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Review

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Acetazolamide and Hydrochlorothiazide in Patients With Acute Decompensated Heart Failure: Insights From Recent Trials

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Abstract

Acetazolamide and thiazide diuretics have been combined with loop diuretics to overcome diuretic resistance in heart failure patients. However, recent studies have assessed the upfront combination of acetazolamide and hydrochlorothiazide with loop diuretics in hospitalized patients with acute decompensated heart failure without loop diuretic resistance. We reviewed two recent randomized controlled trials on the upfront use of acetazolamide and thiazide diuretics in acute decompensated heart failure, respectively. When the two trials on acetazolamide are considered together, adding oral or intravenous acetazolamide to loop diuretics in decompensated heart failure patients resulted in increased diuresis and natriuresis. However, the effects were significantly higher in patients with serum bicarbonate ≥ 27 mmol/L and those with higher baseline glomerular filtration rate (GFR). Similarly, when the two trials on thiazide diuretics are considered together, adding hydrochlorothiazide to loop diuretics in decompensated heart failure patients resulted in increased diuresis and weight loss. However, it increases the risk of impaired renal function. When all the trials are considered together, the upfront use of acetazolamide may be helpful in carefully selected patients, including patients with underlying elevated bicarbonate levels (≥ 27 mmol/L) and those with good renal function (GFR > 50). Conversely, though the upfront use of thiazide diuretic added to intravenous furosemide improved diuretic response in acute decompensated heart failure, it causes an increased risk of worsening renal function and lack of clear evidence of reducing hospital length of stay.

Keywords: Acetazolamide; Hydrochlorothiazide; Acute decompensated heart failure

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Introduction

Intravenous loop diuretics have been the mainstay of treatment in hospitalized acute decompensated heart failure patients. The primary goal of therapy in hospitalized heart failure patients is the resolution of signs and symptoms of decongestion before discharge, as persistent congestion is associated with an increased rate of rehospitalization and mortality. In patients without adequate diuresis with loop diuretics, the addition of acetazolamide or thiazide diuretics, with careful monitoring of serum electrolytes and renal function, has been recommended as a way to improve diuresis and overcome loop diuretics resistance [1, 2]. Recent randomized controlled trials have assessed the benefits of the upfront combination of loop diuretics with acetazolamide and thiazide diuretics in acute decompensated heart failure patients, starting from the first day of hospital admission. Based on these studies, this review aimed to evaluate and compare the benefits of the upfront use of acetazolamide and thiazide diuretics in hospitalized acute decompensated heart failure patients.

Mechanism of Action of Thiazide Diuretics and Acetazolamide

Thiazides achieve diuretic action by inhibiting the sodium-chloride cotransporter (NCC) in the renal distal convoluted tubule. By blocking sodium reabsorption in the distal convoluted tubules, thiazides cause increased delivery of sodium to the collecting duct, promoting natriuresis and increased diuresis [3, 4]. Patients with prolonged exposure to loop diuretics could also develop a renal adaptation, resulting in hypertrophy of the distal renal tubule cells and increased sodium uptake and aldosterone secretion. This could result in decreased efficiency of loop diuretics and loop diuretic resistance. Thiazide diuretics, by blocking the sodium reabsorption in the distal convoluted tubules, can antagonize the effect of renal hypertrophy and potentially improve loop diuretic resistance [5].

Acetazolamide is a carbonic anhydrase inhibitor that works on the proximal tubules and inhibits the formation of bicarbonate (HCO_3) and hydrogen (H^+) from H_2O and CO_2 in the proximal renal tubules [6]. By inhibiting carbonic anhydrase, acetazolamide inhibits sodium reabsorption in the prox-

imal tubules through two main mechanisms. First, around 30% of kidney-filtered sodium (Na) is absorbed through the Na^+/H^+ isoform 3 exchanger (NHe3). Carbonic anhydrase propels this NHe3 enzyme to allow it to function in its role of sodium and water absorption. When this enzyme is inhibited by acetazolamide, NHe3 activity is decreased, allowing mild to moderate natriuresis [7]. Second, acetazolamide reduces sodium reabsorption in the proximal tubules by decreasing the availability of bicarbonate to the Na^+/HCO_3^- cotransporter (NBC) [8]. By blocking sodium reabsorption in the proximal tubules, acetazolamide allows more sodium to reach the distal nephrons. This decreases renin release and improves loop diuretics efficacy, which depends on sodium in the distal nephrons for its actions [5, 9]. Although acetazolamide's diuretic and natriuresis ability is poor, it is very efficient in boosting the efficiency of loop diuretics when combined with loop diuretics [10].

Randomized Controlled Trials With Acetazolamide in Acute Heart Failure

The ADVOR trial published in 2022 [11] and the study conducted by Kosiorek et al in 2023 [12] represent two significant contributions to the study of the upfront use of acetazolamide with loop diuretics in managing acute heart failure with volume overload. Both studies adopted a randomized controlled trial design; however, these trials have notable differences (Table 1) [11-14].

The ADVOR double-blind, randomized controlled trial involved 519 patients in Belgium with acute decompensated heart failure who were randomized on day 1 of admission into the intervention group that received intravenous acetazolamide 500 mg daily for 3 days and the control group that received a placebo. The left ventricular ejection fraction (EF) was similar in both groups, with a mean EF of 43%. Both received intravenous loop diuretics as background therapy. Patients that received acetazolamide had significantly increased urine output after 48 h compared to controls (4,689 mL vs. 4,166 mL, P = 0.001) and increased urine sodium on day 2 than controls (91 mmol/L vs. 80 mmol/L, P < 0.001) [15]. In addition, those in the acetazolamide group were significantly more likely to have a successful decongestion within 3 days of randomization than controls (42% vs. 31%, P < 0.001). However, there was no difference in the length of hospital stay between the acetazolamide and control groups (8.8 days vs. 9.9 days) [11]. Furthermore, the two groups had no differences in side effects, including worsening renal function, hypokalemia, or hypotension. There was also no difference in the two groups on 3 months of rehospitalization for heart failure or death from any cause. In an analysis comparing the subset of patients with elevated bicarbonate levels (≥ 27 mmol/L) and those with normal bicarbonate levels (< 27 mmol/L), patients with elevated bicarbonate had a significantly higher response to acetazolamide, with higher decongestion within 3 days: ((normal vs. elevated HCO_3; odds ratio (OR): 1.37 (0.79 - 2.37) vs. OR: 2.39 (1.35 - 4.22), P-interaction = 0.065)). There was also a higher proportional diuretic and natriuretic response with acetazolamide in those with increased bicarbonate levels (both P-interaction < 0.001). Additionally, the length of stay was significantly lower in acetazolamide patients with increased bicarbonate levels than controls (8.9 vs. 10.9 days, P-interaction = 0.019). The explanation for the increased effect of acetazolamide in those with higher bicarbonate levels is that higher levels of bicarbonate diminished the decongestive effect of the loop diuretics. The use of loop diuretic only (control group) was associated with an increase in the bicarbonate level during treatment, which was prevented by acetazolamide in the intervention group (day 3: control 74.8% vs. acetazolamide 41.3%, P < 0.001) [8]. The study, however, had some limitations. Most patients were Caucasian, which limits the generalizability of the results. Additionally, the primary outcome, congestion score, is based on subjective clinical examination and is not a validated tool frequently used in clinical practice. Furthermore, patients on sodium-glucose cotransporter 2 (SGLT2) inhibitors were excluded from the study [16].

Following the ADVOR trial, Kosiorek et al published a single-center randomized trial in Poland involving 61 patients admitted with acute decompensated heart failure who were randomized into receiving oral acetazolamide 250 mg daily for 2 days (intervention group) and no acetazolamide (control), with both groups receiving background intravenous furosemide [12]. The EF was similar in both groups, with a mean EF of 37%. The study showed increased diuresis and negative fluid balance in the acetazolamide group compared to the control after 48 h (5,300 mL vs. 3,750 mL, P = 0.01) and (-1,232 mL vs. -597 mL, P = 0.04), respectively. There was also more weight loss in the acetazolamide compared to the control group after 48 h (3.25 kg vs. 1.13 kg, P = 0.03). Additionally, there was increased urine sodium in the acetazolamide compared to the control group by day 2 (114.7 mmol/L vs. 74.4 mmol/L, P = 0.003). There was no difference in worsening renal function or hypokalemia in the acetazolamide or control groups. Unlike the ADVOR trial, this study included patients on SGLT2, although only 25% were on SGLT2. However, this study did not report the length of hospital stay, readmission, or mortality data.

When the two trials are considered together, adding oral or intravenous acetazolamide in a dose of 250 - 500 mg to loop diuretics in decompensated heart failure patients resulted in increased diuresis and natriuresis. There was also increased negative fluid balance and weight loss in the acetazolamide patients. However, while the ADVOR study reported a difference of 523 mL in urine output between the acetazolamide group and control in 48 h, Kosiorek et al [12] reported a difference of 1,550 mL, about three times of ADVOR. The reason for such a significant difference is unclear, but a higher baseline glomerular filtration rate (GFR) in the Kosiorek et al [12] study compared to ADVOR (GFR 58 vs. 39 mL/min) could be contributory. The analysis of the ADVOR study showed that higher baseline GFR, higher blood pressure, higher serum sodium, and lower maintenance loop diuretic dose are predictors of natriuresis in patients in the ADVOR study [15].

Furthermore, the ADVOR study showed that the effect of acetazolamide is significantly higher in patients with serum bi-

Table 1. Summary of Studies Included in the Review

Authors	Mullens et al 2022 [11] (ADVOR trial)	Kosiorek et al 2023 [12]	Trullas et al 2023 [13] (CLOROTIC trial)	Piardi et al 2021 [14]
Year[a]	2022	2023	2023	2021
Patients number	519	61	230	51
Location[b]	Belgium	Poland	Spain	Brazil
Enrollment timing (of hospital admission)	Within 24 h	Within 24 h	Within 24 h	Within 24 h
Start time for therapy (of hospital admission)	Day 1	Day 1	Day 1	Day 1
Randomized therapy	Placebo vs. IV acetazolamide 500 mg daily for 3 days (double-blind)	Acetazolamide 250 mg orally daily for 2 days vs. standard care (single-blind)	Hydrochlorothiazide based on patient's GFR: > 50 mL/min: 25 mg daily; 20 - 50 mL/min: 50 mg daily; and < 20 mL/min: 100 mg daily	Hydrochlorothiazide 50 mg
Background therapy	IV loop diuretic	IV furosemide	IV furosemide	IV furosemide
Baseline EF in intervention group	43 ± 15	36 ± 15	55 (40 - 63)	30 ± 8
Baseline renal function	GFR: 39 mL/min	GFR: 58 mL/min	GFR: 43 mL/min	GFR: 30 mL/min
Dyspnea	NA	NS	NS	NS
Diuresis in 48 h	4,689 vs. 4,166 mL at day 2	5,300 vs. 3,750 mL at 48 h	1,775 vs. 1,400 mL at 24 h	NA
Natriuresis	91 vs. 80 mmol/L on day 2	114.7 vs. 74.4 mmol/L on day 2	Higher in the thiazide group at 96 h	NA
Fluid balance	NA	-1,232 mL vs. -597 mL on day 2	NA	NA
Weight loss	NA	3.2 kg vs. 1.13 kg at day 2	2.3 kg vs. 1.5 kg after 72 h	1.78 kg vs. 1.05 kg/day
Length of hospital stay	NS	NA	NS	NS
Worsening renal function	NS	NS	Higher in the thiazide group	NS
Hypokalemia (≤ 3.0 mmol/L)	NS	NS	Higher in the thiazide group	NS
Hypotension	NS	NA	NS	NA
HF rehospitalization within 3 months	NS	NA	NS[c]	NA
Death from any cause within 3 months	NS	NA	NS	NA
Key finding	Successful decongestion in 42.2% vs. 30.5%	The acetazolamide group had significantly higher diuresis, negative fluid balance, and weight loss.	Adding oral hydrochlorothiazide to IV furosemide improves diuretic response in acute decompensated HF patients but has an increased risk of worsening renal function.	Adding hydrochlorothiazide 50 mg to usual treatment resulted in a synergistic effect on weight loss, with a statistically significant increase in the diuretic effect for every 40 mg of IV furosemide used in patients with acute decompensated HF

[a]Year of publication. [b]Locationc of study. [c]Reported all-cause rehospitalization. GFR: glomerular filtration rate; EF: ejection fraction; HF: heart failure; NA: not available; NS: no significant difference between groups.

carbonate ≥ 27 mmol/L due to decreased diuresis in patients with elevated bicarbonate levels. Interestingly, using acetazolamide is not associated with significantly increased worsening renal function, hypokalemia, or hypotension. However, using acetazolamide was not associated with important clinical outcomes such as reduced length of hospital stay, reduced 3-month heart failure readmission rate, or reduced 3-month all-cause mortality.

Randomized Controlled Trials With Thiazides in Decompensated Heart Failure

The CLOROTIC double-blind, randomized controlled trial involving 230 patients in Spain with acute decompensated heart failure, who were randomized on day 1 of admission into the intervention group that received hydrochlorothiazide based on patients' GFR (> 50 mL/min: 25 mg daily; 20 - 50 mL/min: 50 mg daily; and < 20 mL/min: 100 mg daily) and the control group that received placebo [13]. The EF was similar in both groups, with a mean EF of 55% in the intervention group and 57% in the control group. Both groups received intravenous loop diuretics as background therapy. The study showed that patients on hydrochlorothiazide had more significant weight loss than control within 72 h (2.3 kg vs. 1.5 kg). There was also more substantial diuresis in the hydrochlorothiazide group within 24 h compared to the control group (1,775 mL vs. 1,400 mL, P = 0.05). However, the two groups did not differ in patient-reported dyspnea from baseline to 72 h. Furthermore, the two groups did not vary in hospital length of stay, all-cause rehospitalization at 30 and 90 days, and all-cause mortality at 30 and 90 days. The lack of difference in the length of hospital stay could be because, per the study protocol, all the patients could not be discharged during the 5-day study period for close monitoring of side effects.

However, there was increased impaired renal function (46.5% vs. 17.2%, P < 0.001) and increased hypokalemia (44.7% vs. 19%, P < 0.001) in the hydrochlorothiazide group compared to control. There was no difference in hypotension or hyponatremia between the two groups. One limitation of the study is that most of the study population were Caucasians, which limits the generalizability of the study. Furthermore, all patients in the study had an underlying chronic heart failure and were on moderate-to-high doses of home loop diuretics before admission. Thus, the findings may not be generalizable to those with newly diagnosed heart failure or with low diuretic requirements.

A smaller, single-center, double-blind, randomized controlled trial by Piardi et al recruited 51 patients in Brazil with acute decompensated heart failure, who were randomized on day 1 of admission into the intervention group that received hydrochlorothiazide 50 mg daily and the control group that received placebo [14]. The EF was similar in both groups, with a mean EF of 30% in the intervention group and 31% in the control group. Both groups received intravenous furosemide as background therapy. Patients received hydrochlorothiazide for 3 days or until discharge, whichever came first. The study found a greater average daily weight loss in the hydrochlorothiazide group compared to the control (1.78 vs. 1.05 kg/day; P = 0.062). The groups did not differ in length of stay, hypokalemia, in-hospital mortality, congestion score, dyspnea, or thirst. Although the proportion of patients with increased creatinine > 0.3 mg/dL was higher in the chlorothiazide group compared to the control, this was not statistically significant (58% vs. 41%; P = 0.38). However, in absolute numbers, there was a borderline significant increase in creatinine in the hydrochlorothiazide group compared to the control (0.50 vs. 0.27; P = 0.05).

When the two trials are considered together, adding hydrochlorothiazide to loop diuretics in decompensated heart failure patients resulted in increased diuresis and weight loss. However, adding hydrochlorothiazide to loop diuretics in patients with acute decompensated heart failure increases the risk of impaired renal function. Unfortunately, we do not know if the impaired renal function is transient or more persistent because the studies did not report follow-up renal function data. However, the hydrochlorothiazide and control group did not differ in hospital length of stay, in-hospital mortality, all-cause rehospitalization at 30 and 90 days, and all-cause mortality at 30 and 90 days.

Comparing Acetazolamide and Thiazide Up-front Use in Acute Heart Failure

Combining acetazolamide and thiazide with loop diuretics increased diuresis in patients with acute decompensated heart failure. Although an earlier study has suggested that thiazide outperforms acetazolamide as an add-on diuretic based on comparing the ADVOR and CLOROTIC studies, it is unclear whether acetazolamide or thiazide has a more diuretic effect when added to loop diuretics when all the trials are considered together [17]. However, it appears that the diuretic effects of either acetazolamide or thiazide diuretic are dependent on the baseline GFR of the patients with urine output of 523 mL in 48 h in the ADVOR study with GFR of 39 mL/min, 375 mL in 24 h in the CLOROTIC study with GFR of 43 mL/min, and 1,550 mL in 48 h in the study of Kosiorek et al [12], with GFR of 58 mL/min. This is consistent with the analysis of the ADVOR study, which showed that higher baseline GFR is a predictor of natriuresis in patients in the ADVOR study and that higher natriuresis is associated with greater diuresis and decongestion [15]. Unlike the ADVOR and Kosiorek et al [12] studies that gave patients a fixed dose of acetazolamide, the CLOROTIC study increased the dose of hydrochlorothiazide with decreasing GFR of the patients. However, even with the increasing doses of the thiazide diuretic in those with lower GFR, the CLOROTIC study found that the diuresis was directly related to baseline GFR, with the highest diuresis seen in the group with the highest GFR [18].

The studies suggest that acetazolamide is the medication of choice to combine with loop diuretics in patients with metabolic alkalosis. In the ADVOR study, patients with elevated bicarbonate levels (≥ 27 mmol/L) had a significantly higher response to acetazolamide with higher decongestion within 3 days, higher diuretic and natriuretic response, and decreased length of stay compared to those with normal bicarbonate levels. While previous studies have suggested the use of acetazolamide as an add-on in patients with loop diuretic resistance and metabolic alkalosis [5], the ADVOR study shows that the up-front use of acetazolamide prevents the development of metabolic alkalosis in patients on loop diuretics, thereby preventing loop diuretic resistance from metabolic alkalosis [8].

The side effects reported with hydrochlorothiazide appear to be greater than with acetazolamide. Unlike the thiazide studies, the acetazolamide studies showed no statistically signifi-

cant worsening of renal functions with acetazolamide use. The worsening renal function with thiazide is consistent with prior studies that reported worsening, albeit transient, azotemia and increased creatinine with combined loop and thiazide diuretic therapy [19, 20]. The mechanism for worsening renal function with thiazide is unclear; however, possible mechanisms suggested in the past include direct renal injury, renal changes caused by thiazide-induced metabolic abnormalities (hypokalemia, hyperuricemia), overt volume depletion or stimulation of the renin-angiotensin-aldosterone system (RAAS) from volume depletion [21].

Furthermore, unlike the acetazolamide studies, there was increased hypokalemia with thiazide diuretic use in the CLOROTIC study. This finding is consistent with other studies that showed an increased risk of hypokalemia with thiazide diuretics [19, 20]. Although thiazides do not directly affect potassium transport like loop diuretics, they indirectly stimulate increased renal excretion of potassium. Hypokalemia results from increased sodium and fluid delivery to the distal convoluted tubules due to upstream sodium transport inhibition, resulting in increased physiological secretion of potassium. Additionally, aldosterone secretion in response to volume contraction further promotes potassium secretion [22, 23]. However, these studies did not report other side effects, such as hyponatremia and hypotension, previously reported with thiazide diuretic use [20].

The acetazolamide and thiazide studies did not report any difference in hospital readmission rates or mortality in the intervention and control groups. This finding is consistent with other studies that showed that diuresis with medications that inhibit renal tubular sodium reabsorption does not confer a long-term beneficial clinical effect in heart failure patients [24-26], even when the medication is taken for a long time [26]. Surprisingly, acetazolamide and thiazide diuretics were not associated with reduced hospital length of stay in acute heart failure compared to the controls. While the lack of difference in the CLOROTIC study might be because all the patients were required to be admitted for a minimum of 5 days per study protocol, the ADVOR study showed a significant difference in the length of hospital stays in the subset of patients with elevated bicarbonate levels. Although Kosiorek et al [12] did not report the difference in length of stay between the acetazolamide group and control, given the significantly large diuresis in the intervention group, we expect a lower length of stay in the acetazolamide group in that study.

Conclusion and Future Directions

When all the trials are considered together, the upfront use of acetazolamide may be helpful in carefully selected patients, including patients with underlying elevated bicarbonate levels (≥ 27 mmol/L) and those with good renal function (GFR > 50). Conversely, though the upfront use of thiazide diuretic added to intravenous furosemide improved diuretic response in acute decompensated heart failure, we will not recommend its upfront use because of an increased risk of worsening renal function and lack of clear evidence of reducing hospital length of stay. Further research is needed to determine if the impaired renal function noticed with the upfront use of hydrochlorothiazide with loop diuretics is transient or more persistent.

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Conflict of Interest

The authors declare no conflict of interest concerning this article.

Author Contributions

All the authors were involved in conceptualizing the paper. CU, TM, GK, RT, PD, CV and VBC wrote the initial draft. CU and RG reviewed and substantially revised the paper. All the authors have read and approved the final version of the paper.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

GFR: glomerular filtration rate; H+: hydrogen; NBC: sodium bicarbonate cotransporter; NCC: sodium-chloride cotransporter; HCO_3: bicarbonate; NHe3: sodium hydrogen isoform 3 exchanger; RAAS: renin-angiotensin-aldosterone system; SGLT2: sodium-glucose cotransporter 2 inhibitors

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