

Expert Opinion

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Can we improve the treatment of congestion in heart failure?

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Introduction: Dyspnoea and peripheral oedema, caused by fluid redistribution to the lungs and/or by fluid overload, are the main causes of hospitalization in patients with heart failure and are associated with poor outcomes. Treatment of fluid overload should relieve symptoms and have a neutral or favorable effect on outcomes.

Areas covered: We first consider the results obtained with furosemide administration, which is still the mainstay of treatment of congestion in patients with heart failure. We then discuss important shortcomings of furosemide treatment, including the development of resistance and side effects (electrolyte abnormalities, neurohormonal activation, worsening renal function), as well as the relationship of furosemide – and its doses – with patient prognosis. Finally, the results obtained with potential alternatives to furosemide treatment, including different modalities of loop diuretic administration, combined diuretic therapy, dopamine, inotropic agents, ultrafiltration, natriuretic peptides, vasopressin and adenosine antagonists, are discussed.

Expert opinion: Relief of congestion is a major objective of heart failure treatment but therapy remains based on the administration of furosemide, an agent that is often not effective and is associated with poor outcomes. The results of the few controlled studies aimed at the assessment of new treatments to overcome resistance to furosemide and/or to protect the kidney from its untoward effects have been mostly neutral. Better treatment of congestion in heart failure remains a major unmet need.

Keywords: acute heart failure, congestion, diuretics

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1. Introduction

The current treatment of heart failure (HF) with antagonists of the renin–angiotensin–aldosterone (RAA) system, beta-blockers and devices, including cardiac resynchronization therapy and implantable defibrillators, has improved the prognosis for patients [1,2]. Treatment of episodes of acute decompensation may seem satisfactory as dyspnoea and other symptoms have been reported to improve in > 60 – 70% of patients within the first hours of admission [3–6]. However, this percentage may be much lower [7–11] when patients are selected more accurately by using levels of natriuretic peptides as the inclusion criterion [9,11,12]. Prognosis after a hospitalization for acute decompensation also remains poor, with mortality and hospitalization rates of 9 – 15% and 30 – 45%, respectively, in the following 6 months [4,13–19]. Thus, there is room for improvement in the treatment of episodes of fluid retention.

We discuss here the hypothesis that current treatment of fluid retention in HF, based on the administration of loop diuretics, is unsatisfactory both with respect to relief of congestion and to patients' outcomes. Potential tools – both pharmacological and not – to better treat congestion are then illustrated.

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Article highlights.

- In patients with heart failure, dyspnoea and peripheral oedema (caused by fluid redistribution to the lungs and by fluid overload) are the main causes of hospitalization and are associated with poor outcomes. Treatment of fluid overload should relieve symptoms without any negative effects on outcome.
- Furosemide remains the mainstay of treatment of congestion in patients with heart failure.
- The current treatment of congestion in the patients with heart failure is far from optimal: up to 50% of the patients hospitalized for congestion may fail to show relief of dyspnoea during the first days of hospitalization and have a high event rate (death or re-hospitalization) in the following months.
- Shortcomings of furosemide treatment include the development of resistance and side effects (electrolyte abnormalities, neurohormonal activation, worsening renal function).
- Furosemide treatment, particularly at high doses, has been associated with poor outcomes.
- Potential alternatives to furosemide include different modalities of loop diuretic administration, combined diuretic therapy, administration of dopamine, inotropic agents, natriuretic peptides, vasopressin antagonists, adenosine antagonists, and ultrafiltration. Results with these treatments have been insufficient (dopamine, ultrafiltration) or – mostly – neutral.
- Better treatment of congestion in heart failure remains a major unmet need.

This box summarizes key points contained in the article.

2. Current clinical practice of prevention and treatment of fluid retention in heart failure: How much is effective? How much is good for outcomes?

2.1 The in-hospital patient: is symptoms improvement satisfactory?

Despite an apparent early and easy improvement in symptoms, many patients hospitalized for acute HF remain symptomatic and with signs of congestion at discharge [20]. In the IMPACT-HF (Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure) Trial, > 60% of patients were dyspnoeic, 30 – 40% were in New York Heart Association (NYHA) functional class III or IV, and 9 – 15% had pulmonary rales and/or peripheral oedema at discharge [7,13]. In the ADHERE (Acute Decompensated Heart Failure National Registry) database, at the time of discharge 45% of the patients, although improved compared to admission, were still symptomatic and approximately 70% had a weight loss of < 10 lb, despite evidence of congestion at presentation [8].

It is probable that the high rates of response reported in some trials [3-5] were caused by the inclusion of patients who did not actually have HF as a cause of their symptoms.

Accordingly, lower rates of response are found when patients are diagnosed based on more objective criteria (e.g., by natriuretic peptide levels). In ADHERE, plasma levels of B-type natriuretic peptide (BNP) were measured within 24 h of admission in 48,629 hospitalizations. BNP quartiles were independently predictive of in-hospital mortality. They were also predictive of the proportion of patients asymptomatic at discharge, with a decrease from 48 – 49 to 43.6% in the patients in the highest quartile of BNP levels on admission (> 1730 pg/ml) [12]. The PROTECT (A Placebo-controlled Randomized study of the selective A1 adenosine receptor antagonist rolofylline for patients hospitalized with acute HF and volume Overload to assess Treatment Effect on Congestion and renal function) pilot trial excluded patients with BNP or NT-proBNP levels < 250 and < 1000 pg/ml. A moderate to marked improvement in dyspnoea at both 24 and 48 h by the Likert scale, as prospectively defined as dyspnoea relief in the trial, was found in only 49.8% of the patients [9], and a similar proportion (54%) with dyspnoea relief was found in the much larger main PROTECT trial [21]. Even lower percentages (25%) were found in the Pre-RELAX-AHF (Relaxin for the treatment of patients with Acute Heart Failure) trial, in which patients were assessed at an earlier stage (i.e., at 6, 12, and 24 h) by visual analogue scale (VAS) [11,22].

The method used for symptoms assessment is also important, as highlighted in a recent registry. When dyspnoea was assessed using a 7-point Likert scale, improvement occurred early, with 58% of patients grading dyspnoea as improved on the second day after admission and no further improvement thereafter. By contrast, improvement was much more gradual when it was assessed by a 100-point VAS, with a further improvement from day 2 to day 7 after admission. A similar behaviour was found with general well-being scores [23].

2.2 The patient after discharge: have we achieved a satisfactory prophylaxis of readmissions?

Fluid retention is the main cause of HF hospitalizations and chronic administration of loop diuretics is therefore the mainstay for the prevention of episodes of acute decompensation [1,2,19,20,24,25]. The implementation of a flexible diuretic dose regimen, based on daily monitoring of body weight, frequent contacts with medical personnel in disease-management programs, and/or monitoring or telemonitoring of biological parameters (right ventricular or pulmonary artery pressures, oxygen saturation, etc.) [26-30] is one of the major advances in the current treatment of chronic HF. Despite this, an effective prevention of episodes of fluid retention is a long way from being achieved. Patients with HF generally present a further increase in body weight in the first weeks after a hospitalization for acute HF, and such increase is predictive of further rehospitalization [31].

A vulnerable phase for the further decompensation of HF has recently been identified soon after discharge, when the patient is confronted with changes in: the physician(s)

providing care, diet, modality of administration of new and complex drug therapies, demands for more physical activity, and new familial and social stresses [32]. Accordingly, the first weeks after a hospitalization are associated with the highest rate of re-hospitalizations [33,34], and early assessment and follow-up in this phase are associated with significant improvement in prognosis [35,36]. It is clear that more persistent relief of congestion during the inpatient and the subsequent outpatient phase will also be effective in improving patient outcomes.

The chronic administration of diuretics seems insufficient for the prevention of fluid retention and HF hospitalizations. This may be related to the relative lack of efficacy of diuretics. However, it may also be hypothesized that diuretic treatment, although effective in the short-term, may contribute to the activation of mechanisms, namely the renin-angiotensin-aldosterone system [37] and the renal adenosine system [38], leading to reduced renal function, fluid retention and – ultimately – HF hospitalizations. Consistently with this hypothesis, diuretic therapy has been associated with worse prognosis in patients with chronic HF.

3. Pitfalls and limitations of current diuretic treatment in patients with heart failure

3.1 Loop diuretics and prognosis

Three retrospective analyses from the SOLVD (Studies of Left Ventricular Dysfunction) trials suggested, for the first time, that administration of non-potassium-sparing diuretics – namely furosemide – may worsen patient outcomes. The first study, performed on 6797 patients enrolled in SOLVD, showed an increased risk of arrhythmic death associated with diuretic use [relative risk (RR) 1.85, $p = 0.0001$], which remained significant after adjustment for important baseline factors (RR 1.37, $p = 0.009$) [39].

In a second analysis, Domanski *et al.* showed that treatment with loop diuretics or thiazides was associated with an increase both in total mortality [adjusted RR 1.28, 95% confidence interval (CI) 1.19 – 1.49] and HF hospitalization (adjusted RR 1.38, 95% CI 1.11 – 1.71) [40]. By contrast, treatment with a potassium-sparing diuretic, alone or in combination with the other diuretics, was associated with a reduction in the risk of death or hospitalizations [40]. This protective effect of potassium-sparing diuretics, mostly represented by spironolactone, was probably related to protection from hypokalaemia and aldosterone antagonism.

Knight *et al.* showed that diuretic use was an independent predictor of decreased kidney function in the patients studied in SOLVD, thus showing a third mechanism, in addition to electrolyte disturbances and neurohormonal activation, by which loop diuretics may worsen patients' prognosis [41].

These data were confirmed by a retrospective analysis of 7788 patients included in the Digitalis Investigation Group (DIG) trial. Diuretic therapy was associated with an increase in

all-cause mortality (RR 1.31; 95% CI 1.11 – 1.55; $p = 0.002$) and HF hospitalizations (RR 1.37; 95% CI 1.13 – 1.65; $p = 0.001$), which were independent from concomitant variables, including those related to severity of HF and concomitant treatment [42]. This study represents a further step forward, compared to the SOLVD analyses. First, it used propensity score methods of multivariable analysis, with adjustment for many variables, more than what it was possible in the SOLVD analyses. Second, > 90% of the patients were also treated with an ACE-inhibitor and about 80% were in NYHA class I and II. These data show that ACE inhibitors may not fully protect from the untoward effects of diuretics and diuretics may have unfavourable effects also at the early stages of disease progression. Similar results were obtained in other multivariable analyses of the same trial [43,44].

3.2 Clinical significance of furosemide dose

A role of diuretic therapy is further suggested by studies showing the independent prognostic value of the doses of loop diuretic. The administration of high doses of furosemide has been associated with increased mortality in patients with advanced HF [45-47], elderly patients [48] and in patients hospitalized for acute decompensation of HF [49,50]. These relations remained significant after adjustment for other variables at multivariable analyses, suggesting that high doses of furosemide may have a role as a cause of the poor outcomes of HF patients. One important exception to these multivariable analyses was the study by Mielniczuk *et al.* [47], which showed that diuretic dose was no longer a significant determinant of prognosis when clinical stability was taken into account, thus suggesting that furosemide dose is more a marker than a cause of instability. The dose of furosemide is included in a prognostic model to predict mortality in patients with HF [51]. Administration of high doses is also independently associated to an increased risk of worsening renal function [41,52,53], an event with known prognostic role [54,55].

All these data are, however, based on retrospective analyses. A prospective trial comparing a strategy based on low doses of i.v. furosemide with one based on high doses of furosemide for the treatment of acutely decompensated chronic HF was, therefore, extremely necessary [55]. Low-dose i.v. furosemide was defined as the same dose the patients were receiving orally, before hospital admission, whereas high-dose furosemide was 2.5 the usual oral dose. Treatment with high doses of diuretics was associated with higher serum creatinine levels and with a slight and non-significantly greater proportion of patients who developed worsening renal function. However, the intensified diuretic regimen was also associated with a better response of dyspnoea, as assessed by area under the curve (AUC) of VAS, and with a numerically lower rate of events (death, rehospitalizations or visits to the emergency department) [56]. These last data suggest that an increase in diuretic dose may actually have beneficial effects when used in patients with fluid overload [57].

How can we therefore reconcile studies showing an increased mortality with higher furosemide doses with these last studies actually showing better symptoms relief and, to some extent, short-term outcomes with intensified diuretic treatment? The key issue is probably represented by the patient's fluid status and the difficulties in accurately estimating this. When diuretic therapy is administered at excessive doses it may cause fluid contraction with further neurohormonal activation and HF progression. By contrast, when it is administered at insufficient doses, persistent fluid overload and congestion may cause persistent symptoms, further deterioration in renal function, through the effects of increased pressure in the renal veins, and neurohormonal activation through the effects of increased myocardial stress. These observations may also explain the seemingly unexpected beneficial effects of sodium loading in patients undergoing diuretic treatment for acute HF or, even chronically, the favorable effects of diets with a normal to high sodium content in patients on chronic furosemide therapy [57,58].

3.3 Potential limitations and untoward effects of loop diuretics in patients with heart failure

Mechanisms activated by loop diuretics treatment and which may have unfavourable effects on the prognosis of patients with HF include electrolyte abnormalities, neurohormonal activation and worsening renal function. All these untoward effects can be magnified by resistance to loop diuretics.

Resistance to furosemide consists of a progressive loss of sensitivity to its administration so that increasing doses are necessary to obtain diuresis and natriuresis; peak response to maximal doses is also reduced. The mechanisms to resistance to loop diuretics (namely, furosemide) in patients with HF are multiple and hence treatment may vary. They have been thoroughly examined in a recent reviews [57,59,60] and are outlined in Table 1.

Electrolyte abnormalities associated with furosemide administration include hypokalaemia and hypomagnesaemia. Their mechanisms and clinical significance have been previously described [61]. It is likely that the beneficial effects on prognosis of potassium-sparing diuretics are partially related to their effects on serum potassium levels.

Neurohormonal activation occurs in all patients with HF, even if untreated [62]. Further activation has been shown after both acute and chronic furosemide administration. Initial studies showed an elevation of plasma renin activity and of plasma levels of aldosterone, vasopressin and norepinephrine after the initiation of furosemide treatment [63,64]. In another study, neurohormonal activation after bolus administration of intravenous furosemide, 1.3 ± 0.6 mg/kg body weight, was attended by peripheral vasoconstriction with a decrease in the stroke volume index and an increase in left ventricular filling pressure and raised pulmonary artery pressures. Neurohormonal activation and peripheral vasoconstriction were followed after 3.5 h by the expected diuresis and fall in left ventricular filling

pressure [63]. In 1990, the analysis of plasma hormone levels in the patients enrolled in the SOLVD trials confirmed the relationship between diuretic therapy and neurohormonal activation with only the patients on diuretic therapy showing an increase in plasma renin activity, compared to normal subjects, among those enrolled in the SOLVD Prevention trial [37]. Neurohormonal activation may contribute to diuretic resistance and to HF progression as shown in experimental models [65]. Interestingly, neurohormonal activation has not been shown after fluid removal with ultrafiltration, compared with standard diuretic therapy [66,67].

A third untoward effect of furosemide administration is worsening renal function. In addition to neurohormonal activation, furosemide may contribute to the deterioration of renal function through a local mechanism, the so-called tubuloglomerular feedback [38]. The increased delivery of sodium at the level of the distal tubule of the nephron is sensed by the juxtaglomerular cells of the macula densa with a secondary constriction of the glomerular afferent arteriole causing a decline in the glomerular filtration rate and, ultimately, of sodium excretion. Tubuloglomerular feedback is therefore a mechanism ideally aimed at avoiding excessive sodium loss as well as reducing kidney oxygen consumption.

As adenosine is the mediator of the tubuloglomerular feedback, research has recently focused on the administration of adenosine A1-receptor antagonists to maintain renal function and enhance diuresis in patients hospitalized for acutely decompensated HF. Data from large randomized trials have not, however, proven the hypothesis that adenosine A1-receptor antagonism may have beneficial effects on renal function (see below).

4. How can the treatment of congestion be improved?

4.1 Other loop diuretics

The available loop diuretics include bumetanide, ethacrynic acid, furosemide and torasemide; furosemide is used in by far the largest proportion of patients with HF. The main difference between loop diuretics lies mostly in their pharmacokinetics, rather than their efficacy [68]. Between 80 and 100% of the oral doses of bumetanide or torasemide are absorbed by the gut, compared with only 50% of an oral dose of furosemide. Hence, switching from an intravenous to an oral dose of bumetanide or torasemide does not require significant dose adjustments. However, torasemide seems to have its greatest effects at a dose of 50 mg (100 mg in patients with renal insufficiency) and more frequent administrations, rather than an increase in the dose, have been recommended in diuretic resistant patients [69]. Although torasemide has been associated with better outcomes, less hypokalaemia and favorable effects on left ventricular remodeling in some studies [67,70], these data need to be confirmed by large, prospective, randomized trials, which have not yet been performed.

Table 1. Causes of resistance to furosemide.

Cause	Mechanism	Treatment
Excessive dietary sodium	↑tubular sodium load	Sodium restriction
Gut congestion	Furosemide malabsorption	Switch to torasemide/Start i.v. loop diuretic infusion
Chronic renal dysfunction	↓Glomerular filtration rate	Stop NSAIDs/↓dose or withdraw ACEi/ARBs/ Consider hemofiltration
↓cardiac output	↓Glomerular filtration rate	Add Inotropic agents/hemodynamic support
↑renal venous pressure		
Diuretic induced nephron hyperfunction: post-diuretic effect and braking effect	↑proximal tubule and loop of Henle sodium absorption	↑diuretic dose/use multiple diuretic daily doses or continuous i.v. infusion
Diuretic induced nephron hypertrophy	Distal tubule cell hypertrophy: ↑sodium absorption	Combination of loop diuretics with thiazide diuretics
Renin- angiotensin activation	↑proximal and distal tubule sodium absorption Renal hypoperfusion	Add ACEi/ARBs
Aldosterone activation	↑distal tubule sodium/potassium exchange	Add aldosterone antagonist
Vasopressin activation	Free water retention at the distal tubule and collector duct	Water restriction/ add vasopressin antagonist

4.2 Combination with thiazide diuretics

Three options are considered in the recent guidelines when diuresis is inadequate to relieve congestion [2]: i) administration of higher doses of loop diuretics; ii) continuous infusion of a loop diuretic; and iii) addition of a second diuretic (such as a spironolactone, a thiazide or metolazone) (Figure 1).

Continuous infusion of the loop diuretic has the advantage that it may avoid rebound reabsorption of sodium occurring when blood levels of the diuretic are low and may reduce the risks of ototoxicity. However, it did not prove to be as effective as the administration of furosemide boluses in a recent prospective randomized trial [57].

When not contraindicated, spironolactone should always be administered to patients with NYHA class III or IV HF, not because of its diuretic effects but because of its beneficial effects on outcomes [1,2]. Concomitant administration of a thiazide diuretic is therefore potentially indicated in patients with persistent fluid overload despite the administration of high doses of loop diuretics and on neurohormonal antagonists, when tolerated, including renin, angiotensin and aldosterone antagonists.

4.3 Dopamine

When administered at low doses, dopamine may rather selectively improve renal blood flow through its action on dopamine 1 (DA1) receptors. This effect has also been demonstrated in small study groups of patients with HF [71,72]. However, the effects of dopamine administration, both with respect to mortality and to the prevention of renal replacement therapy, have been neutral both in controlled trials and in meta-analyses [73,74]. There is no evidence to recommend dopamine administration for the protection of renal function in patients with fluid overload and need of diuretic treatment.

4.4 Inotropic agents

Renal dysfunction is related both to low cardiac output with renal hypoperfusion and to increased intrabdominal pressure, central venous pressure and hence renal venous pressure in patients with HF [75,76]. Renal dysfunction may therefore be secondary to a severe haemodynamic impairment and inotropic therapy may – theoretically – be indicated to improve systolic function. Accordingly, recent data have shown an improvement in renal function after the administration of the inotropic agent levosimendan. However, these data were obtained in small, single-centre trials and need confirmation by larger studies [77]. Importantly, renal dysfunction also occurs in patients with HF and preserved left ventricular ejection fraction, a condition in which increased renal venous pressure and intraglomerular pressure, but not low cardiac output, are probably the main determinants. Inotropic agents cannot be of help in this condition.

4.5 Vasopressin antagonists

Patients with advanced HF have an activation of vasopressin release. Vasopressin causes water retention by its action on the collector duct, which is mediated by V1 receptors activation. The administration of antagonists of the vasopressin type 2 receptors is associated with increased diuresis and aquaresis in normal subjects and in patients with HF. Hyponatremia, an abnormality caused by vasopressin activation, is also corrected by the administration of vasopressin antagonists [78,79].

The effects of the selective vasopressin V1 receptors antagonist tolvaptan on mortality, hospitalizations and on the symptoms and signs of HF (dyspnoea, body weight, oedema) were assessed in 4133 patients in the EVEREST trial [4,80]. Compared with

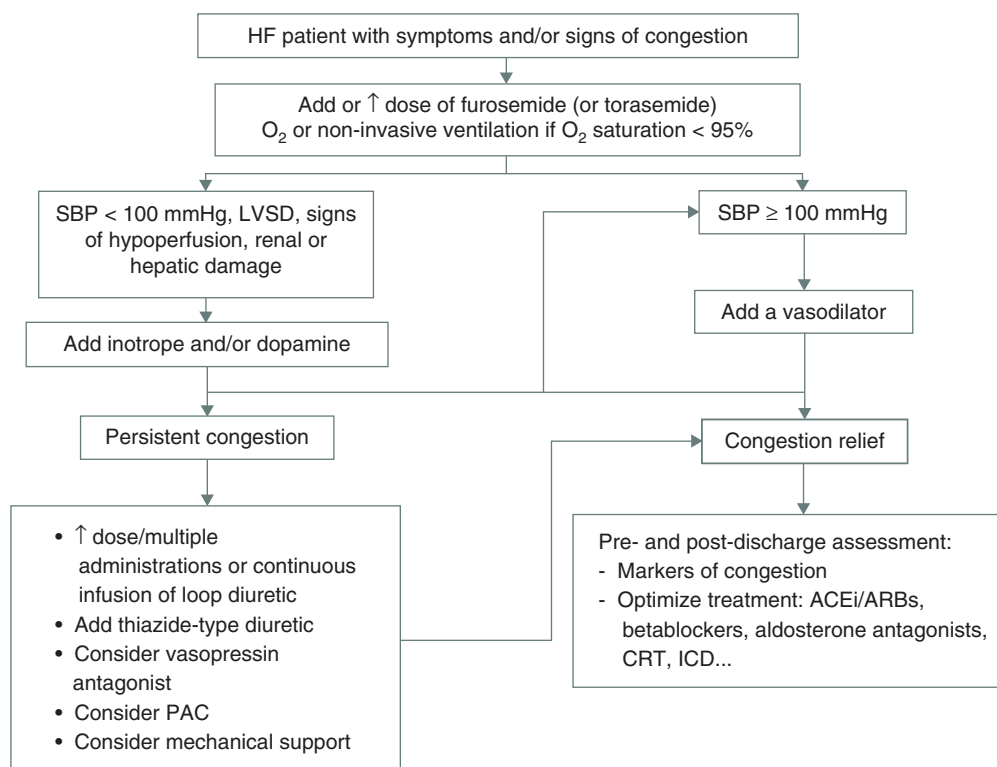


Figure 1. A treatment algorithm of congestion based on systolic blood pressure in patients with acute heart failure.

CRT: Cardiac resynchronization therapy; ICD: Implantable cardioverter defibrillator; PAC: Pulmonary artery catheterization; SBP: Systolic blood pressure.

placebo, the administration of tolvaptan was associated with a greater reduction in body weight and with an improvement in dyspnoea, but with no change in outcomes. It may be that the lack of effects on outcomes is related to the mechanism of action of vasopressin antagonists, causing an increased water excretion but no sodium loss while patients with HF primarily have sodium retention. The drug effects may be greater in patients with greater activation of the vasopressin system, as shown by hyponatremia, which was, however, present only in small percentage of the patients enrolled in EVEREST.

Based on the data of randomized controlled trials, the role of vasopressin antagonists seems limited to the patients with hyponatremia rather than being generally applicable for the treatment of fluid retention in patients with HF. Further trials are, however, either ongoing or will start soon.

4.6 Ultrafiltration

Unlike vasopressin antagonists, ultrafiltration can rapidly and predictably remove extracellular and intravascular fluid volume, allowing loss of an isotonic fluid (e.g., water and sodium). As patients with HF have an activation of primarily sodium-retentive mechanisms, isotonic fluid loss, as achieved by ultrafiltration, may be a better tool for the treatment of congestion [81,82].

Ultrafiltration has been compared with standard diuretic treatment in a few randomized trials involving a limited

number of patients [83]. In the only reasonably large multicentre, controlled trial accomplished to date, which compared ultrafiltration with standard diuretic treatment in 200 patients with HF and fluid overload, ultrafiltration was associated with no difference in symptom improvement, and with a slight increase in serum creatinine and a reduction in the rehospitalization rates after discharge [84].

4.7 Antagonists of the renin-angiotensin-aldosterone system

Antagonists of the RAA system act by antagonizing some of the untoward effects of diuretic treatment, namely neurohormonal activation and the consequent decline in renal function, diuretic resistance, electrolyte abnormalities and progression of cardiac dysfunction. Unfortunately, patients with diuretic resistance and advanced HF also frequently show intolerance to the hemodynamic and renal effects of RAA antagonists [85].

4.8 Adenosine receptor antagonists

Stimulation of adenosine A1 receptors in the kidney is associated with enhanced reuptake of water and sodium at the level of the distal tubule and collector duct, and with afferent glomerular arteriole constriction with reduction in glomerular filtration rate and diuresis. Both these actions can be regarded as part of the general mechanism of action of adenosine, which

acts as a mediator, causing oxygen and energy sparing in the different organs and tissues. In the kidney, glomerular filtration is actually the main cause of oxygen consumption [38].

The release of adenosine is enhanced by increased sodium delivery to the distal tubule, where it is sensed by the cells in the macula densa, which stimulate adenosine release by the juxtaglomerular cells. Adenosine therefore acts as a feedback mechanism to avoid excessive natriuresis. In the setting of acute HF in patients undergoing intensified diuretic treatment, generally by furosemide administration, adenosine release has the effect of reducing glomerular filtration rate and of limiting the natriuretic response to the furosemide administration. This is the rationale for the administration of adenosine A1 receptor antagonists, combined with furosemide treatment, to enhance the diuretic and saluretic response to furosemide administration and preserve – or improve – renal function. Many, relatively small, controlled studies had confirmed this hypothesis, showing that the administration of adenosine A1 receptor antagonists was associated with increased diuresis and improvement in renal function, assessed either through serum creatinine levels and/or glomerular filtration rate in patients with advanced HF [86,87].

It was on this basis that the Placebo-controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) trial was designed [21,88]. In this trial, for the first time, renal function was included among the components of the primary end-point and, as renal protection was considered a primary mechanism of action of the drug, the hypothesis that renal protection could be associated with an improvement in outcomes was tested. Unfortunately, the results of the trial were neutral, both with respect of the primary end-point, including dyspnoea relief combined with the absence of worsening HF at 1 week and worsening renal function at 7 and 14 days, and with respect to the pre-specified secondary outcomes of death from any cause or rehospitalization for cardiovascular or renal causes by day 60 and the proportion of patients with persistent renal impairment. Paradoxically and unexpectedly, the administration of the study drug, the adenosine A1 antagonist rolofylline, was not associated with favorable effects on renal outcomes, although dyspnoea was slightly improved. These results can be interpreted as showing that changes in serum creatinine levels, the variable used to assess renal function in this study, may have different and often opposite causes. An increase in serum creatinine may, in fact, be caused either by overdiuresis with contraction of the effective plasma volume and renal hypoperfusion (so-called vasomotor nephropathy) [24] or by an organic renal damage eventually leading to end-stage renal failure, hemofiltration or dialysis, an event occurring in only in 0.9 and 0.4% of the patients assigned to placebo and rolofylline, respectively, in the PROTECT trial.

Central nervous system adenosine receptors increase the threshold for seizures. Unlike previous studies, rolofylline was associated with an increased risk of seizures in PROTECT and this, in addition to the neutral effect on the primary end-point, resulted in discontinuation of any further development of the drug by the sponsoring company [86].

5. Conclusions

Treatment and prevention of fluid overload in patients with HF remain based on the administration of loop diuretics. However, the efficacy of these agents may decrease and they may be associated with neurohormonal activation, electrolyte abnormalities and worsening renal function. There is a need of further interventions to treat congestion. Dopamine and inotropic agents are often administered to patients with persistent fluid overload and renal dysfunction based on the observation that the latter may be secondary to hemodynamic abnormalities. A further increase in aquaresis has been shown with vasopressin antagonists, and in diuresis and saluresis with adenosine antagonists and ultrafiltration, respectively. In large, multicentre studies, vasopressin antagonists had no effects on outcome and the adenosine antagonist, rolofylline, was associated with seizures and had a neutral effect on the primary outcome. Ultrafiltration has been effective in hospitalizations, compared with standard diuretic therapy, but these results need to be confirmed by other studies.

6. Expert opinion

Fluid overload remains the main cause of hospitalization for the patients with HF. Its treatment is still based on loop diuretics, despite their limited efficacy and the fact that the use of high doses has been associated with poorer outcomes. New treatments have failed to improve outcomes. However, at least in the case of adenosine A1 receptor antagonists, this has been also related to the inclusion of changes in serum creatinine levels as a component of the primary end-point, in addition to the central nervous system side effects. Serum creatinine levels tend to increase whenever the patient undergoes excessive diuresis, a common finding with high furosemide doses, adenosine A1-receptor antagonists and ultrafiltration, although they are not necessarily associated with a poorer outcome. Better assessment of dyspnoea and better focus on meaningful end-points is important for future research.

Declaration of interest

M Metra has received honoraria for advisory board meetings and speeches from Cardiokine, Corthera, Merck, Otsuka and Servier.

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