Diuretics In Stable Outpatients with Mild Heart Failure – May I Discontinue Them?

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Heart failure: congestion and diuretic therapy

Congestion is a key component of the pathophysiology of heart failure (HF) and causes some of the cardinal symptoms of the disease, such as edema, orthopnea, and dyspnea on exertion. Congestion management is, therefore, of utmost importance for a successful HF treatment. Management is based on the prescription of loop diuretics for symptomatic patients according to different guidelines, although there are no placebo-controlled studies that support their use for reducing mortality.[1,2] When they are administered alone or in combination with other drugs, diuretics improve functional capacity and quality-of-life scores by reducing preload, ventricular filling pressures, and mitral regurgitation, resulting in increased cardiac output.[3]

Congestion assessment is essential in diuretic optimization. Within this context, we should consider the low accuracy of clinical signs of congestion, especially when these signs are used alone.[4] Conversely, concomitant assessment of several factors – including New York Heart Association (NYHA) functional class, orthopnea or paroxysmal nocturnal dyspnea, edema, pulmonary rales, third heart sound, hepatojugular reflux, and jugular venous distension – can identify patients at higher risk when they are grouped together by congestion scores.[5] Additional tests increase predictive value and contribute to decision-making. The most common methods are serum natriuretic peptide measurement and imaging tests such as chest radiography, lung ultrasound, and echocardiography. They may be considered before diuretic discontinuation and for monitoring blood volume, especially in doubtful cases.

Loop diuretics are potentially associated with electrolyte disturbances, worsening renal function, and hypovolemia, causing hypotension and limiting the adjustment of disease-modifying drugs (DMDs).[6] Thus, the optimal dose of loop diuretics in HF should be the minimum dose capable of keeping the patient euvolemic. In Table 1, the mechanisms of action, indications, and adverse effects of different diuretic drugs are specified. The discussion herein is essentially about the discontinuation of loop diuretics when they have already fulfilled their role and become potentially harmful, since, in addition to various adverse effects, they may also limit the therapeutic optimization of drugs that will in fact impact the natural history of HF and patient survival.

Observational data suggest that high-dose diuretics are associated with poor clinical outcomes.[7] Eshaghian et al. evaluated a cohort of 1,354 patients and demonstrated, even after adjusting for all other disease severity factors, a strong and independent association of high-dose furosemide with worsening survival.[8] Dini et al. also evaluated a cohort and identified a threshold furosemide dose of 50 mg/day as a predictor of 3-year mortality regardless of renal function, left ventricular filling pattern on echocardiography, and background therapy.[9] Coiro et al.[10] used a patient sample from the EMPHASIS-HF study and demonstrated that the use of loop diuretics is a prognostic factor in HF with reduced ejection fraction (HFrEF) with an impact comparable to traditional markers, such as recent hospitalization and B-type natriuretic peptide. Higher doses lead to a higher risk.[10]

Conversely, the prescription of high-dose diuretics is linked to more advanced HF, as shown by Pellicori et al.[11] Therefore, the need for diuretics would be the factor that is associated with a higher risk, not their potential deleterious effects. We should also consider that not prescribing diuretics or prescribing suboptimal doses would lead to residual congestion, especially in the period following hospitalization for acute HF, and this is associated with poor outcomes.[12] Thus, the safety and benefit of diuretic discontinuation in patients with HFrEF will only be determined by placebo-controlled, randomized clinical trials.

Compensated heart failure: safety of diuretic discontinuation – ReBIC-1 (Figure)[13]

Furosemide is commonly prescribed for symptomatic relief in patients with chronic HF, although few studies have provided robust data on the benefit of diuretics in compensated patients with mild symptoms and in a euvolemic state. Until the publication of the ReBIC-1 study in 2019, there was tremendous concern about the safety and tolerability of furosemide withdrawal in stable patients. This prospective, double-blind, randomized study included 188 patients with left ventricular ejection fraction (LVEF) < 45% for diuretic discontinuation or standard treatment. Inclusion criteria were being on low-dose furosemide (40 to 80 mg), no visits or hospitalizations in the past 6 months, being stable and NYHA class I or II, and receiving optimal therapy with DMD.[13] Patients with clinical congestion, based on a clinical congestion score > 5 points,[5] were excluded. Primary endpoints were

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Table 1 – Diuretics: mechanism of actions, indications, and potential side effects

	Mechanism of action	Effect on mortality	Indication	Side effects
Loop diuretic	Reduces sodium reabsorption in the thick ascending limb of the loop of Henle by inhibiting the Na-K-Cl^{-2} transporter.	No	Congestion management	Allergic and hypersensitivity reactions such as rash, electrolyte disturbances (hypokalemia, metabolic alkalosis), hyperuricemia, interstitial nephritis, and ototoxicity
Thiazide diuretic	Primarily inhibits sodium transport in the distal convoluted tubule.	No	Refractory congestion management	Hyponatremia, hypokalemia, elevated plasma glucose and cholesterol concentrations and magnesium depletion, hyperuricemia, hypercalciuria, and increased risk of kidney stones
Mineralocorticoid receptor antagonist	Acts on the principal cells of the collecting tubules. Reabsorption of cationic sodium without an anion creates a negative electrical gradient into the lumen, which favors secretion of potassium and hydrogen ions.	Yes	Patients with HFrEF (≤35%) who remain symptomatic despite optimal initial drug therapy	Hyperkalemia and endocrine effects (gynecomastia, breast pain, menstrual irregularities, impotence, and decreased libido)
SGLT2i	Inhibits the effects of the sodium-glucose cotransporter 2, which promotes osmotic diuresis and natriuresis, and may reduce preload and, through effects on the endothelium, promote vasodilatation and consequently reduce afterload.	Yes	Patients with HFrEF, with or without T2D, in combination with optimized treatment	Genitourinary infections, reduced bone mineral density, ulcerations with risk of amputation, and increased predisposition to diabetic ketoacidosis

T2D: type 2 diabetes; HFrEF: heart failure with reduced ejection fraction; SGLT2i: sodium-glucose cotransporter 2 inhibitor.

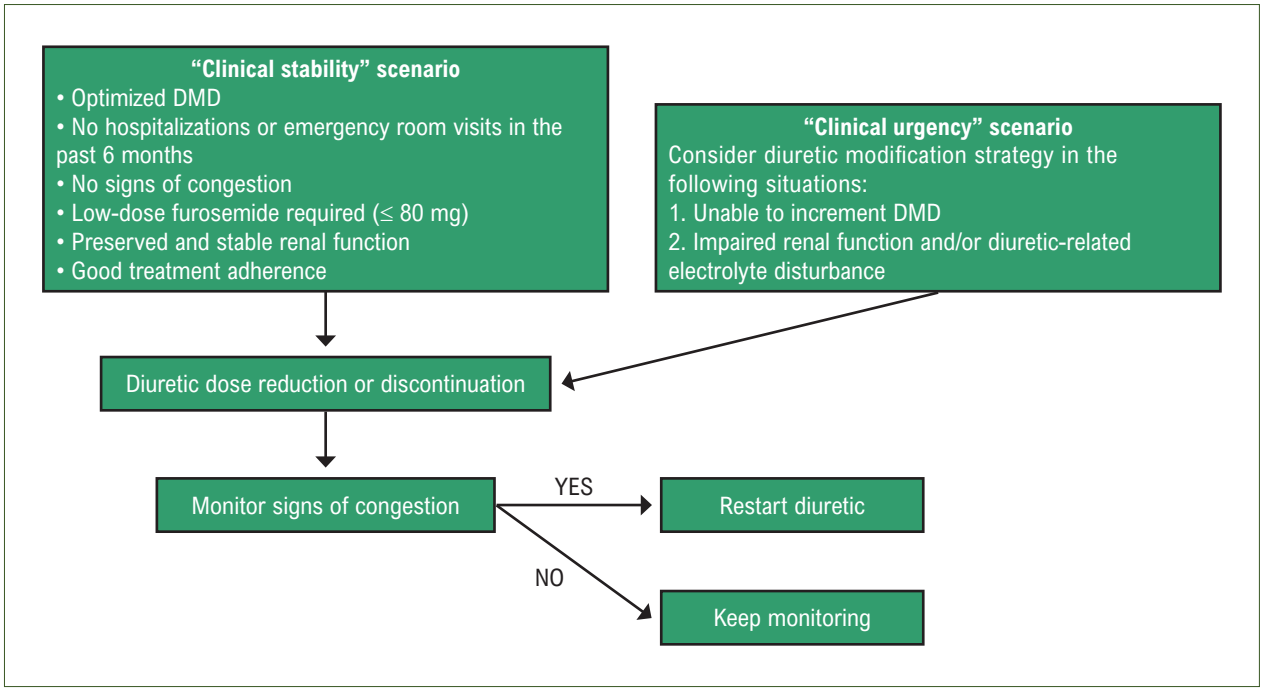

Figure 1 – *Suggested flowchart for using loop diuretics in patients with HFrEF. DMD: disease-modifying drug; HFrEF: heart failure with reduced ejection fraction.*

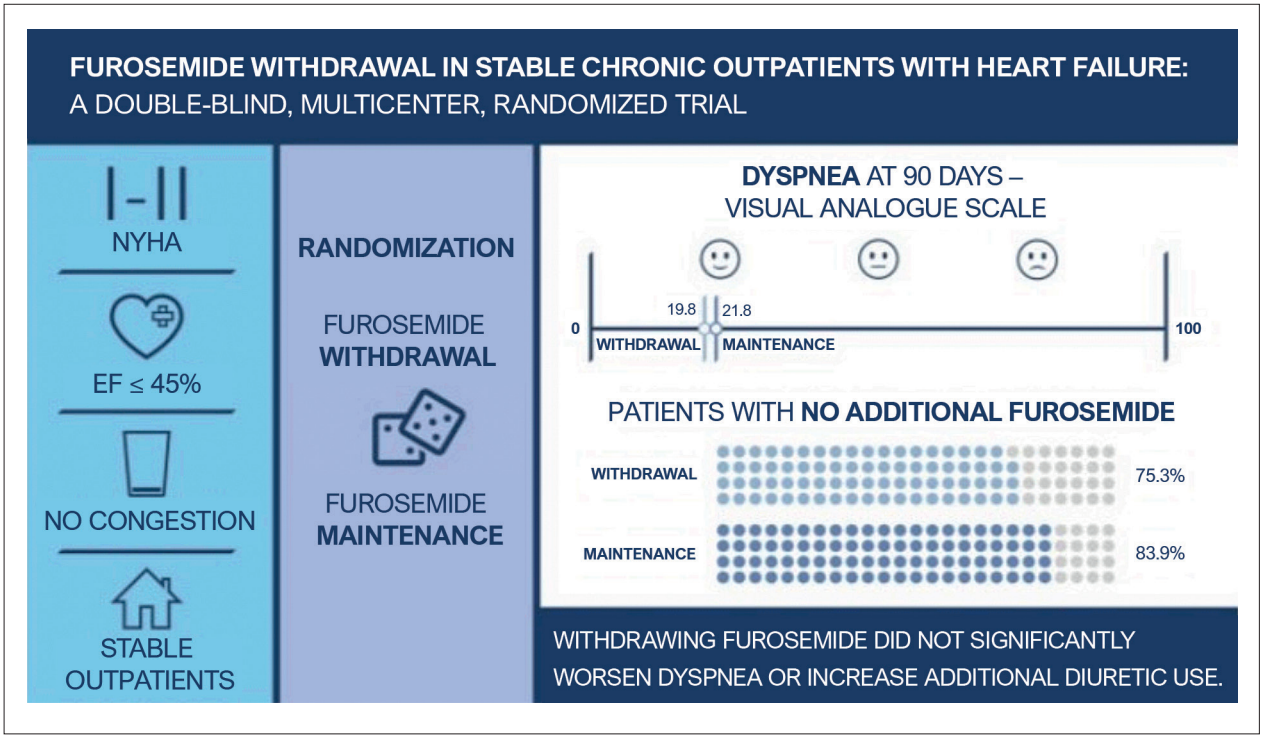

Figure 2 – *Stable chronic outpatients with HF and mild symptoms were randomized to furosemide maintenance or withdrawal – a double-blind, placebo-controlled trial showed no significant change in self-reported dyspnea or increase in the need to reuse furosemide when the groups were compared.*

symptoms measured by a visual analog scale for dyspnea and the proportion of patients maintained without diuretics over the 90-day follow-up period.

Regarding the results, there was no significant difference between the two intervention groups (furosemide maintenance vs. withdrawal) for the co-primary endpoint of patient-reported dyspnea assessed on a visual analog scale ($p = 0.94$). Similarly, no statistically significant difference was observed in the percentage of patients who needed to reuse loop diuretics ($p = 0.16$). The risk of reusing diuretics in the withdrawal group was 1.69 with a wide confidence interval, suggesting statistical uncertainty in the assessment of this endpoint. Patients were followed-up for a short period, during which there was no difference in clinical outcomes between the groups. Because it was a placebo-controlled, randomized clinical trial that evaluated loop diuretic withdrawal, ReBIC-1 can be considered a great contribution to decision-making regarding the safety of discontinuing furosemide in stable patients with chronic disease.

The study had limitations of sample size and follow-up duration, which preclude a conclusion about the effect that diuretic discontinuation would eventually have on the risk of hospitalization and death. Also, as the study was conducted between October 2015 and August 2018, treatment with sodium-glucose cotransporter 2 (SGTL2) inhibitors was not routinely established. DAPA-HF was published in 2019 and showed a 26% reduction in the primary outcome of cardiovascular death or worsening HF, which was significantly lower in the dapagliflozin group.[14] EMPEROR-Reduced evaluated empagliflozin in 3,730 patients with HFrEF, 50.2% of whom had type 2 diabetes. There was a 25% reduction in the primary outcome of cardiovascular death or hospitalization for HF in favor of empagliflozin.[15] These data confirm the results of DAPA-HF and support the rationale for using SGLT2 inhibitors in patients with HFrEF to attenuate symptoms, improve quality of life, and reduce the risk of hospitalization and cardiovascular death. This class may be used to keep patients euvolemic with DMD. Thus, the decision to reduce or discontinue loop diuretics becomes easier and safer in stable patients without congestion in the face of another drug with a diuretic effect that directly reduces cardiovascular events and hospitalizations for HF.

Optimizing blood volume can facilitate the introduction and achievement of the target DMD dose.[16] Reduced diuretic use may decrease hypotension due to initiation of sacubitril-valsartan. In patients with HFrEF, both systolic blood pressure (SBP) and pulse pressure depend primarily on left ventricular stroke volume, while blood pressure and diastolic blood pressure vary according to total blood volume and degree of vasodilatation.[17] Both components are affected by the treatment used in HFrEF. Escalation to target DMD dose may be limited by the presence of hypotension. SBP < 90 mm Hg is an established marker of poor prognosis in acute HF.[18] However, its implications in chronic HF are more complex. SBP is a component of prognostic scores (eg, Seattle model) but does not

necessarily have a causal relationship with adverse events. Patients with lower blood pressure obtain similar benefits from treatment with sacubitril-valsartan and carvedilol compared to patients with higher blood pressure.[19,20]

Conclusion: when to discontinue loop diuretics?

In view of the evidence discussed and considered above, loop diuretics play a crucial role in patients with decompensated HF and signs of congestion. In stable patients with compensated chronic disease, it is increasingly necessary that diuretic use is reduced to make room for therapeutic optimization of drugs that impact the natural history of HF. Hypotension is common in this group of patients and becomes a limiting factor for dose increments. In this setting, the first step should be to reduce or discontinue medications that are not the mainstays of HF treatment, such as calcium channel blockers and alpha-blockers. If symptoms of hypotension persist, the diuretic should be adjusted and even discontinued in euvolemic patients.[17] Importantly, it is essential to monitor these patients frequently and pay attention to signs of congestion and the need to restart the diuretic.

Another specific situation consists of patients with recovered ejection fraction, either through the action of DMD, natural recovery from a condition (eg, myocarditis), or the effect of cardiac resynchronization.[21-23] It is believed that LVEF can be recovered in approximately half of patients.[23] In such cases, DMDs should be maintained as tolerated, and diuretics may be discontinued provided that no associated conditions require their maintenance.

Future randomized studies that evaluate diuretic discontinuation in patients receiving contemporary therapy for HF, including sacubitril-valsartan and SGLT2 inhibitors, and have reduced clinical events as an outcome will be able to solidify the recommendations.

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Conception and design of the research: Rover MM, Jaccottet AC, Sant´Anna RT; Writing of the manuscript and Critical revision of the manuscript for intellectual contente: Rover MM, Jaccottet AC, Calle DV, Sant´Anna RT.

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Ethics approval and consent to participate

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