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Tackling Congestion in Acute Heart Failure: Is It the Primetime for "Combo Diuretic Therapy?"

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Abstract
Symptoms and signs of congestion are the primary reason for hospitalization of patients with acute heart failure. Efficient fluid and sodium removal remain the main goals of therapy, and loop diuretics are the recommended agents in this setting. However, the therapeutic response to these medications is known to be variable, and a significant subset of patients is discharged from the hospital with residual fluid overload. Therefore, sequential blockade of the nephron has been proposed as a more effective decongestive strategy. Pilot studies have suggested significant increase in diuresis and natriuresis with combination diuretic therapy. Recently, two groups of investigators examined this hypothesis on a larger scale in randomized placebo-controlled trials; one targeted the proximal tubules upstream of the loop of Henle (Acetazolamide in Decompensated Heart Failure with Volume Overload – ADVOR), while the other one blocked sodium-chloride cotransporters in the distal convoluted tubules (Combination of Loop with Thiazide Diuretics for Decompensated Heart Failure – CLOROTIC). Herein, we discuss the results of these two trials with special focus on their impact on extraction of sodium, i.e., the main determinant of extracellular volume, and put them in the context of previous studies of combination diuretic therapy as well as extracorporeal ultrafiltration.

Targeting Congestion

Signs and symptoms of congestion are the primary reason for hospitalization of patients with acute heart failure. While renal sodium avidity, the prevailing renal mechanism for fluid overload, is typically addressed with loop diuretics, a significant subset of patients do not get optimally decongested prior to their discharge. Inadequate response to diuretics and residual congestion is associated with higher risk of rehospitalization, adverse outcomes, and cost of care [1]. In order to overcome what has conventionally been referred to as loop diuretic resistance, a number of strategies have been used such as extracorporeal fluid removal, low-dose dopamine, and hypertonic saline. Sequential blockade of sodium absorption in the nephron by using an add-on agent to loop diuretics (combination diuretic therapy [CDT]) has proven appealing as diuretics are generally inexpensive,

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Table 1. Randomized controlled trials of dual nephron blockade in AHF

Secondary nephron site blockade	Trial name	Year of publication	Patients, *n*	Add-on agent	Baseline renal function	Primary endpoints	Diuresis	Natriuresis	Weight loss	Key finding	Comments
Proximal tubule (SGLT2)	EMPA-RESPONSE-AHF [3]	2020	80	Empagliflozin 10 mg	eGFR: 55 mL/min	Change in dyspnea, diuretic response LOS, NT-proBNP	3,442 versus 2,400 mL at day 1*, 3,449 mL difference in cumulative urine output at day 4*	NA	2.83 versus 2.3 kg at day 4**	No difference in any of the four primary endpoints	Significantly improved HF readmission or WHF or death at 60 days
Proximal tubule (CA)	ADVOR [4]	2022	519	Acetazolamide 500 mg	eGFR: 39 mL/min	Successful decongestion (no edema, pleural effusion and ascites)	4,600 versus 4,100 mL at day 2*	468 versus 369 mmol at day 2*	NA	Successful decongestion in 42.2 versus 30.5%*	Shorter LOS in intervention arm by 1.1 day
Distal convoluted tubule (NCC)	CLOROTIC [5]	2022	230	Hydrochlorothiazide 25, 50, 100 mg	eGFR: 43 mL/min	Change in body weight and dyspnea	1,775 versus 1,440 mL in 24 h**	64 versus 47 mmol/L at 96 h*	2.3 versus 1.5 kg at 72 h*	Successful decongestion (weight, diuresis, natriuresis) without change in dyspnea	The trial was halted prematurely due to slow recruitment, higher weight loss per 40 mg of furosemide in intervention arm
Distal convoluted tubule (MR)	ATHENA-HF [6]	2017	360	Spironolactone 100 mg	eGFR: 56 mL/min	change in NT-proBNP	6,086 versus 5,584 mL at day 4**	NA	3.3 versus 2.8 kg at 96 h**	No difference in the primary or secondary endpoints between the two groups	No difference in serum potassium or renal function
Collecting duct (V2R)	EVEREST [7]	2007	4,133	Tolvaptan 30 mg	Serum creatinine: 1.4 mg/dL	Change in global clinical status and body weight	NA	NA	3.35 versus 2.73 kg at day 7* in trial A, 3.77 versus 2.79* in trial B	Improvement in weight but not in global clinical status	Improvement in dyspnea and edema

ADVOR, Acetazolamide in Decompensated Heart Failure with Volume Overload; ATHENA-HF, Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure; CA, carbonic anhydrase; CLOROTIC, Combination of Loop with Thiazide Diuretics for Decompensated Heart Failure; EMPA-RESPONSE-AHF, Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure; EVEREST, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan; HF, heart failure; LOS, length of hospital stay; MR, mineralocorticoid receptor; NA, not available; NCC, sodium-chloride cotransporter; NT-proBNP, N-terminal pro b-type natriuretic peptide; SGLT2, sodium-glucose cotransporter-2; V2R, vasopressin-2 receptor; WHF, worsening heart failure. *The intervention arm versus the control arm, any statistically significant p value < 0.05 reported by the authors. **The intervention arm versus the control arm, any statistically insignificant p value of 0.05 or more reported by the authors.

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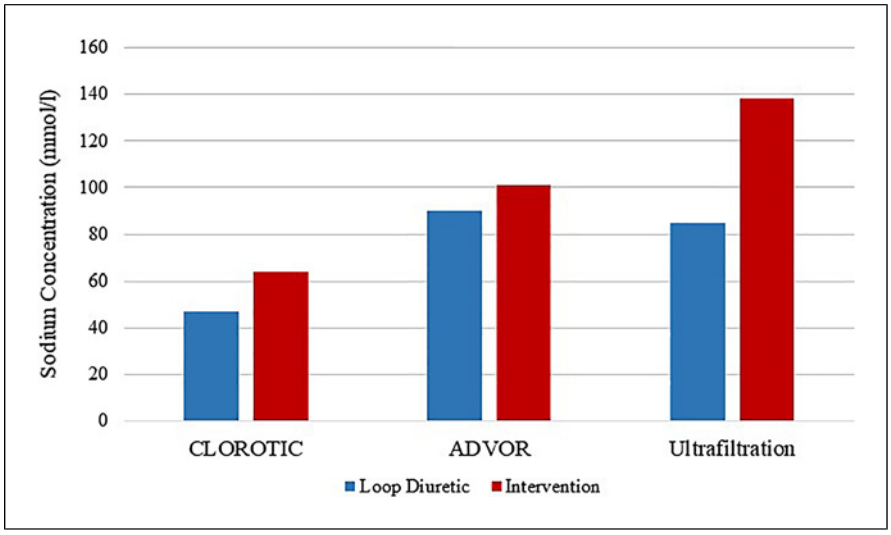

Fig. 1. Comparison of the urine sodium concentration generated by loop diuretics versus the intervention, which includes either an add-on diuretic (ADVOR or CLOROTIC) or the ultrafiltrate. The data for ADVOR and CLOROTIC are obtained from the reported diuresis and natriuresis at 48 and 96 h, respectively. The data for ultrafiltration are adopted from Chung ES et al. [Korean Circ J. 2014;44:156–161].

have been readily available for decades, their safety profiles are well known to clinicians, and would need no specific technology, training, or care setting. Several sites of action, receptors, and transporters, starting from proximal tubules down to collecting ducts, have been explored for this purpose (selected landmark trials are summarized in Table 1). However, high-quality evidence on the efficacy and safety of CDT remains fairly limited. Besides, due to the relative safety of high-dose loop diuretics in the landmark Diuretic Optimization Strategy Evaluation in Acute Decompensated Heart Failure (DOSE) trial, many experts give preference to initial intensification of the loop diuretic dose before considering a second agent [2]. Recently, two trials of CDT were published and resulted in regeneration of interest in this approach.

CLOROTIC

Combination of Loop with Thiazide Diuretics for Decompensated Heart Failure (CLOROTIC) is a double-blind, placebo-controlled trial from Spain that randomized 230 patients with acute heart failure (AHF) to receive either oral hydrochlorothiazide or placebo for 5 days in addition to an intravenous furosemide regimen [5]. The loop diuretic protocol was based on the low-dose arm of the DOSE trial. Patients assigned to hydrochlorothiazide experienced a more significant weight loss compared to those who received placebo (53% higher). Moreover, the hydrochlorothiazide group had a higher median urinary sodium excretion (see Table 1). While there was no difference in patient-reported dyspnea score, more patients in the hydrochlorothiazide arm experienced a rise in serum creatinine, which we now know is not necessarily synonymous with worsening renal function. A variety of metrics for rehospitalization and mortality were found to be similar in both groups. CLOROTIC was halted due to slow enrollment.

ADVOR

Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) is a double-blind, placebo-controlled trial from Belgium that randomized 519 patients with AHF to receive either intravenous acetazolamide or placebo in addition to an intravenous furosemide regimen (twice the oral home dose) [4]. Successful decongestion (defined as no more than trace edema and no residual pleural effusion or ascites) within 3 days was achieved more often in the acetazolamide arm than placebo. At 48 h, the cumulative diuresis and natriuresis were higher in the acetazolamide arm as well (see Table 1). The patients who received acetazolamide had a shortened length of stay, but there was no difference in all-cause mortality or heart failure readmission.

Connecting the Dots

Taken together, these trials suggest that CDT results in greater decongestion among patients with AHF. In both trials, randomization happened soon after admission to the hospital (within 24 h), which is different from common practice where the second diuretic is typically used as rescue therapy for those patients with inadequate response to the initial treatment. Importantly, these two studies convincingly showed that initial dual diuretic therapy has an acceptable safety profile.

Unfortunately, the decongestive benefits of CDT as initial treatment for AHF proved to be fairly modest. The

therapy in both trials was guided by conventional measures such as urine output, change in weight, and clinical manifestations of fluid overload rather than more objective, but less practical, timed spot urine sodium. While this approach does increase the applicability of their findings to real-life settings, it may also have inadvertently diminished the benefits of dual therapy. In CLOROTIC, the 3-day urine output was only 0.8 L more than the CDT arm, with only 37% higher urine sodium excretion. The dosing scale and oral route of administration of hydrochlorothiazide are likely to have played a role in the small differences observed between the two groups, whereas the low-dose loop diuretic is possibly the primary reason for overall modest natriuresis in both arms (47–64 mmol/L). In comparison, urine sodium concentration was 92 mmol/L in the overall population of ADVOR (unpublished data – presented by the investigators at the American Heart Association meeting in 2022). Similarly, the patients in the acetazolamide arm of ADVOR experienced only a small increment in their urine output (0.5 L over 2 days), with only 27% higher urine sodium excretion (Table 1). In fact, post hoc analysis revealed that urine sodium concentration was only 12 mmol/L higher in patients who received acetazolamide in addition to furosemide, which is in line with the studies confirming that proximal tubular absorption of sodium has a negligible role in suboptimal response to loop diuretics [8]. Therefore, while the differences in diuresis and natriuresis were found statistically significant, the clinical relevance of these findings remains to be determined.

In conclusion, these two studies are a welcome addition to the sparse evidence on CDT for AHF. The results imply that sequential nephron blockade can be an initial decongestive strategy. However, it should be noted that the additive effects are fairly modest (e.g., less than 50% increase in natriuresis) and may be transient in the case of acetazolamide (due to tachyphylaxis). It also remains unknown whether the observed salutary effects would translate into improved rate of rehospitalization or mortality. In the setting of diuretic resistance and nephron remodeling, it is prudent to consider a non-renal strategy (extracorporeal ultrafiltration) in which decongestion process can be fully controlled and the ultrafiltrate may achieve a sodium concentration almost twice the urine generated by loop diuretics (Fig. 1). Since ultrafiltration is also more efficient in fluid removal, the total sodium extraction would be significantly higher than diuretics [9]. The reported salutary impact of ultrafiltration therapy on heart failure rehospitalization and mortality may in part be related to more efficient decongestion [10, 11].

Conflict of Interest Statement

Amir Kazory has the following potential conflicts of interest: NuWellis, Inc. (Medical Advisory Board and consultancy fee), W.L. Gore, Inc. (consultancy fee), and Elsevier (consultancy fee). Claudio Ronco in the last 3 years has been consulting or part of advisory boards for Astute, Baxter, Biomerieux, B. Braun, Cytosorbents, ESTOR, FMC, GE, Jafron, Medtronic, and Toray.

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Author Contributions

Amir Kazory: conceptualization, gathering the data, and preparing the draft. Claudio Ronco: conceptualization and critical review of the manuscript.

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