Heart Failure Reviews (2019) 24:17–30
https://doi.org/10.1007/s10741-018-9735-7

Loop diuretics in chronic heart failure: how to manage congestion?

Justas Simonavičius[1,2,3] · Christian Knackstedt[3] · Hans-Peter Brunner-La Rocca[3]

Published online: 7 September 2018

Abstract
Loop diuretics remain the cornerstone of congestion management in contemporary chronic heart failure care. However, their use is not supported by high quality data, and there is doubt about the safety in the outpatient heart failure setting. Still, congestion is related to a worse outcome, and there is general consensus among experts that congestion should not be tolerated in heart failure patients. Recommendations in international guidelines, regarding decongestion strategies in chronic heart failure, are limited. Thus, there is an emerging need for clinical decision-making support about the best strategy for using loop diuretics and decongestion in the chronic setting. The present review provides a comprehensive overview over the evidence of chronic loop diuretic use. Strategies for the assessment of congestion in the outpatient setting and decongestion algorithm are provided to assist health care specialists in delivering high-quality heart failure care.

Keywords Chronic heart failure · Volume overload · Decongestion · Loop diuretic · Diuretic therapy · Diuretic resistance

Introduction

The majority of patients with stage C and D heart failure (HF) is treated with loop diuretics, particularly after admission for HF decompensation [1–3]. In ASCEND-HF trial, 64% of patients admitted for acute HF were already on loop diuretic therapy, which increased to 91% of patients at discharge [1]. However, there are no sufficiently large, randomized, placebo-controlled trials showing that chronic loop diuretic therapy improves outcome [4–6].

The present review outlines current evidence of loop diuretic administration in chronic HF and provides recommendations for guiding loop diuretic therapy in daily outpatient practice.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10741-018-9735-7) contains supplementary material, which is available to authorized users.

✉ Justas Simonavičius
j.simonavicius@gmail.com

[1] Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania

[2] Centre of Cardiology and Angiology, Vilnius University Hospital Santaros Klinikos, Santariskiu Str. 2, LT-08406 Vilnius, Lithuania

[3] Department of Cardiology, Maastricht University Medical Centre, Maastricht, The Netherlands

Loop diuretics in chronic heart failure: the evidence

A meta-analysis of diuretics in chronic HF published in 2012 included 14 trials (7 placebo controlled, 7 against other HF therapy) but only 525 patients [6]. Mortality data was available only in 3 of the placebo-controlled trials (202 participants), and the marked reduction by diuretics is therefore very questionable (odds ratio (OR) 0.24, 95% confidence interval (CI) 0.07–0.83; $p = 0.02$). The same holds true regarding admission for worsening HF (two trials, 169 participants, OR 0.07, $p = 0.01$). In 4 trials comparing diuretics to active control (91 participants), exercise capacity was improved. The included trials lasted from 4 to 24 weeks only, and the use of diuretic drug was not standardized across the studies. Finally, the trials were published between 1977 and 1997 and cannot be transferred to today's HF care. Taken together, the conclusion that diuretics are beneficial not only for symptomatic relief, but also regarding hard endpoints remains unclear.

The ESC guidelines recommend diuretics to reduce the risk of HF hospitalization in patients with signs and/or symptoms of congestion (class of recommendation IIa, level of evidence B) [4]; the recommendation is solely based on the abovementioned meta-analysis [6].

The 2013 ACCF/AHA Guidelines for the Management of HF recommend diuretics in patients with HF and fluid retention, unless contraindicated, to improve symptoms (class I recommendation, level of evidence C) [5]. This

recommendation was not changed in the 2017 focused update [7]. The question therefore arises as to whether this recommendation on a liberal use of diuretics in chronic HF is justified or not.

Diuretic use in chronic heart failure: reflection of risk or direct harm?

Several studies uniformly concluded that diuretic administration is accompanied by a worse outcome [8–19] (Table 1). In addition, up-titration of diuretics was related to worsening renal function (WRF), increased readmission rate, and mortality [8]. In severely symptomatic patients, an independent, dose-dependent association between loop diuretic use and impaired outcome was found [9]. Similar findings were obtained in a large cohort study [10] (Supplementary Table).

Although a dose-dependent relation between loop diuretic use and outcome is established, intensified treatment with loop diuretics is prescribed for advanced HF patients with impaired functional capacity, relevant comorbidities, older age, and difficulties to establish evidence-based treatment due to low blood pressure or other adverse events [3, 9, 10, 14, 20]. All those factors indicate more advanced diseases and worse prognoses. In fact, the severity of HF has been graded according to the diuretic dose [21]. It may be questionable if full statistical adjustment is possible given the significant differences among high-/low-/non-users.

In order to overcome the shortcoming of significant selection bias, the potential prognostic impact of loop diuretics was tested by propensity score matching, seemingly confirming the negative influence of loop diuretic therapy in HF [14–19] (Table 1). In the large DIG trial, diuretic use was associated with significantly increased risk of cardiovascular mortality and HF hospitalization, both in patients above 65 years [15] and regardless of age [16]. Similar results were found in other large cohorts [14, 17, 18]. The association between loop diuretics and increased mortality was also observed in subjects without HF and renal failure (hazard ratio (HR) 1.82, the number needed to harm 7.2 [19]).

Propensity score matching has become an increasingly popular statistical method to simulate randomization in observational studies. However, full adjustment may not always be possible as not all relevant variables may be available, and factors potentially influencing the outcome may be unknown. Moreover, the lower the sample size, the lower the probability is to find suitable matching [22]. Many quality issues are noted in papers that draw conclusions with the help of propensity matching [23, 24], and there is serious doubt regarding the reliability of such data [25]. Therefore, the results of all abovementioned studies cannot reliably investigate the prognostic impact of loop diuretic therapy in HF.

Still, response to diuretic therapy may not be uniform in all HF patients. High diuretic doses may be deleterious in chronic euvolemic HF patients [12], whereas in hypervolemic patients, the diuretic dose may not have prognostic implications [11]. In a retrospective analysis of ASCEND-HF, initiation of loop diuretic therapy was associated with better outcome as compared with no dose change [1]. One of the reasons contributing to the positive effect of loop diuretics may be that patients not using diuretics before hospitalization had fluid overload requiring decongestion.

Potential mechanisms of harm and benefit

There are several potential mechanisms of loop diuretic-related harm (Fig. 1a). Loop diuretics can stimulate the renin-angiotensin-aldosterone system (RAAS) [26–29] as well as lead to electrolyte imbalance (hypokalemia, hyponatremia, hypomagnesaemia) in a dose-dependent manner [26]. Hypokalemia and hypomagnesaemia can lead to life-threatening arrhythmias [10, 30], especially in the presence of severe myocardial fibrosis and digoxin use. Volume depletion can cause hypotension (potentially resulting in falls and injuries), impair cognitive status, or worsen renal function. Also, hypovolemia can reduce cardiac output and impair blood supply to vital organs [31]. Long-term use of high doses of loop diuretics may trigger thiamine deficiency [26, 32, 33]. Loop diuretics (especially furosemide) may increase systemic sympathetic activity [27], potentially contributing to worse outcome.

However, there are also effects of loop diuretics that can be beneficial in HF patients (Fig. 1b). Loop diuretics decrease systemic, venous, and pulmonary overload as well as extracellular edema [26, 27, 34], leading to more favorable end-diastolic pressure, decreased ventricular wall stress, and increased cardiac output [27]. Decreased volume overload results in decreased secondary mitral and tricuspid regurgitations and improved cardiac hemodynamic profiles. There is some evidence that loop diuretics (especially long acting) can suppress cardiac sympathetic activity [35, 36]. This is in line with vasodilation-induced cardiac sympathetic tone reduction in patients with HF [37]. As cardiac autonomous sympathetic activation is particularly deleterious on outcome [38], its inhibition by reducing filling pressure may be beneficial. Additionally, venous congestion is the most important hemodynamic factor driving WRF [39]. Venous overload in the splanchnic venous system results in increased intra-abdominal pressure. By reducing fluid overload, diuretics reduce intra-abdominal pressure, resulting in improved renal function [40]. Thus, high doses of loop diuretics may not only result in worsening but also in improving renal function [27, 34], depending on the individual need. Moreover, cardiac status as determined by NT-proBNP seems to be more important than renal function regarding prognosis [41].

Finally, there might be some differences between loop diuretics. In a rat model of induced autoimmune myocarditis,

Table 1 Major observational studies of loop diuretics in chronic heart failure

Author/trial	Data collected (year)	Year published	Propensity score matching	Subjects (*n*)	Follow-up (months)	Mean age (years)	NYHA III/IV (%)	EF (%)	Conclusion
Martens et al. [8]	2008–2015	2017	No	648	6	71–74	61	29–31	LD dose down-titration after CRT system implantation related to lower rate of HF readmissions and all-cause mortality
Eshaghian et al. [9]	1985–2004	2006	No	1029	48	53	86	24	Independent, dose-dependent association between LD use and impaired survival was found.
Abdel-Quadir et al./EFFECT [10]	1999–2001	2010	No	4270	60	77–79	NA	NA	Dose-dependent increase in risk of mortality and hospitalization was found among LD users
Martins et al. [11]	NA	2011	No	244	48	68	8	NA*	Higher LD doses were associated strongly and independently with adverse long-term outcome in chronic HF
Dini et al. [12]	NA	2012	No	400	32	69	45	31	The study group identified furosemide dose as a major determinant of prognosis in patients with chronic HF but without ongoing signs and symptoms of congestion
Neuberg et al./PRAISE [13]	1992–1994	2002	No	1, 153	14	64–66	100	21–22	High LD doses were independently associated with mortality, sudden death, and pump failure death
Damman et al./CORONA [14]	2003–2005	2016	Yes	1659 pairs (50% LD users)	32.8	72–74	53–59	30–32	The use of LD (compared with no use) and higher LD doses (compared with lower doses) were associated with higher risks of CV mortality and hospitalization owing to HF
Ahmed et al./DIG ≥ 65 years [15]	1991–1995	2008	Yes	651 pairs (50% LD users)	36.7	71.5	14	35	Chronic LD therapy was associated with increased mortality and hospitalization rate
Ahmed et al./DIG [16]	1991–1995	2006	Yes	1391 pairs (50% LD users)	40	62.9	20	36	Chronic LD therapy was associated with increased mortality rate
Dini et al. [17]	NA	2013	Yes	813	44	65	34	31	The risk of death increased linearly across quartiles of furosemide daily dose
Hamaguchi et al./JCARE-CARD registry† [18]	NA	2012	Yes	2549 (79% LD users)	26.4	71	6	42	Before and after propensity matching, LD use was associated with all-cause death, cardiac death and all-cause death and hospitalization
Schartum-Hansen et al./WENBIT‡ [19]	199–2004	2015	Yes	109 pairs	26.4	65	9.6–11.9	66–67	LD use was associated with all-cause mortality.

*Median EF is not provided. The distribution according to EF is as follows: 24%, preserved EF; 15%, mildly depressed EF; 24%, moderately depressed EF; 37%, severely depressed EF

† Sufficient data how the propensity was done is not provided. Data in this table reflect the entire study population before the propensity matching

‡ Patients with systolic HF were excluded from the study

CORONA Controlled Rosuvastatin Multinational Trial in Heart Failure, *CRT* cardiac resynchronization therapy, *CV* cardiovascular, *DIG* digitalis investigation group, *EF* ejection fraction, *EFFECT* enhanced feedback for effective cardiac treatment, *HF* heart failure, *JCARE-CARD* Japanese Cardiac Registry of Heart Failure in Cardiology, *LD* loop diuretic, *NA* not available, *NYHA* New York Heart Association functional class, *PRAISE* prospective randomized amlodipine survival evaluation, *WENBIT* Western Norway B Vitamin Intervention trial

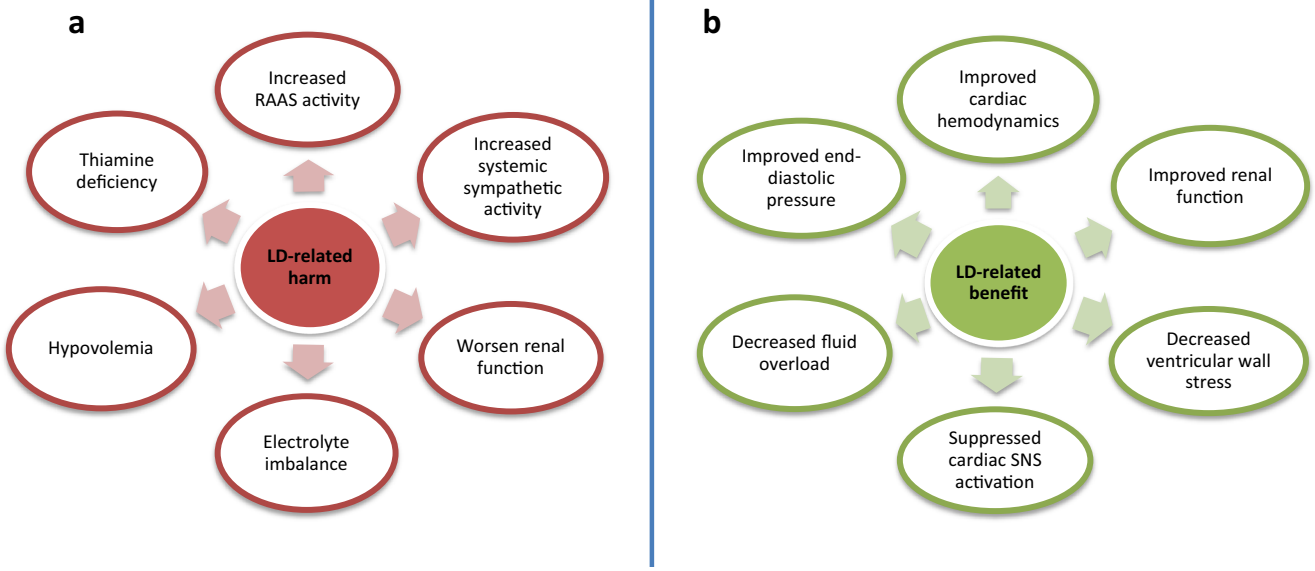

Fig. 1 Potential mechanisms of loop diuretic-related harm (**a**) and benefit (**b**). LD, loop diuretic; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system

torasemide significantly improved cardiac function and left ventricular remodeling as compared to furosemide [42]. In humans, retrospective data suggest that torasemide might be superior to furosemide in HF [43–45]. The prospective, randomized, though open label TORIC study was the largest study comparing furosemide with a newer class loop diuretic, it was found that patients treated with torasemide had better outcome than those treated with furosemide [46]. The superiority of torasemide to other loop diuretics is attributed to its relatively stable and predictable oral bioavailability, longer half-life, and RAAS-suppressing properties, as well as torasemide-mediated cardiac sympathetic nerve deactivation and left ventricular remodeling suppression [43–46].

Animal models of loop diuretic therapy

In a rat model of ischemic HF, both valsartan and hydrochlorothiazide, but not furosemide, improved cardiac function (left ventricular ejection fraction (LVEF) 49.5 ± 1.8%, 49.4 ± 2.1%, and 39.9 ± 1.9%, respectively) as compared to control animals (LVEF 40.1 ± 2.2%). Similar differences were seen regarding interstitial cardiac fibrosis and collagen volume fraction (10.0 ± 1.3% and 9.7 ± 1.2% versus 14.1 ± 0.8% and 15.9 ± 1.1%, respectively) [47]. In a tachycardia-induced porcine model of HF, furosemide was related to significant acceleration of both contractile and metabolic features of chronic HF [48]. A rat model was used to investigate the impact of furosemide on survival in rats with ischemia induced HF. The survival rate in furosemide group was lower than in the placebo group (HR 3.39, 95% CI 1.14 to 10.09, $p = 0.028$), whereas ramipril improved survival [49]. On the other hand, another rat model of ischemic HF showed that furosemide has no effect on collagen content, LVEF, and mortality rate [50]. Testing the impact of ramipril vs. furosemide or a combination of both showed that all treatment regimens improved cardiac remodeling and decreased angiotensin-converting enzyme (ACE) activity. However, mortality was only reduced in ramipril-treated animals, irrespectively if they received furosemide or not [51]. The results of animal model studies of diuretic safety are therefore controversial and inconclusive as well. Still, the latter studies suggest that loop diuretics may have different effects if combined with ACE-inhibition (and possibly other treatment improving prognosis), which would be relevant to the clinical setting.

Loop diuretics in chronic heart failure: clinical practice

Diuretics must be adjusted according to the individual needs [4, 5]. Still, the significance of clinical signs and symptoms, instrumental monitoring, and blood biomarkers for assessing (de)congestion has not yet been studied extensively. Right heart catheterization may be seen as a gold standard for fluid status assessment [52], but due to its invasive nature, large trials in the outpatient setting are difficult to carry out. No congestion evaluation and management algorithm has been widely implemented into daily clinical practice. Therefore, identification of the individual needs remains challenging.

Outpatient fluid status assessment

Signs and symptoms

Clinical signs and symptoms of congestion (Table 2) lack sensitivity and specificity [52, 53]. This is particularly true for elderly patients and those with an advanced HF stage and significant comorbidities, impaired mental status and limited physical capacity. Therefore, additional laboratory and/or instrumental assessment in daily outpatient practice is advisable. Still, clinical signs and symptoms of congestion are key elements to a guide of HF management [4, 5].

HF patients should be encouraged to monitor symptoms of congestion, including daily measurement of their body weight. Worsening of symptoms of congestions or weight gain may indicate fluid accumulation [4, 5], potentially requiring temporary increase in diuretic dose or consulting a medical professional. If a physical or mental status limits self-care, this should be ensured by the caregivers. Also, nursing professionals should play an active role in educating patients to recognize signs and symptoms of fluid overload [54]. However, congestion might trigger appetite loss and contribute to malnutrition leading to loss of lean body mass. Thus, fluid accumulation can occur without significant change in the absolute body weight. Importantly, individual patients may have their own pattern of signs and symptoms in case of fluid accumulation. Knowing such individual pattern may increase accuracy significantly.

The role of telemonitoring-based symptom monitoring systems in chronic HF has been investigated [55], but results are mixed and improvement of outcome is not yet clear. Several clinical congestion scores have been proposed; however, their diagnostic value is still uncertain [52]. Moreover, no studies have tested their value for diuretic dose adjustment in clinical practice.

Hypovolemia-related signs and symptoms, e.g., hypotension, thirst, and dry mouth and skin, are even less reliable than those caused by volume overload and clinical examination does not provide sufficient evidence in volume depletion states [56]. Thus, laboratory and/or instrumental assessment may be even more important to detect hypovolemia than hypervolemia.

Table 2 Clinical signs and symptoms of heart failure-related congestion

Signs and symptoms of left-sided congestion
• (Increasing) dyspnea
• Orthopnea
• Paroxysmal nocturnal dyspnea
• Bendopnea
• (Bilateral) pulmonary rales
• (Bilateral) pleural effusion
• Third heart sound
• Weight gain
Signs and symptoms of right-sided congestion
• Jugular venous dilation
• Bilateral peripheral edema
• Congested hepatomegaly
• Hepatojugular reflux
• Ascites
• Symptoms of gut congestion (e.g., appetite loss)
• Weight gain

Instrumental monitoring

If signs and symptoms leave uncertainties, the second step should be instrumental evaluation. Although easily accessible even for primary care physicians, chest X-ray examination is more helpful in the acute setting [4]; therefore, X-ray-guided diuretic therapy is of little value in chronic HF. Doppler echocardiography requires specific training; however, it enables assessment of volume status (ventricular filling pressures) with reasonable accuracy [57, 58], but limitations of echocardiographic fluid assessment must be considered. Three-step echocardiographic fluid status assessment algorithm is shown in Fig. 2. A small study found that echocardiography-guided therapy may decrease HF morbidity [59]. A recent study compared two HF treatment approaches (echocardiography and BNP vs. clinically guided): the daily dose of loop diuretics did not change in echocardiography and BNP-guided group, while it increased in 65% of patients in a clinically guided group, resulting in more deaths and WRF [60]. However, additional studies are required to define the value of echocardiography-guided diuretic therapy.

Bioimpedance is widely used in many dialysis centers to guide fluid removal [61]. However, its routine use in HF is not advocated. A recent IMPEDANCE-HF trial suggested that lung bioimpedance-guided treatment of chronic HF might reduce hospitalizations for HF and mortality [62]. Diuretics were less often up-titrated as well as more often down-titrated in the bioimpedance-guided group compared to the controls [62]. Intrathoracic bioimpedance is being investigated; however, current evidence does not support its routine use today [63, 64]. A wearable bioimpedance measuring vest has been proposed; however, its value is not yet known [65]. Thus, bioimpedance might improve fluid management in HF, but a standardized method must be validated before its wide implementation.

B-lines visualized by means of lung ultrasound have been shown to reflect pulmonary fluid accumulation in the outpatient setting [66]. In the emergency department, lung ultrasound may improve accuracy of acute decompensated HF (ADHF) diagnosis [67]. However, lung ultrasound does not

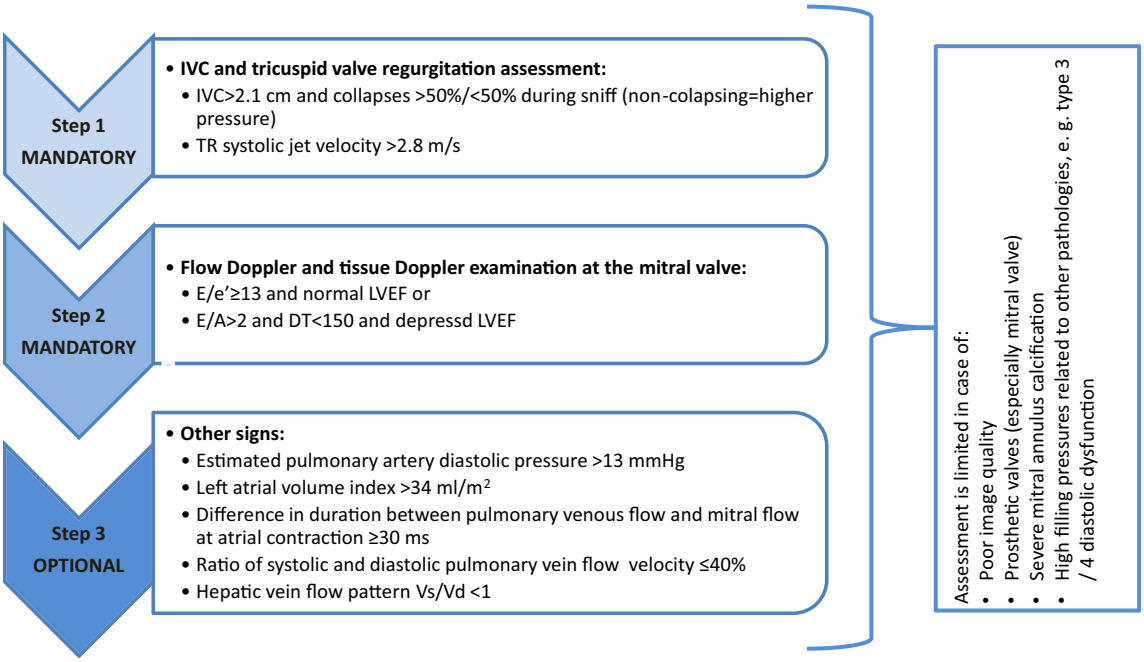

Fig. 2 Three-step echocardiographic fluid status assessment algorithm. Every examination should include Step 1 and Step 2; Step 3 is required if fluid status still remains uncertain. IVC, inferior vena cava; LVEF, left ventricular ejection fraction

seem to be superior to echocardiography in chronic HF, and its routine use remains to be better defined, since B-lines are a later finding of pulmonary water accumulation [68].

In a large randomized trial, wireless pulmonary artery hemodynamic monitoring (PAHM) in HF patients with New York Heart Association class III has been shown to reduce HF-related hospitalizations at 6 months by 28% and by 37% at 15 months [69]. Changes in medication, particularly diuretic dose adjustments, were more often initiated in the treatment group [69, 70]. The treatment group had a significant uptitration of loop diuretic total daily dose [71]. Cost-effectiveness of PAHM is supported by economic modeling [72]. Still, PAHM is not yet a part of standard care in many countries, mainly due to its invasive nature requiring a device implantation and its costs.

Blood biomarkers

Although a single sensitive and specific biomarker of congestion does not exist, blood analysis may serve as a valuable tool for congestion management. This may include changes in hematocrit, hemoglobin, albumin, and total protein over time, reflecting the shift from hemoconcentration to hemodilution and vice versa [73]. Hemoconcentration is a reasonable means to guide diuretic therapy in both acute and chronic HF [73, 74], but accuracy and clinical value needs to be shown.

The rise in creatinine during diuretic administration is a red flag, since rising creatinine can reflect hypovolemia, effective decongestion, but also (remaining) congestion. Thus, a significant change in creatinine requires careful, possibly instrumental fluid status assessment and potentially indicates management modification.

Liver damage-related markers should be tested once a year as persistent congestion can potentially lead to liver injury [75]. If they are elevated, careful fluid status assessment is required and effects of decongestion on liver markers should be evaluated. Elevated cholestasis markers have been associated with systemic congestion, whereas the increase in aminotransferases is more common in hypoperfusion-related liver damage [76]. The rise in bilirubin but not in aminotransferases in HF decompensation was also associated with increased mortality [77].

Natriuretic peptides play an important role in the diagnosis of HF [4, 5] and have been investigated to guide chronic HF therapy [78]. Although they are released from the myocardium in response to stretching [79], they poorly correlate with congestion [80–82]. In addition, NT-proBNP-guided therapy studies mainly focusing on intensifying of diuretic therapy did not improve outcome, whereas intensifying of other HF drugs did. Therefore, the use of natriuretic peptides to monitor congestion is limited despite their excellent prognostic value and being biomarkers of cardiac dysfunction.

Soluble CD146, a novel congestion biomarker, is released from the peripheral vasculature in response to venous stretch [83] and has been shown to reflect congestion [80]; however, its value in acute and chronic HF setting is yet uncertain. Further studies of its potential role in daily clinical practice are needed.

Successful outpatient decongestion approach

Step 1: identification of congestion

The responsibility for regular screening should be organized regionally or nationally and can be done by a trained HF nurse, general practitioner, cardiologists, or a HF specialist. However, an active role of general practitioners and HF nurses is encouraged, following the recommendations of multidisciplinary care [4]. Screening of congestion should be done regularly. The intervals may vary depending on the severity of HF. More importantly, if patients develop symptoms, clinical evaluation is required and laboratory testing should be done in every patient, including at least creatinine/glomerular filtration rate (GFR), blood urea nitrogen, sodium, and potassium (if stable every 6 months). Liver function testing should be done every 12 months for all stable HF patients and if clinical congestion is present. An increase in liver enzymes by more than two times the upper normal reference level or total bilirubin concentration higher than 50 μmol/L requires—if congestion is not obvious—instrumental fluid status assessment and abdominal ultrasound if no congestion is present or values do not normalize after decongestion.

There is no uniform definition for severity of congestion, but severe congestion may be equivalent to ADHF. The difference between mild and moderate congestion is more difficult to establish. A NYHA class II or III patient with obvious signs and symptoms of congestion but without acute deterioration fits the picture of moderate congestion. Mild congestion might not be clinically noted and is detected by means of blood analysis and (or) instrumental investigation. Some severely congested (ADHF) patients can be managed in the outpatient setting if done by sufficiently experienced care providers [84, 85], but hospital admission is often required. Importantly, rapid treatment of ADHF is recommended as it may improve outcome [4, 5]. Mild to moderate congestion can usually be treated in an outpatient setting.

Step 2: treatment of congestion

HF patients with congestion are normally treated with loop diuretics as thiazides are usually not sufficient. Two main factors are important to consider before choosing the dose. Firstly, the decision depends on if the patient is already taking loop diuretics or not and at which dose. Secondly, kidney function is important as it influences the response to loop diuretic therapy (Fig. 3).

In patients with chronic kidney disease (CKD), higher doses are usually needed to achieve the same diuresis as in non-CKD patients [86]. If there is no urgent clinical need, it is still reasonable to initiate a low loop diuretic dose (Table 3) regardless of renal function, because initial response to a loop diuretic is difficult to predict. If the patient already takes a loop diuretic, the baseline dose serves as a starting point. Loop diuretic initiation and modification strategy is shown in Fig. 3.

Torasemide and bumetanide have a roughly consistent oral bioavailability [29], whereas furosemide represents a drug with a highly variable oral bioavailability (from 10 to 90 in percentage [29]; thus, precise equipotent oral doses between furosemide and other loop diuretics are difficult to establish. The authors suggest using equipotent doses of loop diuretics shown in Table 3. Loop diuretics with better bioavailability (bumetanide, torasemide) and longer half-lives (torasemide) are recommended as first-line loop diuretics. If a short-acting loop diuretic (furosemide, bumetanide) is chosen, it should be administered twice or three times a day.

Step 3: reassessment

Patients with mild congestion and normal renal function should be reassessed in 2 weeks after the initial visit. However, CKD patients are vulnerable; they might not respond to the initial therapy and develop ADHF; they are susceptible for acute kidney injury (AKI) [87] that requires timely intervention; they often have more comorbidities that might worsen. Therefore, all patients with a GFR < 60 ml/min should receive an intensified follow-up strategy with a follow-up visit in 1 week. The same is true regarding patients with moderate congestion, since the risk of acute decompensation is higher in such setting. The follow-up interval needs to be adjusted to the individual need of patients, but the timing has not been investigated so far and remains at the discretion of the treating physician.

Reassessment protocol covers the same laboratory work-up as in the identification step. Instrumental assessment needs to be done if the clinical situation is not clear. In particular, remaining (mild) congestion may not be detected clinically and may be accompanied with a worse outcome.

There are a few common scenarios that can be identified at the reassessment step:

1. WRF (i.e., deterioration of GFR ≥ 25%) is most likely related to congestion-related cardiorenal syndrome or iatrogenic hypovolemia. It is noted that WRF translates into poor outcome if it develops in the presence of persistent congestion [88], whereas in case of successful decongestion its prognostic implication is limited [73]. Therefore, further decisions depend on the results of congestion status determined by means of a clinical, laboratorical, and if uncertain, instrumental investigation. If congestion is no longer present, loop diuretic doses should be reduced by 50%, whereas persistent congestion should be treated with intensified diuretic therapy despite WRF, possibly in the clinical setting. Other drugs potentially leading to kidney injury (e.g., non-steroidal drugs, some antibiotics)

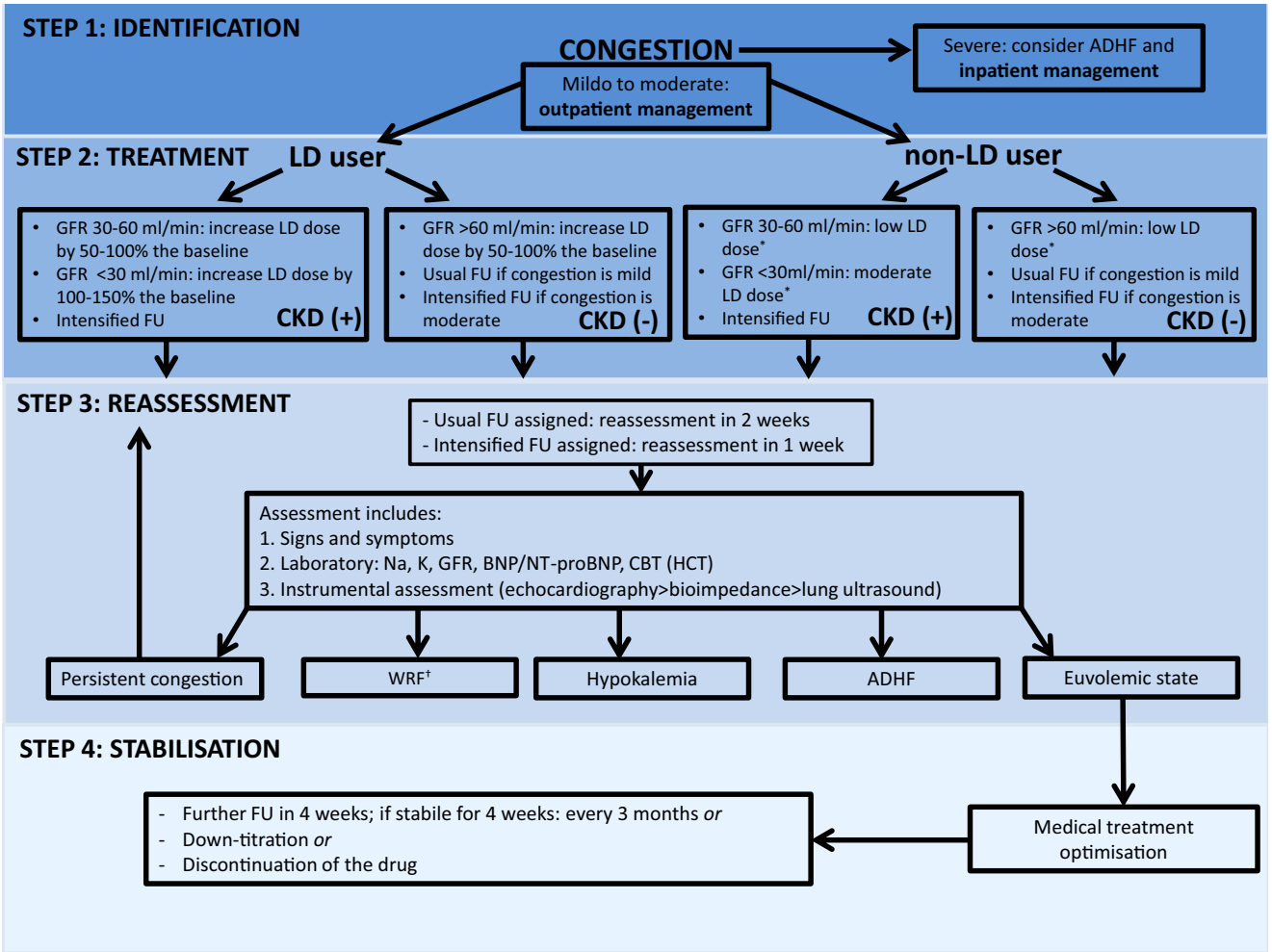

Fig. 3 Outpatient congestion management algorithm in chronic heart failure. The 4-step congestion management algorithm should be initiated as soon as congestion is identified. ADHF, acute decompensated heart failure; BNP, B-type natriuretic peptide; CBT, complete blood count; CKD, chronic kidney disease; FU, follow-up; GFR, glomerular filtration rate; HCT, hematocrit; LD, loop diuretic; NT-proBNP, N-terminal pro B-type natriuretic peptide; WRF, worsening renal function. (See * - Table 3; † - deterioration of GFR ≥ 25%)

should be discontinued or reconsidered. Patients with AKI (increase in serum creatinine by ≥ 26.5 μmol/L/≥ 0.3 mg/dL or decrease in GFR ≥ 25% within 48 h, or urine volume < 0.5 mL/kg/h for 6 h [87]) must be admitted to hospital for adequate monitoring and treatment.

2. Persistent congestion is common, often because a loop diuretic dose at *Step 2* was too low to control fluid overload. Unless treated with very high loop diuretic dose, the dose should be doubled and the patient reassessed at a usual or intensified interval. If dose is very high (Table 3) or escalation is not effective, diuretic resistance or pseudoresistance may be present (Table 4, see chapter Diuretic resistance). If patients deteriorate and/or present with ADHF, admission to hospital should be considered.

Table 3 Oral loop diuretic dosage in chronic heart failure

	Low dose	Moderate dose	High dose	Very high dose	Max dose*
Furosemide	≤ 40mg/day	> 40–100 mg/day	> 100–200 mg/day	> 200 mg/day	600-1500 mg/day
Torasemide	≤ 10 mg/day	> 10-25 mg/day	> 25–50 mg/day	> 50 mg/day	200 mg/day
Bumetanide	≤ 1 mg/day	> 1–2.5 mg/day	> 2.5–5 mg/day	> 5 mg/day	10 mg/day

*Maximal doses of loop diuretics are not well studies; thus, higher doses might be used in different centers worldwide

LD loop diuretic

3. Hypokalemia is a known and potentially life-threatening side effect of loop diuretics. Even potassium levels < 4.1 mmol/L have been associated with increased risk of death in chronic HF [89]. In case of potassium levels < 4.1 mmol/L, potassium supplementation or mineralocorticoid-receptor antagonists (MRA), unless contraindicated, should be given. If a single-drug treatment approach is not effective, the combination of potassium supplementation and MRA can be considered, but requires an intensified follow-up regimen or hospitalisation.
4. If the initial treatment was effective, the patient might no longer be congested. In this case, the stabilization step should take place (see Step 4: stabilization).

Step 4: stabilization

Some euvolemic patients may benefit from loop diuretic dose reduction or even discontinuation of the drug, particularly after establishment of optimal HF therapy (drugs and devices). Such approach may be considered in patients with good functional capacity and no history of unsuccessful down-titration, after medical treatment with evidence-based drugs was established and the probability of relapse was considered as low. Careful monitoring is important and some patients need maintaining loop diuretic dose as otherwise congestion reoccurs. This recommendation applies particularly to patients with previous relapse after loop diuretic dose down-titration or those who have experienced frequent decompensations. However, optimal regiment in individual patients has not been sufficiently studied. The CHAMPION trial suggests that optimal euvolemic fluid status with the according dose of diuretics encompasses the best outcome [69–71]. In general, the aim should be to use the lowest loop diuretic dose that is sufficient to keep the patient euvolemic, but this needs to be carefully evaluated. Partial decongestion and some degree of residual volume overload are potentially harmful [90].

Medical treatment with evidence-based HF medication should remain unchanged during recompensation whenever possible. After recompensation, HF treatment must be revised and optimized if needed. It is important to continuously re-evaluate compliance because congestion in HF is closely related to non-compliance (medication, excess water, and salt intake). Compliance problems should be managed by educational programs mainly led by HF nursing team.

Diuretic resistance

The lack of decongestion despite adequate/high (very high) dose of loop diuretic (Table 3) is called diuretic resistance. Although diuretic resistance is noted in up to one third of HF patients [91], there is no uniform definition [92]. It is related to increased morbidity and mortality [92, 93] and can be attributed to both renal and non-renal causes [29, 92–94]. There is a number of reasons that resemble diuretic resistance (e.g., non-compliant patient). These reasons must be clearly identified, because true resistance requires different management approach [92, 95]. Possible causes of diuretic resistance/pseudoresistance are listed in Table 4. Obviously, identified causes should be treated specifically if possible.

Loop diuretic agent, dose and route of administration as well as timing play important roles in the diuretic efficacy. Switching furosemide to another loop diuretic with stable pharmacokinetic profile (torasemide, bumetanide) can be sufficient to increase efficacy. Also, timing should be adjusted to

Table 4 Possible causes of diuretic resistance and pseudoresistance

Usage-/compliance- or diagnosis-related causes
- Unrestricted water intake
- Not taking the drug
- Excessive sodium intake
- No monitoring of body weight
- Inadequate diuretic therapy (too low or too infrequent)
- Incorrect diagnosis (e.g., lymphatic edema)

Renal causes
- Tubular uptake of diuretic impaired by uremic toxins
- Decreased kidney blood flow
- Decreased functional kidney mass
- Low GFR
- RAAS activation-related non-responding
- Nephron adaptation
- Proteinuria

Cardiovascular causes
- Severe HF
- Arrhythmias
- Hypertension and hypotension
- Ischemia
- Valvular disease
- Endocarditis

Pharmacological causes
- NSAIDs use
- Negative inotropes
- Probenecid
- Lithium
- Some antihypertensive drugs

Acute and chronic comorbidities
- Pneumonia
- Pulmonary embolism
- COPD
- Thyroid disease
- Anemia
- Surgery-related stress
- Electrolyte imbalance
- Gut edema impaired absorption
- Intestinal hypoperfusion
- Hypoproteinemia
- SIADH

COPD chronic obstructive pulmonary disease, *GFR* glomerular filtration rate, *HF* congestive heart failure, *NSAIDs* non-steroid anti-inflammatory drugs, *RAAS* renin-angiotensin-aldosterone system, *SIADH* syndrome of inappropriate antidiuretic hormone secretion

Table 5 Possible designs of diuretic management trials

1. A large, randomized, prospective, single-blind, controlled clinical trial where clinically stable chronic HF patients are randomized to one of three arms:
   1.1. No deliberate attempt to minimalize the dose or discontinue the drug
   1.2. Attempt to minimalize diuretic dose or discontinue the drug as soon as clinically determined euvolemia is achieved (clinically guided approach)
   1.3. Attempt to reduce/tailor diuretic dose or discontinue the drug according to the evidence of fluid retention determined by means of instrumental monitoring (e.g., echocardiography/bioimpedance-guided approach)
2. A large, randomized, prospective, double-blind, placebo-controlled trial where euvolemic HF patients are randomly assigned to either receive:
   2.1. The same diuretic dose
   2.2. The dose reduced by 50% (or discontinued if the dose of loop diuretic administrated was low)

HF heart failure

the half-life of the drugs; thus, two or even three times daily administration is usually more effective (applies particularly to furosemide and bumetanide), because a rebound effect may be seen during the loop diuretic-free period [86, 93].

Chronic administration of loop diuretics results in several functional and structural changes in the kidney leading to so-called "braking phenomenon". This adaptation contributes to the diminished effect of loop diuretics. As sodium reabsorption is blocked in the ascending loop of Henle, more sodium ions reach distal convoluted tubule. This effect induces hypertrophy and hyperplasia of distal tubular cells and increases their sodium reabsorption capacity [86]. Therefore, dual [94] or even triple [92] nephron blockage with a loop diuretic and thiazide/thiazide-like diuretic and (or) MRA may overcome diuretic resistance, as these drugs block sodium reabsorption in the distal convoluted tubule. However, such treatment should be administrated with caution because of potential side effects, such as hypokalemia, hypomagnesemia, hypovolemia, and renal dysfunction [92]. Some authors describe possible benefits of acetazolamide [93, 96] or mannitol [93] in the treatment of diuretic resistance, but further research is required before this can be recommended.

If the abovementioned means are ineffective to overcome diuretic resistance, congestion is likely to lead to ADHF. ADHF and diuretic resistance represent a challenging clinical scenario [29]. Treatment with vasopressin receptor antagonists [92], hypertonic salt solution co-administrated with diuretics [29, 92, 97], ultrafiltration [98, 99], and inotropic support [100] are all being investigated. Recently, published results of a small randomized study suggest that a novel subcutaneously administered furosemide formulation is as effective as intravenous form in decompensated HF; thus, this possibility might open new cost-effective outpatient decongestion options in the nearest future [101]. ADHF is not the scope of this review; therefore, the abovementioned modalities are not further discussed.

Limitations

Many of the above outlined recommendations and the four-step congestion management algorithm (Fig. 3) represent an authors' opinion-based consensus, since evidence is lacking. On the other hand, the lack of evidence-based guidelines makes this decision support tool valuable, given the uncertainties about loop diuretic dosage in chronic HF [8–18]. The aspects suggested in this document need to be prospectively studied in appropriate clinical trials.

Conclusion

High doses of loop diuretics identify HF patients at increased risk; however, it remains unclear if this is due to more advanced disease severity or a direct negative effect of loop diuretics. The importance of extensive evaluation of fluid retention has not yet been properly investigated, but indirect evidence suggests that decongestion using diuretic therapy might improve outcome. Which patients benefit from diuretics and which experience potential harm remains uncertain, but it is likely that this is not uniform across all HF patients. Large, randomized, prospective clinical trials of chronic HF patients are urgently needed testing different approaches for the clinical use of diuretics and means of fluid status assessment (Table 5). A small randomized double-blind trial evaluating the safety and tolerability of furosemide withdrawal in stabile chronic HF patients is currently ongoing [102]. Until such data is available, careful screening, including instrumental monitoring for congestion and treating it whenever present with the minimum effective diuretic dose may be the best approach.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. DeVore Adam D, Vic H, Mentz RJ et al (2015) Loop diuretic dose adjustments after a hospitalization for heart failure: insights from ASCEND-HF. Eur J Heart Fail 17:340–346. https://doi.org/10.1002/ejhf.235
2. Pfisterer M, Buser P, Rickli H, Gutmann M, Erne P, Rickenbacher P, Vuillomenet A, Jeker U, Dubach P, Beer H, Yoon SI, Suter T, Osterhues HH, Schieber MM, Hilti P, Schindler R, Brunner-la Rocca HP, TIME-CHF Investigators (2009) BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive

Heart Failure (TIME-CHF) randomized trial. JAMA 301:383–392. https://doi.org/10.1001/jama.2009.2
3. Rodriguez-Cillero C, Menu D, d'Athis P, et al (2017) Potentially inappropriate use of furosemide in a very elderly population: an observational study. Int J Clin Pract 71. doi: https://doi.org/10.1111/ijcp.12975
4. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group (2016) 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 Heart J 37:2129–2200. https://doi.org/10.1093/eurheartj/ehw128
5. Yancy CW, Jessup M, Bozkurt B et al (2013) 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 128: e240–e327. https://doi.org/10.1161/CIR.0b013e31829e8776
6. Faris RF, Flather M, Purcell H, et al (2012) Diuretics for heart failure. Cochrane Database Syst Rev CD003838. doi: https://doi.org/10.1002/14651858.CD003838.pub3
7. Yancy CW, Jessup M, Bozkurt B et al (2017) 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. https://doi.org/10.1161/CIR.0000000000000509
8. Martens P, Verbrugge FH, Nijst P, Dupont M, Mullens W (2017) 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 120:267–273. https://doi.org/10.1016/j.amjcard.2017.04.021
9. Eshaghian S, Horwich TB, Fonarow GC (2006) Relation of loop diuretic dose to mortality in advanced heart failure. Am J Cardiol 97:1759–1764. https://doi.org/10.1016/j.amjcard.2005.12.072
10. Abdel-Qadir HM, Tu JV, Yun L et al (2010) Diuretic dose and long-term outcomes in elderly patients with heart failure after hospitalization. Am Heart J 160:264–271.e1. https://doi.org/10.1016/j.ahj.2010.05.032
11. Martins J, Lourenço P, Araújo JP, Mascarenhas J, Lopes R, Azevedo A, Bettencourt P (2011) Prognostic implications of diuretic dose in chronic heart failure. J Cardiovasc Pharmacol Ther 16:185–191. https://doi.org/10.1177/1074248410388807
12. Dini FL, Guglin M, Simioniuc A, Donati F, Fontanive P, Pieroni A, Orsini E, Caravelli P, Marzilli M (2012) Association of furosemide dose with clinical status, left ventricular dysfunction, natriuretic peptides, and outcome in clinically stable patients with chronic systolic heart failure. Congest Heart Fail 18:98–106. https://doi.org/10.1111/j.1751-7133.2011.00252.x
13. Neuberg GW, Miller AB, O'Connor CM et al (2002) Diuretic resistance predicts mortality in patients with advanced heart failure. Am Heart J 144:31–38
14. Damman K, Kjekshus J, Wikstrand J, Cleland JGF, Komajda M, Wedel H, Waagstein F, McMurray JJV (2016) Loop diuretics, renal function and clinical outcome in patients with heart failure and reduced ejection fraction. Eur J Heart Fail 18:328–336. https://doi.org/10.1002/ejhf.462
15. Ahmed A, Young JB, Love TE, Levesque R, Pitt B (2008) A propensity-matched study of the effects of chronic diuretic therapy on mortality and hospitalization in older adults with heart failure. Int J Cardiol 125:246–253. https://doi.org/10.1016/j.ijcard.2007.05.032
16. Ahmed A, Husain A, Love TE, Gambassi G, Dell'Italia LJ, Francis GS, Gheorghiade M, Allman RM, Meleth S, Bourge RC (2006) Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods. Eur Heart J 27:1431–1439. https://doi.org/10.1093/eurheartj/ehi890
17. Dini FL, Ghio S, Klersy C, Rossi A, Simioniuc A, Scelsi L, Genta FT, Cicoira M, Tavazzi L, Temporelli PL (2013) Effects on survival of loop diuretic dosing in ambulatory patients with chronic heart failure using a propensity score analysis. Int J Clin Pract 67: 656–664. https://doi.org/10.1111/ijcp.12144
18. Hamaguchi S, Kinugawa S, Tsuchihashi-Makaya M et al (2012) Loop diuretic use at discharge is associated with adverse outcomes in hospitalized patients with heart failure: a report from the Japanese cardiac registry of heart failure in cardiology (JCARE-CARD). Circ J 76:1920–1927
19. Schartum-Hansen H, Løland KH, Svingen GFT, et al (2015) Use of loop diuretics is associated with increased mortality in patients with suspected coronary artery disease, but without systolic heart failure or renal impairment: an observational study using propensity score matching. PLoS ONE 10. doi: https://doi.org/10.1371/journal.pone.0124611
20. Hamaguchi S, Kinugawa S, Goto D et al (2011) Predictors of long-term adverse outcomes in elderly patients over 80 years hospitalized with heart failure. - A report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). Circ J 75:2403–2410
21. Andersson C, Norgaard ML, Hansen PR, Fosbøl EL, Schmiegelow M, Weeke P, Olesen JB, Raunsø J, Jørgensen CH, Vaag A, Køber L, Torp-Pedersen C, Gislason GH (2010) Heart failure severity, as determined by loop diuretic dosages, predicts the risk of developing diabetes after myocardial infarction: a nationwide cohort study. Eur J Heart Fail 12:1333–1338. https://doi.org/10.1093/eurjhf/hfq160
22. Nguyen T-L, Collins GS, Spence J, Daurès JP, Devereaux PJ, Landais P, le Manach Y (2017) Double-adjustment in propensity score matching analysis: choosing a threshold for considering residual imbalance. BMC Med Res Methodol 17:78. https://doi.org/10.1186/s12874-017-0338-0
23. Austin PC (2007) Propensity-score matching in the cardiovascular surgery literature from 2004 to 2006: a systematic review and suggestions for improvement. J Thorac Cardiovasc Surg 134: 1128–1135.e3. https://doi.org/10.1016/j.jtcvs.2007.07.021
24. Ali MS, Groenwold RHH, Belitser SV, Pestman WR, Hoes AW, Roes KCB, Boer A, Klungel OH (2015) Reporting of covariate selection and balance assessment in propensity score analysis is suboptimal: a systematic review. J Clin Epidemiol 68:122–131. https://doi.org/10.1016/j.jclinepi.2014.08.011
25. King G, Nielsen R (2016) Why propensity scores should not be used for matching. Gary King Website. https://gking.harvard.edu/files/gking/files/psnot.pdf. Accessed 29 Aug 2018
26. Weber KT (2004) Furosemide in the long-term management of heart failure: the good, the bad, and the uncertain **editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACCor the American College of Cardiology. J Am Coll Cardiol 44:1308–1310. https://doi.org/10.1016/j.jacc.2004.06.046
27. Huang X, Dorhout Mees E, Vos P, Hamza S, Braam B (2016) Everything we always wanted to know about furosemide but were afraid to ask. Am J Physiol Ren Physiol 310:F958–F971. https://doi.org/10.1152/ajprenal.00476.2015
28. van Kraaij DJW, Jansen RWMM, Sweep FCGJ, Hoefnagels WHL (2003) Neurohormonal effects of furosemide withdrawal in elderly heart failure patients with normal systolic function. Eur J Heart Fail 5:47–53

29. Ellison DH, Felker GM (2017) Diuretic treatment in heart failure. N Engl J Med 377:1964–1975. https://doi.org/10.1056/NEJMra1703100
30. Cooper HA, Dries DL, Davis CE, Shen YL, Domanski MJ (1999) Diuretics and risk of arrhythmic death in patients with left ventricular dysfunction. Circulation 100:1311–1315. https://doi.org/10.1161/01.CIR.100.12.1311
31. Harjola V-P, 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, Schäfer A, Seferovic PM, Skouri H, Yilmaz MB, Mebazaa A (2017) 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 19:821–836. https://doi.org/10.1002/ejhf.872
32. Katta N, Balla S, Alpert MA (2016) Does long-term furosemide therapy cause thiamine deficiency in patients with heart failure? A focused review. Am J Med 129:753.e7–753.e11. https://doi.org/10.1016/j.amjmed.2016.01.037
33. Zenuk C, Healey J, Donnelly J et al (2003) Thiamine deficiency in congestive heart failure patients receiving long term furosemide therapy. Can J Clin Pharmacol 10:184–188
34. House AA, Haapio M, Lassus J et al (2010) Therapeutic strategies for heart failure in cardiorenal syndromes. Am J Kidney Dis 56:759–773. https://doi.org/10.1053/j.ajkd.2010.04.012
35. Matsuo Y, Kasama S, Toyama T, Funada R, Takama N, Koitabashi N, Ichikawa S, Suzuki Y, Matsumoto N, Sato Y, Kurabayashi M (2016) Comparative effects of long-acting and short-acting loop diuretics on cardiac sympathetic nerve activity in patients with chronic heart failure. Open Heart 3:e000276. https://doi.org/10.1136/openhrt-2015-000276
36. Kasama S, Toyama T, Hatori T, Sumino H, Kumakura H, Takayama Y, Ichikawa S, Suzuki T, Kurabayashi M (2006) Effects of torasemide on cardiac sympathetic nerve activity and left ventricular remodelling in patients with congestive heart failure. Heart 92:1434–1440. https://doi.org/10.1136/hrt.2005.079764
37. Kaye DM, Jennings GL, Dart AM, Esler MD (1998) Differential effect of acute baroreceptor unloading on cardiac and systemic sympathetic tone in congestive heart failure. J Am Coll Cardiol 31:583–587
38. Coats AJ (2001) A sympathetic heart and the art of dying. Eur Heart J 22:1069–1071. https://doi.org/10.1053/euhj.2000.2763
39. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB, Tang WHW (2009) Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol 53:589–596. https://doi.org/10.1016/j.jacc.2008.05.068
40. Mullens W, Abrahams Z, Skouri HN, Francis GS, Taylor DO, Starling RC, Paganini E, Tang WHW (2008) Elevated intra-abdominal pressure in acute decompensated heart failure: a potential contributor to worsening renal function? J Am Coll Cardiol 51:300–306. https://doi.org/10.1016/j.jacc.2007.09.043
41. Salah K, Kok WE, Eurlings LW, Bettencourt P, Pimenta JM, Metra M, Verdiani V, Tijssen JG, Pinto YM (2015) Competing risk of cardiac status and renal function during hospitalization for acute decompensated heart failure. JACC Heart Fail 3:751–761. https://doi.org/10.1016/j.jchf.2015.05.009
42. Tanaka H, Watanabe K, Harima M et al (2009) Effects of various diuretics on cardiac function in rats with heart failure. Yakugaku Zasshi 129:871–879
43. Wargo KA, Banta WM (2009) A comprehensive review of the loop diuretics: should furosemide be first line? Ann Pharmacother 43:1836–1847. https://doi.org/10.1345/aph.1M177
44. Murray MD, Deer MM, Ferguson JA, Dexter PR, Bennett SJ, Perkins SM, Smith FE, Lane KA, Adams LD, Tierney WM, Brater DC (2001) Open-label randomized trial of torsemide compared with furosemide therapy for patients with heart failure. Am J Med 111:513–520
45. Müller K, Gamba G, Jaquet F, Hess B (2003) Torasemide vs. furosemide in primary care patients with chronic heart failure NYHA II to IV–efficacy and quality of life. Eur J Heart Fail 5:793–801
46. Cosín J, Díez J, TORIC investigators (2002) Torasemide in chronic heart failure: results of the TORIC study. Eur J Heart Fail 4:507–513
47. Luo J, Chen X, Luo C, et al (2017) Hydrochlorothiazide modulates ischemic heart failure-induced cardiac remodeling via inhibiting angiotensin II type 1 receptor pathway in rats. Cardiovasc Ther 35. doi: https://doi.org/10.1111/1755-5922.12246
48. McCurley JM, Hanlon SU, Wei S et al (2004) Furosemide and the progression of left ventricular dysfunction in experimental heart failure. J Am Coll Cardiol 44:1301–1307. https://doi.org/10.1016/j.jacc.2004.04.059
49. Rokutan H, Suckow C, von Haehling S, Strassburg S, Bockmeyer B, Doehner W, Waller C, Bauersachs J, von Websky K, Hocher B, Anker SD, Springer J (2012) Furosemide induces mortality in a rat model of chronic heart failure. Int J Cardiol 160:20–25. https://doi.org/10.1016/j.ijcard.2011.03.005
50. Seeland U, Kouchi I, Zolk O, Itter G, Linz W, Böhm M (2002) Effect of ramipril and furosemide treatment on interstitial remodeling in post-infarction heart failure rat hearts. J Mol Cell Cardiol 34:151–163. https://doi.org/10.1006/jmcc.2001.1497
51. Seeland U, Kouchi I, Zolk O, Jockenhövel F, Itter G, Linz W, Böhm M (2003) Effects of diuretic treatment on cardiac and circulating RAS in chronic heart failure post-myocardial infarction in rats. Eur J Heart Fail 5:241–246
52. Girerd N, Seronde M-F, Coiro S, Chouihed T, Bilbault P, Braun F, Kenizou D, Maillier B, Nazeyrollas P, Roul G, Fillieux L, Abraham WT, Januzzi J Jr, Sebbag L, Zannad F, Mebazaa A, Rossignol P, INI-CRCT, Great Network, and the EF-HF Group (2017) Integrative assessment of congestion in heart failure throughout the patient journey. JACC Heart Fail 6:273–285. https://doi.org/10.1016/j.jchf.2017.09.023
53. Miller WL (2016) Fluid volume overload and congestion in heart failure: time to reconsider pathophysiology and how volume is assessed. Circ Heart Fail 9:e002922. https://doi.org/10.1161/CIRCHEARTFAILURE.115.002922
54. Piano MR, Prasun MA, Stamos T, Groo V (2011) Flexible diuretic titration in chronic heart failure: where is the evidence? J Card Fail 17:944–954. https://doi.org/10.1016/j.cardfail.2011.10.001
55. Chaudhry SI, Mattera JA, Curtis JP, Spertus JA, Herrin J, Lin Z, Phillips CO, Hodshon BV, Cooper LS, Krumholz HM (2010) Telemonitoring in patients with heart failure. N Engl J Med 363:2301–2309. https://doi.org/10.1056/NEJMoa1010029
56. Fortes MB, Owen JA, Raymond-Barker P, Bishop C, Elghenzai S, Oliver SJ, Walsh NP (2015) Is this elderly patient dehydrated? Diagnostic accuracy of hydration assessment using physical signs, urine, and saliva markers. J Am Med Dir Assoc 16:221–228. https://doi.org/10.1016/j.jamda.2014.09.012
57. Ritzema JL, Richards AM, Crozier IG, Frampton CF, Melton IC, Doughty RN, Stewart JT, Eigler N, Whiting J, Abraham WT, Troughton RW (2011) Serial Doppler echocardiography and tissue Doppler imaging in the detection of elevated directly measured left atrial pressure in ambulant subjects with chronic heart failure. J

Am Coll Cardiol Img 4:927–934. https://doi.org/10.1016/j.jcmg.2011.07.004
58. Porter TR, Shillcutt SK, Adams MS, Desjardins G, Glas KE, Olson JJ, Troughton RW (2015) Guidelines for the use of echocardiography as a monitor for therapeutic intervention in adults: a report from the American Society of Echocardiography. J Am Soc Echocardiogr 28:40–56. https://doi.org/10.1016/j.echo.2014.09.009
59. Rohde LE, Palombini DV, Polanczyk CA, Goldraich LA, Clausell N (2007) A hemodynamically oriented echocardiography-based strategy in the treatment of congestive heart failure. J Card Fail 13:618–625. https://doi.org/10.1016/j.cardfail.2007.05.003
60. Simioniuc A, Carluccio E, Ghio S, Rossi A, Biagioli P, Reboldi G, Galeotti GG, Lu F, Zara C, Whalley G, Temporelli PL, Dini FL, investigators of the Network Labs Ultrasound (NEBULA) in Heart Failure Study Group (2016) Echo and natriuretic peptide guided therapy improves outcome and reduces worsening renal function in systolic heart failure: an observational study of 1137 outpatients. Int J Cardiol 224:416–423. https://doi.org/10.1016/j.ijcard.2016.09.034
61. Davies SJ, Davenport A (2014) The role of bioimpedance and biomarkers in helping to aid clinical decision-making of volume assessments in dialysis patients. Kidney Int 86:489–496. https://doi.org/10.1038/ki.2014.207
62. Shochat MK, Shotan A, Blondheim DS, Kazatsker M, Dahan I, Asif A, Rozenman Y, Kleiner I, Weinstein JM, Frimerman A, Vasilenko L, Meisel SR (2016) Non-invasive lung IMPEDANCE-guided preemptive treatment in chronic heart failure patients: a randomized controlled trial (IMPEDANCE-HF trial). J Card Fail 22:713–722. https://doi.org/10.1016/j.cardfail.2016.03.015
63. Conraads VM, Tavazzi L, Santini M, Oliva F, Gerritse B, Yu CM, Cowie MR (2011) Sensitivity and positive predictive value of implantable intrathoracic impedance monitoring as a predictor of heart failure hospitalizations: the SENSE-HF trial. Eur Heart J 32:2266–2273. https://doi.org/10.1093/eurheartj/ehr050
64. Böhm M, Drexler H, Oswald H, Rybak K, Bosch R, Butter C, Klein G, Gerritse B, Monteiro J, Israel C, Bimmel D, Käab S, Huegl B, Brachmann J, OptiLink HF Study Investigators (2016) Fluid status telemedicine alerts for heart failure: a randomized controlled trial. Eur Heart J 37:3154–3163. https://doi.org/10.1093/eurheartj/ehw099
65. Gastelurrutia P, Cuba-Gyllensten I, Lupon J, Zamora E, Llibre C, Caballero Á, Riistama J, Aarts R, Bayes-Genis A (2016) Wearable vest for pulmonary congestion tracking and prognosis in heart failure: a pilot study. Int J Cardiol 215:77–79. https://doi.org/10.1016/j.ijcard.2016.04.024
66. Miglioranza MH, Gargani L, Sant'Anna RT et al (2013) Lung ultrasound for the evaluation of pulmonary congestion in outpatients: a comparison with clinical assessment, natriuretic peptides, and echocardiography. J Am Coll Cardiol Img 6:1141–1151. https://doi.org/10.1016/j.jcmg.2013.08.004
67. Pivetta E, Goffi A, Lupia E, Tizzani M, Porrino G, Ferreri E, Volpicelli G, Balzaretti P, Banderali A, Iacobucci A, Locatelli S, Casoli G, Stone MB, Maule MM, Baldi I, Merletti F, Cibinel GA, Baron P, Battista S, Buonafede G, Busso V, Conterno A, del Rizzo P, Ferrera P, Pecetto PF, Moiraghi C, Morello F, Steri F, Ciccone G, Calasso C, Caserta MA, Civita M, Condo' C, D'Alessandro V, del Colle S, Ferrero S, Griot G, Laurita E, Lazzero A, Lo Curto F, Michelazzo M, Nicosia V, Palmari N, Ricchiardi A, Rolfo A, Rostagno R, Bar F, Boero E, Frascisco M, Micossi I, Mussa A, Stefanone V, Agricola R, Cordero G, Corradi F, Runzo C, Soragna A, Sciullo D, Vercillo D, Allione A, Artana N, Corsini F, Dutto L, Lauria G, Morgillo T, Tartaglino B, Bergandi D, Cassetta I, Masera C, Garrone M, Ghiselli G, Ausiello L, Barutta L, Bernardi E, Bono A, Forno D, Lamorte A, Lison D, Lorenzati B, Maggio E, Masi I, Maggiorotto M, Novelli G, Panero F, Perotto M, Ravazzoli M, Saglio E, Soardo F, Tizzani A, Tizzani P, Tullio M, Ulla M, Romagnoli E, SIMEU Group for Lung Ultrasound in the Emergency Department in Piedmont (2015) Lung ultrasound-implemented diagnosis of acute decompensated heart failure in the ED: a SIMEU multicenter study. Chest 148:202–210. https://doi.org/10.1378/chest.14-2608
68. Dini FL, Carluccio E, Montecucco F, et al (2017) Combining echo and natriuretic peptides to guide heart failure care in the outpatient setting: a position paper. Eur J Clin Invest 47. doi: https://doi.org/10.1111/eci.12846
69. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, Strickland W, Neelagaru S, Raval N, Krueger S, Weiner S, Shavelle D, Jeffries B, Yadav JS (2011) Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet 377:658–666. https://doi.org/10.1016/S0140-6736(11)60101-3
70. Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB (2016) Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomised trial. Lancet 387:453–461. https://doi.org/10.1016/S0140-6736(15)00723-0
71. Adamson PB, Abraham WT, Stevenson LW, et al (2016) Pulmonary artery pressure-guided heart failure management reduces 30-day readmissions. Circ Heart Fail 9. doi: https://doi.org/10.1161/CIRCHEARTFAILURE.115.002600
72. Martinson M, Bharmi R, Dalal N, Abraham WT, Adamson PB (2017) Pulmonary artery pressure-guided heart failure management: US cost-effectiveness analyses using the results of the CHAMPION clinical trial. Eur J Heart Fail 19:652–660. https://doi.org/10.1002/ejhf.642
73. Breidthardt T, Weidmann ZM, Twerenbold R, Gantenbein C, Stallone F, Rentsch K, Rubini Gimenez M, Kozhuharov N, Sabti Z, Breitenbücher D, Wildi K, Puelacher C, Honegger U, Wagener M, Schumacher C, Hillinger P, Osswald S, Mueller C (2017) Impact of haemoconcentration during acute heart failure therapy on mortality and its relationship with worsening renal function. Eur J Heart Fail 19:226–236. https://doi.org/10.1002/ejhf.667
74. Vaduganathan M, Greene SJ, Fonarow GC, Voors AA, Butler J, Gheorghiade M (2014) Hemoconcentration-guided diuresis in heart failure. Am J Med 127:1154–1159. https://doi.org/10.1016/j.amjmed.2014.06.009
75. Alvarez AM, Mukherjee D (2011) Liver abnormalities in cardiac diseases and heart failure. Int J Angiol 20:135–142. https://doi.org/10.1055/s-0031-1284434
76. Čerlinskaitė K, Javanainen T, Cinotti R, Mebazaa A, on behalf of the Global Research on Acute Conditions Team (GREAT) Network (2018) Acute heart failure management. Korean Circ J 48:463–480. https://doi.org/10.4070/kcj.2018.0125
77. Samsky MD, Dunning A, DeVore AD et al (2016) Liver function tests in patients with acute heart failure and associated outcomes: insights from ASCEND-HF. Eur J Heart Fail 18:424–432. https://doi.org/10.1002/ejhf.440
78. Troughton RW, Frampton CM, Brunner-La Rocca H-P et al (2014) Effect of B-type natriuretic peptide-guided treatment of chronic heart failure on total mortality and hospitalization: an individual patient meta-analysis. Eur Heart J 35:1559–1567. https://doi.org/10.1093/eurheartj/ehu090
79. Koratala A, Kazory A (2017) Natriuretic peptides as biomarkers for congestive states: the cardiorenal divergence. Dis Markers 2017:1454986–1454989. https://doi.org/10.1155/2017/1454986
80. Van Aelst LNL, Arrigo M, Placido R et al (2017) Acutely decompensated heart failure with preserved and reduced ejection fraction present with comparable haemodynamic congestion. Eur J Heart Fail 20:738–747. https://doi.org/10.1002/ejhf.1050

81. Kociol RD, McNulty SE, Hernandez AF et al (2013) Markers of decongestion, dyspnea relief, and clinical outcomes among patients hospitalized with acute heart failure. Circ Heart Fail 6: 240–245. https://doi.org/10.1161/CIRCHEARTFAILURE.112.969246
82. Omar HR, Guglin M (2016) A single BNP measurement in acute heart failure does not reflect the degree of congestion. J Crit Care 33:262–265. https://doi.org/10.1016/j.jcrc.2016.02.023
83. Arrigo M, Truong QA, Onat D, Szymonifka J, Gayat E, Tolppanen H, Sadoune M, Demmer RT, Wong KY, Launay JM, Samuel JL, Cohen-Solal A, Januzzi JL Jr, Singh JP, Colombo PC, Mebazaa A (2017) Soluble CD146 is a novel marker of systemic congestion in heart failure patients: an experimental mechanistic and transcardiac clinical study. Clin Chem 63:386–393. https://doi.org/10.1373/clinchem.2016.260471
84. Buckley LF, Carter DM, Matta L, Cheng JW, Stevens C, Belenkiy RM, Burpee LJ, Young MA, Weiffenbach CS, Smallwood JA, Stevenson LW, Desai AS (2016) Intravenous diuretic therapy for the management of heart failure and volume overload in a multidisciplinary outpatient unit. JACC Heart Fail 4:1–8. https://doi.org/10.1016/j.jchf.2015.06.017
85. Ryder M, Murphy NF, McCaffrey D, O'Loughlin C, Ledwidge M, McDonald K (2008) Outpatient intravenous diuretic therapy; potential for marked reduction in hospitalisations for acute decompensated heart failure. Eur J Heart Fail 10:267–272. https://doi.org/10.1016/j.ejheart.2008.01.003
86. Shah N, Madanieh R, Alkan M, Dogar MU, Kosmas CE, Vittorio TJ (2017) A perspective on diuretic resistance in chronic congestive heart failure. Ther Adv Cardiovasc Dis 11:271–278. https://doi.org/10.1177/1753944717718717
87. Khwaja A (2012) KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 120:c179–c184. https://doi.org/10.1159/000339789
88. Damman K, Testani JM (2015) The kidney in heart failure: an update. Eur Heart J 36:1437–1444. https://doi.org/10.1093/eurheartj/ehv010
89. Aldahl M, Jensen A-SC, Davidsen L, Eriksen MA, Møller Hansen S, Nielsen BJ, Krogager ML, Køber L, Torp-Pedersen C, Søgaard P (2017) Associations of serum potassium levels with mortality in chronic heart failure patients. Eur Heart J 38:2890–2896. https://doi.org/10.1093/eurheartj/ehx460
90. 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 (2012) 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 5:54–62. https://doi.org/10.1161/CIRCHEARTFAILURE.111.963413
91. Dupont M, Mullens W, Tang WHW (2011) Impact of systemic venous congestion in heart failure. Curr Heart Fail Rep 8:233–241. https://doi.org/10.1007/s11897-011-0071-7
92. Regolisti G, Antoniotti R, Pastorini G, Fani F, Fiaccadori E (2016) Management of congestion and diuretic resistance in heart failure. Nephrol Point Care 2:pocj.5000200. https://doi.org/10.5301/pocj.5000200
93. ter Maaten JM, Valente MAE, Damman K, Hillege HL, Navis G, Voors AA (2015) Diuretic response in acute heart failure-pathophysiology, evaluation, and therapy. Nat Rev Cardiol 12:184–192. https://doi.org/10.1038/nrcardio.2014.215
94. Hoorn EJ, Ellison DH (2017) Diuretic Resistance. Am J Kidney Dis 69:136–142. https://doi.org/10.1053/j.ajkd.2016.08.027
95. Bruyne LKMD (2003) Mechanisms and management of diuretic resistance in congestive heart failure. Postgrad Med J 79:268–271. https://doi.org/10.1136/pmj.79.931.268
96. Verbrugge FH, Grieten L, Mullens W (2014) New insights into combinational drug therapy to manage congestion in heart failure. Curr Heart Fail Rep 11:1–9. https://doi.org/10.1007/s11897-013-0174-4
97. Gandhi S, Mosleh W, Myers RBH (2014) Hypertonic saline with furosemide for the treatment of acute congestive heart failure: a systematic review and meta-analysis. Int J Cardiol 173:139–145. https://doi.org/10.1016/j.ijcard.2014.03.020
98. Siddiqui WJ, Kohut AR, Hasni SF, Goldman JM, Silverman B, Kelepouris E, Eisen HJ, Aggarwal S (2017) Readmission rate after ultrafiltration in acute decompensated heart failure: a systematic review and meta-analysis. Heart Fail Rev 22:685–698. https://doi.org/10.1007/s10741-017-9650-3
99. 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 (2016) Aquapheresis versus intravenous diuretics and hospitalizations for heart failure. JACC Heart Fail 4:95–105. https://doi.org/10.1016/j.jchf.2015.08.005
100. Reed BN, Devabhakthuni S (2017) Diuretic resistance in acute decompensated heart failure: a challenging clinical conundrum. Crit Care Nurs Q 40:363–373. https://doi.org/10.1097/CNQ.0000000000000173
101. Gilotra NA, Princewill O, Marino B, Okwuosa IS, Chasler J, Almansa J, Cummings A, Rhodes P, Chambers J, Cuomo K, Russell SD (2018) Efficacy of intravenous furosemide versus a novel, pH-neutral furosemide formulation administered subcutaneously in outpatients with worsening heart failure. JACC Heart Fail 6:65–70. https://doi.org/10.1016/j.jchf.2017.10.001
102. da Rosa PR, Rohde LE, Doebber M, Ribeiro ALP, Prado DP, Bertoldi EG, Figueiredo Neto JA, Kohler I, Beck-da-Silva L, Danzmann LC, Moura LZ, Rover M, Simões MV, Sant'Anna RT, Biolo A (2017) Rational and design of a randomized, double-blind, multicenter trial to evaluate the safety and tolerability of furosemide withdrawal in stable chronic outpatients with heart failure: the ReBIC-1 trial. Am Heart J 194:125–131. https://doi.org/10.1016/j.ahj.2017.08.012