ESC European Society of Cardiology

European Journal of Heart Failure (2019)
doi:10.1002/ejhf.1369

POSITION PAPE

The use of diuretics in heart failure with congestion — a position statement from the Heart Failure Association of the European Society of Cardiology

Wilfried Mullens[1,2]*, Kevin Damman[3], Veli-Pekka Harjola[4], Alexandre Mebazaa[5], Hans-Peter Brunner-La Rocca[6], Pieter Martens[1,2], Jeffrey M. Testani[7], W.H. Wilson Tang[8], Francesco Orso[9], Patrick Rossignol[10], Marco Metra[11], Gerasimos Filippatos[12,13], Petar M. Seferovic[14], Frank Ruschitzka[15], and Andrew J. Coats[16]

[1]Ziekenhuis Oost Limburg, Genk, Belgium; [2]University of Hasselt, Hasselt, Belgium; [3]University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [4]Emergency Medicine, University of Helsinki, Helsinki University Hospital, Helsinki, Finland; [5]University of Paris Diderot, Hôpitaux Universitaires Saint Louis Lariboisière, APHP, U 942 Inserm, F-CRIN INI-CRCT, Paris, France; [6]Maastricht University Medical Center, Maastricht, The Netherlands; [7]Yale University, New Haven, CT, USA; [8]Cleveland Clinic, Cleveland, OH, USA; [9]University of Florence, Florence, Italy; [10]Université de Lorraine, Inserm, Centre d'Investigations Clinique 1433 and Inserm U1116; CHRU Nancy; F-CRIN INI-CRCT, Nancy, France; [11]University of Brescia, Brescia, Italy; [12]National and Kapodistrian University of Athens, Athens, Greece; [13]University of Cyprus, Nicosia, Cyprus; [14]University of Belgrade, Faculty of Medicine, Belgrade, Serbia; [15]UniversitätsSpital Zürich, Zürich, Switzerland; and [16]IRCCS, San Raffaele Pisana, Rome, Italy

Received 19 July 2018; revised 14 October 2018; accepted 27 October 2018

The vast majority of acute heart failure episodes are characterized by increasing symptoms and signs of congestion with volume overload. The goal of therapy in those patients is the relief of congestion through achieving a state of euvolaemia, mainly through the use of diuretic therapy. The appropriate use of diuretics however remains challenging, especially when worsening renal function, diuretic resistance and electrolyte disturbances occur. This position paper focuses on the use of diuretics in heart failure with congestion. The manuscript addresses frequently encountered challenges, such as (i) evaluation of congestion and clinical euvolaemia, (ii) assessment of diuretic response/resistance in the treatment of acute heart failure, (iii) an approach towards stepped pharmacologic diuretic strategies, based upon diuretic response, and (iv) management of common electrolyte disturbances. Recommendations are made in line with available guidelines, evidence and expert opinion.

Keywords Diuretics • Heart failure • Acute heart failure • Pharmacotherapy • Loop diuretics

Introduction

The natural history of heart failure is characterized by acute decompensation episodes, which are associated with increased morbidity and mortality and pose an economic burden on our society .[1,2] Increasing signs and symptoms of congestion are the main reasons why patients with acute heart failure seek urgent medical care.[3–5] Even though congestion often develops over an extended period of time before acute presentation, the remainder of this manuscript will refer to this setting as acute heart failure. Only a minority of patients with acute heart failure present acutely with signs and symptoms of low perfusion.[4] Given the pivotal role of congestion in heart failure, diuretics are a cornerstone of therapy in heart failure.[6] Guidelines strongly recommend the use of loop diuretics to alleviate signs and symptoms of fluid overload (class I, level of evidence B).[7] This paper discusses the practical use of diuretics in patients with acute and chronic heart failure, based on contemporary evidence and expert opinion.

*Corresponding author. Department of Cardiology, Ziekenhuis Oost-Limburg, Schiepse Bos 6, 3600 Genk, Belgium. Tel: +32 89 327160, Fax: +32 89 327918, Email: wilfried.mullens@zol.be

Congestion in heart failure

Definition and mechanisms of congestion

Congestion in heart failure is defined as signs and symptoms of extracellular fluid accumulation that result in increased cardiac filling pressures.[8] Filling pressures are the integrated result of the cardiac systolic and diastolic function, plasma volume, and venous capacitance/compliance.[9–11] Heart failure with increased neurohumoral activation induces a state of increased renal sodium and water avidity resulting in an increased plasma volume.[11,12] Also, increased sympathetic output leads to splanchnic arterial and venous constriction resulting in blood redistribution from the splanchnic capacitance vasculature to the circulatory volume. This increases the effective circulating volume by redistribution, in a state where volume expansion is already present.[13] As a result, venous return and cardiac filling pressures increase.[11] Indeed, the venous capacitance function becomes compromised during states of longstanding venous congestion and/or increased sympathetic activation in acute heart failure.[11,14,15] Importantly, the term volume overload and congestion are often used interchangeably. However, it has been demonstrated that 54% of patients hospitalized for acute heart failure gain ≤ 1 kg during the month prior to admission, suggesting that volume overload incompletely characterizes the pathophysiology of acute heart failure and redistribution of volume may also contribute to the development of signs and symptoms of congestion.[16,17] Furthermore, heart failure is often associated with cachexia which makes the interpretation of weight changes difficult. Additionally, cachexia might result in a loss of plasma proteins, reducing plasma oncotic pressure, hampering plasma refilling from the interstitium.[18,19] Additionally, weight loss during hospitalization is not necessarily associated with improved in-hospital or post-discharge morbidity or mortality, however weight gain has been associated with poor outcome.[20,21] Therefore, the European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure recommend to distinguish acute fluid redistribution from true volume overload in patients presenting with congestion (no class recommendation).[7] As diuretics are mainly used to relieve excessive volume, the remainder of this manuscript will focus on congestion with excessive volume overload.

Detecting congestion in heart failure

Although the intravascular pressure–volume relationship may vary across individuals and clinical conditions, the gold standard for diagnosing congestion in heart failure is cardiac catheterization with direct measurement of right atrial pressure and pulmonary capillary wedge pressure (PCWP).[22] However, the invasive nature of this technique limits its routine use in clinical practice. Furthermore, the use of pulmonary artery catheterization to guide decongestive therapy did not improve outcome in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) study in comparison to serial clinical assessment, despite significantly improving haemodynamics.[23] The diagnostic accuracy of non-invasive clinical and technical assessments of congestion has been validated against invasive haemodynamic evaluation and shown a variable sensitivity and specificity (*Table 1*).[22–28] Physical signs and symptoms of congestion are based on detecting increased filling pressures and/or the extravascular fluid build-up secondary to the increased filling pressures. As such, the jugular venous pulse is the most useful physical finding for determining a patient's volume status. Not only does an elevated jugular venous pulsation (JVP) detect systemic congestion, but there is good sensitivity (70%) and specificity (79%) between high JVP and elevated left-sided filling pressure. Changes in JVP with therapy usually parallel changes in left-sided filling pressure although significant inter-observer variability regarding the extent of JVP elevation exist.[29–31] However, in a series of 50 patients with chronic heart failure it was shown that physical signs of congestion (rales, oedema and JVP elevation) were absent in 42% of patients with a PCWP ≥ 22 mmHg.[32] Additionally, there is a waning of skills in performing physical examination in current practice.[33] Also, while a chest X-ray can show signs of lung congestion and pleural fluid, 20% of patients with congestion exhibit a normal chest X-ray.[34] In comparison to chest X-ray, lung ultrasound is better in ruling out interstitial oedema and pleural effusions. Lung ultrasound detects B-lines originating from extravasated fluid into the interstitium and alveoli.[35,36] More than three B-lines in more than two intercostal spaces bilaterally are considered diagnostic for the detection of interstitial and alveolar oedema in acute heart failure. Echocardiographic parameters (*Table 1*) can be used to estimate right- and left-sided filling pressures, although with less certainty in acute heart failure.[25] Estimation of right atrial pressures can be performed by assessing the collapsibility and width of the vena cava. Doppler imaging and tissue Doppler can be used to assess left-sided filling pressures. With rising filling pressures, an increase in early diastolic mitral inflow velocities (E wave) occurs. This is indicative of increased filling pressures in the presence of a low e', especially if E-wave deceleration time is short and A-wave velocities are low.[28] Nevertheless, the use of e' might be limited in advanced heart failure.[25] Guidelines suggest the measurement of natriuretic peptides (NPs) in all patients with acute heart failure, especially to distinguish from non-cardiac causes of dyspnoea (class I recommendation, level of evidence A).[7] NPs have a high negative predictive value for ruling out acute heart failure with congestion [thresholds for excluding acute heart failure; B-type natriuretic peptide (BNP) < 100 pg/mL, N-terminal pro BNP (NT-proBNP) < 300 ng/mL and mid-regional pro atrial natriuretic peptide < 120 pg/mL].[7,37] In patients with history of heart failure or cardiac disease, the combination of signs and symptoms of congestion, an indicative chest X-ray and the measurement of elevated NPs allows for the diagnosis of congestion.[22,38] According to local availability, these tests can be supplemented with transthoracic echocardiography or lung ultrasound. In line with the ESC guidelines, direct haemodynamic evaluation should be reserved for patients with cardiogenic shock, refractory pulmonary oedema or suspected mismatch between left and right-sided filling pressures (class IIb recommendation, level of evidence C) or in cases of uncertainty of the haemodynamic status.[7]

Table 1 Sensitivity and specificity of different clinical and technical parameters to detect congestion

Parameter	Sensitivity	Specificity	Comparator	Comment
Clinical evaluation				
Right-sided				
JVP > 8 cm	48%	78%	RAP > 7 mmHg	Difficult in obese patient
Jugular venous reflux	50%	75%	RAP > 7 mmHg	Difficult in obese patient
Hepatomegaly	51%	62%	RAP > 7 mmHg	Difficult in obese patient, non-HF causes
Bilateral leg oedema	94%	10%	RAP > 7 mmHg	Non-HF oedema gives false positive
Left-sided				
Dyspnoea	50%	73%	PCWP > 18 mmHg	Multiple reasons for dyspnoea
Dyspnoea on exertion	66%	52%	PCWP > 18 mmHg	Multiple reasons for dyspnoea on exertion
Orthopnoea	66%	47%	PCWP > 18 mmHg	May be non-cardiac in origin or absent
S3	73%	42%	PCWP > 18 mmHg	Intra-observer variability
Rales	13%	90%	PCWP > 18 mmHg	May be non-cardiac in origin or absent
Echocardiographic evaluation				
Right-sided				
Collapse (< 50%) IVC	12%	27%	RAP > 7 mmHg	Difficult to use in positive pressure ventilated patients
Inspiratory diameter IVC < 12 mm	67%	91%	RAP > 7 mmHg	Cannot be used in positive pressure ventilated patients
Left-sided				
Mitral inflow E-wave velocity > 50 (cm/s)	92%	28%	PCWP > 18 mmHg	Difficult when fusion of E and A wave
Lateral E/e' > 12	66%	55%	PCWP > 18 mmHg	Less accurate in advanced heart failure and CRT
Deceleration time < 130 ms	81%	80%	PCWP > 18 mmHg	Difficult when fusion of E and A wave
Pulmonary vein S/D < 1	83%	72%	PCWP > 18 mmHg	Intra-observer variability in Doppler measurements of the vein
Diffuse B-lines on lung ultrasound[a]	85.7%	40%	PCWP > 18 mmHg	B-lines might be present in non-cardiac conditions

CRT, cardiac resynchronization therapy; HF, heart failure; IVC, inferior vena cava; JVP, jugular venous pulsation; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; S/D, systolic diastolic velocity.
[a]More than three B-lines in more than two intercostal spaces bilaterally.
Adapted from Gheorghiade,[22] Nagueh,[24] Mullens,[25] Parrinello[26] and Volpicelli.[27]

Determination of euvolaemia

Many patients are discharged with residual clinical congestion.[39–41] For example, only 15% of patients were assessed to be euvolaemic by their treating physician in the Diuretic Optimization Strategies Evaluation (DOSE-AHF) study after decongestive therapy.[42] Importantly, clinical congestion at discharge is a strong predictor of poor outcome and readmission, especially in the setting of worsening of renal function.[20,43,44] However, even in patients with limited clinical signs and symptoms of congestion at discharge, outcome can remain poor, pointing towards a role of subclinical congestion.[45] Relief of dyspnoea is a poor marker of decongestion, as patients without dyspnoea frequently still have significant clinical or haemodynamic congestion.[39,46] The same applies to attaining a similar body weight loss when the patient was stable.[47] Determining euvolaemia or the optimal stopping point for decongestive therapy remains a major challenge in heart failure. At the moment no reliable practical bedside test exists to determine euvolaemia as it is not yet clear what euvolaemia encompasses. Theoretically, it relates to an optimal fluid volume allowing the body to meet metabolic demands without excessive interstitial fluid or the development of a detrimental increase in cardiac filling pressures. Indeed, most non-invasive clinical tests to detect congestion have been used as surrogates for the presence of increased filling pressures (right atrial pressure > 7 mmHg or PCWP > 18 mmHg).[48] However, their performance in detecting the euvolaemic point without residual haemodynamic congestion is unclear. Increasing interest is being placed on biomarkers in detecting a state of decongestion, as they have the advantage of being easy to measure. To serve as a biomarker for decongestion, markers do not only need to be correlated with congestion at a certain time point, but also need to respond to changes in congestion status rapidly and reliably. NPs are released in response to increased myocardial wall stress, hereby reflecting intracardiac filling pressures. However, many additional factors may influence the NP levels in addition to wall stress.[37,49] To date, no randomized controlled trial has demonstrated that NP-guided decongestive therapy in acute heart failure improves clinical outcome.[50] However, changes in NP concentrations over time may help to further stratify risk, as reductions in previously elevated NP levels, whether achieved spontaneously or through application of appropriate medical therapy, appear to be associated with an improvement in clinical outcomes[50,51] Soluble CD146, carbohydrate antigen-125 and adrenomedulin are novel biomarkers more precisely reflecting vascular congestion. They could potentially offer incremental information in addition to the value of

NPs reflecting cardiac congestion. However, their use is currently restricted to the field of research and less embedded in clinical practice.[52–54] An increase in haemoglobin (haemoconcentration) after decongestion has been proposed as a marker of the reduction of intravascular volume.[55–57] However, haemoconcentration only provides a surrogate for a relative reduction in plasma volume between two time points and it therefore does not provide an indication of the absolute plasma volume (which might be the target).[58] Only late haemoconcentration (e.g. during the last days of hospitalization) was associated with improved outcome, making it a poor candidate to guide decongestive therapy.[56] In addition, changes in haematocrit are small, and can also relate to bleeding, phlebotomy, splenic pooling of blood and postural changes. Importantly, an increase in plasma creatinine is frequently interpreted in clinical practice as a decrease in effective circulating volume, prompting physicians to reduce decongestive therapy, based on the often false assumption that further decongestion might result in renal tubular damage. Indeed, during decongestion, an increase in creatinine should not automatically stop further decongestive therapy, especially if congestion persists. Additionally, an increase in creatinine during decongestion is not associated with intrinsic renal tubular damage.[59,60] Clinical outcomes are extremely poor if patients are discharged with ongoing congestion in the face of worsening of renal function.[20] In addition, an overemphasis on serial biomarker level assessment as a surrogate for changes in volume status might lead to inappropriate dose escalation of loop diuretics among patients without significant residual congestion, potentially increasing the rate of hypotension, renal dysfunction, and other adverse events. In contrast, improved biomarker levels may provide false reassurance that decongestion has been achieved. In line with a previous position paper, the use of a multi-parameter-based evaluation of congestion pre-discharge, using clinical assessment at rest and during dynamic manoeuvres as well as biomarkers, supplemented with technical assessments according to local expertise, is probably the best contemporary strategy (*Figure 1*), but has never been prospectively evaluated.[22,61,62]

	Variable	EUVOLEMIA → CONGESTED				
Clinical congestion	Orthopnea	None		Mild	Moderate	Severe/worst
	JVP (cm)	<8 and no HJR	<8	8-10 or HJR+	11-15	>16
	Hepatomegaly		Absent	Liver edge	Moderate pulsatile enlargement	Massive enlargement and tender
	Edema		None	+1	+2	+3/+4
	6MWT	>400m	300-400m	200-300m	100-200m	<100m
Technical evaluation	NP (one of both): -BNP -NT-proBNP		<100 <400°	100-299 400-1500	300-500 1500-3000	>500 >3000
	Chest X-ray	clear	clear	cardiomegaly	- pulmonary venous congestion* - small pleural effusions*	- Interstitial or alveolar edema
	Vena Cava imaging [45]	**none of two:** - Max diameter >2.2 cm - collapsibility <50%		**One of two:** - Max diameter >2.2 cm - collapsibility <50%		**Both:** - Max diameter >2.2 cm - collapsibility <50%
	Lung Ultrasound [44]	<15 B-lines when scanning 28-sites		15-30 B-lines when scanning 28-sites		>30 B-lines when scanning 28-sites

Figure 1 Integrative euvolaemia/congestion evaluation at discharge. 6MWT, 6-minute walk test; BNP, B-type natriuretic peptide; HJR, hepato-jugular reflux; HR, heart rate; JVP, jugular venous pulsation; NP, natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide; SBP, systolic blood pressure. °The cut-off for NT-proBNP to exclude congestion as endorsed by the Heart Failure Association position paper on grading congestion is higher than the cut-off endorsed by the European Society of Cardiology guidelines to exclude acute heart failure. *Chest X-ray can be clear but presence of abnormalities suggests higher degree of congestion. Partially adapted from the Heart Failure Association position paper on assessing and grading congestion in acute heart failure.[22]

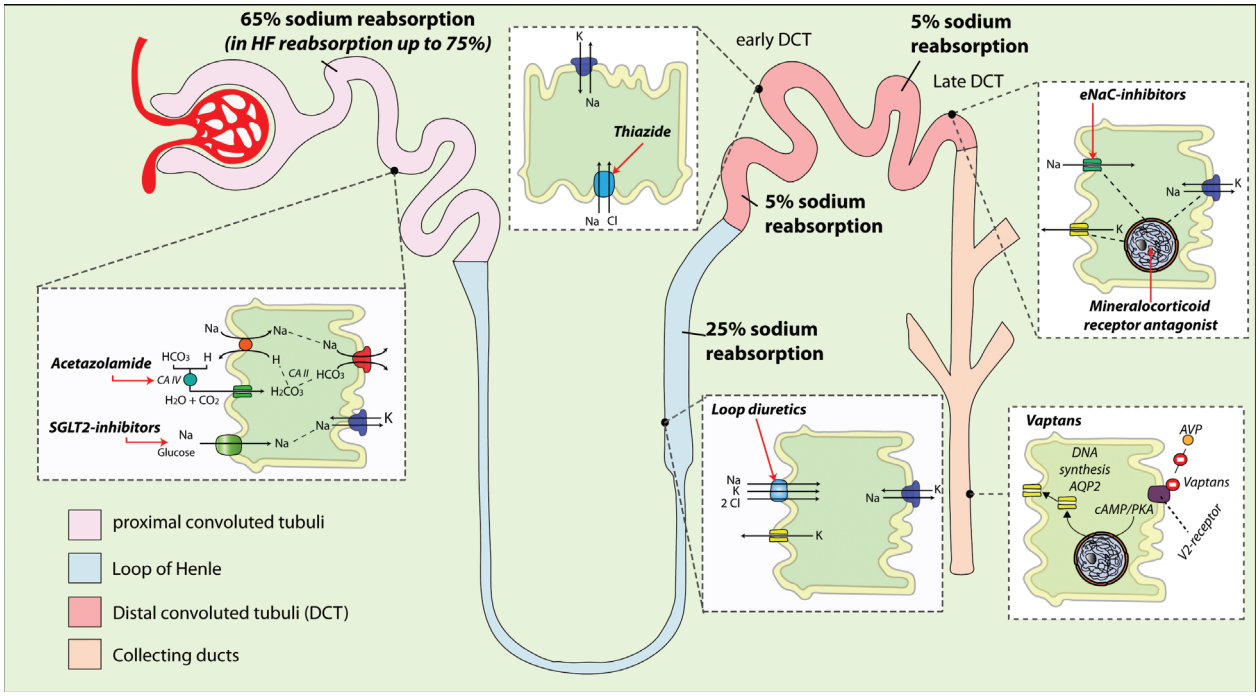

Figure 2 Sites and mode of action and effects on sodium reabsorption in the nephron of different diuretics. AQP2, aquaporin-2; AVP, arginine vasopressin; cAMP, cyclic adenosine monophosphate; eNaC, epithelial sodium channel; HF, heart failure; PKA, protein kinase A; SGLT2, sodium–glucose linked transporter-2.

Mechanisms of action of diuretics in heart failure

In the case of congestion with volume overload, chronic retention of sodium and water further expands intravascular volume, resulting in excessive extravascular fluid build-up. Other than ultrafiltration, the only pathway to get rid of sodium and water is through increased renal natriuresis and diuresis. Diuretics increase renal sodium and water output. Thorough knowledge of their pharmacokinetics and pharmacodynamics are mandatory for their successful employment.[63] The site of action of cellular mechanisms of different diuretics are listed in *Figure 2* and a synopsis of their pharmacologic properties is presented in *Table 2*.[64]

Diuretic response and resistance in heart failure

In achieving euvolaemia, the degree of volume overload and diuretic response will determine the success of therapy.[65] The capacity of inducing natriuresis or diuresis following diuretic administration is defined as diuretic response. Diuretic resistance is defined as an impaired sensitivity to diuretics resulting in reduced natriuresis and diuresis limiting the possibility to achieve euvolaemia.[66] Diuretic response should always be interpreted in light of the dose and type of the diuretic agent administered and the degree of volume overload, body composition and kidney function. As loop diuretics form the mainstay of diuretic therapy in heart failure, the terms diuretic resistance and loop diuretic resistance are often used interchangeably.[65,67–69] To assess the response to an initiated diuretic regimen, physicians need an indicator of the diuretic response. Currently, net fluid output and changes in body weight are frequently used. While assessment of weight might appear to be a simple measurement, it is technically challenging and fluctuations in weight might not represent changes in volume redistribution.[47] Furthermore, there is a poor correlation between weight loss and fluid output.[47]

As the objective of diuretic therapy is to get rid of excessive sodium (and accompanying water), the measurement of urinary sodium content has recently experienced a renewed interest as an indicator for diuretic response.[70–73] In addition to measuring sodium in a continuous urinary collection, a spot urine sample 1–2 h following loop diuretic administration has recently demonstrated an excellent correlation with total urine sodium output in a 6 h urine collection.[73] This strategy might allow the clinician to determine loop diuretic response in a systematic and timely fashion, potentially allowing for more timely adjustments in therapy. However, during consecutive days of loop diuretic therapy in acute heart failure, urinary sodium composition changes significantly.[74] Despite persistent increased urinary volume output (diuresis), renal sodium output (natriuresis) diminishes over time. Therefore, increasingly hypotonic urine is produced during consecutive days of loop diuretic therapy, which might relate to numerous factors including altered renal haemodynamics, differential substrate

Table 2 Pharmacology of diuretics

	Acetazolamide	Loop diuretics	Thiazide-like diuretics	MRA[a]	Amiloride
Site of action	Proximal nephron	Ascending loop of Henle	Early distal convoluted tubule	Late distal tubuie	Late distal tubule
Starting dose/usual chronic dose	Oral: 250–375 mg Intravenous: 500 mg	Furosemide: 20–40/40–240 mg[b] Bumetanide: 0.5–1.0/1–5 mg[b] Torsemide: 5–10/10–20 mg[b]	HCTZ: 25/12.5–100 mg[c] Metolazone: 2.5/2.5–10 mg[c] Chlorthalidone: 25/25–200 mg[c] Chlorothiazide: 500–1000 mg (IV formulation available)	Spironolactone: 25/25–50 mg Eplerenone: 25/25–50 mg Potassium canrenoate: 25–200 mg/not for chronic use	5/10 mg
Maximum recommended total daily dose	Oral: 500 mg 3x/day Intravenous: 500 mg 3x/day	Furosemide: 400–600 mg Bumetanide: 10–15 mg Torsemide: 200–300 mg	HCTZ: 200 mg Metolazone: 20 mg Chlorthalidone: 100 mg Chlorothiazide: 1000 mg	50–100 mg (doses up to 400 mg are used in hepatology)	20 mg
Half-life	2.4–5.4 h	Furosemide: 1.5–3.0 h Bumetanide: 1–1.5 h Torsemide: 3–6 h	HCTZ: 6–15 h Metolazone: 6–20 h Chlorthalidone: 45–60 h	Canrenone: 16.5 h[d] Eplerenone: 3–6 h	Normal GFR: 6–9 h GFR < 50 mL/min: 21–144 h
Onset	PO: 1 h IV: 15–60 min	PO: 0.5–1 h[e] IV: 5–10 min[e] SC: 0.5 h[e]	PO: 1–2.5 h IV: Chlorothiazide is IV available, onset action: 30 min	PO: 48–72 h[d] IV: potassium canrenoate; 2.5 h	PO: 2 h IV: not available
Oral bioavailability	Absorption is dose-dependent, dose >10 mg/kg exhibit variable uptake	Furosemide: 10–100% Bumetanide: 80–100% Torsemide: 80–100%	HCTZ: 65–75% Metolazone: 60–65%[f] Chlorthalidone: unknown Chlorothiazide: 9–56%	Spironolactone: ~90% Eplerenone: 69%	30–90%
Enteral absorption affected by food	May be taken with food. Food decreases symptoms of GI upset.	Furosemide: yes (slowed) Bumetanide: yes (slowed) Torsemide: no	HCTZ: unknown Metolazone: unknown Chlorthalidone: unknown	Spironolactone: bioavailability increase with high fat food Eplerenone: unknown	Unknown
Potency (FENa%)[g]	4%	20–25%[e]	5–8%	2%	2%

FENa, fractional excretion of sodium; GFR, glomerular filtration rate; GI, gastrointestinal; HCTZ, hydrochlorothiazide; HF, heart failure; IV, intravenous; MRA, mineralocorticoid receptor antagonist; PO, per oral; SC, subcutaneous. Diuretic agents are reflected from the site of action; from proximal nephron to distal nephron.

[a]Minimal diuretic effect.

[b]Dose of intravenous and oral loop diuretics are similar.

[c]Only PO use in acute HF, thiazides are not recommended for daily ambulatory use in chronic stable HF.

[d]Canrenone is the active metabolite of spironolactone. Intravenous potassium canrenoate is the intravenous formulation and is metabolized to canrenone resulting in significant plasma levels after 2.5 h of administration.

[e]Generally similar for different loop diuretics.

[f]Variations between pharmaceutical brands of metolazone exist.

[g]Tested in non-HF patients. FENa is the percentage of the sodium filtered by the kidney, which is ultimately excreted in the urine. It is measured based on plasma and urinary sodium. In clinical use, FENa can be calculated as part of the evaluation of diuretic effectiveness. The normal value depends primarily on the GFR of the patient but is commonly <2% in patients with relatively intact renal function. Diuretic agents increase FeNa with loop diuretic agents to be the most potent ones. FENa = 100 × (Na urine × creatinine plasma)/(Na plasma × creatinine urine).

delivery (sodium and/or diuretics), neurohormonal factors and structural kidney alterations. Although several studies have illustrated the prognostic value of urinary sodium following a first administration of a loop diuretic, its prognostic value during consecutive days remains unstudied.

The pathophysiology of diuretic resistance is multi-factorial and involves sympathetic nervous system activation, renin–angiotensin–aldosterone system (RAAS) activation, nephron remodelling, pre-existing renal function alterations, disrupted pharmacokinetics and dynamics of diuretics and intravascular fluid depletion due to slow plasma refilling.[65,75,76] Therefore, a stepped pharmacologic approach focused on achieving successful decongestion with alterations in diuretic therapy based on early and repetitive treatment assessment is suggested to be superior to standard high-dose loop diuretics in patients with worsening of renal function (serum creatinine increase of > 0.3 mg/dL within previous 12 weeks before decompensation), as assessed in a post-hoc analysis of the DOSE-AHF and the Renal Optimization Strategies Evaluation (ROSE-AHF) trials.[77,78]

Practical use of diuretics in acute heart failure

Goals of therapy in acute decompensated heart failure

Before initiating decongestive therapies in acutely decompensated patients, the distinction should be made if volume overload or volume redistribution is contributing to congestion.[79] The goals of therapy in patients presenting with congestion and volume overload consists of (i) achieving thorough decongestion without residual volume overload. Nevertheless, the optimal stopping point of decongestive therapy is often difficult to determine, as alluded to above. (ii) Ensuring adequate perfusion pressures to guarantee organ perfusion. (iii) Maintaining guideline-directed medical therapies as these medications may also increase diuretic response and improve long-term survival.[80,81] When patients with heart failure with reduced (HFrEF) or preserved ejection fraction (HFpEF) decompensate, they often can present with a similar profile of congestion.[82,83] Therefore, the goal of decongestive therapy is similar in terms of diuretic use in patients with HFrEF and HFpEF.[7] A practical stepped approach to diuretic treatment and assessment in acute heart failure is reflected in *Figure 3*. Once euvolaemia has been achieved, loop diuretic therapy should be continued at the lowest dose that can maintain euvolaemia.[7,8] Additionally, enrolment of patients in a detailed multi-disciplinary heart failure care management programme, promoting medication adherence, up-titration of disease-modifying therapy, cardiac rehabilitation, treatment of underlying co-morbidities, timely follow-up with the health care team, and screening for additive device-based and medical interventions therapies is essential.[7]

Loop diuretics

Loop diuretics form the backbone of diuretic therapy in acute heart failure, being used in over 90% of patients.[3] Loop diuretics are heavily protein-bound (> 90%) and need to be secreted into the proximal convoluted tubule through several organic anion transporters. Therefore, adequate dosing with sufficient plasma levels is pivotal as renal perfusion is often reduced in heart failure, resulting in diminished secretion of loop diuretics. Additionally, decreased plasma protein content can result in reduced secretion of loop diuretics. Loop diuretics inhibit the Na-K-2Cl symporter at the ascending loop of Henle, and have the most potent diuretic effect, promoting excretion of sodium and chloride (and potassium, albeit to a lesser extent than thiazides).[64] The pharmacological properties of the different loop diuretics are presented in *Table 2*. The bioavailability of orally administered furosemide is highly variable (10–90%), and is determined by absorption from the gastrointestinal tract into the bloodstream.[6] The oral bioavailability for torsemide and bumetanide are consistently higher than 80–90%. In addition, torsemide has a longer half-life in heart failure patients when compared to furosemide or bumetanide.[84] Although some smaller studies suggested superior diuretic effect of torsemide, no large randomized studies have compared the difference between different loop diuretics.[85] The Torsemide Comparison with Furosemide for Management of Heart Failure (TRANSFORM-HF) trial (NCT03296813) is planned to randomize 6000 heart failure patients who are hospitalized. While heart failure need not to be the reason for hospitalization, its objective is to detect a difference between furosemide vs. torsemide for the primary endpoint all-cause mortality. Given the wide range of bioavailability of oral furosemide, variance exists in the conversion calculation. Therefore an oral dose of 40 mg of furosemide is generally equivalent to 10–20 mg of torsemide and 0.5–1 mg of bumetanide. Importantly, loop diuretics may also lead to renin release by the macula densa by blocking chloride uptake, further stimulating RAAS. Furthermore, chronic use of loop diuretics induces compensatory distal tubular sodium reabsorption through hypertrophy of tubular cells, leading to reduced natriuresis.[8] Guidelines recommend the use of intravenous loop diuretics in acute heart failure, as the uptake of oral diuretics (particularly furosemide) can be diminished in the face of congestion due to bowel oedema (class I, level of evidence B).[7] Optimal dosing and timing of intravenous loop diuretics are pertinent. Loop diuretics exhibit a threshold concentration to invoke natriuresis, necessitating a minimal drug dose prior to exceeding the baseline rate of sodium excretion.[6,86] Afterwards a log-linear increase in the dose is necessary to achieve a ceiling in natriuretic response. Further increasing the loop diuretic dose beyond this ceiling will not result in a greater rate of peak natriuresis, however it will lead to a longer period of loop diuretic over the threshold level and thus increases total natriuresis. Similarly, multiple administrations can cause additional natriuresis, as it increases the duration of time above a natriuretic threshold. These pharmacologic characteristics lead to the following recommendation in acute heart failure: (i) diuretic naïve patients with acute heart failure should receive a dose of intravenous furosemide of at least 20–40 mg furosemide equivalent. The higher dose should be considered in patients with pre-existing kidney dysfunction as it is associated with a rightward shift in the dose–response curve.[6,86] (ii) Patients on an ambulatory diuretic regimen should receive at least the pre-existing oral dose

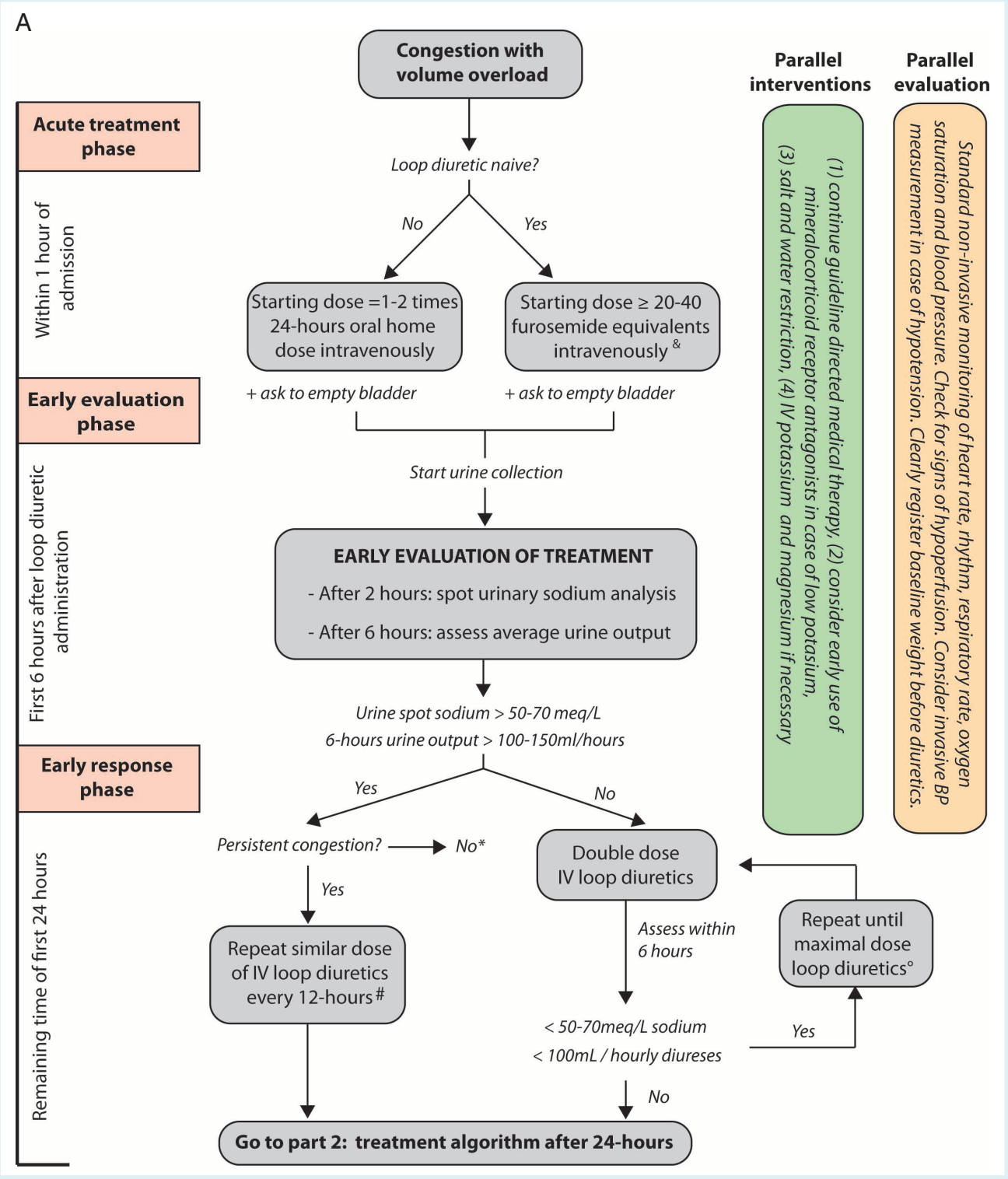

Figure 3 Flowchart to diuretic use in acute heart failure. (*A*) Congestion with volume overload. (*B*) Treatment algorithm after 24 h. Total loop diuretic dose can be administered either as continuous infusion or bolus infusion. BP, blood pressure; HF, heart failure; IV, intravenous; SGLT2-I, sodium–glucose linked transporter 2 inhibitor; UF, ultrafiltration; UO, urine output. &Higher dose should be considered in patients with reduced glomerular filtration rate. *Consider other reasons for dyspnoea given the quick resolution of congestion. °The maximal dose for IV loop diuretics is generally considered furosemide 400–600 mg or 10–15 mg bumetanide. #In patients with good diuresis following a single loop diuretic administration, once a day dosing can be considered.

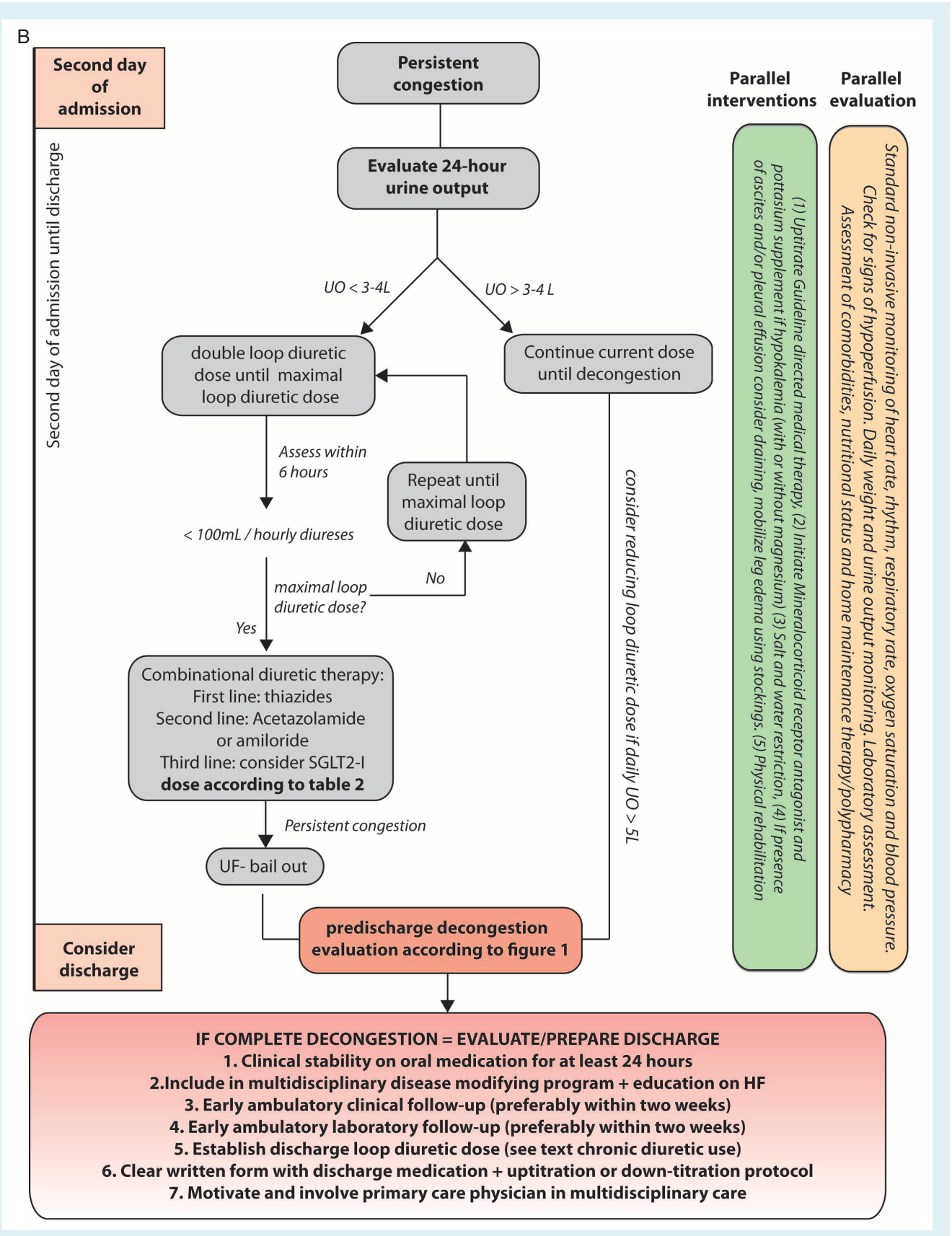

Figure 3 Continued.

administered intravenously. The DOSE-AHF trial demonstrated that high loop diuretic dose (2.5 times the usual home dose, with at least 80 mg/day furosemide equivalents) in comparison to low dose (equal to home dose) resulted in a favourable effect on secondary endpoints of dyspnoea relief, change in weight and net fluid loss.[42] Worsening of renal function (defined as an increase in creatinine by more than 0.3 mg/dL) occurred more in the high-dose group. However, a post-hoc analysis of the DOSE-AHF trial illustrated that this increase in creatinine did not portend a worse outcome.[87] In addition, the high-dose group was associated with better outcomes when adjusted for the total amount of loop diuretics received, suggesting that adequacy of loop diuretic dosing to reach the 'ceiling' threshold is key.[88] Determining the individual ceiling dose in a patient is difficult and is influenced by numerous factors, including previous treatment with loop diuretics, body composition, degree of volume overload and kidney function. However, an intravenous dose ranging between 400–600 mg furosemide vs. 10–15 mg bumetanide is generally considered as the maximal total daily dose above which limited additional natriuresis should be expected but side effects will continue to increase. Generally, loop diuretics are given in multiple doses (twice to three times daily). Intravenous loop diuretics should be administered as early as possible, since early loop diuretic administration is associated with lower in-hospital mortality.[89] In the DOSE-AHF trial, no difference was seen in the primary endpoint between continuous or bolus infusion. However, continuous infusion was not preceded by a bolus loading dose which might have resulted in not reaching the threshold dose in the continuous infusion group. If bolus infusion is given, doses should be split-up into doses with at least 6 h intervals, to maximize the time above the natriuretic threshold and to avoid rebound sodium retention.[90] Continuous infusion should be preceded by a loading dose, which assures the prompt achievement of a steady-state of plasma loop diuretic concentration.[6]

Stepped pharmacologic care

Early evaluation and loop diuretic intensification

The majority of the diuretic effect of intravenous loop diuretics occurs within the first couple of hours with a return to baseline sodium excretion by 6–8 h. Early evaluation of the diuretic response is therefore warranted and will allow for the identification of patients with a poor diuretic response.[67,69,73,74] This will permit early intensification of loop diuretic dose and/or using a strategy of sequential nephron blockade (combining diuretics with a different mode of action). Although this concept has yet to be formally tested in prospective trials, such a strategy is important in several aspects. Firstly, persisting congestion further compromises organ function.[91] Secondly, the plasma refill rate (the rate at which fluid is mobilized from the interstitium into the plasma compartment) might drop during decongestion.[92,93] Thirdly, patients are often hospitalized in acute care units for the first days, where intensive adaptation of therapy is more likely to occur than in a regular ward. Additionally, faster decongestion might be especially valuable in health care systems where length of hospital stay needs to be short.

In addition to the evaluation of vital signs, daily weights, and signs/symptoms of congestion as endorsed by ESC guidelines (class I recommendation, level of evidence C), this Cardio-Renal Dysfunction Study Group proposes the active evaluation of diuretic response early after start of therapy. Diuretic response may be evaluated using urinary volume output and post-diuretic (spot) urinary sodium content as outlined in *Figure 3*. To allow for standardization and reliable results, patients presenting with congestion need to empty their bladder before the administration of diuretics. The degree of bladder emptying could potentially be checked using a bladder scan. Afterwards, determination of urinary spot sodium content allows the clinician to interpret diuretic response, thereby generating the opportunity to intervene if sodium content is low. In the face of congestion with volume overload, a spot urine sodium content of $< 50–70$ mEq/L after 2 h, and/or an hourly urine output $< 100–150$ mL during the first 6 h, generally identifies a patient with an insufficient diuretic response.[72,73,94] In patients who produce sufficient urinary volumes following a first intravenous loop diuretic administration, urinary sodium is almost universally high. However, more recent data indicate that in patients with a low to medium volume output, spot urinary sodium content offers independent prognostic information on heart failure admissions on top of urinary volume output.[71] Prompt doubling of loop diuretic dose might allow the attainment of a loop diuretic ceiling dose earlier (as alluded to in the loop diuretic section). After these doses are achieved, addition of another diuretic agent should be considered, as increasing the loop diuretic dose any further does not induces incremental diuresis/natriuresis. In the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF), a strategy of stepped pharmacologic therapy was compared with ultrafiltration in acute decompensated heart failure patients with worsened renal function and persistent congestion (online supplementary *Figure S1*). The pharmacologic care approach using early assessment of urinary output with adjustment of loop diuretic dosing and the addition of a thiazide-like diuretic, resulted in equal decongestion compared to ultrafiltration, however with fewer serious adverse events.[95] Post-hoc comparisons with the DOSE-AHF and ROSE-AHF trials indicates that a stepped pharmacologic care approach was also associated with greater net fluid and weight loss, without compromising renal function.[77,78] As urine sodium content rarely changes discordantly to urine output during the first day of decongestive therapy (in the absence of excessive fluid intake by the patient), it seems reasonable to assess urinary sodium content always together with urine volume to adjust diuretic intensity during the first day. Insufficient data are available to support the use of urinary sodium during consecutive days of decongestion. In the CARRESS-HF trial, a urinary output of > 5 L per day allowed the physicians to reduce diuretic intensity, however continuation of the diuretic regimen may be acceptable if renal function and blood pressure remain stable.

Thiazide or thiazide-like co-administration

Thiazide and thiazide-like diuretics encompass a large class of agents that block the sodium–chloride co-transporter (NCC) in the distal convoluted tubule.[96] Therefore, from a theoretical point of view, they may partially overcome distal increased sodium avidity accompanied with chronic loop diuretic use. Large

geographical differences exist in the use of thiazide-like diuretics with metolazone being the most used thiazide-like diuretic in the United States.[97] The different molecules have a similar blocking effect of NCC, however they differ in terms of half-lives and off-target effects (*Table 2*). In contrast with loop diuretics, metolazone and chlorthalidone have a slow gastrointestinal absorption (time to peak up to 8 h) and a very long half-life, therefore if low oral doses are started, they should be given hours before the intravenous loop diuretic is administered as it will take a long time until a steady state is achieved. However, chlorothiazide has a short half-life so it should be given closer to the loop diuretic. In healthy individuals, the maximal diuretic effect of a thiazide is limited, generating a diuretic response of maximum 30–40% of a loop diuretic when used in monotherapy.[96] Thiazides are also protein bound requiring adequate renal blood flow to be secreted into the tubules. Furthermore, thiazides can induce significant kaliuresis, as per sodium ion lost 2–3 ions of potassium are excreted.[98] This potassium losing effect is especially pronounced in high aldosterone states, such as heart failure.[99] The rationale for using thiazides in acute heart failure is based on the finding of increased distal nephron sodium avidity in the case of (prolonged) loop diuretic administration.[100] Indeed, animal data indicate that distal nephron hypertrophy occurs following chronic loop diuretic administration, which might explain loop diuretic resistance to an extent.[101] In contrast to conventional teaching, more recent evidence does support the effectiveness of thiazides in patients with a reduced glomerular filtration rate (< 30 mL/min).[102] There are no randomized controlled trials published in heart failure testing the use of thiazide diuretics. Currently, there is a study ongoing comparing Metolazone Versus Chlorothiazide for Acute Decompensated Heart Failure With Diuretic Resistance (NCT03574857). A meta-analysis of existing observational data underscores the frequent occurrence of hypokalaemia. In a propensity-matched analysis of real-world use of thiazides (combined with lower-dose loop diuretics) and high-dose loop diuretics in heart failure patients, thiazides, but not high-dose loop diuretics, were independent predictors of the occurrence of hyponatraemia and hypokalaemia with an indication towards a higher risk for all-cause mortality.[103] Given the relative safety of high-dose loop diuretics in the DOSE-AHF trial, a preference might be given to initial intensification of the loop diuretic dose before adding a thiazide diuretic.[42] However, in the CARRESS-HF-trial, the addition of metolazone was an intrinsic part of the stepped pharmacologic algorithm, resulting in the recommendation of thiazides as a second-line agent in the Heart Failure Society of America practical guidelines.[90]

Mineralocorticoid receptor antagonists

Mineralocorticoid receptor antagonists (MRAs) exhibit pleiotropic effects, but their renal effects consist of modulating the expression/activity of sodium and potassium channels in the distal nephron. MRAs have a class I recommendation as a disease-modifying therapeutic agent in symptomatic chronic HFrEF, counteracting the aldosterone escape generated by neurohormonal over-activation.[104,105] Recently in acute heart failure, the incremental diuretic effect of high-dose MRA therapy in addition to standard loop diuretic therapy has been tested in the Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure (ATHENA-HF) trial.[106] Therapy with 100 mg of spironolactone per day was not superior to 25 mg per day in reducing NT-proBNP or increase urine output after 96 h. However, as illustrated in *Table 2*, spironolactone is a pro-drug with onset of action only 48–72 h after oral intake, which could account for the observed nil-effect. However, high-dose MRA was safe, as it did not result in hyperkalaemia or worsening of renal function. Furthermore, MRA therapy might be useful in offsetting the hypokalaemic effect of potassium-wasting loop and thiazide diuretics.[106–108] Importantly, data indicate marked under-utilization of MRAs as a disease-modifying drug class in HFrEF.[109] It is the opinion of the expert panel that early initiation of a MRA, in a regular dose (25 mg), might be useful in reducing treatment-induced hypokalaemia and may lead to higher chance of HFrEF patients being discharged on an optimized disease-modifying therapy regimen. However, the use of MRA in the acute settings needs to be individualized with temporarily discontinuation in case of the development of hyperkalaemia.

Acetazolamide

Due to haemodynamic alterations in heart failure with a reduction in renal blood flow with a correspondingly increased filtration fraction, important increases in proximal nephron sodium avidity occur.[9,63] From a pathophysiological point of view, targeting sodium reabsorption in the proximal tubules has several potential benefits in heart failure. First, most sodium is reabsorbed in the proximal nephron, especially in decompensated heart failure. Second, greater delivery of chloride to the macula densa cells decreases renin production, reducing neurohumoral activation.[9] Third, endogenous natriuretic peptides (acting in the distal nephron) will possibly regain their effects.[110] The carbonic anhydrase inhibitor acetazolamide inhibits sodium reabsorption in the proximal tubules. An observational study in patients with decompensated heart failure and marked volume overload indicated that the addition of acetazolamide (500 mg intravenous bolus on top of loop diuretic) improved loop diuretic response with ~100 mmol Na^+ excreted per 40 mg of furosemide dose equivalents.[69] Additionally, acetazolamide efficiently boosts the diuretic response in combination with loop diuretics, as illustrated by one small randomized trial including 24 patients with acute volume overload refractory to loop diuretic therapy.[110] A multicentre, randomized, double-blind, phase IV clinical trial of the diuretic effects of Acetazolamide in Decompensated heart failure with Volume OveRload (ADVOR, NCT03505788) will investigate if combination therapy with acetazolamide improves loop diuretic response to increase diuresis in decompensated heart failure patients.[111] Observational studies have only assessed the role of intravenous acetazolamide, and no data are available supporting the role of oral acetazolamide.

Other potential agents

In addition, the new diabetic drug class of sodium–glucose linked transporter-2 (SGLT2 inhibitors) also inhibit proximal sodium

absorption (*Figure 2*).[9,112,113] Two trials in diabetic patients with mostly established cardiovascular disease, illustrated that SGLT2 inhibitors reduced heart failure hospitalizations and resulted in a less steep slope of glomerular filtration rate decline over time.[114,115] However, the potential of SGLT2 inhibitors in heart failure with or without diabetes remains unknown. Several trials are ongoing in testing the disease-modifying effect of SGLT2 inhibitors in the setting of both chronic and acute heart failure. Amiloride inhibits distal epithelial sodium channels (ENaC), and anecdotal evidence suggests that ENaC inhibition can result in decongestion with a lowering of filling pressures.[116] Furthermore, chronic over-expression of ENaC has been implicated in the thiazolidinedione-mediated volume retention witnessed in diabetics. Finally, vasopressin antagonists limit distal nephron free water re-uptake by counteracting arginine vasopressin, which results in a limited availability of luminal aquaporin water channels in the renal collecting ducts. This results in increased aquaresis without significantly impacting natriuretic response. The selective V_2- receptor antagonist tolvaptan did not result in a reduction of morbidity or mortality in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) study in acute heart failure patients when added to standard therapy.[117] This limits its use in heart failure with congestion, as extracellular volume expansion is mainly driven by sodium retention. However, in more advanced stages of heart failure inappropriately high levels of arginine vasopressin contribute to plasma expansion and dilutional hyponatraemia. More recently, early use of tolvaptan and use in patients with diuretic resistance, renal dysfunction or hyponatraemia, did result in more weight loss, but no significant improvement in dyspnoea relief.[118,119] Currently, vasopressin antagonists are only indicated in patients with severe hyponatraemia, and their widespread use might be limited by the high drug costs. In Europe, tolvaptan is available but not officially approved for heart failure by the European Medicines Agency.

Ultrafiltration

Ultrafiltration removes plasma water across a semipermeable membrane driven by a machine generated transmembrane pressure gradient. There is limited compelling evidence to support ultrafiltration as first-line therapy over loop diuretics in patients with acute heart failure.[95,120] Therefore, in most centres, ultrafiltration is reserved as a bail-out therapy to relieve congestion if stepped pharmacologic care fails.[121] Of note, the Peripheral Ultrafiltration for the RElief From Congestion in Heart Failure (PURE-HF) trial (NCT03161158) is evaluating whether tailored, peripheral veno–venous ultrafiltration (CHIARA System) complementary to low-dose diuretics is associated with a reduction in cardiovascular mortality and heart failure hospitalization in 90 days after randomization compared to usual care including stepped intravenous diuretics in acutely decompensated chronic heart failure with fluid overload (not fully responsive to diuretic therapy). Renal replacement therapy allows for management of metabolic complications of anuria/oliguria such as hyperkalaemia, acidosis and uraemia,[95,121] although in a large proportion of cases such use has poor long-term prognosis, especially when systemic perfusion pressures are low.[122] Additionally, in the CARRESS-HF trial, the proportion of patients with catheter-related access site bleeding and infection was numerically higher in the ultrafiltration group.

Diuretic use and electrolyte abnormalities

Electrolyte abnormalities resulting from neurohormonal activation, kidney dysfunction, or iatrogenic due to the employed diuretic regimen occur frequently during episodes of acute heart failure, mostly affecting sodium and potassium handling.[121,123,124] Recently, also alterations in chloride metabolism have been recognized to independently predict adverse outcomes.[125] Hyponatraemia, defined as a plasma sodium concentration < 135 mEq/L, is the main abnormality of sodium homeostasis occurring in acute heart failure whereas hypernatraemia rarely occurs. A sub-analysis of the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) illustrated that 20% of patients had hyponatraemia at the time of admission.[126] The incidence of hospital acquired hyponatraemia during decongestive therapy for acute heart failure ranges between 15–25%.[127] The pathophysiology of hyponatraemia in heart failure is either due to the inability to excrete free water (dilution hyponatraemia) or either due to a depletion of sodium (depletion hyponatraemia),[123] or a combination of these factors. A practical approach to hyponatraemia is reflected in *Table 3*. After confirmation of a low serum osmolality, the differentiation between dilution and depletion is made on the basis of the clinical picture and urinary analysis. Abnormalities in the potassium homeostasis are typically the result of the employed pharmacologic therapy in heart failure in combination with pre-existing renal impairment. Hypokalaemia (plasma K < 3.5 mEq/L) occurs typically in acute heart failure secondary to diuretic-induced diuresis with potassium wasting.[110] In clinical practice, loop diuretic use is the most common reason for hypokalaemia, however thiazide diuretics do exhibit an even stronger kaliuretic effect.[110] Treatment consists of adding upfront MRA therapy during decongestion, increasing RAAS blockade and supplementation of potassium (*Table 3*). In addition to potassium wasting, diuretics often induce the loss of magnesium, potentially resulting in therapy-refractory hypokalaemia. Although not supported by strong evidence, magnesium supplementation could be considered during diuretic treatment. Although less common than hypokalaemia during acute heart failure, hyperkalaemia (K > 5.0 mEq/L) can occur in patients on RAAS blockade, especially in the case of pre-existing renal impairment.[128] A clinical approach to hyperkalaemia is reflected in *Table 3*.

Diuretics in chronic heart failure

The ambulatory loop diuretic dose is variable

Loop diuretics are recommended in chronic heart failure to prevent signs and symptoms of congestion.[7] This recommendation is valid across the entire spectrum of left ventricular ejection

Table 3 Approach to electrolyte disturbances in acute heart failure

	Hyponatraemia	Hypokalaemia	Hyperkalaemia
Definition	$Na^+ < 135$ mEq/L	$K^+ < 3.5$ mEq/L	$K^+ > 5$ mEq/L
Diagnostic tests	• **P_{osm}**: should be <285 mOsm/L (else pseudo-hyponatraemia) • **Physical examination:** to differentiate between volume overload or volume depletion • **Urinary analysis:** U_{osm} and U_{Na}	• **ABG**: confirm on ABG, check pH status • **ECG**: check potential abnormalities • **Physical examination**: usually normal, however muscle weakness or paralysis present in severe cases • **Lab:** check for Mg deficit	• **ABG**: confirm on ABG, check pH status • **ECG**: check potential abnormalities • **Lab:** check renal function, exclude haemolysis as cause of pseudo-hyperkalaemia
Pathophysiology	• **Dilution**: impaired free water excretion. Clinical picture of volume overload with inappropriate high U_{osm} ($\geq$ 100 mOsm/L). Typical in the setting of ADHF • **Depletion:** true body deficit of Na^+. Typical in the setting of chronic excessive diuretic use (and strict Na^+ intake). Clinical picture of volume depletion with low U_{osm} (< 100 mOsm/L) and U_{Na} (< 50 mEq/L)	• **Diuretic** use results in hypokalaemia • **Predisposing** factors in HF can play a role, for instance: cachexia with low K^+ intake and chronic hypomagnesaemia	Most likely due to combination of RAAS blocker agent and poor renal function with diminished renal potassium excretion capacity
Treatment	• **Dilution:** temporarily stop distal acting diuretics[a], limit water intake, promote distal nephron flow (loop diuretics, hypertonic saline, acetazolamide/SGLT2 inhibitor) or vaptans, correction of K^+ and Mg^{2+} deficiencies • **Depletion:** stop distal acting diuretics[a], calculate Na deficit and administer IV Na^+ correction of K^+ and Mg^{2+} deficiencies	• **Consider** discontinuation of thiazide diuretics • **Upfront** use of MRA during decongestion • **Increase** dose of RAAS blocking agent • **IV** substitution of K^+ and Mg^{2+}: peripheral or central depending on severity of K^+ deficit.	• **Acute hyperkalaemia:** if ECG abnormalities present, then prevent arrhythmias by IV calcium. Intermediate strategies include: insulin/albuterol/sodium HCO_3 IV. Ultimately potassium must be removed from the body with either diuretics, potassium binding resins, or RRT. • **Chronic hyperkalaemia:** reduces dose RAAS blocker, increase loop diuretic, potassium binders

ABG, arterial blood gas analysis; ADHF, acute decompensated heart failure; AVP, arginine vasopressin; ECG, electrocardiogram; HCO_3, bicarbonate; HF, heart failure; IV, intravenous; MRA, mineralocorticoid receptor antagonist; P_{osm}, plasma osmolality; RAAS, renin–angiotensin–aldosterone system; RRT, renal replacement therapy; SGLT2, sodium–glucose linked transporter-2; U_{osm}, urine osmolality; U_{Na}, urine sodium.
[a]Distal acting diuretics included thiazide-like diuretics, MRA and amiloride.

fraction. Indeed, diuretics are the only group of drugs with a class I recommendation in patients with heart failure with reduced, mid-range, or preserved ejection fraction.[7] However, the effects of diuretics in chronic heart failure on morbidity and mortality have not been studied in large prospective randomized controlled trials. Several observational studies have linked loop diuretic use to increased mortality, even after multivariate adjustment or propensity matching.[129] However, potential bias remains as sicker patients are generally prescribed (higher doses of) loop diuretics. A Cochrane meta-analysis has shown that in patients with chronic heart failure, loop diuretics and thiazides might reduce the risk of death and worsening of heart failure in comparison to placebo and could lead to improved exercise capacity.[86] However, this meta-analysis included only small studies with limited follow-up, showing unrealistically large reductions in events. Moreover, this analysis was not updated in 2016 as requested by the Cochrane Institute and subsequently withdrawn. Therefore, the prognostic effect of diuretic therapy is still unknown. Clearly, patients at risk for congestion would benefit from maintenance therapy with a loop diuretic. However, in patients at low risk for developing worsening of congestion, the use of loop diuretics might indeed result in electrolyte disturbances, further neurohormonal activation, accelerated kidney function decline, and symptomatic hypotension.[130] The latter might especially be relevant in patients with HFrEF as it could result in treatment with lower doses of neurohormonal blockers.[43] Therefore, it is generally advised to use to the lowest possible dose of diuretics and the dose of the loop diuretic often needs to be adjusted to the individual need.[131,132] Importantly, the individual diuretic need significantly changes over time. This was clearly illustrated by a post-hoc analysis of the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in Class III Heart Failure (CHAMPION) trial, which indicated that mainly increases but also decreases in loop diuretic dose were the most common therapy changes made by treating physicians.[133] Nevertheless, uncertainty exists about the optimal dose of loop diuretics following discharge. For patients who developed an acute heart failure episode while previously taking a loop diuretic before admission, a higher dose following discharge might need to be used. Additionally, in case that this previous loop diuretic was furosemide, a switch to either bumetanide or torsemide might be considered, as they have a more predictable absorption pattern and bioavailability, especially in the face of subclinical congestion. However, defining the most appropriate outpatient dose of diuretic can be difficult and requires careful follow-up, particularly early in the post-discharge period. The chronic use of thiazides in the stable ambulatory setting (sequential nephron blocking) should be avoided, if possible, as this practice often induces severe electrolyte disturbances that could go undetected in the ambulatory setting. Additional research is needed to evaluate ambulatory metrics (in addition to pulmonary pressures) of volume status, which might allow easier adaptation of loop diuretic therapy. Registry data indicate that mildly symptomatic heart failure patients [New York Heart Association (NYHA) class I and II] are generally treated with similar doses of loop diuretics as more symptomatic heart failure patients (NYHA class III and IV).[134] This underscores the importance to re-assess loop diuretic need following the initiation of therapies that improve cardiac status (such as cardiac resynchronization therapy or sacubitril/valsartan).[112,135] A recent pilot study illustrated the potential of self-measuring urine chloride content after loop diuretic intake using a dipstick to determine the need for maintenance loop diuretics in stable ambulatory heart failure patients.[136] Despite the guideline recommendation to use the lowest possible dose of diuretics and discontinue loop diuretics if possible, little information is available on discontinuing loop diuretics in contemporary treated heart failure patients.[137,138] A prospective interventional study in 50 stable ambulatory heart failure patients assessed the feasibility of loop diuretic down-titration and discontinuation.[138] At 30 days, down-titration remained successful in 62% of patients, however baseline investigations including physical examination, echocardiography and NP measurement were not capable to predict in which patients loop diuretic down-titration would be successful or not.[138]

Heart failure disease management strategy

The goals of heart failure care are dynamic and vary according to the stage of heart failure. In the ambulatory patient, care should focus on up-titrating disease-modifying drugs, evaluating the need for device-based therapies, enrolling patients in multidisciplinary disease-modifying programmes, focusing on self-management, physical activity, and dietary interventions.[7] Furthermore, efforts should be made to reduce readmission and improve quality and longevity of life. With average salt intake in the western world reaching up to 6–8 g, it has been recommended by the ESC guidelines to avoid excessive high salt intake (>6 g NaCl = 2.4 g Na per day) and excessive fluid intake (no class recommendation).[7] Salt and fluid restriction are often underscored in disease-modifying programmes. Yet, animal and epidemiologic data suggest that an excessively low sodium intake (<2 g Na^+ per day) is associated with cardiac remodelling and worse clinical outcome.[139] Currently four trials are evaluating the benefit of sodium restriction, including one trial assessing a hard clinical endpoint.[140] A meta-analysis on fluid restriction did not indicate benefit or harm when performed in heart failure patients.[141] Therefore, dietary restrictions should be adapted according to the clinical context. In the case of acute heart failure with dilution hyponatraemia, more stringent fluid restriction is necessary.

Gaps in knowledge and future directions

Evidence-based medicine with respect to diuretic treatment in heart failure remains difficult as only a limited number of small prospective studies have been performed. Ongoing research is necessary to determine the ideal diuretic strategy and to optimally evaluate full decongestion (euvolaemia) in heart failure. The role of urinary sodium to assess the adequacy of diuretic therapy in acute heart failure should be further assessed prospectively. The role of hypertonic NaCl infusion in conjunction with high-dose loop diuretics in hyponatraemic volume overloaded patients needs

to be studied as this concept is supported by several analyses, however suffering from methodologic restrains.[142] Randomized controlled trials are necessary assessing the decongestive properties of diuretics other than loop diuretics or MRAs. Novel effective and safe pharmacologic or mechanical methods to achieve decongestion without inducing end-organ damage are needed. Furthermore, several upcoming studies will investigate the optimal use of current diuretic treatment options. The TRANSFORM-HF will assess the superiority of torsemide in comparison to furosemide in reducing all-cause mortality. Furthermore, ongoing studies are testing the effect of subcutaneous furosemide in comparison to oral furosemide.[143]

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.
Figure S1. Summary overview of the CARRESS-HF trial.

Conflict of interest: W.M. has received research grants from Novartis, Vifor, Medtronic, Biotronik, Abbott and Boston Scientific. V.P.H. has received research grants from Abbott Laboratories, and personal fees from Bayer, Boehringer-Ingelheim, MSD, Orion Pharma, Pfizer, Roche Diagnostics, Thermo Fisher and Vifor. A.M. received speaker's honoraria from Abbott, Orion, Roche and Servier and fee as member of advisory board and/or Steering Committee and/or research grant from BMS, Adrenomed, Neurotronik, Roche, Sanofi and Sphyngotec. H.P.B.L.R. has received research grants from Roche Diagnostics, Novartis, Servier and Vifor pharma, and advisory board fees from Novartis, Roche Diagnostics, Vifor Pharma and Servier. P.M. has received a research grant from Vifor pharma and Fonds Wetenschappelijk Onderzoek (grant number: 1127917N) and consultancy fees from AstraZeneca, Boehringer-Ingelheim, Novartis and Vifor pharma. J.M.T. has received research grants from the NIH, FDA, Boehringer Ingelheim, Sanofi, Abbott, FIRE1, Sequana Medical, Otsuka and consulting fees from Sanofi, Boehringer Ingelheim, Novartis, BMS, AstraZeneca, FIRE1, Sequana Medical, Cardionomic, and RenalGuard. W.H.W.T. has been supported by grants from the NIH (R01HL103931) and has served as a consultant for the Advisory Board Company, MyoKardia Inc, and Sequana Medical Inc. P.R. reports personal fees (consulting) from Fresenius, Grünenthal, Idorsia, Novartis, Novo-Nordisk, Relypsa, Stealth Peptides, Vifor Fresenius Medical Care Renal Pharma, Vifor, as well as lecture fees from Bayer and CVRx; he is a cofounder of CardioRenal. M.M. has received consulting honoraria from Bayer, Novartis, and Servier, and speaker's fees from Abbott Vascular and Novartis. G.F. has served on the committees of trials supported by Bayer, Novartis, Servier, Vifor, BI and Medtronic. P.S. reports grants/research supports from Ministry of education, science and technological development of Republic of Serbia; and honoraria or consultation fees from Servier, Boehringher Ingelheim, Hemofarm, Novartis, Astra Zeneca; he participated in a company sponsored speaker's bureau: Fondazione Internationale Menarini. F.R. reports grants and personal fees from SJM/Abbott, Novartis, Bayer, Servier; personal fees from Zoll, Astra Zeneca, Sanofi, Amgen, BMS, Pfizer, Fresenius, Vifor, Roche, Cardiorentis, Boehringer Ingelheim, other from Heartware, grants from Mars, during the conduct of the study; since 1st January 2018: no personal payments/all payments directly to the University of Zurich. A.J.C. reports personal fees from Respicardia, Vifor and Servier. The other authors have no conflicts of interest to declare.

References

1. Filippatos G, Zannad F. An introduction to acute heart failure syndromes: definition and classification. *Heart Fail Rev* 2007;**12**:87–90.
2. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart* 2007;**93**:1137–1146.
3. Chioncel O, Mebazaa A, Harjola VP, Coats AJ, Piepoli MF, Crespo-Leiro MG, Laroche C, Seferovic PM, Anker SD, Ferrari R, Ruschitzka F, Lopez-Fernandez S, Miani D, Filippatos G, Maggioni AP; ESC Heart Failure Long-Term Registry Investigators. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017;**19**:1242–1254.
4. Gheorghiade M, Pang PS. Acute heart failure syndromes. *J Am Coll Cardiol* 2009;**53**:557–573.
5. Nunez J, Nunez E, Fonarow GC, Sanchis J, Bodi V, Bertomeu-Gonzalez V, Minana G, Merlos P, Bertomeu-Martinez V, Redon J, Chorro FJ, Llacer A. Differential prognostic effect of systolic blood pressure on mortality according to left-ventricular function in patients with acute heart failure. *Eur J Heart Fail* 2010;**12**:38–44.
6. Ellison DH, Felker GM. Diuretic treatment in heart failure. *N Engl J Med* 2017;**377**:1964–1975.
7. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
8. Martens P, Nijst P, Mullens W. Current approach to decongestive therapy in acute heart failure. *Curr Heart Fail Rep* 2015;**12**:367–378.
9. Mullens W, Verbrugge FH, Nijst P, Tang WH. Renal sodium avidity in heart failure: from pathophysiology to treatment strategies. *Eur Heart J* 2017;**38**:1872–1882.
10. Nijst P, Verbrugge FH, Grieten L, Dupont M, Steels P, Tang WH, Mullens W. The pathophysiological role of interstitial sodium in heart failure. *J Am Coll Cardiol* 2015;**65**:378–388.
11. Verbrugge FH, Dupont M, Steels P, Grieten L, Malbrain M, Tang WH, Mullens W. Abdominal contributions to cardiorenal dysfunction in congestive heart failure. *J Am Coll Cardiol* 2013;**62**:485–495.
12. Miller WL. Fluid volume overload and congestion in heart failure: time to reconsider pathophysiology and how volume is assessed. *Circ Heart Fail* 2016;**9**:e002922.
13. Fudim M, Jones WS, Boortz-Marx RL, Ganesh A, Green CL, Hernandez AF, Patel MR. Splanchnic nerve block for acute heart failure. *Circulation* 2018;**138**:951–953.
14. Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. *J Am Coll Cardiol* 2009;**53**:582–588.
15. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB, Tang WH. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol* 2009;**53**:589–596.
16. Dovancescu S, Pellicori P, Mabote T, Torabi A, Clark AL, Cleland JG. The effects of short-term omission of daily medication on the pathophysiology of heart failure. *Eur J Heart Fail* 2017;**19**:643–649.
17. Chaudhry SI, Wang Y, Concato J, Gill TM, Krumholz HM. Patterns of weight change preceding hospitalization for heart failure. *Circulation* 2007;**116**:1549–1554.
18. Clark AL, Coats AJ, Krum H, Katus HA, Mohacsi P, Salekin D, Schultz MK, Packer M, Anker SD. Effect of beta-adrenergic blockade with carvedilol on cachexia in severe chronic heart failure: results from the COPERNICUS trial. *J Cachexia Sarcopenia Muscle* 2017;**8**:549–556.

19. Loncar G, Springer J, Anker M, Doehner W, Lainscak M. Cardiac cachexia: hic et nunc: "hic et nunc" - here and now. *Int J Cardiol* 2015;**201**:e1–e12.
20. Metra M, Davison B, Bettari L, Sun H, Edwards C, Lazzarini V, Piovanelli B, Carubelli V, Bugatti S, Lombardi C, Cotter G, Dei Cas L. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. *Circ Heart Fail* 2012;**5**:54–62.
21. Ambrosy AP, Cerbin LP, Armstrong PW, Butler J, Coles A, DeVore AD, Dunlap ME, Ezekowitz JA, Felker GM, Fudim M, Greene SJ, Hernandez AF, O'Connor CM, Schulte P, Starling RC, Teerlink JR, Voors AA, Mentz RJ. Body weight change during and after hospitalization for acute heart failure: patient characteristics, markers of congestion, and outcomes: findings from the ASCEND-HF trial. *JACC Heart Fail* 2017;**5**:1–13.
22. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, Dickstein K, Drazner MH, Fonarow GC, Jaarsma T, Jondeau G, Sendon JL, Mebazaa A, Metra M, Nieminen M, Pang PS, Seferovic P, Stevenson LW, van Veldhuisen DJ, Zannad F, Anker SD, Rhodes A, McMurray JJ, Filippatos G. Assessing and grading congestion in acute heart failure: a scientific statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. *Eur J Heart Fail* 2010;**12**:423–433.
23. Binanay C, Califf RM, Hasselblad V, O'Connor CM, Shah MR, Sopko G, Stevenson LW, Francis GS, Leier CV, Miller LW; ESCAPE Investigators and ESCAPE Study Coordinators. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA* 2005;**294**:1625–1633.
24. Nagueh SF. Non-invasive assessment of left ventricular filling pressure. *Eur J Heart Fail* 2018;**20**:38–48.
25. Mullens W, Borowski AG, Curtin RJ, Thomas JD, Tang WH. Tissue Doppler imaging in the estimation of intracardiac filling pressure in decompensated patients with advanced systolic heart failure. *Circulation* 2009;**119**:62–70.
26. Parrinello G, Greene SJ, Torres D, Alderman M, Bonventre JV, Di Pasquale P, Gargani L, Nohria A, Fonarow GC, Vaduganathan M, Butler J, Paterna S, Stevenson LW, Gheorghiade M. Water and sodium in heart failure: a spotlight on congestion. *Heart Fail Rev* 2015;**20**:13–24.
27. Volpicelli G, Skurzak S, Boero E, Carpinteri G, Tengattini M, Stefanone V, Luberto L, Anile A, Cerutti E, Radeschi G, Frascisco MF. Lung ultrasound predicts well extravascular lung water but is of limited usefulness in the prediction of wedge pressure. *Anesthesiology* 2014;**121**:320–327.
28. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016;**29**:277–314.
29. Caldentey G, Khairy P, Roy D, Leduc H, Talajic M, Racine N, White M, O'Meara E, Guertin MC, Rouleau JL, Ducharme A. Prognostic value of the physical examination in patients with heart failure and atrial fibrillation: insights from the AF-CHF trial (Atrial Fibrillation and Chronic Heart Failure). *JACC Heart Fail* 2014;**2**:15–23.
30. Chakko S, Woska D, Martinez H, de Marchena E, Futterman L, Kessler KM, Myerberg RJ. Clinical, radiographic, and hemodynamic correlations in chronic congestive heart failure: conflicting results may lead to inappropriate care. *Am J Med* 1991;**90**:353–359.
31. McGee SR. Physical examination of venous pressure: a critical review. *Am Heart J* 1998;**136**:10–18.
32. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA* 1989;**261**:884–888.
33. Thibodeau JT, Drazner MH. The role of the clinical examination in patients with heart failure. *JACC Heart Fail* 2018;**6**:543–551.
34. Collins SP, Lindsell CJ, Storrow AB, Abraham WT. Prevalence of negative chest radiography results in the emergency department patient with decompensated heart failure. *Ann Emerg Med* 2006;**47**:13–18.
35. Platz E, Merz AA, Jhund PS, Vazir A, Campbell R, McMurray JJ. Dynamic changes and prognostic value of pulmonary congestion by lung ultrasound in acute and chronic heart failure: a systematic review. *Eur J Heart Fail* 2017;**19**:1154–1163.
36. Al Deeb M, Barbic S, Featherstone R, Dankoff J, Barbic D. Point-of-care ultrasonography for the diagnosis of acute cardiogenic pulmonary edema in patients presenting with acute dyspnea: a systematic review and meta-analysis. *Acad Emerg Med* 2014;**21**:843–852.
37. Maeder MT, Mueller C, Pfisterer ME, Buser PT, Brunner-la Rocca HP. Use of B-type natriuretic peptide outside of the emergency department. *Int J Cardiol* 2008;**127**:5–16.
38. Philipson H, Ekman I, Forslund HB, Swedberg K, Schaufelberger M. Salt and fluid restriction is effective in patients with chronic heart failure. *Eur J Heart Fail* 2013;**15**:1304–1310.
39. Gheorghiade M, De Luca L, Fonarow GC, Filippatos G, Metra M, Francis GS. Pathophysiologic targets in the early phase of acute heart failure syndromes. *Am J Cardiol* 2005;**96**:11G–17G.
40. O'Connor CM, Stough WG, Gallup DS, Hasselblad V, Gheorghiade M. Demographics, clinical characteristics, and outcomes of patients hospitalized for decompensated heart failure: observations from the IMPACT-HF registry. *J Card Fail* 2005;**11**:200–205.
41. Vaduganathan M, Greene SJ, Fonarow GC, Voors AA, Butler J, Gheorghiade M. Hemoconcentration-guided diuresis in heart failure. *Am J Med* 2014;**127**:1154–1159.
42. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM; NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med* 2011;**364**:797–805.
43. Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Crespo LM, Drozdz J, Fruhwald F, Gullestad L, Logeart D, Fabbri G, Urso R, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors AA, Nielsen OW, Zannad F, Tavazzi L; Heart Failure Association of the European Society of Cardiology (HFA). EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail* 2013;**15**:808–817.
44. Rubio-Gracia J, Demissei BG, Ter Maaten JM, Cleland JG, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Davison BA, Givertz MM, Bloomfield DM, Dittrich H, Damman K, Perez-Calvo JI, Voors AA. Prevalence, predictors and clinical outcome of residual congestion in acute decompensated heart failure. *Int J Cardiol* 2018;**258**:185–191.
45. Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC, Traver B, Maggioni AP, Cook T, Swedberg K, Burnett JC Jr, Grinfeld L, Udelson JE, Zannad F, Gheorghiade M; EVEREST Trial Investigators. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. *Eur Heart J* 2013;**34**:835–843.
46. Lala A, McNulty SE, Mentz RJ, Dunlay SM, Vader JM, AbouEzzeddine OF, DeVore AD, Khazanie P, Redfield MM, Goldsmith SR, Bart BA, Anstrom KJ, Felker GM, Hernandez AF, Stevenson LW. Relief and recurrence of congestion during and after hospitalization for acute heart failure: insights from Diuretic Optimization Strategy Evaluation in Acute Decompensated Heart Failure (DOSE-AHF) and Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARESS-HF). *Circ Heart Fail* 2015;**8**:741–748.
47. Testani JM, Brisco MA, Kociol RD, Jacoby D, Bellumkonda L, Parikh CR, Coca SG, Tang WH. Substantial discrepancy between fluid and weight loss during acute decompensated heart failure treatment. *Am J Med* 2015;**128**:776–783.
48. Drazner MH, Rame JE, Stevenson LW, Dries DL. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. *N Engl J Med* 2001;**345**:574–581.
49. Letsas KP, Filippatos GS, Pappas LK, Mihas CC, Markou V, Alexanian IP, Efremidis M, Sideris A, Maisel AS, Kardaras F. Determinants of plasma NT-pro-BNP levels in patients with atrial fibrillation and preserved left ventricular ejection fraction. *Clin Res Cardiol* 2009;**98**:101–106.
50. Stienen S, Salah K, Moons AH, Bakx AL, van Pol P, Kortz M, Ferreira JP, Marques I, Schroeder-Tanka JM, Keijer JT, Bayes-Genis A, Tijssen JG, Pinto YM, Kok WE. NT-proBNP (N-terminal pro-B-type natriuretic peptide)-guided therapy in acute decompensated heart failure: PRIMA II randomized controlled trial (Can NT-ProBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?). *Circulation* 2018;**137**:1671–1683.
51. Desai AS. Are serial BNP measurements useful in heart failure management? Serial natriuretic peptide measurements are not useful in heart failure management: the art of medicine remains long. *Circulation* 2013;**127**:509–516.
52. Nunez J, Llacer P, Bertomeu-Gonzalez V, Bosch MJ, Merlos P, Garcia-Blas S, Montagud V, Bodi V, Bertomeu-Martinez V, Pedrosa V, Mendizabal A, Cordero A, Gallego J, Palau P, Minana G, Santas E, Morell S, Llacer A, Chorro FJ, Sanchis J, Facila L; CHANCE-HF Investigators. Carbohydrate antigen-125-guided therapy in acute heart failure: CHANCE-HF: a randomized study. *JACC Heart Fail* 2016;**4**:833–843.
53. Kremer D, Ter Maaten JM, Voors AA. Bio-adrenomedullin as a potential quick, reliable, and objective marker of congestion in heart failure. *Eur J Heart Fail* 2018;**20**:1363–1365.
54. Gayat E, Caillard A, Laribi S, Mueller C, Sadoune M, Seronde MF, Maisel A, Bartunek J, Vanderheyden M, Desutter J, Dendale P, Thomas G, Tavares M,

Cohen-Solal A, Samuel JL, Mebazaa A. Soluble CD146, a new endothelial biomarker of acutely decompensated heart failure. *Int J Cardiol* 2015;**199**:241–247.
55. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. *Circulation* 2010;**122**:265–272.
56. Testani JM, Brisco MA, Chen J, McCauley BD, Parikh CR, Tang WH. Timing of hemoconcentration during treatment of acute decompensated heart failure and subsequent survival: importance of sustained decongestion. *J Am Coll Cardiol* 2013;**62**:516–524.
57. Greene SJ, Gheorghiade M, Vaduganathan M, Ambrosy AP, Mentz RJ, Subacius H, Maggioni AP, Nodari S, Konstam MA, Butler J, Filippatos G; EVEREST Trial Investigators. Haemoconcentration, renal function, and post-discharge outcomes among patients hospitalized for heart failure with reduced ejection fraction: insights from the EVEREST trial. *Eur J Heart Fail* 2013;**15**:1401–1411.
58. Breidthardt T, Weidmann ZM, Twerenbold R, Gantenbein C, Stallone F, Rentsch K, Rubini GM, Kozhuharov N, Sabti Z, Breitenbucher D, Wildi K, Puelacher C, Honegger U, Wagener M, Schumacher C, Hillinger P, Osswald S, Mueller C. Impact of haemoconcentration during acute heart failure therapy on mortality and its relationship with worsening renal function. *Eur J Heart Fail* 2017;**19**:226–236.
59. Ahmad T, Jackson K, Rao VS, Tang WH, Brisco-Bacik MA, Chen HH, Felker GM, Hernandez AF, O'Connor CM, Sabbisetti VS, Bonventre JV, Wilson FP, Coca SG, Testani JM. Worsening renal function in patients with acute heart failure patients undergoing aggressive diuresis is not associated with tubular injury. *Circulation* 2018;**137**:2016–2028.
60. Maisel AS, Wettersten N, van Veldhuisen DJ, Mueller C, Filippatos G, Nowak R, Hogan C, Kontos MC, Cannon CM, Muller GA, Birkhahn R, Clopton P, Taub P, Vilke GM, McDonald K, Mahon N, Nunez J, Briguori C, Passino C, Murray PT. Neutrophil gelatinase-associated lipocalin for acute kidney injury during acute heart failure hospitalizations: the AKINESIS study. *J Am Coll Cardiol* 2016;**68**:1420–1431.
61. Coiro S, Rossignol P, Ambrosio G, Carluccio E, Alunni G, Murrone A, Tritto I, Zannad F, Girerd N. Prognostic value of residual pulmonary congestion at discharge assessed by lung ultrasound imaging in heart failure. *Eur J Heart Fail* 2015;**17**:1172–1181.
62. Thavendiranathan P, Yingchoncharoen T, Grant A, Seicean S, Landers SH, Gorodeski EZ, Marwick TH. Prediction of 30-day heart failure-specific readmission risk by echocardiographic parameters. *Am J Cardiol* 2014;**113**:335–341.
63. Verbrugge FH, Dupont M, Steels P, Grieten L, Swennen Q, Tang WH, Mullens W. The kidney in congestive heart failure: 'are natriuresis, sodium, and diuretics really the good, the bad and the ugly?'. *Eur J Heart Fail* 2014;**16**:133–142.
64. Brater DC. Pharmacokinetics of loop diuretics in congestive heart failure. *Br Heart J* 1994;**72**:S40–S43.
65. Ter Maaten JM, Valente MA, Damman K, Hillege HL, Navis G, Voors AA. Diuretic response in acute heart failure – pathophysiology, evaluation, and therapy. *Nat Rev Cardiol* 2015;**12**:184–192.
66. Ellison DH. Diuretic therapy and resistance in congestive heart failure. *Cardiology* 2001;**96**:132–143.
67. Testani JM, Brisco MA, Turner JM, Spatz ES, Bellumkonda L, Parikh CR, Tang WH. Loop diuretic efficiency: a metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. *Circ Heart Fail* 2014;**7**:261–270.
68. Verbrugge FH, Nijst P, Dupont M, Reynders C, Penders J, Tang WH, Mullens W. Prognostic value of glomerular filtration changes versus natriuretic response in decompensated heart failure with reduced ejection. *J Card Fail* 2014;**20**:817–824.
69. Verbrugge FH, Dupont M, Bertrand PB, Nijst P, Penders J, Dens J, Verhaert D, Vandervoort P, Tang WH, Mullens W. Determinants and impact of the natriuretic response to diuretic therapy in heart failure with reduced ejection fraction and volume overload. *Acta Cardiol* 2015;**70**:265–273.
70. Ferreira JP, Girerd N, Bettencourt MP, Bento RM, Almeida T, Rola A, Zannad F, Rossignol P, Aragao I. Lack of diuretic efficiency (but not low diuresis) early in an acutely decompensated heart failure episode is associated with increased 180-day mortality. *Cardiorenal Med* 2017;**7**:137–149.
71. Brinkley DM Jr, Burpee LJ, Chaudhry SP, Smallwood JA, Lindenfeld J, Lakdawala NK, Desai AS, Stevenson LW. Spot urine sodium as triage for effective diuretic infusion in an ambulatory heart failure unit. *J Card Fail* 2018;**24**:349–354.
72. Singh D, Shrestha K, Testani JM, Verbrugge FH, Dupont M, Mullens W, Tang WH. Insufficient natriuretic response to continuous intravenous furosemide is associated with poor long-term outcomes in acute decompensated heart failure. *J Card Fail* 2014;**20**:392–399.
73. Testani JM, Hanberg JS, Cheng S, Rao V, Onyebeke C, Laur O, Kula A, Chen M, Wilson FP, Darlington A, Bellumkonda L, Jacoby D, Tang WH, Parikh CR. Rapid and highly accurate prediction of poor loop diuretic natriuretic response in patients with heart failure. *Circ Heart Fail* 2016;**9**:e002370.
74. Verbrugge FH, Nijst P, Dupont M, Penders J, Tang WH, Mullens W. Urinary composition during decongestive treatment in heart failure with reduced ejection fraction. *Circ Heart Fail* 2014;**7**:766–772.
75. Damman K, Testani JM. The kidney in heart failure: an update. *Eur Heart J* 2015;**36**:1437–1444.
76. Filippatos G, Farmakis D, Parissis J. Renal dysfunction and heart failure: things are seldom what they seem. *Eur Heart J* 2014;**35**:416–418.
77. Grodin JL, Stevens SR, de Las FL, Kiernan M, Birati EY, Gupta D, Bart BA, Felker GM, Chen HH, Butler J, Davila-Roman VG, Margulies KB, Hernandez AF, Anstrom KJ, Tang WH. Intensification of medication therapy for cardiorenal syndrome in acute decompensated heart failure. *J Card Fail* 2016;**22**:26–32.
78. Grodin JL, Carter S, Bart BA, Goldsmith SR, Drazner MH, Tang WH. Direct comparison of ultrafiltration to pharmacological decongestion in heart failure: a per-protocol analysis of CARRESS-HF. *Eur J Heart Fail* 2018;**20**:1148–1156.
79. Martens P, Mullens W. How to tackle congestion in acute heart failure. *Korean J Intern Med* 2018;**33**:462–473.
80. Butler J, Gheorghiade M, Metra M. Moving away from symptoms-based heart failure treatment: misperceptions and real risks for patients with heart failure. *Eur J Heart Fail* 2016;**18**:350–352.
81. Kula AJ, Hanberg JS, Wilson FP, Brisco MA, Bellumkonda L, Jacoby D, Coca SG, Parikh CR, Tang WH, Testani JM. Influence of titration of neurohormonal antagonists and blood pressure reduction on renal function and decongestion in decompensated heart failure. *Circ Heart Fail* 2016;**9**:e002333.
82. Van Aelst LN, Arrigo M, Placido R, Akiyama E, Girerd N, Zannad F, Manivet P, Rossignol P, Badoz M, Sadoune M, Launay JM, Gayat E, Lam CS, Cohen-Solal A, Mebazaa A, Seronde MF. Acutely decompensated heart failure with preserved and reduced ejection fraction present with comparable haemodynamic congestion. *Eur J Heart Fail* 2018;**20**:738–747.
83. Ambrosy AP, Bhatt AS, Gallup D, Anstrom KJ, Butler J, DeVore AD, Felker GM, Fudim M, Greene SJ, Hernandez AF, Kelly JP, Samsky MD, Mentz RJ. Trajectory of congestion metrics by ejection fraction in patients with acute heart failure (from the Heart Failure Network). *Am J Cardiol* 2017;**120**:98–105.
84. Felker GM, Mentz RJ. Diuretics and ultrafiltration in acute decompensated heart failure. *J Am Coll Cardiol* 2012;**59**:2145–2153.
85. Bikdeli B, Strait KM, Dharmarajan K, Partovian C, Coca SG, Kim N, Li SX, Testani JM, Khan U, Krumholz HM. Dominance of furosemide for loop diuretic therapy in heart failure: time to revisit the alternatives? *J Am Coll Cardiol* 2013;**61**:1549–1550.
86. Faris RF, Flather M, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. *Cochrane Database Syst Rev* 2012;**2**:CD003838.
87. Brisco MA, Zile MR, Hanberg JS, Wilson FP, Parikh CR, Coca SG, Tang WH, Testani JM. Relevance of changes in serum creatinine during a heart failure trial of decongestive strategies: insights from the DOSE trial. *J Card Fail* 2016;**22**:753–760.
88. Hanberg JS, Tang WH, Wilson FP, Coca SG, Ahmad T, Brisco MA, Testani JM. An exploratory analysis of the competing effects of aggressive decongestion and high-dose loop diuretic therapy in the DOSE trial. *Int J Cardiol* 2017;**241**:277–282.
89. Matsue Y, Damman K, Voors AA, Kagiyama N, Yamaguchi T, Kuroda S, Okumura T, Kida K, Mizuno A, Oishi S, Inuzuka Y, Akiyama E, Matsukawa R, Kato K, Suzuki S, Naruke T, Yoshioka K, Miyoshi T, Baba Y, Yamamoto M, Murai K, Mizutani K, Yoshida K, Kitai T. Time-to-furosemide treatment and mortality in patients hospitalized with acute heart failure. *J Am Coll Cardiol* 2017;**69**:3042–3051.
90. Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, Katz SD, Klapholz M, Moser DK, Rogers JG, Starling RC, Stevenson WG, Tang WH, Teerlink JR, Walsh MN. HFSA 2010 comprehensive heart failure practice guideline. *J Card Fail* 2010;**16**:e1–e194.
91. Harjola VP, Mullens W, Banaszewski M, Bauersachs J, Brunner-la Rocca HP, Chioncel O, Collins SP, Doehner W, Filippatos GS, Flammer AJ, Fuhrmann V, Lainscak M, Lassus J, Legrand M, Masip J, Mueller C, Papp Z, Parissis J, Platz E, Rudiger A, Ruschitzka F, Schafer A, Seferovic PM, Skouri H, Yilmaz MB, Mebazaa A. Organ dysfunction, injury and failure in acute heart failure: from pathophysiology to diagnosis and management. A review on behalf of the Acute Heart Failure Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2017;**19**:821–836.
92. Iimura O, Tabei K, Nagashima H, Asano Y. A study on regulating factors of plasma refilling during hemodialysis. *Nephron* 1996;**74**:19–25.
93. Pietribiasi M, Katzarski K, Galach M, Stachowska-Pietka J, Schneditz D, Lindholm B, Waniewski J. Kinetics of plasma refilling during hemodialysis sessions with different initial fluid status. *ASAIO J* 2015;**61**:350–356.
94. Buckley LF, Carter DM, Matta L, Cheng JW, Stevens C, Belenkiy RM, Burpee LJ, Young MA, Weiffenbach CS, Smallwood JA, Stevenson LW, Desai AS.

Intravenous diuretic therapy for the management of heart failure and volume overload in a multidisciplinary outpatient unit. *JACC Heart Fail* 2016;**4**:1–8.
95. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, Redfield MM, Deswal A, Rouleau JL, LeWinter MM, Ofili EO, Stevenson LW, Semigran MJ, Felker GM, Chen HH, Hernandez AF, Anstrom KJ, McNulty SE, Velazquez EJ, Ibarra JC, Mascette AM, Braunwald E; Heart Failure Clinical Research Network. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med* 2012;**367**:2296–2304.
96. Knauf H, Mutschler E. Pharmacodynamic and kinetic considerations on diuretics as a basis for differential therapy. *Klin Wochenschr* 1991;**69**:239–250.
97. Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. *J Am Coll Cardiol* 2010;**56**:1527–1534.
98. Sorensen MV, Grossmann S, Roesinger M, Gresko N, Todkar AP, Barmettler G, Ziegler U, Odermatt A, Loffing-Cueni D, Loffing J. Rapid dephosphorylation of the renal sodium chloride cotransporter in response to oral potassium intake in mice. *Kidney Int* 2013;**83**:811–824.
99. Hoorn EJ, Nelson JH, McCormick JA, Ellison DH. The WNK kinase network regulating sodium, potassium, and blood pressure. *J Am Soc Nephrol* 2011;**22**:605–614.
100. Rao VS, Planavsky N, Hanberg JS, Ahmad T, Brisco-Bacik MA, Wilson FP, Jacoby D, Chen M, Tang WH, Cherney DZI, Ellison DH, Testani JM. Compensatory distal reabsorption drives diuretic resistance in human heart failure. *J Am Soc Nephrol* 2017;**28**:3414–3424.
101. Kaissling B, Bachmann S, Kriz W. Structural adaptation of the distal convoluted tubule to prolonged furosemide treatment. *Am J Physiol* 1985;**248**(3 Pt 2):F374–F381.
102. Agarwal R, Sinha AD. Thiazide diuretics in advanced chronic kidney disease. *J Am Soc Hypertens* 2012;**6**:299–308.
103. Brisco-Bacik MA, Ter Maaten JM, Houser SR, Vedage NA, Rao V, Ahmad T, Wilson FP, Testani JM. Outcomes Associated With a Strategy of Adjuvant Metolazone or High-Dose Loop Diuretics in Acute Decompensated Heart Failure: A Propensity Analysis. *J Am Heart Assoc* 2018;**7**(18):e009149.
104. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;**341**:709–717.
105. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**:11–21.
106. Butler J, Anstrom KJ, Felker GM, Givertz MM, Kalogeropoulos AP, Konstam MA, Mann DL, Margulies KB, McNulty SE, Mentz RJ, Redfield MM, Tang WH, Whellan DJ, Shah M, Desvigne-Nickens P, Hernandez AF, Braunwald E; National Heart Lung and Blood Institute Heart Failure Clinical Research Network. Efficacy and safety of spironolactone in acute heart failure: the ATHENA-HF randomized clinical trial. *JAMA Cardiol* 2017;**2**:950–958.
107. Ferreira JP, Santos M, Almeida S, Marques I, Bettencourt P, Carvalho H. Mineralocorticoid receptor antagonism in acutely decompensated chronic heart failure. *Eur J Intern Med* 2014;**25**:67–72.
108. Verbrugge FH, Martens P, Ameloot K, Haemels V, Penders J, Dupont M, Tang WHW, Droogne W, Mullens W. Spironolactone to increase natriuresis in congestive heart failure with cardiorenal syndrome. *Acta Cardiol* 2018;1–8.
109. Ferreira JP, Rossignol P, Machu JL, Sharma A, Girerd N, Anker SD, Cleland JG, Dickstein K, Filippatos G, Hillege HL, Lang CC, Ter Maaten JM, Metra M, Ng L, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zwinderman AH, Voors A, Zannad F. Mineralocorticoid receptor antagonist pattern of use in heart failure with reduced ejection fraction: findings from BIOSTAT-CHF. *Eur J Heart Fail* 2017;**19**:1284–1293.
110. Knauf H, Mutschler E. Sequential nephron blockade breaks resistance to diuretics in edematous states. *J Cardiovasc Pharmacol* 1997;**29**:367–372.
111. Mullens W, Verbrugge FH, Nijst P, Martens P, Tartaglia K, Theunissen E, Bruckers L, Droogne W, Troisfontaines P, Damman K, Lassus J, Mebazaa A, Filippatos G, Ruschitzka F, Dupont M. Rationale and design of the ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload) trial. *Eur J Heart Fail* 2018;**20**:1591–1600.
112. Martens P, Mathieu C, Verbrugge FH. Promise of SGLT2 inhibitors in heart failure: diabetes and beyond. *Curr Treat Options Cardiovasc Med* 2017;**19**:23.
113. Butler J, Hamo CE, Filippatos G, Pocock SJ, Bernstein RA, Brueckmann M, Cheung AK, George JT, Green JB, Januzzi JL, Kaul S, Lam CS, Lip GY, Marx N, McCullough PA, Mehta CR, Ponikowski P, Rosenstock J, Sattar N, Salsali A, Scirica BM, Shah SJ, Tsutsui H, Verma S, Wanner C, Woerle HJ, Zannad F, Anker SD; EMPEROR Trials Program. The potential role and rationale for treatment of heart failure with sodium-glucose co-transporter 2 inhibitors. *Eur J Heart Fail* 2017;**19**:1390–1400.
114. Neal B, Perkovic V, Mahaffey KW, de ZD, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**:644–657.
115. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117–2128.
116. Cheitlin MD, Byrd R, Benowitz N, Liu E, Modin G. Amiloride improves hemodynamics in patients with chronic congestive heart failure treated with chronic digoxin and diuretics. *Cardiovasc Drugs Ther* 1991;**5**:719–725.
117. Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA* 2007;**297**:1319–1331.
118. Felker GM, Mentz RJ, Cole RT, Adams KF, Egnaczyk GF, Fiuzat M, Patel CB, Echols M, Khouri MG, Tauras JM, Gupta D, Monds P, Roberts R, O'Connor CM. Efficacy and safety of tolvaptan in patients hospitalized with acute heart failure. *J Am Coll Cardiol* 2017;**69**:1399–1406.
119. Konstam MA, Kiernan M, Chandler A, Dhingra R, Mody FV, Eisen H, Haught WH, Wagoner L, Gupta D, Patten R, Gordon P, Korr K, Fileccia R, Pressler SJ, Gregory D, Wedge P, Dowling D, Romeling M, Konstam JM, Massaro JM, Udelson JE; SECRET of CHF Investigators, Coordinators, and Committee Members. Short-term effects of tolvaptan in patients with acute heart failure and volume overload. *J Am Coll Cardiol* 2017;**69**:1409–1419.
120. Costanzo MR, Negoianu D, Jaski BE, Bart BA, Heywood JT, Anand IS, Smelser JM, Kaneshige AM, Chomsky DB, Adler ED, Haas GJ, Watts JA, Nabut JL, Schollmeyer MP, Fonarow GC. Aquapheresis versus intravenous diuretics and hospitalizations for heart failure. *JACC Heart Fail* 2016;**4**:95–105.
121. Costanzo MR, Ronco C, Abraham WT, Agostoni P, Barasch J, Fonarow GC, Gottlieb SS, Jaski BE, Kazory A, Levin AP, Levin HR, Marenzi G, Mullens W, Negoianu D, Redfield MM, Tang WH, Testani JM, Voors AA. Extracorporeal ultrafiltration for fluid overload in heart failure: current ststus and prospects for future research. *J Am Coll Cardiol* 2017;**69**:2428–2445.
122. Patarroyo M, Wehbe E, Hanna M, Taylor DO, Starling RC, Demirjian S, Tang WH. Cardiorenal outcomes after slow continuous ultrafiltration therapy in refractory patients with advanced decompensated heart failure. *J Am Coll Cardiol* 2012;**60**:1906–1912.
123. Verbrugge FH, Steels P, Grieten L, Nijst P, Tang WH, Mullens W. Hyponatremia in acute decompensated heart failure: depletion versus dilution. *J Am Coll Cardiol* 2015;**65**:480–492.
124. Verbrugge FH, Grodin JL, Mullens W, Taylor DO, Starling RC, Tang WH. Transient hyponatremia during hospitalization for acute heart failure. *Am J Med* 2016;**129**:620–627.
125. Ter Maaten JM, Damman K, Hanberg JS, Givertz MM, Metra M, O'Connor CM, Teerlink JR, Ponikowski P, Cotter G, Davison B, Cleland JG, Bloomfield DM, Hillege HL, van Veldhuisen DJ, Voors AA, Testani JM. Hypochloremia, diuretic resistance, and outcome in patients with acute heart failure. *Circ Heart Fail* 2016;**9**:e003109.
126. Gheorghiade M, Abraham WT, Albert NM, Gattis SW, Greenberg BH, O'Connor CM, She L, Yancy CW, Young J, Fonarow GC; OPTIMIZE-HF Investigators and Coordinators. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. *Eur Heart J* 2007;**28**:980–988.
127. Konishi M, Haraguchi G, Ohigashi H, Sasaoka T, Yoshikawa S, Inagaki H, Ashikaga T, Isobe M. Progression of hyponatremia is associated with increased cardiac mortality in patients hospitalized for acute decompensated heart failure. *J Card Fail* 2012;**18**:620–625.
128. de DS, Tardif JC, White M, Bourassa MG, Racine N, Levesque S, Ducharme A. Quantification of the risk and predictors of hyperkalemia in patients with left ventricular dysfunction: a retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD) trials. *Am Heart J* 2006;**152**:705–712.
129. Damman K, Kjekshus J, Wikstrand J, Cleland JG, Komajda M, Wedel H, Waagstein F, McMurray JJ. Loop diuretics, renal function and clinical outcome in patients with heart failure and reduced ejection fraction. *Eur J Heart Fail* 2016;**18**:328–336.
130. Martens P, Verbrugge FH, Nijst P, Dupont M, Mullens W. Changes in loop diuretic dose and outcome after cardiac resynchronization therapy in patients with heart failure and reduced left ventricular ejection fractions. *Am J Cardiol* 2017;**120**:267–273.
131. Galve E, Mallol A, Catalan R, Palet J, Mendez S, Nieto E, Diaz A, Soler-Soler J. Clinical and neurohumoral consequences of diuretic withdrawal in patients with chronic, stabilized heart failure and systolic dysfunction. *Eur J Heart Fail* 2005;**7**:892–898.

132. Grinstead WC, Francis MJ, Marks GF, Tawa CB, Zoghbi WA, Young JB. Discontinuation of chronic diuretic therapy in stable congestive heart failure secondary to coronary artery disease or to idiopathic dilated cardiomyopathy. *Am J Cardiol* 1994;**73**:881–886.
133. Costanzo MR, Stevenson LW, Adamson PB, Desai AS, Heywood JT, Bourge RC, Bauman J, Abraham WT. Interventions linked to decreased heart failure hospitalizations during ambulatory pulmonary artery pressure monitoring. *JACC Heart Fail* 2016;**4**:333–344.
134. Beygui F, Anguita M, Tebbe U, Comin-Colet J, Galinier M, Bramlage P, Turgonyi E, Lins K, Imekraz L, de Frutos T, Bohm M. A real-world perspective on the prevalence and treatment of heart failure with a reduced ejection fraction but no specific or only mild symptoms. *Heart Fail Rev* 2015;**20**:545–552.
135. Martens P, Belien H, Dupont M, Mullens W. Insights into implementation of sacubitril/valsartan into clinical practice. *ESC Heart Fail* 2018;**5**:275–283.
136. Verbrugge FH, Martens P, Boonen L, Nijst P, Verhaert D, Noyens P, De Vusser P, Dupont M, Tang WH, Mullens W. Loop diuretic down-titration in stable chronic heart failure is often achievable, especially when urinary chloride concentration is low. *Acta Cardiol* 2017;**73**:335–341.
137. Kapelios CJ, Kaldara E, Ntalianis A, Nana E, Pantsios C, Repasos E, Margari Z, Sousonis V, Malliaras K, Nanas JN. Lowering furosemide dose in stable chronic heart failure patients with reduced ejection fraction is not accompanied by decompensation: a randomized study. *Int J Cardiol* 2014;**177**:690–692.
138. Martens P, Verbrugge FH, Boonen L, Nijst P, Dupont M, Mullens W. Value of routine investigations to predict loop diuretic down-titration success in stable heart failure. *Int J Cardiol* 2018;**250**:171–175.
139. Gupta D, Georgiopoulou VV, Kalogeropoulos AP, Dunbar SB, Reilly CM, Sands JM, Fonarow GC, Jessup M, Gheorghiade M, Yancy C, Butler J. Dietary sodium intake in heart failure. *Circulation* 2012;**126**:479–485.
140. Colin-Ramirez E, Ezekowitz JA. Salt in the diet in patients with heart failure: what to recommend. *Curr Opin Cardiol* 2016;**31**:196–203.
141. Li Y, Fu B, Qian X. Liberal versus restricted fluid administration in heart failure patients. A systematic review and meta-analysis of randomized trials. *Int Heart J* 2015;**56**:192–195.
142. Paterna S, Fasullo S, Parrinello G, Cannizzaro S, Basile I, Vitrano G, Terrazzino G, Maringhini G, Ganci F, Scalzo S, Sarullo FM, Cice G, Di Pasquale P. Short-term effects of hypertonic saline solution in acute heart failure and long-term effects of a moderate sodium restriction in patients with compensated heart failure with New York Heart Association class III (Class C) (SMAC-HF Study). *Am J Med Sci* 2011;**342**:27–37.
143. Gilotra NA, Princewill O, Marino B, Okwuosa IS, Chasler J, Almansa J, Cummings A, Rhodes P, Chambers J, Cuomo K, Russell SD. Efficacy of intravenous furosemide versus a novel, pH-neutral furosemide formulation administered subcutaneously in outpatients with worsening heart failure. *JACC Heart Fail* 2018;**6**:65–70.