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Practical outpatient management of worsening chronic heart failure:

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Abstract

Management of worsening heart failure (WHF) has traditionally been hospital-based, but with the rising burden of HF, the pressure on health care systems exerted by this disease necessitates a different strategy than long (and costly) hospital stays. A strategy for outpatient intravenous (IV) diuretic treatment of WHF has been developed in certain American centers in the past 10 years, whereas European centers have been mostly favoring “classic” in-hospital management of WHF. Embracing novel, outpatient approaches for treating WHF could substantially reduce the burden on healthcare systems while improving patient’s satisfaction and quality of life. The present article is intended to provide essential knowledge and practical guidelines aimed at helping clinicians implement these new ambulatory approaches using day hospital and/or at-home hospitalization. The topics addressed by our group of HF experts include the pathophysiological background of diuretic therapy, the most suitable profile of WHF that may be managed in an ambulatory setting, the pharmacological protocols that can be used, as well as a detailed description of healthcare structures that can be proposed to deliver these ambulatory care interventions. The practical aspects of day hospital and Hospital-at-Home (HaH) IV diuretics administration are specifically emphasized. The algorithm provided along with the practical IV diuretics protocols should assist HF clinicians in implementing this new approach in their local clinical setting.

Practical outpatient management of worsening chronic heart failure

Keywords: heart failure; diuretics; cardiac congestion; cardiovascular diseases; ambulatory management

Introduction

Heart failure (HF) is widely recognized as a major global public health burden. HF affects 2% to 3% of the adult population in Western countries¹⁻³ and is the most common cardiovascular cause of hospital admission over the age of 60 years. It is estimated that HF consumes approximately 9 billion euros/year of the European healthcare budget.

Congestion, related to pressure and/or volume overload, is fundamental to the pathophysiology, presentation and prognosis of HF^{5, 6}, irrespectively of its typology (i.e. HF with reduced vs. preserved ejection fraction [HF_rEF, HF_pEF]). Specifically, increased fluid filtration due to elevated pulmonary capillary pressure leads to an increase in extravascular lung water resulting in pulmonary congestion and severe breathlessness in patients with HF.^{7, 8} Consequently, systemic congestion may also occur, often causing intestinal oedema and reduced absorption of guideline-directed medical therapies (GDMT) for HF, including loop diuretics. It usually presents – clinically – with various degree of lower limb edema and substantial weight gain. Worsening symptomatic congestion is one of the main causes leading to urgent HF hospitalization and subsequent poor patient outcomes.^{5, 9} The cornerstone of worsening HF (WHF) treatment is intravenous (IV) loop diuretic, usually administered during hospital stays of 5 to 15 days (usually less in the US) according to the severity of the congestive episode and the regional differences in healthcare structure. Importantly, patients hospitalized for worsening WHF have a high-risk of readmission, reaching up to 50% at 6-months.^{10, 11} Iterative hospital admissions have a major impact on quality of life.¹² In addition, hospitalizations by themselves can be associated with iatrogenic and nosocomial complications including malnutrition, infections, dependency, etc., especially in elderly patients. If they could choose, many patients with chronic illnesses, including heart failure, would prefer to be treated at home, particularly during, and presumably after, the COVID-19 pandemic.¹³

Given the projected substantial rise in HF burden in Western populations over the next decades, the ensuing pressure on healthcare systems exerted by HF will undoubtedly increase. In Europe, the median length of hospital stay is approximately 8 days in units with 24/7 trained nurses and physicians, which largely explains the high cost of WHF management. An ambulatory management strategy for WHF has been developed in American centers in the past 10 years (even if used heterogeneously across centers/regions),¹⁴ whereas European centers (along with a number of American centers) have been mostly favoring “classic” in-hospital management of WHF. Embracing new approaches for managing WHF could substantially reduce the “burden” of the diagnosis on European healthcare systems while improving quality of life. We believe that there is a common interest for both patients and healthcare providers to favor these ambulatory approaches to WHF. The present review article is intended to provide

essential knowledge and practical guidelines aimed at helping clinicians implement these new ambulatory approaches using day hospital and/or at-home hospitalization.

Herewith, our panel of HF experts will review the pathophysiological background of diuretic therapy, describe the most suitable profile of WHF which may be managed in an ambulatory setting as well as the pharmacological protocols that can be used, and detail the healthcare setting that can be proposed to deliver these ambulatory care interventions.

Part I: Pathophysiological background relevant to diuretics

Patients with WHF typically have clinically significant congestion with volume overload due to chronic retention of sodium and water in the intravascular and extravascular compartments.¹⁵ In this context, diuretics are used to relieve congestion through increased renal natriuresis and diuresis. In an ambulatory setting, it is therefore important to have a sound knowledge on how to use and combine the different diuretic classes together,¹⁶ keeping in mind that only a few small trials have provided, so far, evidence for their best use.¹⁷

As recently presented in a position paper of the HFA¹⁶, the goal of diuretic therapy is to:

- 1) obtain efficient decongestion
- 2) maintain sufficient renal and organ perfusion pressures

An important facet when using diuretics in WHF patients is to understand their pharmacokinetics. In routine practice, many patients with WHF have HF GDMT down-titrated or discontinued due to a mistaken interpretation of apparent worsening renal function (WRF)¹⁸ without an attempt to increase – substantially – or combine diuretics to achieve complete decongestion. It is hence important to i) define the optimal diuretic loading dose, ii) rapidly assess the patient’s diuretic response, and iii) upgrade doses in instances of insufficient response with possible use of sequential nephron blockade.^{16, 19} Patients with WHF usually present with a combination of volume overload accompanied by interstitial and bowel edema, kidney dysfunction and altered organ perfusion, which impairs both bioavailability of, and response to, diuretic therapy. Furthermore, activation of the renin-angiotensin-aldosterone system (RAAS) renders the patient further resistant to oral diuretics; rising blood urea nitrogen—an indirect measure of RAAS activation—also may occur, masquerading as worsening kidney function.

The principal pharmacological properties (including site of action) of the various diuretic classes are presented in Table 1 and Figure 1. In this review, we will not address the use of acetazolamide and amiloride, being less documented, not routinely available in clinical practice in many countries and recently overviewed in detail somewhere else.¹⁶

The most potent diuretic class includes loop diuretics, with the effect of WHF on their dose-response curve presented in Figure 2.²⁰ In the context of WHF and the consequent reduced bioavailability of oral loop diuretics, guidelines recommend the use of IV loop diuretics⁵ to rapidly and more efficiently achieve a natriuretic ceiling.²⁰ Different loop diuretics exist and they have different pharmacokinetics and bioavailability;¹⁷ a large (~6,000 participants to be enrolled) ongoing trial is comparing oral torasemide to furosemide as treatment for congestion at the time of discharge from an episode of heart failure

(TRANSFORM-HF, NCT03296813²¹) following the favorable effect of torasemide on HF hospitalizations suggested in observational studies and the meta-analysis of small trials.²²

Thiazide-like diuretics can be used in severe HF patients who responded poorly to loop diuretics in a sequential nephron blockade strategy. These diuretic agents potentialize the natriuretic effect of loop diuretics (Figure 1) and in the case of oral metolazone or intravenous hydrodiuril remain effective with reduced filtration rate ($<30 \text{ mL/min/1.73m}^2$).²³ This effect can significantly increase diuresis and should be closely monitored with serum potassium and sodium measurements.

Mineralocorticoid antagonists (MRAs) are seldom used in the acute setting although their introduction at this phase should nonetheless be considered. Together with their direct inhibition of aldosterone and their potassium-sparing effect, they can partially offset certain significant side-effects of loop and thiazide diuretics.²⁴ In addition, MRA initiated in acute settings have been shown to have natriuretic effects.²⁵ Since the action of the MRA spironolactone occurs 48-72h after oral intake (Table 1), eplerenone or canrenoate potassium could be favored in the setting of WHF.²⁶ In the ATHENA-HF trial, spironolactone use at 100 mg/day was deemed safe and did not result in hyperkalemia or worsening of renal function (but did not improve outcome either possibly because of the short follow-up and slow pharmacokinetics of spironolactone).²⁷

Finally, assessment of diuretic response is critical in routine practice. Clinical signs of decongestion, diuresis, weight loss and renal function have limited sensitivity for guiding diuretic therapy.²⁸ Urinary sodium monitoring is a simple indicator of diuretic response that is associated with prognosis and has the potential of becoming a useful tool for routine practice guidance of diuretic therapy.^{16, 29} Serial measurement of natriuretic peptide concentrations are commonly utilized in US institutions for monitoring trajectory of decongestion. Given stability of N-terminal pro-B type natriuretic peptide (NT-proBNP) even home-based phlebotomy with centralized measurement may be performed. The use of ultrasound, including serial assessment of lung B-lines, inferior vena cava or jugular vein diameter, or intra-renal venous flow have also shown potential to be useful in this setting and is currently under evaluation.³⁰

Diuretic resistance

As noted, diuretic resistance (defined as the need for progressive dosage up-titration in order to achieve a net fluid balance) is common in those with WHF, and corresponds to an impaired sensitivity to diuretics resulting in reduced natriuresis. Diuretic resistance translates into a rightward shift of the dose-

response curve of sodium excretion rate with a lowering of the sodium ceiling excretion rate (Figure 2). Furthermore, WRF-associated diuretic resistance is an indicator of advanced HF (as poor perfusion can favor WRF) and the need for more advanced therapies.³¹ Loop and thiazide-diuretics may provide immediate symptom relief, albeit without necessarily decreasing patient mortality. Conversely, consistent data have established that large doses of diuretics^{32, 33} and/or the need for intensification of diuretic treatments³⁴ are associated with increased mortality in HF, reflecting the severity of congestion and advanced cardiac dysfunction as drivers of poor outcomes.³⁵

The impact of GDMT drugs on congestion

Both persistent congestion and excessive decongestion can lead to down-titration of GDMT, mostly through renal function- and blood pressure-related effects.^{36, 37} Several studies have focused on the interaction between use of diuretics and these life-saving HF/EF medication. In a post-hoc analysis of the EPHESUS trial, patients taking eplerenone had their loop diuretic dose significantly reduced during follow-up while eplerenone benefit was not dependent on diuretic dose.³⁸ In a post-hoc analysis of the PARADIGM-HF trial, patients randomized to sacubitril/valsartan had a lower subsequent use of diuretics, with fewer loop diuretic dose increases and more frequent dose reductions compared with those taking enalapril. The treatment effect of sacubitril/valsartan to reduce hospitalizations appeared within 30 days,³⁹ and among those patients hospitalized during PARADIGM-HF, readmissions were lower among those treated with sacubitril/valsartan.⁴⁰ Natriuresis is also potentialized by sacubitril through the natriuretic peptide pathway.⁴¹ In the PARADIGM-HF trial, loop diuretic dose reduction was significantly more frequent in the sacubitril-valsartan group compared to the enalapril group.⁴² These results prompted the recommendation in all subsequent trials evaluating sacubitril/valsartan (including PIONEER-HF) to consider a dose reduction in loop diuretics. Moreover, in those patients with acute HF randomized to receive sacubitril/valsartan in the PIONEER-HF trial, rehospitalization for HF was substantially reduced (hazard ratio 0.61; P=0.02). This impact of sacubitril/valsartan on congestive complications may have to do with a modest effect of sacubitril to promote natriuresis through boosting of natriuretic peptide concentrations.⁴² Supporting the indirect results from PARADIGM-HF, Desai and colleagues reported early, significant reduction in pulmonary artery pressures among those treated with sacubitril/valsartan (N=96) compared to a matched control group of 406 patients (-2.9 mm Hg; P < 0.001); the reduction of mean pulmonary artery pressure was greatest among those with a baseline pressure ≥ 30 mm Hg. No predicate data exist to suggest sacubitril/valsartan has a direct effect on ambulatory outpatients with WHF, however these recent analyses are in keeping with a meta-analysis of older trials focusing on RAASi showing that these latter drugs have a significant decongestion effect⁴³ and with likely benefit on those with congestive complications.

In the last 2 years, sodium-glucose cotransporter-2 (SGLT2) inhibitors have been shown to improve HF-related outcomes.⁴⁶ These inhibitors induce significant natriuresis and glucosuria, particularly when combined with loop diuretics (Figure 1), resulting in reduction in blood and plasma volume. Importantly, SGLT2i have a proximal effect, leading to a shift of tubular fluid from the proximal to the distal segments of the nephron. This shift can increase natriuresis depending on the sodium-retaining capacity of these distal segments (i.e. volume status, neurohumoral activation, use of diuretics). This natriuretic effect is not associated with any significant electrolyte wasting, renal dysfunction or neurohormonal activation.⁴⁷ Importantly, the efficacy, tolerability and safety profile of SGLT2i is unaffected by concomitant treatment (or dosage) with a conventional diuretic.⁴⁹ Most patients in the DAPA-HF trial did not undergo a change in diuretics dose during follow-up, and the mean daily dose of diuretics did not differ between the dapagliflozin and placebo groups.⁵⁰ In line with these results, in a moderately-sized trial study, Boorsma et al. reported that empagliflozin at a dose of 10 mg increased plasma osmolality without affecting fractional sodium, chloride excretion or urinary osmolality.¹⁵ However, two studies conversely reported favorable decongestion effects with higher doses of empagliflozin^{47, 51}. Despite natriuresis being unchanged following empagliflozin initiation in the aforementioned studies, diuresis did increase in the study by Mordi et al.⁵¹ whereas fractional sodium excretion increased in the Griffin et al. study.⁴⁷ Lastly, in keeping with the impact of neprilysin inhibition on pulmonary artery pressures, Nassif and colleagues similarly reported an average 12 week treatment effect of -1.7 mm Hg (P=0.02) on mean pulmonary artery pressures among patients treated with empagliflozin versus placebo. Trials testing use of SGLT2i in patients with diuretic resistance are ongoing (DAPA-RESIST, NCT04860011). In addition, SGLT2i were reported recently to be favorably associated with better overall clinical outcome in the setting of worsening HF in the EMPULSE trial.⁵² This positive result in acute HF, in which congestion is a key issue, parallels the results reported in the SOLOIST trial, where the rate of the primary event in patients randomized to Sotagliflozin was 30% lower than in the placebo group (HR=0.67; 0.52 to 0.85; P<0.001).⁵³ The efficacy and safety of dapagliflozin in acute HF will further be evaluated in the ongoing DICTATE-AHF trial.⁵⁴ Of note, SGLT2 inhibitors appear similarly effective in patients with HFpEF: In the EMPEROR Preserved trial, an impressive 27% reduction in the total number of hospitalizations for HF in the empagliflozine group.⁵⁵

Importantly, all of these observations are derived from protocolized clinical and biological monitoring allowing to titrate loop diuretic doses to patient status and no predicate data exist focusing on use of SGLT2 inhibitors specifically on patients with WHF exist however their safety/efficacy among those with congestion appears promising.

Part II: Identification of patients eligible for IV diuretic therapy

The identification of patients with WHF who are more likely to benefit from outpatient treatment with IV diuretics remains insufficiently documented to date. We propose an approach to the use of IV diuretics in an ambulatory setting (Figure 3) along with factors to be considered to select eligible patients (Table 2).

Clinical situations unlikely to fit an ambulatory IV diuretics program (Table 2)

We suggest that patients with severe *de novo* HF (p.e. patients with markedly reduced LVEF and NYHA 3+) should be managed in an in-hospital setting; Indeed, these patients usually require further diagnostic and prognostic workup typically performed in-hospital.⁵⁶

Secondly, patients presenting with signs of shock/low cardiac output, low oxygen saturation levels (ie: SpO₂<92%) and/or symptoms at rest (NYHA 4) should be also managed in-hospital. The clinical suspect, or identification, of specific and potentially fatal triggers of clinical deterioration, for instance a rapid conduction of supraventricular arrhythmias, pulmonary embolism or acute coronary syndromes^{14, 57} should also prompt in-hospital management.

Explosive/rapid worsening does not leave an adequate window for intervening in an outpatient setting. Nevertheless, this clinical scenario does not exclude early discharge with subsequent ambulatory IV diuretic management.

Clinical situations most likely to fit an ambulatory IV diuretics program

Episodes of progressive, worsening HF are very common, and represent the most frequent causes of a HF hospitalization (65% of cases in the EuroHeart Failure Survey II⁵⁸). Refractory symptoms and signs of congestion despite high doses of oral loop diuretics are major concerns for patients with severe HF. Indeed, these patients represent the main target population of ambulatory treatment with IV diuretics, as they spend a substantial amount of time in hospital (“frequent flyers”), which impairs their quality of life further and is associated with substantial costs. This particular phenotype corresponds to the population originally targeted by the Brigham and Women’s Hospital group in their initial experience of ambulatory IV diuretics: most (80%) had mild-moderate symptoms, with a median maintenance diuretic dose of 240 mg oral furosemide.⁵⁷

Similarly, this approach has been proposed in patients with cardiac amyloidosis,⁵⁹ a population

who also experiences multiple episodes of WHF and poor quality of life.

It is likely that these ambulatory IV diuretics program could be especially efficient in patients implanted with a CardioMEMS device,⁶⁰ as it allows an early detection of increased pulmonary pressure.

Importantly, a number of patients do not feel sufficiently ill to require in-hospital admission. Yet their management based solely on oral diuretics is troublesome. There is thus a “grey-zone” of patients too ill to be managed with oral diuretics but not sufficiently ill to necessitate an emergency room visit. In these “grey-zone” scenarios, local availability of an ambulatory IV diuretics service can be widely accepted and effective to improve congestion before it reaches the threshold for in-hospital admission.

In all instances, the clinical response to IV diuretic sessions should be carefully assessed, through a dedicated local disease management protocol, involving one or several of the following healthcare professionals: HF nurses, local nurses, GPs and treating cardiologists.

Part III/ IV diuretics in ambulatory settings – How to proceed?

The protocol published by Buckley et al.⁵⁷ (adapted in Figure 4) has been used in more than 250 patients^{14, 61} and sets a good foundation for implementation strategies. This protocol has also been used, with some local adjustments/amendments,⁶² by our group on a regular basis in the last few years.

Briefly, diuretic sessions consist in a 3-hour IV diuretic infusion, performed the same day or next-day treatment. The pharmacological approach is contingent on the maintenance diuretic dose: patients with the highest oral diuretic maintenance dose would receive the highest IV diuretics (and possibly co-diuretics such as thiazides). Generally, hydrochlorothiazide doses between 12.5 to 50 mg/session are used; metolazone 2.5 to 5 mg may have even greater impact in those with eGFR <30 mL/min/1.73m². In such patients, IV hydrodiuril may also be given, however the advantage of oral thiazide administration makes it preferred. If sequential nephron blockade is utilized with an oral thiazide, the oral medication is administered 30 minutes prior to the IV loop diuretic. Thiazide has occasionally been replaced by an high-dose IV MRA by some members of our group in similar settings given the natriuretic and diuretic properties of MRAs,⁶³ including IV MRAs.²⁶ The main advantage of MRA in this setting is to offset the *primus movens* of diuretic resistance, i.e. the key involvement of RAAS – in sharp contrast with thiazide that further increases RAAS activation. Acetazolamide is another option to consider in multi-site nephron blockade.⁶⁴ In the setting of HaH, only IV boluses of loop diuretics are typically used, singly or divided to twice a day.

Importantly SC form of furosemide have been developed in recent years.⁶⁵ These SC injections are particularly useful in at home hospital settings as they are logistically demanding and do not require the hurdle/inconvenience of repeated venous puncture.

Careful consideration should be paid to dyskalemia following the IV diuretic session. Briefly, with this protocol, only patients with prior IV diuretic potassium >4 mEq/l (regardless of renal function) or patients with K>3.7 if creatinine is 2.0 mg/dL (175 umol/l) or above will not receive potassium supplements during the IV diuretic sessions (Figure 4). In our experience, these patients with low serum potassium should receive MRAs whenever possible. Indeed, patients receiving IV diuretic sessions are likely to have increased doses of oral diuretics in the following weeks, which could further decrease serum potassium levels.

Of importance, GDMT drugs should not be withheld during this IV diuretic period, unless symptomatic hypotension occurs. Indeed, as already emphasized above, RAAS is a key driver of sodium/water retention.

There are sparse data assessing the optimal number of diuretic sessions. Very early follow-up overviewed by a physician should be undertaken to assess the clinical efficacy of the IV sessions (ideally within 48-72H). Additional sessions should be performed if substantial congestion persists. Clinical deterioration or a decrease in diuretic efficacy should prompt in-hospital admission in most instances. Our general threshold to discontinue iterative ambulatory IV diuretics is reported in Figure 3, and includes a mixture of clinical response, objective evaluation, and laboratory testing (which can include natriuretic peptides quantification).

Part IV/ How to organize healthcare in order to successfully perform ambulatory IV diuretics?

A/ Hospital at home

“Hospital at home” (HaH) or "home hospitalization" may be used following in-hospital care. This approach can favor the reduction in length of intra-hospital stay, as patients will be closely followed in this home setting following a short initial in-hospital admission. During HaH, in addition to the use of IV diuretics, high-risk behaviors limiting HF care efficacy can be identified (since home is the setting of care).^{66, 67}

Not all patients are eligible for this HaH approach. Patient selection begins with a geriatric and social assessment, involving patient, caregiver(s), attending physician and, if applicable, nurses and social workers. The second step is to determine who will be responsible for the patient’s treatment – either the patient’s GP or a cardiologist.

In our experience, the success of HaH following in-hospital management of WHF relies on daily nursing assessment (weight, blood pressure, heart rate, oximetry and symptoms), home biology and electrocardiogram, remote access to online patient chart, secured remote prescription, close nursing duty, medical on-call service and a process for urgent consultation or rehospitalization.

The efficacy of HaH for HF has been recently systematically reviewed by Qaddoura et al.⁶⁸ The conclusion of this meta-analysis was that only a limited number (3 trials totalizing 203 patients and 3 cohorts totalizing 329 patients) of modest-quality studies were available, in which HaH appears to increase time to readmission, reduce index costs, and improve quality of life.⁶⁸ Notwithstanding the latter, larger trials such as the SAFE-HOME (NCT03156686) and FIL-EAS (NCT04878263) trials are needed to accumulate definitive evidence.

B/ Day hospital

Much of the published clinical experience regarding ambulatory IV diuretics is currently derived from a day hospital setting.⁵⁷ This outpatient venue enables delivering 3-hour IV diuretic infusion, which is obviously not possible in a consultation setting and requires dedicated space and resources. A nurse would be devoted to the surveillance of the patient's vitals every hour, as well as verify diuresis and natriuresis, and perform blood tests if needed. In a day hospital setting, early low diuresis can be offset using thiazide or MRA during the second half of the infusion session, thanks to the close monitoring of the nurse.

At the end of the session, the patient's status is reassessed to determine whether the IV infusion was sufficiently effective for the patient to be discharged and plans are made for subsequent infusions. Typically, 2 to 3 infusions during the first week of treatment for WHF are needed to achieve decongestion and improve clinical status. In most severe cases, a continuous infusion of IV diuretics for 6 hours may be required, which will be perceived much less negatively by the patient than regular hospitalizations requiring overnight stay. In the next days, an ambulatory short-term telemonitoring is useful to verify the favorable impact of the diuretic assault. Repeated natriuretic peptides measurements can also be useful to monitor decongestion.

A day hospital setting has additional benefits. For instance, it can favor a multidisciplinary approach and, during the day-hospital management, patients can be cared for by therapeutic education nurses, dieticians, and other healthcare professionals for additional counseling and reevaluation aiming at preventing further episodes of decongestion.

In order to be efficiently used, as in the case of home hospitalization, this facility should be easily accessible to eligible patients. Typically, day hospital sessions should be performed within 24 to 48 hours of the identification of moderate WHF during a consultation at an HF clinic, within disease-management programs or home monitoring. To maximize efficacy, the coordinative link between the day hospital and these other facilities should be optimal, possibly included in the same parent organization/network. This integration is crucial since a close follow-up is needed following the IV infusions to determine whether additional sessions are required. As for "classical" WHF requiring ward hospitalizations, congestion episodes tend to recur. These relapses need to be quickly managed in additional day-hospital sessions, within an organized healthcare network.

Part V/ Management following ambulatory IV diuretic treatment

A/ Background HFrEF treatment optimization

Given the significant decongestion effect of RAASi⁴³ and rapid improvement in outcome after initiation of contemporary GDMT, every attempt should be made to optimize the non-loop diuretic HF GDMT after the resolution of congestive episodes following ambulatory IV diuretic therapy. The up-titration of drugs (initiation/switch to sacubitril/valsartan, as well as initiation of MRA and SGLT2 inhibitors) could be perceived as difficult to achieve in this context given that WRF is often observed during or following WHF. A practical approach to HF treatment management in the setting of WRF¹⁸ and low blood pressure³⁷ has moreover been published. Importantly, in the month following the IV diuretic session, we recommend a weekly assessment by an HF physician or nurse practitioner in order to adjust the diuretic dose and optimize/up-titrate the GDMT.

B/ HFpEF and HFmrEF treatment optimization

Importantly, patients with HFpEF and HFrEF are similarly affected by WHF and diuretic strategies in ambulatory clinics appear to have similar benefit for those with HFpEF as it did for HFrEF⁵⁷. Medical optimization is advisable for patients with HFpEF (LVEF $\geq 50\%$) or HF with mildly reduced EF (HFmrEF; LVEF 41-49%) following decongestion. Initiation/up-titration of MRAs⁷⁰ in this setting may be associated with better outcome and should be considered in patients with HFpEF. In the PARAGON-HF study, use of sacubitril/valsartan for patients with LVEF $\geq 45\%$ was associated with reduction of HF hospitalization in patients with LVEF $< 55\%$ and women⁷¹. In the EMPEROR-Preserved trial, empagliflozin reduced the HF hospitalization by 27% ($p < 0.001$) in patients with LVEF $> 40\%$.⁵⁵

C/ How to down-titrate diuretics after a temporary increase in ambulatory patients?

Despite the importance of loop diuretics in HF management and related adverse events, little effort has focused on “optimizing” diuretics. A number of tools could help optimize diuretic treatment, including natriuretic peptide monitoring⁷⁵, pulmonary arterial pressure remote monitoring⁶⁰ or serial ultrasound imaging of the inferior vena cava, but in routine practice only clinical assessment is used in the vast majority of cases. Importantly, the first step should be to establish whether the previous dose should be considered as the correct posology or whether a higher dose is required. As a general rule, if the previous dose did not prevent WHF, a higher dose should be maintained for at least 3-4 weeks. Reinforcing GDMT will eventually help the down-titration of loop diuretics.

Part VI Barriers to the implementation of these healthcare organizations

There are several existing barriers to overcome in the application of these new patient management pathways (Table X).

- 1) Limited clinical trial evidence (despite a larger use in observational studies¹⁴) to document the efficacy or non-inferiority of these alternative therapeutic approaches.
- 2) Further validation of the protocols for the use of diuretics and associated drugs: dose validation, intravenous access, periodicity, clinical and laboratory monitoring.
- 3) Formal endorsement by healthcare insurance providers: these pathways need to be funded (and possibly promoted) by the health insurance sector.
- 4) Formalized approach to medical responsibility. In an ambulatory setting, determining who is the physician in charge of the patient's management may be less straightforward than in an inpatient setting.
- 5) Formalized process 24/7 for "rescue" management by emergency departments.
- 6) Health data transfer/ exchange between the different healthcare providers.

The main limitation of the implementation of the approach proposed herein could be its actual integration within the patient's immediate healthcare environment. Ambulatory care may be impossible or impractical if the local health network is not sufficiently reliable or adapted to perform such management. The minimum requirements for the implementation of ambulatory IV management likely include: 1) clinicians available for clinical reassessment, treatment adjustments, and triage toward hospitalization or urgent visits in HF clinics, 2) nurses available at home for blood sampling/tests, clinical assessment (weight, vital signs), 3) social support (meals at home, for instance), 4) a direct link of these professionals with a dedicated HF team. All should be efficiently connected through a healthcare coordination framework, ideally available 24/7, but more realistically, operating during regular hours. Importantly, some of these issues could be alleviated by telemonitoring, e.g. for changes in weight or symptoms, and empowering patients and their careers.⁷⁶

Conclusion

The rising pressure on healthcare systems will preclude continuing treating all episodes of worsening heart failure with lengthy hospital admissions. Therefore, there is a mutual interest for both patients and healthcare providers to favor ambulatory therapeutic approaches that deliver IV diuretics to improve congestion and well-being, and save costs and resources. Future trials will clarify safety and effectiveness of these models of care and identify patients more likely to gain benefits. It is likely that ambulatory delivery of IV diuretics will soon no longer be an option, but rather a new norm.

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Conflict of interest

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Idorsia, NovoNordisk, Ablative Solutions, G3P, Corvidia, Relypsa, and is the cofounder of CardioRenal, a company developing a telemonitoring loop in heart failure (including potassium measurements). Dr Roubille reports grants, personal fees and non-financial support from Novartis, Servier, Abbott, MSD, Sanofi, Bayer, BMS-Pfizer, Air Liquide, Abiomed, Resmed and Medtronic.

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Table 1: Principal pharmacological properties (PPP) of drugs with diuretic effects (adapted from Mullens et al.¹⁶).

	Natriuretic effect when used in monotherapy (FENa%)	Time to peak efficacy	Half-life	Bioavailability	Side effects
Loop diuretics	25-30%	PO: 0.5-1hour IV: 5-10 minutes	3 hours	Highly variable for oral furosemide 90% for bumetanide/torsemide	Important RAAS activation Diuretic resistance induced by compensatory DCT hypertrophy Hypokalemia Hypomagnesemia Hyperuricemia Gout
Thiazide-like diuretics	10% Loop-diuretics potentializing ++++	PO: 1-6 hours IV: only chlorothiazide with onset of 30 minutes	HCTZ=6-15 hours Metozalone=6-20h Chlortalidone=45-60h	HCTZ=65-75% Metozalone=60-65% Chlortalidone=NA	RAAS activation Hypokalemia Hyponatremia Hyperuricemia Gout Hypercalcemia Hypomagnesemia
MRAs	2%	PO: 48-72 hours IV: potassium canreonate: 2.5 hours	Eplerenone=3-6 hours Canrenone=17 hours	Spironolactone=90% Eplerenone=70%	Hyperkalemia Average increase in serum potassium=0.4 mmol/l
SGLT2i	3% Loop-diuretics potentializing ++	PO: 1.5-2 hours	12 hours	80-90%	keto-acidosis (in patients treated with insulin)
Acetazolamide	Heavily depends on subsequent tubular segments	PO: 2 hours	6 hours	>90%	Hypokalemia Metabolic acidosis Hyponatremia
Amiloride	2%	PO: 6 hours	6-9 hours	50%	Hyperkalemia Hyponatremia

Table 2: Factors to be considered to select patients to be treated with IV diuretics in an ambulatory setting.

	In favor	Against
Clinical scenarios	Progressive worsening HF ^{57, 61} HR : 50-120bpm ⁷⁷ PAs >100mmHg ⁷⁷ SaO2 >92% ⁷⁷ Alert from remote HF monitoring ⁷⁷	First episode of HF ⁵⁶ Critical trigger ⁷⁷ (Rapid arrhythmias, acute coronary syndrome) NYHA IV ⁷⁷ Anasarca ^{57, 61}
Heart Failure profiles	Cardiac amyloidosis ⁵⁹	Very high dose of oral diuretics (500mg or more furosemide/day)
Comorbidities	Frailty ⁷⁸ Palliative care ⁷⁸ (especially for Hospital at home)	Severely impaired eGFR (p.e. <25) ⁷⁷ Severe dysnatremia, dyskalemia or anemia ⁷⁷
Social criteria	Patient preference ⁷⁸ Adequate living support ⁷⁸	Difficult/Unsanitary living conditions ⁷⁸ (for at home hospital)

Figure 1. Nephron sites and target ion channels with approximate natriuresis/diuresis effect of the various diuretic classes. Na, sodium; K, potassium; Cl, chloride; RAAS, renin-angiotensin and aldosterone system; GFR, glomerular filtration rate; IV, intravenous; SGLT2, sodium-glucose linked transporter-2.

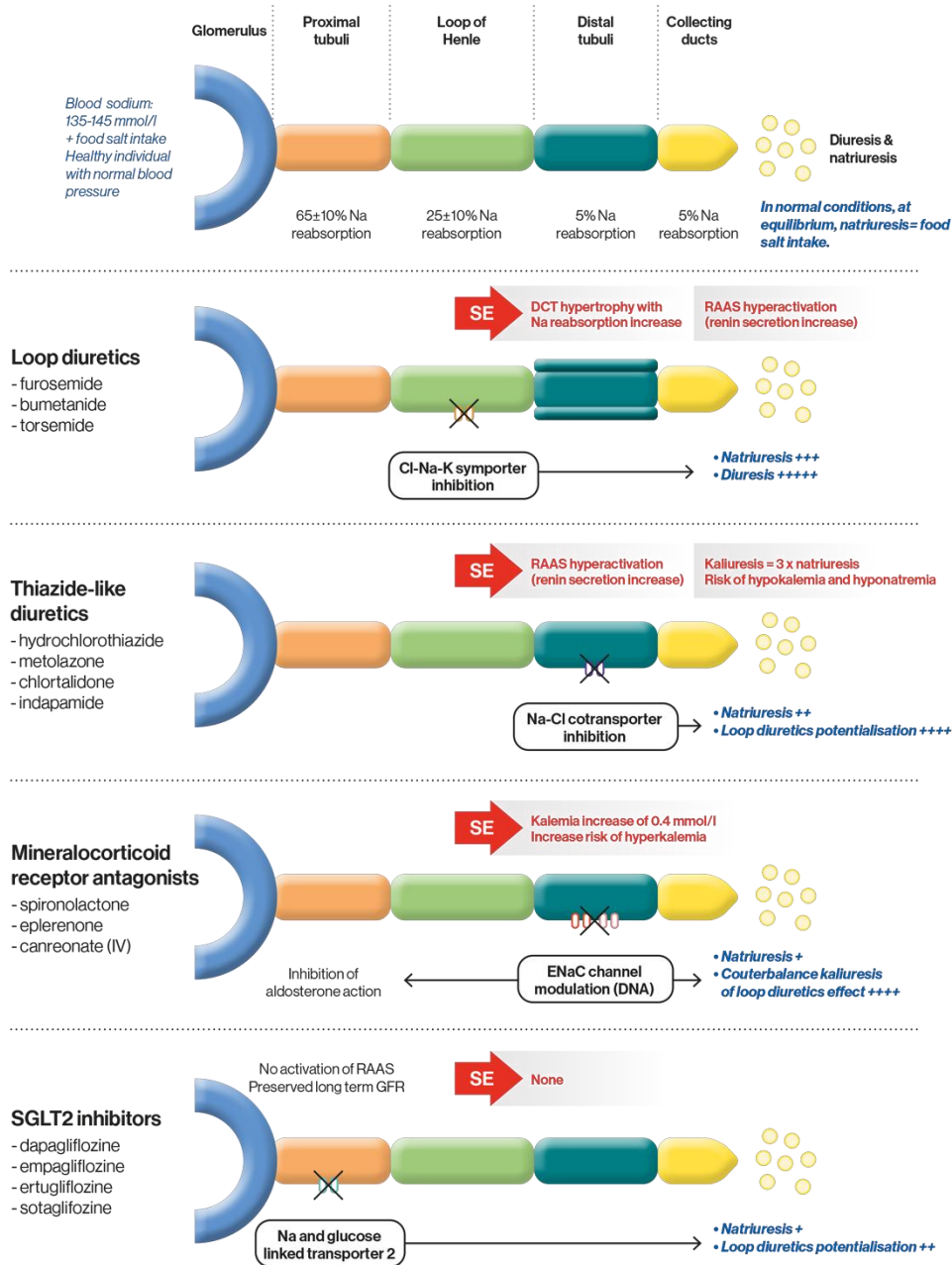
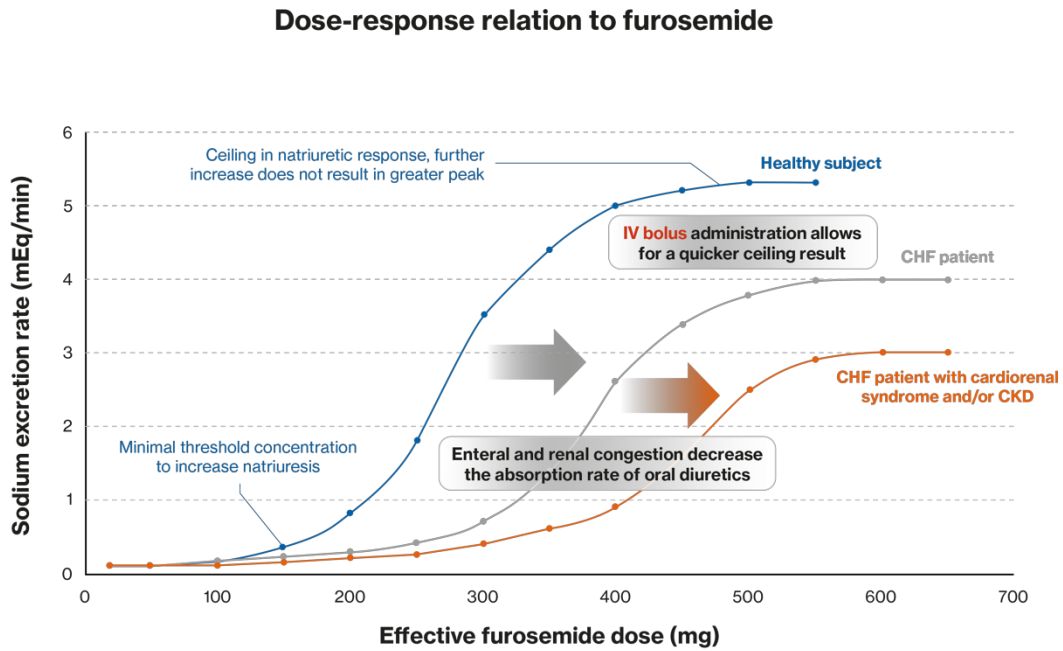


Figure 2. Shift in dose-response relation to furosemide in patients with chronic heart failure (adapted from Brater et al.²⁰).



Renal function (as measured by estimated glomerular filtration rate) has an important impact on the dose-response curve to furosemide: Higher dosing is needed for lower estimated glomerular filtration rate. This is the underlying reason of the right shift observed for patients with CHF and cardiorenal syndrome and/or CKD (orange curve).

Figure 3: Framework for ambulatory IV diuretics use

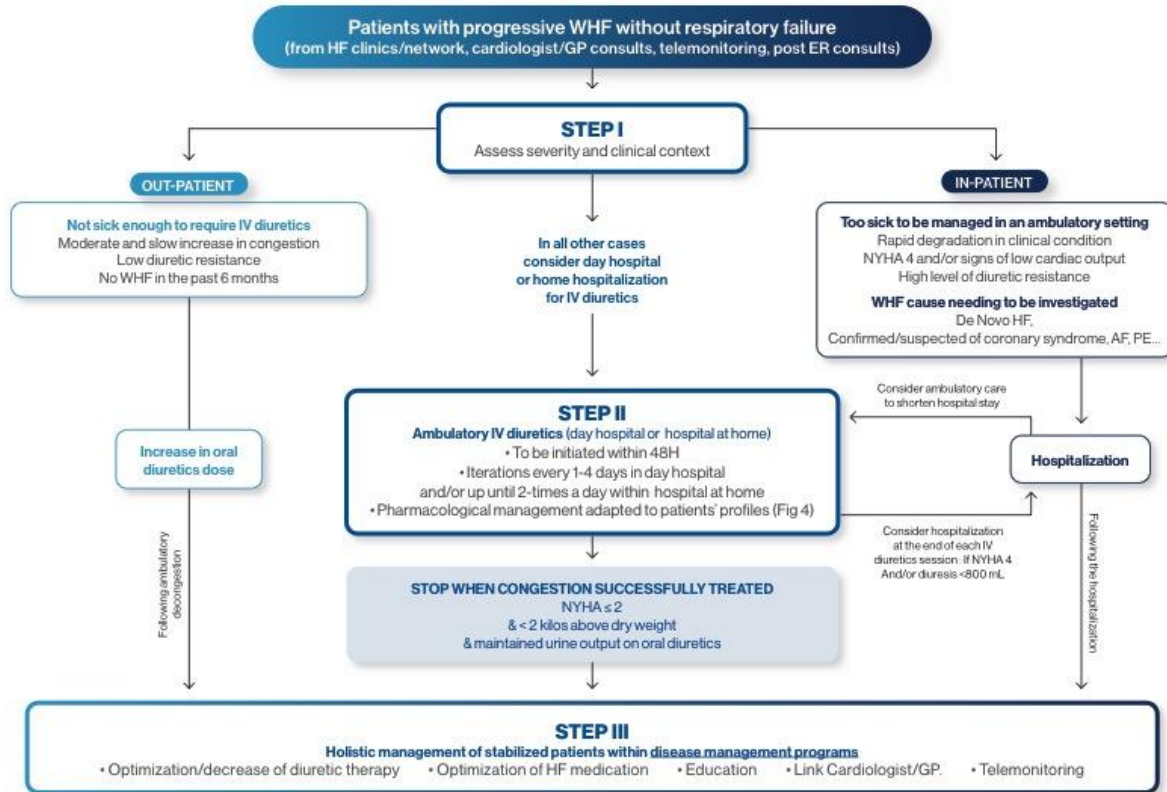
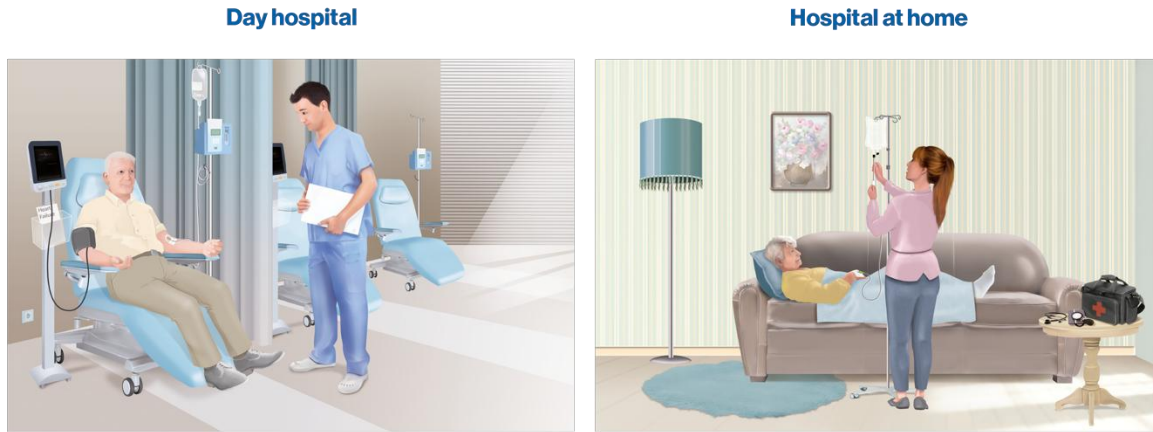


Figure 4: Ambulatory IV diuretics protocol according to maintenance loop diuretic dose



Category	Maintenance furosemide equivalent dose (mg)*	IV Furosemide dose			If inadequate urine output (<500ml) after 90 min of infusion	Oral potassium supplement during the furosemide infusion	Parallel Intervention	Monitoring
		Bolus mg**	Infusion mg/hr During 2 to 3 hours***	SC Furosemide infusion dose				
Low dose	≤ 40	20	20	40 mg over 5 hours				Day hospital setting
Standard dose	41-160	Numeric equivalent of maintenance diuretic dose	20	2/3 of numeric equivalent + 40 mg				<ul style="list-style-type: none"> • Monitor HR & BP, every hour • Quantify diuresis and natriuresis
High dose	161-300	200	20	160 mg				At-home hospitalization setting
Mega dose	≥ 301	200	20	160 mg	Additional 200 mg bolus of furosemide and/or (thiazide diuretic† or 100 mg potassium canrenoate)	<p>K⁺ > 4 mmol/l, No potassium supplement</p> <p>K⁺ 3.7 to 4.0, 20 mEq**** if creatinine <20 mg/L</p> <p>K⁺ 3.4 to 3.6, 40 mEq if creatinine <20 mg/L, 20 mEq if creatinine 20-28, 10 mEq if creatinine >28</p> <p>K⁺ 3.1 to 3.3 40 mEq if creatinine <20 mg/L, 30 mEq if creatinine 20-28, 20 mEq if creatinine >28</p> <p>If K⁺ <3.1, achieve potassium >3.1 before diuretic infusion.</p>	<p>Continue guideline directed medical therapy (RAASi/ SGLT2i /ARNi)</p> <p>Consider increasing / initiating MRAs and/or thiazide in case of diuretic resistance</p>	<ul style="list-style-type: none"> • Monitoring 2 to 3 times a day • Monitor HR & BP prior and 5 minutes after the bolus <p>Following the infusion</p> <ul style="list-style-type: none"> • After the IV diuretic session, in all patients, monitor creatinine and potassium levels within 7 days of IV diuretics infusion

Dose of IV furosemide depends on the maintenance diuretic dose.
 Infusions were administered over 3h. **In home hospital setting, only bolus are usually performed.**
 * Total daily dose expressed in the equivalent of milligrams of oral furosemide.
 ** Bolus infusion, consider prescribe higher dose in patient with low eGFR.
 † Metolazone, 125 mg to 10 mg, hydrochlorothiazide 12.5 mg to 50 mg. IV: intravenous, HR: Heart Rate, BP: Blood pressure, RAASi: renin-angiotensin-aldosterone system inhibitor, SGLT2i: sodium-glucose transporter 2 inhibitors, ARNi: angiotensin receptor neprilysin inhibitors
 *** infusion is usually not possible in the setting of at-home hospitalization
 **** 10 mEq approximately corresponds to 400 mg of potassium ion and 760 mg of potassium chlorur

These doses are general guidelines that need to be adapted to renal function. Patients with eGFR <30 ml/min/1.73m² usually need higher (usually doubled) diuretics dose.