

Should Combination of Diuretics Always Be Early after the ADVOR and CLOROTIC Trials?

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There has been remarkable progress in the treatment of heart failure (HF) over the past years. Medications such as angiotensin receptor-neprilysin inhibitors, beta blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 inhibitors (SGLT2i), often referred to as the “fantastic four,” have been shown to reduce mortality and hospitalization, in addition to improving patients’ quality of life.¹

The natural history of the disease is characterized by recurrent episodes of decompensation and hospital admission linked to pulmonary and/or systemic congestion. Although diuretics doesn’t reduce mortality, they are universally recommended for congestive symptoms relief in all phenotypes of the disease.^{2,3}

Even though normovolemia has been established as a clear therapeutic target and the persistence of congestion is associated with high rates of rehospitalization and mortality after discharge, research indicates that approximately 50% of hospitalized patients are discharged from the hospital with residual congestion.^{3,4} Achieving normovolemia can be a challenge, especially when congestion is subtle, largely due to diuretic resistance, which is characterized by a diminished renal response to diuretics, resulting in reduced natriuresis and diuresis.^{4,5}

The mechanisms behind diuretic resistance in acute HF are intricate, mostly centered around renal adaptation with distal nephron hypertrophy and subsequent sodium retention.^{2,6} The first approach frequently adopted to overcome this resistance is to intensify the dose of loop diuretics, with controversial benefits regarding different continuous and intermittent infusion strategies. In theory, the combination of different diuretics could also address the mechanisms underlying resistance. However, studies are limited, and questions such as the best approach, the ideal time to introduce the combination, and whether it will translate into clinical benefits are still uncertain.²

Keywords

Heart Failure; Diuretics; Drug Utilization

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To clarify these answers, two clinical trials were published in 2022, seeking to determine whether a combination of different diuretics could offer faster and more effective decongestion.

ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload) was a prospective, multicenter, double-blind trial that evaluated the early addition of intravenous acetazolamide to standard loop diuretic therapy in patients with decompensated HF and evident signs of volume overload. Regardless of ejection fraction, this combination of diuretics achieved the primary outcome, defined as successful decongestion within 3 days, without the need for treatment escalation, and reduced clinical signs of overload, such as edema, pleural effusion, and ascites, and it was associated with greater natriuresis and increased urinary output. It is crucial to highlight that there was no significant increase in adverse events, such as metabolic acidosis, worsening renal function, hypokalemia, or hypotension.^{7,8}

On the other hand, the CLOROTIC (Combining loop with thiazide diuretics for decompensated HF) study, which was also multicenter, randomized, and double-blind, evaluated the combination of hydrochlorothiazide and standard loop diuretic therapy in patients hospitalized for acute HF. Patients must have been using oral loop diuretics at doses of 80 to 240 mg for at least 1 month, which was higher than the dose used by patients in the ADVOR study. The main finding was greater weight loss in 72 hours compared to placebo (mean –2.3 kg versus –1.5 kg; $p = 0.002$), with no improvement in dyspnea reported by the patients.⁹

These studies have made it evident that the combination of different diuretic classes enhances the diuretic effect, providing more effective decongestion in patients hospitalized due to decompensated HF. It is important to highlight that, in both studies, randomization occurred early, within the first 24 hours of admission, convincingly showing an acceptable safety profile. This management differs from common practice, where the combination of a second diuretic is used only as rescue therapy for inadequate response to the initial treatment.

It is, thus, understood that the use of intravenous furosemide may not be sufficient to treat congestion in a scenario of HF decompensation, and the combination of different diuretic classes has a beneficial and safe effect. Nevertheless, questions remain about which combination is most appropriate and whether the initial administration is ideal for all patients who are hospitalized for acute HF.⁸⁻¹⁰

In our view, the early combination of different diuretic classes can bring benefits; however, individual analysis is essential to decision-making. It is important to highlight that the ADVOR and CLOROTIC studies did not include patients who had never used diuretics or those with daily doses of less than 40 mg of furosemide for at least 1 month before randomization. Accordingly, combination of diuretics should not be the first choice for patients on lower doses of loop diuretics.^{8,9}

The benefits shown in ADVOR did not have a long-term impact on major outcomes such as death and readmission due to HF, although the study was not designed for this purpose. It is important to mention that the patients were not using SGLT2i; therefore, its concomitant use with acetazolamide was not evaluated. However, considering that SGLT2i are responsible for only 5% of sodium uptake in the proximal convoluted tubule, with no significant increase in natriuresis, there is no solid physiological basis to suppose that the effect of acetazolamide would be affected by the presence of SGLT2i, or that there would be any risk associated with the simultaneous use of both agents. We emphasize that acetazolamide should be considered as a diuretic for temporary use in the treatment of volume overload, while SGLT2i are disease-modifying medications intended for chronic use, and they should be started within 3 days after admission for decompensated HF or maintained in the event of prior use.

For patients hospitalized with decompensated HF who are already using high-dose diuretics or patients with evidence of diuretic resistance (reflected by the dosage and duration of diuretic use in the outpatient setting and baseline renal function), it is recommended to administer an initial loading dose of a loop diuretic (at least double the outpatient dose). The diuretic response in these patients must be rapidly assessed, either by urine sodium concentration or by 6-hour urine volume. Patients who do not demonstrate an adequate response may be candidates for earlier introduction of a combination of diuretics, rather than only escalation of the loop diuretic.

Once the choice has been made to combine diuretics, considering the benefits observed with both acetazolamide and hydrochlorothiazide, we believe that an individualized approach will guide the best strategy. A subanalysis of the ADVOR study revealed that, due to the medication's mechanism of action, patients with serum bicarbonate ≥ 27 mmol/L had a more pronounced diuretic and natriuretic response with acetazolamide. In contrast, hydrochlorothiazide was associated with major electrolyte disturbances, such as hyponatremia and hypokalemia, as well as a greater propensity for arterial hypotension; thus, it is not the first choice for patients with these disorders or with hypotension (Figures 1 and 2). It is important to note that the results of the ADVOR study refer to the intravenous use of acetazolamide, and this formula is not available in Brazil. Therefore, the findings are extrapolated to the oral use of acetazolamide.^{8,9}

In hospitalized patients with decompensated HF who show clear signs of congestion, the primary therapeutic focus is to achieve decongestion quickly and aggressively.

Within this context, the addition of acetazolamide or thiazide diuretics to loop diuretics, aiming for sequential action in the nephron, has been shown to be both safe and effective. However, it is imperative to conduct further studies, including patients using SGLT2i, in order to confirm these findings and clarify the best diuretic approach (Figure 3).^{10,11}

Author Contributions

Writing of the manuscript, Critical revision of the manuscript for important intellectual content and Creation of figures: Kobbaz N, Monferdini L, Andrade FA, Freitas Jr. AF

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

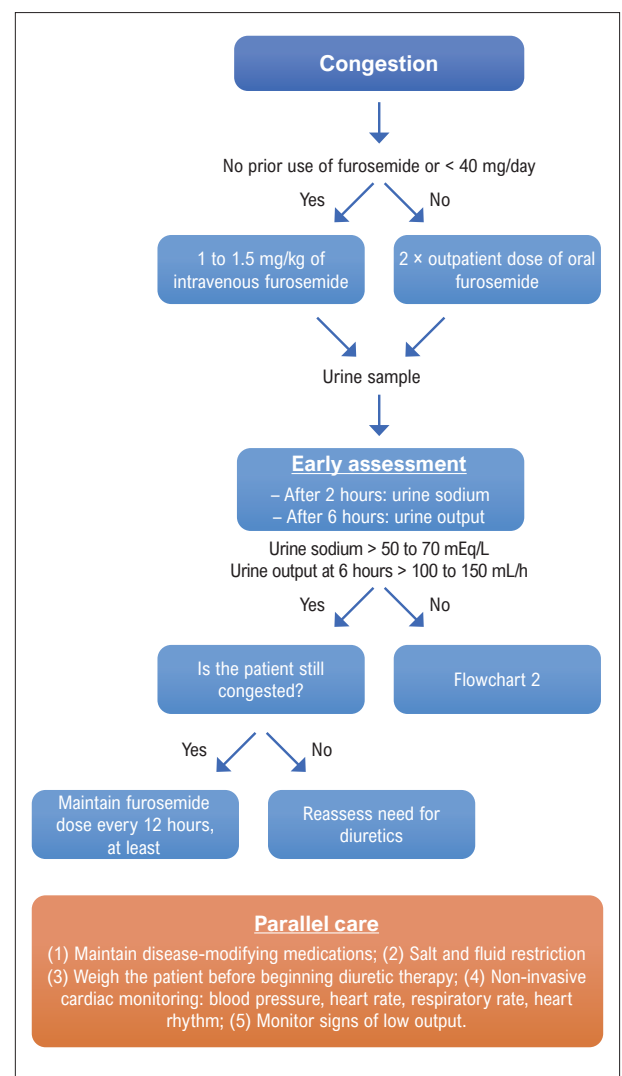


Figure 1 – Flowchart for initial treatment of congestion.

Viewpoint

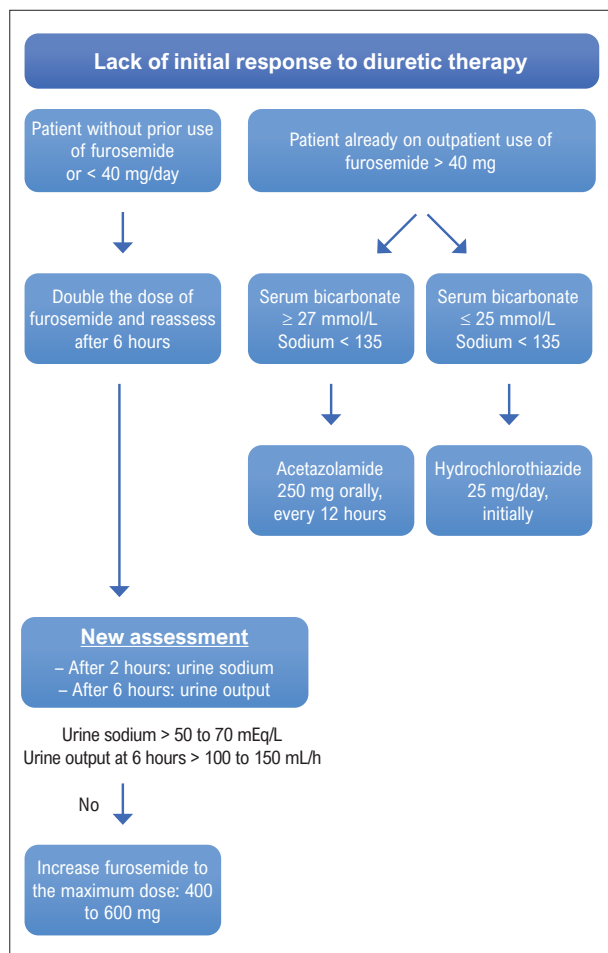


Figure 2 – Flowchart for treatment of congestion refractory to initial diuretic therapy

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This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

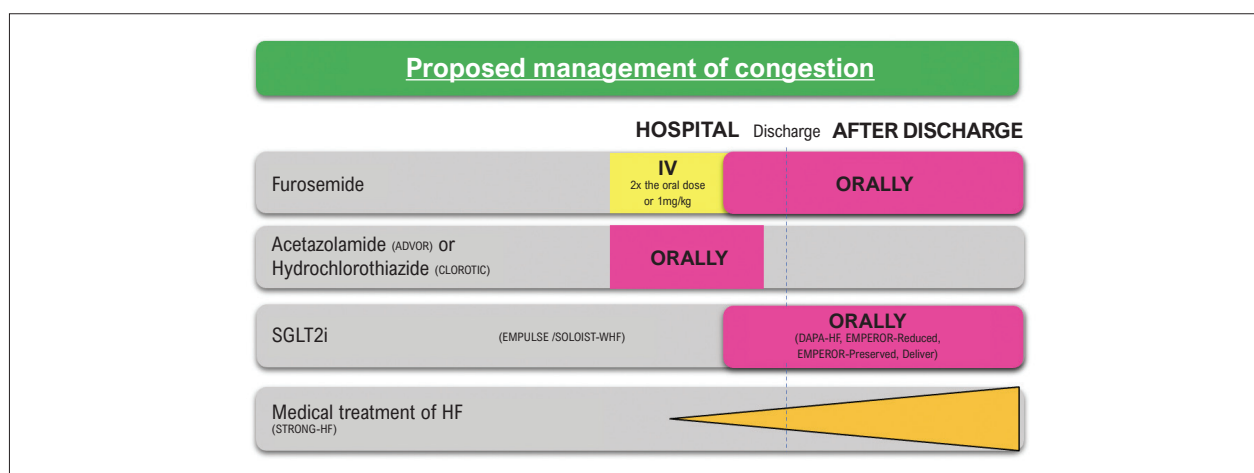


Figure 3 – Proposal for managing congestion during hospital admission and after hospital discharge, including standard treatment of heart failure. Adapted from Mullens et al.¹⁰ HF: heart failure; IV: intravenous; SGLT2i: sodium-glucose cotransporter 2 inhibitors.

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