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POSITION PAPER

Urinary sodium analysis: The key to effective diuretic titration? *European Journal of Heart Failure* expert consensus document

Evelyne Meekers[1,2], Jeroen Dauw[3], Jozine M. ter Maaten[4,5], Pieter Martens[1], Petra Nijst[1], Frederik H. Verbrugge[6,7], Marnicq Van Es[1,2], Jonas Erzeel[1,2], Kevin Damman[4], Joan Carles Trullàs[8,9], Matthias Dupont[1], and Wilfried Mullens[1,2]*

[1]Department of Cardiology, Ziekenhuis Oost-Limburg A.V., Genk, Belgium; [2]Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium; [3]Cardiovascular Center Aalst, OLV Hospital, Aalst, Belgium; [4]University of Groningen, Groningen, The Netherlands; [5]Department of Cardiology, University Medical Centre Groningen, Groningen, The Netherlands; [6]Centre for Cardiovascular Diseases, University Hospital Brussels, Jette, Belgium; [7]Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, Jette, Belgium; [8]Department of Internal Medicine, Hospital d'Olot, Girona, Spain; and [9]Tissue Repair and Regeneration Laboratory (TR2Lab), Institut de Recerca i Innovació en Ciències de la Vida i de la Salut a la Catalunya Central (IrisCC), Faculty of Medicine, University of Vic - Central University of Catalonia (UVic-UCC), Barcelona, Spain

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In patients with heart failure, neurohumoral activation leads to increased renal sodium avidity across the entire renal tubules, resulting in a positive sodium and water balance, leading to decompensated heart failure requiring intravenous diuretics. As the dose of diuretic therapy required to achieve euvolaemia is difficult to estimate due to considerable intra- and interindividual differences, the European Society of Cardiology recommends assessment of the diuretic response within hours either via evaluation of the urinary sodium concentration or via urinary volume after initial diuretic administration. All diuretic agents enhance sodium excretion to a different extent depending on their side of action across the renal tubules, and renal adaptation mechanisms due to neurohumoral stimulation. Impaired sodium excretion, even in the presence of fluid loss, is associated with worse clinical outcomes. Therefore, assessing urinary sodium excretion is considered a good and direct marker of the diuretic efficacy. Such natriuresis-guided protocols have been tested prospectively by the Pragmatic Urinary Sodium-based algoritHm in Acute Heart Failure and the Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure study, both demonstrating increased natriuresis and diuresis. Moreover, the Readily Available Urinary Sodium Analysis in Patients with Acute Decompensated Heart Failure study has demonstrated that a nurse-led natriuresis-guided protocol is feasible through the use of a point-of-care urinary sodium sensor, allowing an immediately readable urinary sodium result, enabling fast changes in diuretic therapy. This review summaries the rationale, current evidence and gaps supporting the role of urinary sodium concentration in patients with acute decompensated heart failure.

Keywords Acute decompensated heart failure • Acute heart failure • Therapy • Diuretics • Natriuresis

Introduction

Acute decompensated heart failure (ADHF) significantly impacts patients with heart failure, contributing to high morbidity, mortality, and healthcare costs.[1–3] Despite advancements in chronic heart failure (CHF) treatment, ADHF episodes remain prevalent, severely affecting patients' quality of life. Congestion is the primary reason for seeking urgent medical attention. Therefore, the primary goal during hospitalization is to achieve and maintain euvolaemia in addition to optimizing guideline-directed medical therapy and treating comorbid conditions. According to current guidelines, judicious use of intravenous (IV) loop diuretics remains the cornerstone in treating ADHF, to relieve signs and symptoms of congestion.[3,4] Nevertheless, only 11–18% of the patients achieved decongestion after 72 h of treatment in the Diuretic Optimization Strategies Evaluation (DOSE) trial.[5] In addition, in the recent Acetazolamide in Acute Decompensated Heart Failure with Volume Overload (ADVOR) trial, not all patients were fully decongested

*Corresponding author. Cardiovascular Physiology, Hasselt University, Heart Failure and Cardiac Rehabilitation Specialist, Ziekenhuis Oost-Limburg, 3600 Genk, Belgium. Tel: +32 89 327087, Fax: +32 89 327918, Email: wilfried.mullens@zol.be

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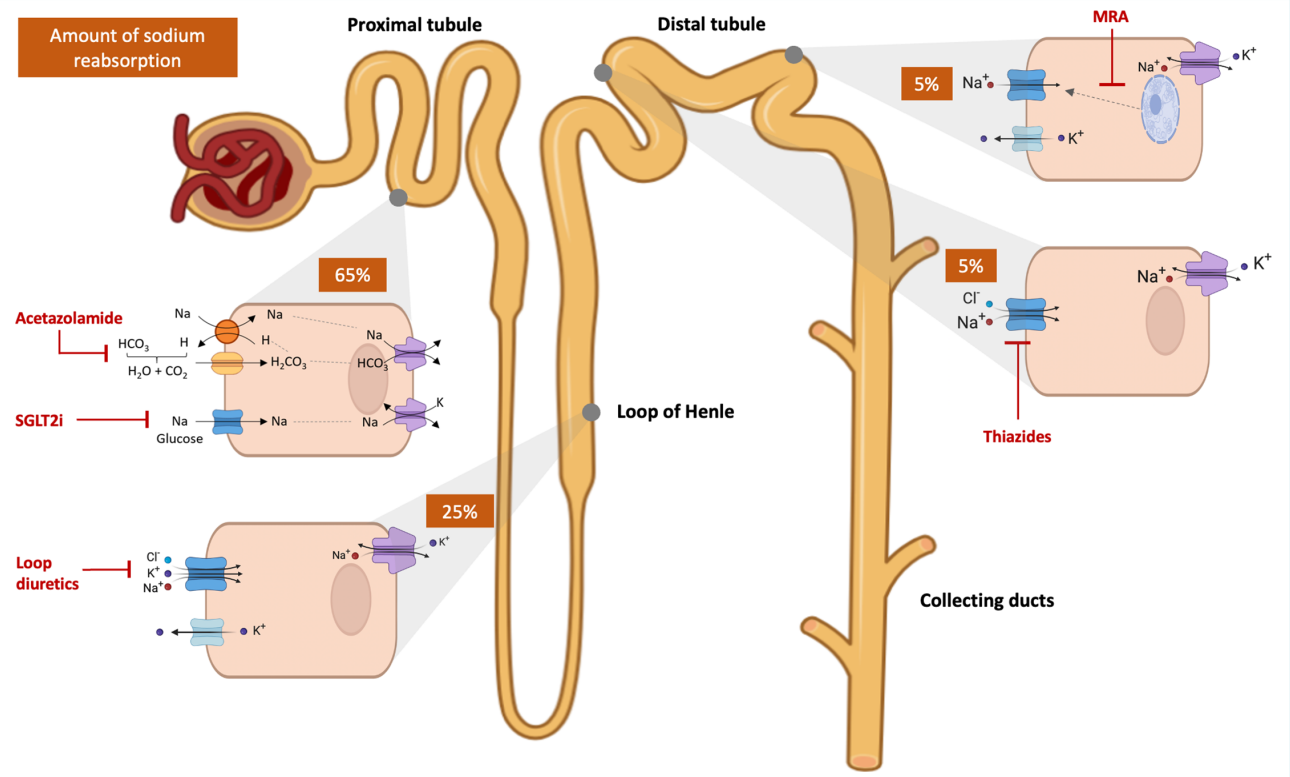

Figure 1 Renal tubules and different diuretic target sides. MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

at the moment of discharge, despite the fact that upfront combination therapy with acetazolamide improves decongestion rate considerably.[6] Therefore, there is a pressing need for effective and pragmatic metrics to optimize diuretic therapy, tailored to each patient's need. Several expert position papers, as well as the 2021 heart failure guidelines of the European Society of Cardiology (ESC) advise early assessment of the diuretic response using spot urinary sodium concentrations within 2 h of diuretic administration, with levels >50–70 mmol/L targeted.[3,7,8] Recent trials have tested various diuretic protocols guided by urinary sodium concentrations in patients with ADHF. This review summarizes the physiological basis and current evidence supporting urinary sodium concentration as a tool to guide diuretic therapy. It proposes practical approaches to titration in daily practice and highlights gaps in evidence, emphasizing its potential role in improving outcomes for ADHF patients.

Impaired natriuresis and diuresis in heart failure

Although sodium is freely filtered across the renal glomerulus, more than 99% is reabsorbed in the renal tubules, primarily in the proximal tubules (*Figure 1*). In heart failure, haemodynamic alterations and neurohumoral stimulation enhance renal sodium avidity. Importantly, heart failure is characterized by disproportionate sodium retention relative to water retention.[9,10] Decreased cardiac output, elevated filling pressures and renal venous congestion lead to reduced renal blood flow, requiring an increase in single-nephron glomerular filtration rate (GFR) to maintain overall GFR.[11] This compensatory increase in single-nephron filtration accelerates nephron loss in heart failure patients.[12] Thus, as renal blood flow decreases, the kidneys autoregulate by increasing the filtration fraction to maintain the GFR. This heightened filtration fraction raises sodium and water reabsorption across the proximal tubule (glomerulotubular balance) due to higher oncotic pressures in the peritubular capillaries. Consequently, the amount of sodium and chloride reaching the loop of Henle and the more distal parts of the tubules is considerably reduced. Neurohumoral upregulation further amplifies sodium and water reabsorption across the nephron. Additionally, reduced chloride delivery to the macula densa triggers renin release, activating the renin–angiotensin–aldosterone axis (tubuloglomerular feedback).

In the distal nephron, aldosterone increases sodium reabsorption by the sodium–chloride co-symporter and by the insertion of the epithelial sodium channels in the distal convoluted tubules and in the collection ducts. Chronic high-dose loop diuretic use promotes distal tubular hypertrophy, further enhancing sodium retention. Reduced tubular flow in the distal nephron segments, combined with decreased blood flow in the vasa recta and increased sodium reabsorption, creates a hypertonic medullary interstitium. This osmotic gradient, along with arginine–vasopressin release stimulated by angiotensin II, promotes free water retention in

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the collection ducts, impairing the diluting capacity of the kidney.[7,13] This highlights that plasma volume regulation is primarily mediated by renal sodium handling. Sodium serves as the primary determinant of extracellular fluid volume, and plasma sodium concentration reflects plasma volume regulation rather than osmoregulation.[14]

Diuretics in heart failure

Under conditions of forced sodium intake of 540 mEq (>12 g) with unrestricted access to water, maximal urinary sodium concentration can reach 280 mEq/L.[15] In contrast, during decongestion therapy with diuretics in the management of heart failure, urinary sodium concentration typically remains lower than serum sodium levels (~140 mEq/L). Therefore, a significant volume of water is required to promote the effective excretion of excess sodium in heart failure. Loop diuretics are strongly recommended (class I) for alleviating signs and symptoms of congestion in patients with ADHF. In patients with diuretic resistance, combination diuretic therapy might be indicated, as it enhances natriuresis and diuresis, although the comparison was not to a higher dose of loop diuretics, but against placebo. Given the varying mechanisms of action of different diuretics along the renal tubules, combination diuretic therapy blocks sodium reabsorption at multiple sites, augmenting the diuretic response (*Figure 1*).

Targeting the loop of Henle

Loop diuretic therapy blocks the $Na^+/K^+/2Cl^-$ symporter at the luminal membrane of the ascending loop of Henle, where 25% of sodium reabsorption occurs. This produces potent diuretic effects as the distal tubules have limited compensatory capacity (*Figure 1*). However, loop diuretics reduce the intracellular chloride load in the macula densa, triggering renin release and consequently higher renin–angiotensin–aldosterone system activation. Importantly, chronic use of loop diuretics may induce distal tubular hypertrophy and increased sodium reabsorption, resulting in diuretic resistance.[7] This effect may be countered by adding thiazides, which block the sodium–chloride cotransporter in the early part of the distal convoluted tubules (*Figure 1*).[7] The Safety and Efficacy of Combination of Loop with Thiazide-type Diuretics in patients with Decompensated Heart Failure (CLOROTIC) trial demonstrated that combining hydrochlorothiazide with IV furosemide was safe and effective in patients with ADHF, improving diuresis, natriuresis and weight loss in patients with chronic high-dose loop diuretics (maintenance therapy of more than 80 mg of furosemide daily), that is patients often classified as having diuretic resistance.[16] Similarly, the Diuresis Efficacy in Ambulatory Congested Heart Failure Patients (DEA-HF) trial showed that patients with intermittent long-term very high-dose IV loop diuretic therapy have a beneficial effect of the addition of thiazides to overcome the distal tubular hypertrophy.[17] With regard to different types of loop diuretics, torsemide has a longer half-life than bumetanide and furosemide.[18] Despite this, the Torsemide Comparison with Furosemide for Management of Heart Failure (TRANSFORM-HF) study was not able to demonstrate a significant difference in all-cause mortality over 12 months between ambulatory heart failure patients treated with torsemide and those with furosemide.[19]

Targeting the proximal tubule

Proximal diuretic agents are acetazolamide and sodium–glucose cotransporter 2 inhibitors (SGLT2i). Acetazolamide, a carbonic anhydrase inhibitor, blocks sodium reabsorption in the proximal tubules (*Figure 1*).[7,20,21] The ADVOR trial revealed that upfront use of IV acetazolamide in addition to IV loop diuretics in patients with ADHF resulted in a greater incidence of successful decongestion within 3 days and at discharge, attributed to higher cumulative urine output and natriuresis.[6] SGLT2i block the sodium and glucose reabsorption at the proximal tubules (*Figure 1*), promoting osmotic diuresis through glucosuria. However, this effect is rather small with only a transient increase in natriuresis.[22] Indeed, the association of an SGLT2i to loop diuretic therapy led to a significant increase in 24-h diuresis, without an increase in urinary sodium excretion at both 3 days and 6 weeks of treatment.[23] The increase in urinary volume due to the osmotic diuretic effect of SGLT2i even weans off 24–48 h after the initiation due to the parallel release of vasopressin, resulting in renal water reabsorption.[24] Furthermore, in patients with diuretic resistance, the addition of dapagliflozin to loop diuretics did not lead to an increase in weight loss after 96 h compared with the addition of metolazone (DAPA-RESIST).[25] Thus, while SGLT2i have limited utility in achieving acute euvolaemia, they are essential in CHF therapy for their disease-modifying benefits.

Targeting the distal nephron

Mineralocorticoid receptor antagonists (MRA) also theoretically induce natriuresis by modulating sodium and potassium channel activity in the distal nephron.[7] However, as they work as a prodrug, they have a slow onset and only work 48–72 h after oral intake. The Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure (ATHENA-HF) trial confirmed that their diuretic properties are limited as high dose (100 mg) spironolactone was not superior to low dose (25 mg) with regard to 96-h diuresis in patients with ADHF.[26] Importantly, like SGLT2i, they are also part of the chronic therapy in all patients with symptomatic heart failure. An auxiliary benefit of early addition of an MRA is the protection against hypokalaemia during aggressive decongestion.[27]

Natriuresis-guided diuretic strategies

The disproportionate increase in sodium retention relative to water avidity in ADHF represents a key pathophysiological mechanism. Therefore, it is logical that assessing urinary sodium content could offer valuable clinical insights. Strategies that enhance natriuresis are prognostically significant in patients hospitalized with ADHF. Among patients receiving high-dose loop diuretics, sodium concentration and excretion demonstrate substantial variability.

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Notably, sodium excretion is strongly correlated with 6-month mortality, whereas traditional fluid-based metrics including diuresis (aquaresis) show limited prognostic value. Impaired sodium excretion, even in the presence of fluid loss, is associated with worse clinical outcomes.[28,29]

Testani *et al.*[30] defined a poor diuretic response as a cumulative urinary sodium output below 50 mmol in a 6-h urinary collection post-diuretic administration. This threshold reflects the pharmacodynamic principle that loop diuretics have a half-life of 1.5–2 h and that their natriuretic effect is completed within 6 h.[31] If diuretics are given twice a day, this would lead to a total sodium excretion below 100 mmol. As the recommended daily sodium intake is limited to 3 g a day, which equals 130 mmol, there would still be a positive sodium balance, leading to salt and fluid retention. While 6-h sodium excretion correlates well with total 24-h urine output,[32] this requires timed urinary collections, prone to sampling errors. Therefore, spot urinary sodium samples offer an alternative, simplified and pragmatic strategy to predict a poor loop diuretic response with a good accuracy.[30,33] This method provides an early diuretic response evaluation within 2 h, enabling rapid adjustments to the diuretic regimen.[34] Guzik *et al.*[35] demonstrated in a small, single-centre study ($n = 50$) that urinary sodium concentration during the first 6 h exhibits an exponential relationship with urinary output, particularly in diuretic-naive patients. This suggests that urinary output might be simplified to once after 24 h rather than every 6 h. However, beyond this initial period, the relationship between urinary sodium concentration and output is less consistent.

Natriuresis-guided protocols

As illustrated, all diuretic agents (except vaptans) block sodium reabsorption along distinct sites along the renal tubule. Measuring urinary sodium concentrations early during decongestive therapy can identify patients requiring diuretic intensification to enhance diuretic efficacy. Observational studies show up to 40% of ADHF patients meet criteria for diuretic resistance, emphasizing the need for early evaluation strategies.[30,36–38] Given the good accuracy of spot urinary sodium concentrations for predicting diuretic resistance, the ESC guidelines recommend natriuresis-guided decongestive protocols. These protocols suggest diuretic up-titration if urinary sodium concentration falls below 50–70 mmol/L or urinary output is less than 100–150 mL/h, measured at 2 and 6 h post-diuretic administration, respectively.[3] As previously used metrics (such as weight change or initial diuresis) were not good predictors for diuretic resistance,[39] urinary spot sodium measurement may be the new kid in the block, leading to early optimization of diuretic treatment in patients with ADHF.

As present, two large trials and one small feasibility trial have tested the protocol prospectively (*Table 1*). The Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure (ENACT-HF) study was a multicentre, international, open-label, non-randomized, two-phase study ($n = 401$), in which a natriuresis-guided protocol ($n = 147$) improved natriuresis after 1 and 2 days (174 vs. 282 mmol, $p < 0.001$; and 365 vs. 538 mmol, $p < 0.001$, respectively), diuresis after 2 days (5.8 L vs. 4.4 L, $p < 0.001$), with a reduction in length of stay (5.8 vs. 7.0 days; $p = 0.036$) compared to the standard of care ($n = 254$).[40,41] Similarly, the Pragmatic Urinary Sodium-based algoritHm in Acute Heart Failure (PUSH-AHF) trial was a single-centre, open-label, randomized-controlled study ($n = 310$), which confirmed that a natriuresis-guided therapy resulted in a significant improvement in 24- and 48-h natriuresis (345 vs. 409 mmol, and 575 vs. 653 mmol, respectively) and diuresis (3.3 vs. 3.9 L, and 5.9 vs. 6.7 L, respectively) compared to the standard of care.[42,43]

There are some discrepancies between the study designs that should be addressed. The ENACT-HF protocol required a minimum home maintenance loop diuretic dose of 40 mg, while 45% of patients in the PUSH-AHF trial were diuretic-naive. The first loop diuretic bolus was double of the oral maintenance dose in all patients in the intervention arm. Up-titration was performed in case of a urinary sodium concentration below 50 mmol/L after 2 h or a urine output below 100 ml/h after 6 h, and doubling of the diuretic dose occurred 6 to 12 h after the first one. If these measurements were adequate, the same dose was repeated 6 to 12 h after the first administration. In case of a urine output below 3 L the next morning (i.e. not per definition after 24 h), diuretic dosage was doubled during the second day of treatment. In the standard of care arm, IV diuretic therapy was left at the discretion of the treating physician.[40]

In the PUSH-AHF study, the cut-off for the urinary sodium concentration was set higher at 70 mmol/L in the intervention arm.[42] The starting dose was equal to the oral home maintenance loop diuretic dose (or 40 mg of furosemide equivalents in loop diuretic naive patients) with a doubling of the dose in patients with an impaired kidney function (eGFR <60 ml/min/1.73 m^2). During the treatment phase in the PUSH-AHF, doubling of the diuretic dose was possible in case of a low urine output (<150 ml/h) or sodium concentration (<70 mmol/L) at any set timepoint (2, 6, 12, 18, 24 and 36 h).

Although the initial diuretic administration was more cautious with loop diuretic titration based on renal function, the PUSH-AHF study employed a more aggressive diuretic protocol with intensification of therapy at any of the previously mentioned time points. The ENACT-HF study used the lower range of the values proposed by the ESC for both the urinary sodium concentration and urinary output, in contrast to the PUSH-AHF which used the upper range. Although the study designs were somewhat different, both protocols seemed to be effective with regard to improving decongestive therapy (i.e. natriuresis and diuresis) in patients with ADHF compared to our current practice. A comparable protocol has been tested through a nurse-led diuretic protocol in the Readily Available Urinary Sodium Analysis in Patients with Acute Decompensated Heart Failure (EASY-HF) study.[44] This open-label, single-centre study randomized 60 patients to a standard of care arm or a nurse-led urinary sodium-guided diuretic up-titration protocol. Urinary sodium concentrations were measured bedside through a urinary sodium sensor (Horiba, LaquaTwin Na-11, Japan), providing an immediately readable result which allowed direct adjustments to the diuretic protocol in case of an insufficient diuretic efficiency (defined as urinary sodium concentration

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Table 1 Comparison of current urinary sodium-guided diuretic protocols

	PUSH-AHF		ENACT-HF		EASY-HF	
Methods						
Study design	Single-centre, open-label		Multicentre, open-label		Single-centre, open-label	
Randomized	+		−		+	
Sample size	310		401		60	
Patient population	ADHF		ADHF with maintenance loop diuretic therapy at home		ADHF	
Exclusion criteria	Severe renal impairment receiving dialysis or requiring ultrafiltration		• Cardiogenic shock or systolic blood pressure <90 mmHg • Use of renal replacement therapy or ultrafiltration • Use or anticipated use of intravenous inotropes		• eGFR <20 ml/min/1.73 m^2 • Patients currently undergoing or with a history of renal replacement therapy	
Intervention	Diuretic intensification if • U_{Na+} <70 mmol/L 2, 6, 12, 18, 24 and 36 h • U_{out} <150 mL/h at 6, 12, 18, 24 and 36 h		Diuretic intensification if • U_{Na+} <50 mmol/L after 2 h • U_{out} <100 ml/h after 6 h • U_{out} <3 L after 1 day		Diuretic intensification if • U_{Na+} <70 mmol/L after 2 h • U_{out} <3 L after 24 h	
Primary endpoint	• 24 h urinary sodium excretion • Combined endpoint of time to all-cause mortality or adjudicated heart failure rehospitalization at 180 days		Natriuresis after 1 day (first diuretic administration until next morning 8–10 AM)		48 h natriuresis	
Patient characteristics						
Age (years)	74 (65–82)		70 ± 14		80 ± 8	
Male sex	55%		250 (62%)		45 (75%)	
EF (%)	38 ± 14		39 ± 15		43 ± 16	
EF <40%	124 (54%)		223 (56%)		24 (40%)	
Baseline therapy						
Loop diuretics at home	114 (37%)		401 (100%)		31 (52%)	
Dose of oral furosemide or equivalents (mg/day)	80 (40–160)		60 (40–90)		40 (40–80)	
ACEi/ARB/ARNI	109 (35%)		270 (67.3%)		23 (38%)	
BB	139 (45%)		317 (79.1%)		39 (65%)	
MRA	69 (22%)		207 (51.6%)		15 (25%)	
SGLT2i	13 (17%)		68 (17.0%)		13 (22%)	
Laboratory						
eGFR (ml/min/1.73 m^2)	53 (35–73)		49 (32–74)		51 ± 18	
NT-proBNP (ng/L)	4710 (2553–8750)		5888 (3200–11 934)		4667 (2667-7709)	
Diuretics	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Loop diuretics after 2 days (furosemide equivalents)	640 (400–960)	320 (200–560)	640 (320–760)	240 (195–391)	320 (160–480)	240 (200–320)
Use of thiazides	24%	3%	18.9%	5.7%	0%	0%
Acetazolamide	0.4%	1%	0.7%	1.6%	0%	17%
Number of up-titration	85%		35%		30%	
Outcome	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Natriuresis after 1 day (mmol)	409 ± 178	345 ± 202	282 (254–312)	174 (154–196)	475 ± 161	420 ± 181
Natriuresis after 2 days (mmol)	653 ± 249	575 ± 290	538 (493–587)	365 (330–403)	820 ± 279	657 ± 273
Diuresis after 1 day (L)	3.9 (3.2–4.9)	3.3 (2.5–4.5)	3.1 (2.3–4.0)	2.2 (1.5–3.1)	4.2 ± 1.5	3.6 ± 1.3
Diuresis after 2 days (L)	6.7 (5.4–7.8)	5.9 (4.6–7.4)	5.8 (5.4–6.2)	4.4 (4.1–4.7)	7.3 ± 2.4	6.0 ± 1.9
Length of stay (days)	6 (5–9)	7 (5–10)	6 (5–7)	7 (6–8)	7 (3–16)	8 (4–17)

ACEi, angiotensin-converting enzyme inhibitor; ADHF, acute decompensated heart failure; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; EF, ejection fraction; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SGLT2i, sodium–glucose cotransporter 2 inhibitor; U_{Na+}, urinary sodium concentration; U_{out}, urinary output.

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below 70 mmol/L 2 h after diuretic administration or urinary output below 3 L after 24 h). This trial demonstrated that individualized titration significantly improved natriuresis (657 ± 273 mmol vs. 820 ± 279 mmol, $p < 0.05$) and diuresis (6.0 ± 1.9 L vs. 7.3 ± 2.4 L, $p < 0.05$) within 48 h (without physician intervention). The incorporation of a point-of-care urinary sodium sensor into the existing protocol enables nurse-led (or other healthcare providers) individualized diuretic titration, potentially establishing it as a standard procedure applicable across various departments beyond cardiology, which could significantly enhance the success of decongestion.

The dosage of loop diuretic therapy administered after 2 days of treatment in both arms in the ENACT-HF (640 [320–760] mg and 240 [195–391] mg) and PUSH-AHF (640 [400–960] mg and 320 [200–560] mg) trials were considerably higher than in the EASY-HF study (320 [160–480] mg and 240 [200–320] mg). The higher loop diuretic dosages in PUSH-AHF and ENACT-HF are related to the fact that the diuretic protocol was more intensive (i.e. the combination of the hourly urine output or the urinary sodium concentration criteria, the lower urine output requirements in the ENACT-HF study and the doubling at any set timepoint irrespective of previous diuretic responses in the PUSH-AHF study) and the more diuretic resistant study population of ENACT-HF. This was also reflected by the proportion of patients requiring up-titration according to the protocol, that is 30% in the EASY-HF study, 35% in the ENACT-HF study, and 85% in the PUSH-AHF study. Notably, diuretic response, measured as natriuresis per 40 mg furosemide equivalents, was lower in PUSH-AHF and ENACT-HF than EASY-HF, highlighting greater diuretic responsiveness in the latter population. Therefore, by taking all differences between the trial protocols into account, it can be postulated that urinary sodium-guided diuretic protocols have demonstrated to be efficient and safe across a broad spectrum of heart failure patients (de novo to more diuretic resistant heart failure patients).

Practical approach

Since the release of the ESC guidelines and position statement, significant new data have emerged regarding diuretic titration in ADHF. These recommendations may seem less practical in daily use due to their broad urinary sodium concentration range (50–70 mmol/L) with the need for hourly urinary volume assessments. The ESC flowchart may be too abstract, while the position statement's detailed recommendations could limit clinical applicability.[3,7] Therefore, based on recent trial data and real-world use of natriuresis-guided diuretic protocols, a novel more pragmatic algorithm is proposed to optimize diuretic therapy in patients with ADHF (*Figure 2*). For diuretic-naive patients, treatment starts with 40 mg IV furosemide (equivalent to 1 mg bumetanide or 10 mg torsemide), doubled for eGFR <60 ml/min/1.73 m^2. Patients on maintenance loop diuretics begin with double their oral dose intravenously, and the upfront addition of IV acetazolamide (500 mg IV once daily) or an oral thiazide (e.g. hydrochlorothiazide, dose adjusted by eGFR) should already be considered. Acetazolamide is the preferred first-line agent for most maintenance patients, while upfront thiazides are reserved for high-dose loop diuretic users. If urinary spot sodium concentration is <70 mmol/L 2 h after administration or a urinary volume <150 ml/h, diuretic therapy should be doubled. Loop diuretics should be titrated to a maximum bolus dose of 200 mg of furosemide (daily maximum 600 mg, with higher doses cautiously considered for patients with impaired renal function, though this increases the risk of ototoxicity). In patients with poor natriuretic or diuretic response, early combination therapy with acetazolamide or thiazides should be considered in diuretic-naive patients. Both acetazolamide (500 mg IV once daily) or a thiazide (hydrochlorothiazide if eGFR >50 ml/min: 25 mg daily; eGFR 20–50 ml/min: 50 mg daily; and eGFR <20 ml/min: 100 mg daily) are administered in a once daily regimen. Diuretic therapy should be optimized during the first day until natriuretic response is sufficient (i.e. ≥70 mmol/L and output ≥150 ml/h). Once achieved, this dose should be repeated every 12 h until decongestion is accomplished. After 24 h of treatment, total diuresis should be taken into consideration. If diuresis remains <3 L and congestion persists, further diuretic escalation should be considered during the second day of treatment. Importantly, other options like ultrafiltration in case of overt diuretic resistant volume overload, IV vasodilator therapy like nitroprusside (or inotropes in low-output states) in case of advanced low-output left ventricular failure with reduced ejection fraction or performing paracentesis in case of ascites should be considered.[45–47] Diuretic therapy should be given at least twice daily to limit the amount of post-diuretic sodium retention. Bolus IV loop therapy is preferred as it allows easier changes. However, when continuous infusions are chosen, an initial bolus should be administered to reach the diuretic threshold. During decongestive treatment, some degree of worsening renal function (WRF) may be anticipated due to haemodynamic alterations.[48] However, in case of adequate diuresis and no signs of hypoperfusion/hypotension, this should be interpreted as pseudo-WRF. Pseudo-WRF generally does not worsen prognosis if effective decongestion is achieved. So, in case of residual signs of congestion, continuation of decongestive therapy is advised under monitoring of electrolytes and serum creatinine. In contrast, if true WRF occurs in the face of a poor diuretic response, diuretic escalation is often necessary and signs of hypoperfusion should be ruled out (*Figure 2*). Consequently, changes in renal markers should be interpreted within the clinical context, focusing on achieving complete decongestion without overly reducing essential therapies based solely on transient increases in serum creatinine.[48] In the process of assessing changes in creatinine with diuresis, urinary sodium is also useful as patients with true WRF will have low urinary sodium concentration. These recommendations differ from the current ESC guidelines as patients with maintenance loop diuretic therapy receive already a different initial diuretic approach as they are considered to be more diuretic resistant (*Table 2*). In addition, the upper value of the target urinary sodium concentration and urine output has been chosen (i.e. ≥70 mmol/L and 150 ml/h). Most importantly, the urinary sodium concentration assessment is limited to the first day of treatment as the composition of the urinary sodium concentration during decongestive therapy changes significantly over time. Although urinary volume output remains relatively stable (diuresis), a drop in natriuresis is

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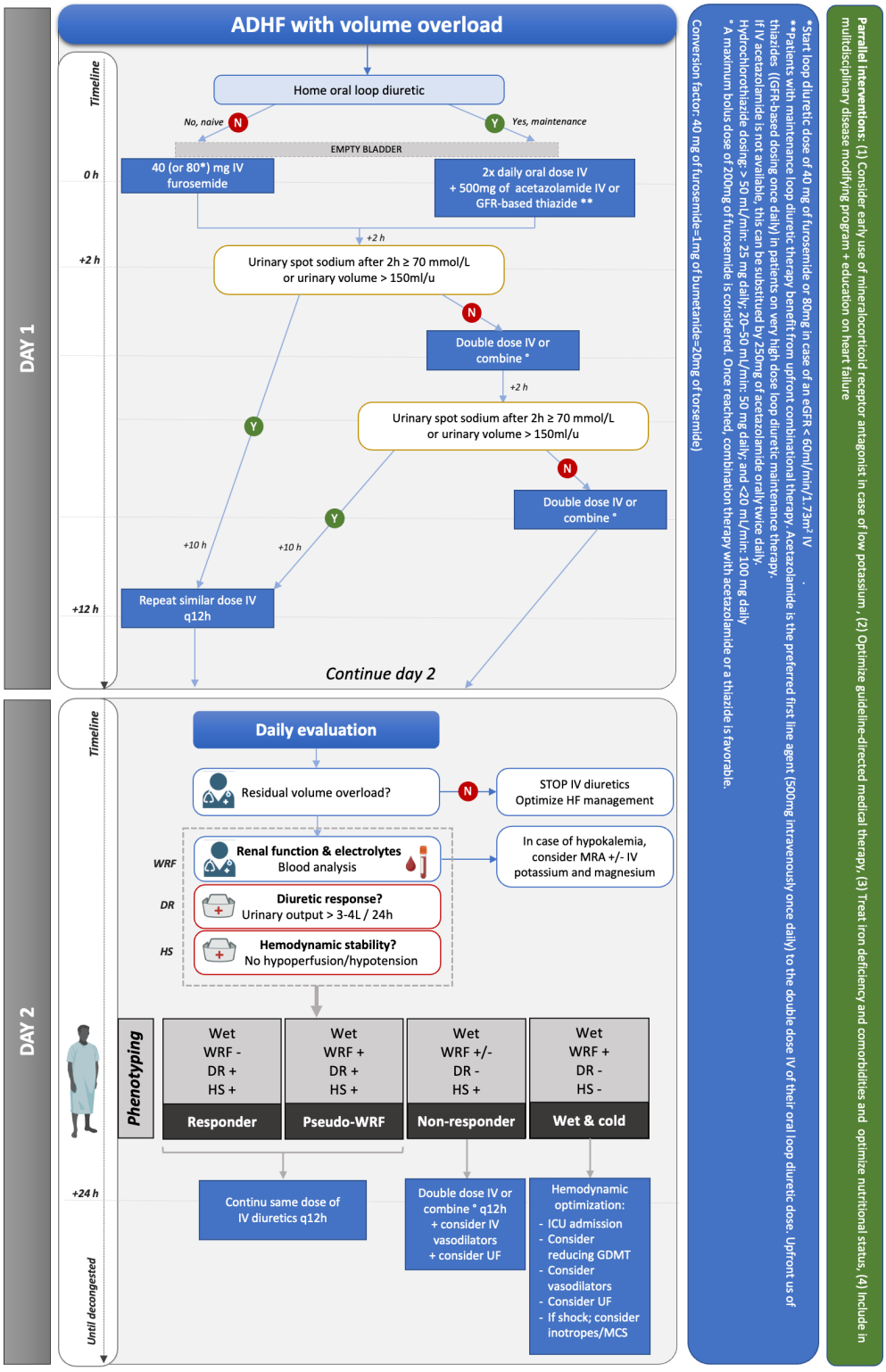

Figure 2 Diuretic titration in patients with acute decompensated heart failure (ADHF) with volume overload. DR, diuretic response; GDMT, guideline-directed medical therapy; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HF, heart failure; HS, haemodynamic stability; ICU, intensive care unit; IV, intravenous; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; UF, ultrafiltration; WRF, worsening renal function. WRF defined as a rise in serum creatinine of >0.3 mg/dl and/or an increase >25%.

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Table 2 What is new?

- Upfront combination therapy in patients who receive oral loop diuretic maintenance therapy at home.
- Urinary sodium concentration assessment after 2 h, possible through a nurse-led protocol. A urinary sodium concentration above 70 mmol/L (not 50 mmol/L) is considered as adequate.
- Use of point-of-care urinary sodium concentration tests or rapid laboratory testing in order to timely optimize diuretic titration.

expected during the consecutive days of loop diuretic therapy.[32] The role of urinary sodium-guided diuretic therapy during the first 24 to 48 h of treatment has been firmly established, however it is rather unsure how it may aid in diuretic titration afterwards as the urine becomes more hypotonic as a result of both haemodynamic and neurohumoral changes.[32,34,49] Most importantly, if decongestive therapy is optimized early, most of the patients are assessed decongested after a short treatment period.[6,44]

Future directions

Some gaps in the current evidence with regard to urinary sodium-guided diuretic titration remain. The ongoing Urine Chemistry Guided Acute Heart Failure Treatment (ESCALATE) trial may aid to provide an answer to the role of the urinary sodium concentration during the later phases of decongestion (i.e. after 48 h). The study randomizes 450 patients with ADHF to standard of care or urinary sodium-guided diuretic titration until euvolaemia is reached (NCT04481919).[50] Such a strategy is also tested in the Diuretic Treatment in Acute Heart Failure With Volume Overload Guided by Serial Spot Urine Sodium Assessment (DECONGEST) trial, which randomizes 107 ADHF patients and evaluates whether a diuretic sodium-guided regimen with low-threshold use of combination diuretic therapy improves decongestion and outcome compared to usual care (NCT05411991). Given the results of the ADVOR and CLOROTIC trials, early combination of diuretic agents might be indicated in a subpopulation of ADHF patients. The DECONGEST trial will evaluate how this might have an impact on the urinary sodium concentration during decongestion. It is important to note that a clinical evaluation of the congestion state remains necessary as a drop in urinary sodium excretion may implicate that euvolaemia is reached. However, it could also imply growing diuretic resistance in case of remaining signs and symptoms of congestion. In addition, the target urinary spot sodium concentration of 50–70 mmol/L is derived from the equation of Testani *et al.*[30] and showed to have a good accuracy, but not excellent. The chosen threshold of 70 mmol/L is therefore somewhat arbitrary and reflects the guidelines, but any value below 100 mmol/L may represent some kind of diuretic resistance.[51] Finally, although most ADHF patients receive dietary restrictions during hospitalizations, these might differ between centres. Dietary salt intake and total volume intake might have an influence on the urinary sodium concentration measured during decongestive treatment.

Beyond its role in the titration of diuretic therapy in ADHF patients, urinary sodium concentration measurements may also provide valuable prognostic and therapeutic insights for patients with CHF. Studies have shown that CHF patients with a low baseline urinary sodium excretion (i.e. <80 mmol/L), who are concurrently on high dose of maintenance loop diuretic therapy (furosemide >80 mg per day) exhibit a higher mortality risk.[52] Martens *et al.*[53] have explored the longitudinal significance of urinary sodium measurements in CHF patients. Their findings indicate that patients who experienced ADHF events generally presented with lower urinary sodium concentration compared to those with stable CHF. Furthermore, in these patients, episodes of congestion were preceded by a drop in urinary sodium concentration, likely due to increased neurohumoral activation. Sodium retention and congestion are inherently dynamic processes, resulting in frequent changes in home loop diuretic therapy. In addition to its potential role in prognostication, evidence suggests that urinary sodium concentration may assist in optimizing loop diuretic maintenance therapy.[49,54–56] However, further research is required to determine whether individual diuretic adjustments based on urinary sodium measurements are feasible and improve outcomes in CHF management, as well as to assess the impact of dietary sodium and fluid intake on these adjustments.

Conclusion

Until recently, no good metrics and lack of interest to guide diuretic therapy in patients with ADHF often lead to relatively late change in dose escalation and initiation of combination therapy, contributing to diuretic resistance. As urinary sodium excretion is a direct reflection of the action of diuretic agents, regular assessment of urinary sodium concentrations holds great promises. The benefit of a natriuresis-guided diuretic protocol, especially during the first 24 to 48 h, has consistently demonstrated to improve diuresis and natriuresis, with a possible reduction in length of hospital stay. Incorporating a point-of-care sensor to the protocol allows individualized (nurse-led) diuretic titration, enhancing heart failure care. Despite the growing evidence, there are still some gaps, which might be answered by the current ongoing trials (DECONGEST, ESCALATE).

Conflict of interest: none declared.

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