Timing for combined diuretic therapy in acute heart failure: should we continue waiting for the poor response?

Van Duc Hanh [1] ✉, Piter Martínez Benítez [2], Bui Vinh Ha [1,3], Yanitsy Chipi Rodriguez [2]
Vu Huy Son [2], Nguyen Thi Quynh [2], Chu Thi Ha My [2]

[1] Vietnam National Heart Institute, Bach Mai Hospital

[2] Hung Vuong General Hospital

[3] Hanoi Medical University

▶ **Correspondence to**
Dr. Van Duc Hanh
Vietnam National Heart Institute, Bach Mai Hospital
Email: duchanhvan@gmail.com

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ABSTRACT

Decongestion is an important primary goal in acute heart failure treatment. Loop diuretics remain a fundamental role in congestion management and symptom improvement in patients with acute heart failure. Diuretic combination contributes to achieving better diuretic efficacy. However, the optimal timing for diuretic combination in clinical practice has not been distinctly recommended in current guidelines.

Keywords: acute heart failure, congestion, diuretic combination.

INTRODUCTION

Acute heart failure (AHF) is a clinically complex condition characterized by severe signs and/or symptoms of heart failure that require unplanned or emergency medical support.[1] In-hospital mortality, short-term, and long-term mortality rates are high in patients with AHF patients especially in the elderly.[2,3] Congestion accounts for nearly 90% of patients with AHF and may predominantly occur in the vascular system (intravascular congestion) or in the interstitium (tissue congestion), or often involves a combination of both mechanisms.[2,4] Congestion which resulting from increased left ventricle filling pressures, plays a significant role in the pathophysiology of organ damage in patients with AHF.[5] Improving congestion is one of the primary goals in the immediate phase of AHF management.[1] Loop diuretic is mentioned as cornerstone therapy in alleviating congestion in AHF patients. Additionally, combining other diuretics such as thiazides, acetazolamide, or tolvaptan with loop diuretics has been shown to improve congestion and symptoms.[1,4,6–8] However, the optimal timing for combining diuretics has not been uniformly established in recommendations.[1,6,8] This review will summarize the evidence regarding the timing of diuretic combination. Should we initiate diuretic combination therapy early or wait for clinical poor response before adding a second diuretic agent in patients with AHF?

METHODOLOGY

A review of the literature related to the therapeutic management of acute heart failure was carried out. The searches were carried out in Vietnamese and English language, in specialized databases of medical

publications such as PubMed/Medline, Scopus, Epistemonikos, SciELO and Trip medical database.

The search terms acute heart failure, decongestion and combined diuretic therapy were used as keywords. The inclusion criteria were established: the period of publication of the articles, between 1994 and 2023; the design of the study: randomized clinical trials, systematic reviews with meta-analysis, systematic reviews without meta-analysis, exploratory reviews, clinical practice guidelines. Approximately 86 original and review articles were consulted and 28 were selected. Articles written in languages other than those mentioned above were excluded.

IMPROVING CONGESTION WITH DIURETIC COMBINATION IN ACUTE HEART FAILURE

Congestion is defined as the accumulation of fluid in the intravascular compartment and the interstitial space, resulting from increased cardiac filling pressures caused by renal sodium and water retention.[9] Fluid accumulation originating in the intravascular compartment leads to decompensated heart failure, progressively elevating venous pressure, resulting in tissue congestion. Most AHF patients exhibit a combination of intravascular and tissue congestion, although dominance of either mechanism may occur. In cases of predominant intravascular congestion, patients often present with high blood pressure along with signs and symptoms such as increased jugular venous pressure, dyspnea, third heart sound (S3), and orthopnea. Vasodilators play a crucial role in managing these cases. Conversely, in cases of typical tissue congestion, patients frequently exhibit pitting edema, rales, and ascites, where intravenous diuretics are a preferred option.[4]

Several congestion scores such as EVEREST, EMPAROSPONSE-AHF, OPTIMIZE-HF, ASCEND-HF, and PROTECT have been established based on peripheral edema, orthopnea, dyspnea, jugular vein distension, rales, fatigue, and NT-proBNP levels. [4,10–15] In clinical practice, assessing congestion levels can be based on orthopnea, jugular venous pulsation, hepatomegaly, edema, 6-minute walk test, NT-proBNP levels, chest X-ray, inferior vena cava diameter, and lung ultrasound.[7]

Loop diuretics which inhibit the Na-K-2Cl symporter at the ascending loop of Henle, promoting sodium and chloride excretion.[16] For congestion management, loop diuretics help improve respiratory status and reduce left ventricular filling pressure.[17] AHF patients exhibit a decreased response to loop diuretics compared to healthy individuals. Additionally, there might be diuretic resistance due to increased catecholamines in those manifesting clinical congestion.[18] Hence, using intravenous loop diuretics with suitable doses is recommended. Moreover, diuretic response should be evaluated every 2 or 6 hours of diuretic therapy to adjust loop diuretic dosage.[1,8] Higher dose of loop diuretics are associated with adverse effects such as diuretic resistance, neurohormonal activation, electrolyte imbalances, and worsening renal function. Combining other diuretics such as thiazides, mineralocorticoid receptor antagonists, acetazolamide, and vasopressin antagonists may enhance the diuretic effect to mitigate these adverse effects and augment efficacy.[19] Although blood filtration may be considered in refractory congested patients despite high-dose diuretics or diuretic combinations, its superiority over conventional pharmacological treatment in AHF patients with renal impairment remains unproven.[1,8,20] Recent trial designed to demonstrate the effectiveness of SGLT2 inhibitors on congestion relief in AHF patients.[21]

TIMING FOR DIURETIC COMBINATION IN ACUTE HEART FAILURE

Some observational or randomized controlled trials with small sample sizes have demonstrated the increased diuretic effect of a second diuretic agent in combination with furosemide in AHF patients (Table 1). However, the timing of combining these medications is not explicitly addressed and lacks consistency across studies.[21–25] Notably, two recent large-scale studies, CLOROTIC and ADVOR trials, observed clinical efficacy but also lacked uniformity regarding the timing of combining diuretics. The CLOROTIC trial, encompassing

230 AHF patients with an average age of 83 years old, of whom 48% were female, indicated that combining hydrochlorothiazide (HCTZ) with loop diuretics improved diuretic response in AHF heart failure patients by enhancing weight loss at 72 and 96 hours. However, there was no difference observed in improving dyspnea between the two groups. Additionally, the HCTZ diuretic group exhibited a significantly higher incidence of renal impairment compared to the placebo group (46.5% in the HCTZ group vs. 17.2% in the placebo group). In CLOROTIC trial, HCTZ or placebo was administered orally and initiated within 24 hours of hospital admission.[27] The ADVOR trial, involving 519 AHF patients with an average age of 78 years old, of whom 62.6% were male, showed the benefit of intravenous acetazolamide in combination with loop diuretics in effectively improving congestion based on criteria such as successful decongestion within 3 days of randomization, congestion score, or successful decongestion at discharge compared to placebo. Moreover, there were no significant differences observed in the incidence of new-onset renal injury, hypokalemia, hypotension, or adverse effects between the two study groups. The timing of combining a second diuretic with loop diuretics was defined as the first-time use of the second diuretic daily.[28]

Both the European Society of Cardiology (ESC) and the Vietnam National Heart Association (VNHA) emphasize considering combining a second diuretic with loop diuretics in patients with persistent or refractory edema unresponsive to escalating loop diuretic doses (Class IIa, level B).[1,8] Similar recommendations are also provided by the American College of Cardiology (ACC) for patients not showing improvement in signs and symptoms of congestion.[6] The optimal timing for combining diuretics remains inconsistent across guidelines. While the ESC and VNHA outline a diuretic use protocol in AHF patients and emphasizes considering combining diuretics after two assessments of clinical response and urinary sodium (4–12 hours after the initial dose of loop diuretics), the American College of Cardiology does not provide a specific time frame for combining diuretics. The improvement of congestion in acute or critically ill AHF patients is a crucial goal that needs to be promptly addressed.[1,6,8] Combining a second diuretic on a loop diuretic background enhances diuretic efficacy and improves congestion symptoms.[1,6,8] The lack of data concerning the timing of combining diuretics and the benefit in improving congestion may be the reason for the lack of consensus regarding the timing of combining diuretics. Future trials are needed to address the question of the optimal timing for combining a second diuretic to rapidly improve congestion and alleviate symptoms in AHF patients.

CONCLUSION

Acute heart failure represents a multifaceted pathological state characterized by substantial fluid retention. Loop diuretics play a crucial role in congestion relief in AHF patients. Diuretics combination can enhance fluid excretion and alleviate symptoms of congestion. However, the optimal timing for combining diuretics lacks consensus across clinical trials and is not explicitly addressed in current treatment guidelines. Future studies will guide strategies to optimize diuretic combinations aiming for early improvement in congestion and symptoms for patients with AHF.

***Table 1**. Timing of diuretic combination in several trials*

Author, Year, Patients number, Design	2nd diuretic and administration timing	Results
Channer et al, 1993, 33 patients, randomised clinical trial[22]	Bendrofluazide and metolazone. Unresponsive to intravenous loop diuretics for 48 hours.	5 – 5.6 kg weight loss after the addition of bendrofluazide and metolazone.
Mouallem, 1995, 32 patients, observational study[23]	Thiazide. During acute period.	4.8 kg weight loss.

Author, Year, Patients number, Design	2nd diuretic and administration timing	Results
Dormans, 1996, 20 patients, observational study[24]	Thiazide. During acute period.	6.7 kg weight loss. increasing daily urine volume. increasing fractional sodium excretion.
Piardi, 2021, 51patients, randomized, single-center, parallel, double-blind, placebo-controlled clinical trial[25]	Thiazide Within 1st day of admission	1,78 kg weight loss/day.
Tien M.H. Ng, 2013, 242 patients, retrospective study[26]	Metolazone At least 6 hours after the first bolus doses of furosemide	increasing hourly urine output.
CLOROTIC trial, 230 patients, prospective, double-blind, placebo-controlled trial[27]double-blind, placebo-controlled trial, including patients with AHF randomized to receive HCTZ or placebo in addition to an intravenous furosemide regimen. The coprimary endpoints were changes in body weight and patient-reported dyspnoea 72 h after randomization. Secondary outcomes included metrics of diuretic response and mortality/rehospitalizations at 30 and 90 days. Safety outcomes (changes in renal function and/or electrolytes	Hydrochlothizide. Within 24 hours after admission.	HCTZ group were more lose weight at 72 hours than placebo group. No significant differencses in patient-reported dyspnea. More impaired renal function in HCTZ group.
ADVOR trial, 519 patients, multicenter, parallel-group, double-blind, randomized, placebo-controlled Trial[28]	Acetazolamide Acetazolamide was administered with the first dose of loop diuretics.	Acetazolamide group were more successful decongestion, higher urine output and natriuresis than placebo group.

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CONFLICTS OF INTEREST

The authors declare no competing interests.

LIST OF ABBREVIATIONS

ACC = American College of Cardiology;
AHF = Acute heart failure;
ESC = European Society of Cardiology;
HCTZ = Hydrochlorothiazide;
VNHA = Vietnam National Heart Association.

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