substantial amount of Na⁺ and Cl⁻, the current dose has to be continued as maintenance therapy to prevent ongoing fluid accumulation.
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## Supplemental Material

### 1. SUPPLEMENTAL TABLES

**Supplemental Table 1. Fractional sodium and chloride excretion to predict low urine output**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>AUC (95%CI)</th>
<th>P-value</th>
</tr>
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<tr>
<td>Urinary sodium concentration (mmol/L)</td>
<td>0.698 (0.619-0.778)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary sodium/creatinine ratio (mmol/g)</td>
<td>0.830 (0.771-0.889)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Fractional sodium excretion (%)</strong></td>
<td><strong>0.760 (0.688-0.831)</strong></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary chloride concentration (mmol/L)</td>
<td>0.727 (0.649-0.806)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary chloride/creatinine ratio (mmol/g)</td>
<td>0.826 (0.766-0.887)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Fractional chloride excretion (%)</strong></td>
<td><strong>0.770 (0.698-0.841)</strong></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AUC, area under the curve; CI, confidence interval.

**Supplemental Table 2. Urinary predictors of low urine output according to acetazolamide use**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Acetazolamide use (n=57)</th>
<th>P-value</th>
<th>No acetazolamide use (n=122)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary sodium concentration (mmol/L)</td>
<td>0.650 (0.451-0.850)</td>
<td>0.124</td>
<td>0.676 (0.580-0.773)</td>
<td>0.001</td>
</tr>
<tr>
<td>Urinary sodium/creatinine ratio (mmol/g)</td>
<td>0.806 (0.677-0.936)</td>
<td>0.002</td>
<td>0.815 (0.741-0.889)</td>
<td>&lt;0.001</td>
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<tr>
<td>Urinary chloride concentration (mmol/L)</td>
<td>0.634 (0.414-0.855)</td>
<td>0.169</td>
<td>0.728 (0.637-0.818)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary chloride/creatinine ratio (mmol/g)</td>
<td>0.779 (0.627-0.931)</td>
<td>0.004</td>
<td>0.820 (0.746-0.893)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary urea concentration (mg/dL)*</td>
<td>0.781 (0.612-0.950)</td>
<td>0.004</td>
<td>0.814 (0.735-0.892)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary urea/creatinine ratio</td>
<td>0.769 (0.611-0.927)</td>
<td>0.006</td>
<td>0.617 (0.515-0.718)</td>
<td>0.030</td>
</tr>
<tr>
<td>Plasma NT-proBNP (ng/L)</td>
<td>0.553 (0.375-0.732)</td>
<td>0.585</td>
<td>0.472 (0.366-0.577)</td>
<td>0.596</td>
</tr>
</tbody>
</table>

* AUC under the inversed receiver operated characteristic curve

AUC, area under the curve; CI, confidence interval; NT-proBNP, amino-terminal of pro-B-type natriuretic peptide; RAS, renin-angiotensin system.
## Supplemental Table 3. Urinary predictors of low urine output according to chlorthalidone use

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Chlorthalidone use (n=44)</th>
<th>P-value</th>
<th>No chlorthalidone use (n=135)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary sodium concentration (mmol/L)</td>
<td>0.632 (0.429-0.834)</td>
<td>0.185</td>
<td>0.700 (0.610-0.790)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary sodium/creatinine ratio (mmol/g)</td>
<td>0.817 (0.690-0.944)</td>
<td>0.001</td>
<td>0.832 (0.764-0.900)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary chloride concentration (mmol/L)</td>
<td>0.597 (0.380-0.813)</td>
<td>0.330</td>
<td>0.740 (0.655-0.826)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary chloride/creatinine ratio (mmol/g)</td>
<td>0.790 (0.646-0.935)</td>
<td>0.003</td>
<td>0.832 (0.764-0.900)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary urea concentration (mg/dL)*</td>
<td>0.866 (0.711-1.000)</td>
<td>&lt;0.001</td>
<td>0.807 (0.732-0.882)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary urea/creatinine ratio</td>
<td>0.645 (0.449-0.841)</td>
<td>0.144</td>
<td>0.649 (0.554-0.744)</td>
<td>0.003</td>
</tr>
<tr>
<td>Plasma NT-proBNP (ng/L)</td>
<td>0.511 (0.316-0.706)</td>
<td>0.914</td>
<td>0.479 (0.379-0.579)</td>
<td>0.680</td>
</tr>
</tbody>
</table>

*AUC under the inversed receiver operated characteristic curve

AUC, area under the curve; CI, confidence interval; NT-proBNP, amino-terminal of pro-B-type natriuretic peptide; RAS, renin-angiotensin system

## Supplemental Table 4. Urinary predictors of low urine output according to RAS blocker use

<table>
<thead>
<tr>
<th>Predictor</th>
<th>RAS blocker use (n=112)</th>
<th>P-value</th>
<th>No RAS blocker use (n=67)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary sodium concentration (mmol/L)</td>
<td>0.690 (0.588-0.792)</td>
<td>0.001</td>
<td>0.723 (0.593-0.853)</td>
<td>0.002</td>
</tr>
<tr>
<td>Urinary sodium/creatinine ratio (mmol/g)</td>
<td>0.830 (0.754-0.906)</td>
<td>&lt;0.001</td>
<td>0.856 (0.769-0.942)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary chloride concentration (mmol/L)</td>
<td>0.737 (0.641-0.834)</td>
<td>&lt;0.001</td>
<td>0.712 (0.575-0.848)</td>
<td>0.004</td>
</tr>
<tr>
<td>Urinary chloride/creatinine ratio (mmol/g)</td>
<td>0.829 (0.752-0.907)</td>
<td>&lt;0.001</td>
<td>0.844 (0.753-0.935)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary urea concentration (mg/dL)*</td>
<td>0.814 (0.730-0.899)</td>
<td>&lt;0.001</td>
<td>0.904 (0.830-0.978)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary urea/creatinine ratio</td>
<td>0.686 (0.581-0.791)</td>
<td>0.001</td>
<td>0.614 (0.475-0.753)</td>
<td>0.116</td>
</tr>
<tr>
<td>Plasma NT-proBNP (ng/L)</td>
<td>0.494 (0.384-0.605)</td>
<td>0.921</td>
<td>0.512 (0.368-0.656)</td>
<td>0.871</td>
</tr>
</tbody>
</table>

*AUC under the inversed receiver operated characteristic curve

AUC, area under the curve; CI, confidence interval; NT-proBNP, amino-terminal of pro-B-type natriuretic peptide; RAS, renin-angiotensin system
2. SUPPLEMENTAL FIGURES & FIGURE LEGENDS

Supplemental Figure 1. Urinary patterns during progressive decongestion were relatively similar regardless whether patients received acetazolamide or not. However, the urinary sodium (Na) and chloride (Cl) concentrations were significantly higher overall (P-value<0.001 and =0.007, respectively), likely reflecting the natriuretic effect of acetazolamide. In contrast, the urinary urea concentration was significantly lower in the acetazolamide group (P-value<0.001), probably reflecting the higher proportion of patients with underlying kidney disease and impaired urinary concentration capacity in this group.
Supplemental Figure 2. Urinary patterns during progressive decongestion were relatively similar regardless whether patients received chlorthalidone or not. However, the urinary sodium (Na) and chloride (Cl) concentrations were significantly higher overall (P-value=0.003 and <0.001, respectively), likely reflecting the natriuretic effect of chlorthalidone. In contrast, the urinary urea concentration was significantly lower in the chlorthalidone group (P-value<0.001), probably reflecting the higher proportion of patients with underlying kidney disease and impaired urinary concentration capacity in this group.
Supplemental Figure 3. Urinary sodium (Na) and chloride (Cl) concentrations were similar whether or not renin-angiotensin system (RAS) blockers were concomitantly administered with decongestive therapy (P-value=0.164 and 0.068 for the pooled results, respectively). In contrast, the absolute urinary urea concentration was significantly higher in patients who concomitantly received a renin-angiotensin system (RAS) blocker compared to them who were not (P-value=0.003 for the pooled results). This probably reflects the higher proportion of patients with underlying kidney disease and impaired urinary concentration capacity in the group that did not receive a RAS blocker. Nevertheless, the pattern of changes during decongestive treatment was remarkably similar between both groups.