ORIGINAL ARTICLE

# Acetazolamide in Acute Decompensated Heart Failure with Volume Overload

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## ABSTRACT

### BACKGROUND

Whether acetazolamide, a carbonic anhydrase inhibitor that reduces proximal tubular sodium reabsorption, can improve the efficiency of loop diuretics, potentially leading to more and faster decongestion in patients with acute decompensated heart failure with volume overload, is unclear.

### METHODS

In this multicenter, parallel-group, double-blind, randomized, placebo-controlled trial, we assigned patients with acute decompensated heart failure, clinical signs of volume overload (i.e., edema, pleural effusion, or ascites), and an N-terminal pro–B-type natriuretic peptide level of more than 1000 pg per milliliter or a B-type natriuretic peptide level of more than 250 pg per milliliter to receive either intravenous acetazolamide (500 mg once daily) or placebo added to standardized intravenous loop diuretics (at a dose equivalent to twice the oral maintenance dose). Randomization was stratified according to the left ventricular ejection fraction (≤40% or >40%). The primary end point was successful decongestion, defined as the absence of signs of volume overload, within 3 days after randomization and without an indication for escalation of decongestive therapy. Secondary end points included a composite of death from any cause or rehospitalization for heart failure during 3 months of follow-up. Safety was also assessed.

### RESULTS

A total of 519 patients underwent randomization. Successful decongestion occurred in 108 of 256 patients (42.2%) in the acetazolamide group and in 79 of 259 (30.5%) in the placebo group (risk ratio, 1.46; 95% confidence interval [CI], 1.17 to 1.82; P<0.001). Death from any cause or rehospitalization for heart failure occurred in 76 of 256 patients (29.7%) in the acetazolamide group and in 72 of 259 patients (27.8%) in the placebo group (hazard ratio, 1.07; 95% CI, 0.78 to 1.48). Acetazolamide treatment was associated with higher cumulative urine output and natriuresis, findings consistent with better diuretic efficiency. The incidence of worsening kidney function, hypokalemia, hypotension, and adverse events was similar in the two groups.

### CONCLUSIONS

The addition of acetazolamide to loop diuretic therapy in patients with acute decompensated heart failure resulted in a greater incidence of successful decongestion. (Funded by the Belgian Health Care Knowledge Center; ADVOR ClinicalTrials.gov number, NCT03505788.)

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*A list of the principal investigators in the ADVOR Study Group is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on August 27, 2022, at NEJM.org.

DOI: 10.1056/NEJMoa2203094

Current guidelines recommend the use of intravenous loop diuretics to ameliorate symptoms of fluid overload in patients with acute decompensated heart failure.[1] Despite the use of high-dose loop diuretics (dose equivalent, 2 to 2.5 times the oral maintenance dose), many patients are discharged from the hospital with residual clinical signs of volume overload, a strong predictor of poor outcome.[2,3] For example, in the Diuretic Optimization Strategies Evaluation (DOSE) trial, only 15% of the patients were free from clinical congestion after 72 hours of treatment.[4] Moreover, in the Acute Decompensated Heart Failure National Registry (ADHERE), approximately 20% of the patients were discharged from the hospital with an increase in body weight.[5] Although sequential diuretic therapy has been suggested as a more effective decongestive strategy than loop diuretic therapy alone, decisive evidence regarding effective diuretic agents, administration schedules, and routes of administration is limited.[1,2,6]

Acetazolamide is a carbonic anhydrase inhibitor that reduces proximal tubular sodium reabsorption and may improve diuretic efficiency when added to loop diuretics, thereby potentially facilitating decongestion. Results from an observational study and a small, prospective, randomized trial suggest that the addition of acetazolamide (at a dose of 500 mg administered intravenously once daily) to intravenous loop-diuretic therapy increased urinary sodium excretion, which is an objective metric of diuretic efficiency in patients with acute decompensated heart failure.[7,8] In the Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial, we examined whether the addition of acetazolamide to standardized intravenous loop-diuretic therapy would improve the incidence of successful decongestion among patients with acute decompensated heart failure.

## Methods

### Trial Design and Oversight

We conducted this multicenter, randomized, parallel-group, double-blind, placebo-controlled, investigator-initiated, academic, clinical trial without industry involvement. Details regarding the trial design and the baseline characteristics of the patients have been published previously,[9,10] and the trial protocol is available with the full text of this article at NEJM.org. Ziekenhuis Oost-Limburg initiated and managed the clinical investigation but was not involved in the data collection or analysis.

The protocol was designed by the first five authors and the last author. A steering committee consisting of 14 academic members, one patient representative, and one independent statistician was responsible for trial oversight and the reporting of results. The trial was conducted and documented in accordance with the protocol and the statistical analysis plan. The trial protocol was approved by a central ethics committee and the Belgian Federal Agency for Medicines and Health Products. All the patients provided written informed consent before any trial-specific procedure commenced.

The clinical trial unit of Ziekenhuis Oost-Limburg oversaw patient recruitment and data collection and storage. An independent clinical endpoint committee adjudicated prespecified events (Section S1 in the Supplementary Appendix, available at NEJM.org). The statistical analyses were conducted by an independent academic statistical center (Data Science Institute–CenStat, University Hasselt). The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

### Patients

Adult patients who were admitted to the hospital because of acute decompensated heart failure and had at least one clinical sign of volume overload (i.e., edema, pleural effusion, or ascites) and an N-terminal pro–B-type natriuretic peptide (NT-proBNP) level of more than 1000 pg per milliliter or a B-type natriuretic peptide level of more than 250 pg per milliliter were eligible for participation.[9] In addition, the receipt of oral maintenance therapy with at least 40 mg of furosemide or an equivalent dose (1 mg of bumetanide or 20 mg of torasemide) for at least 1 month before randomization was required.[9] If pleural effusion or ascites was suspected clinically at any time during the trial, confirmation with radiography or ultrasonography of the chest or with ultrasonography of the abdomen was obtained.

The main exclusion criteria were the receipt of acetazolamide maintenance therapy or treatment with another proximal tubular diuretic including a sodium–glucose cotransporter 2 (SGLT2) inhibitor, a systolic blood pressure of less than 90

mm Hg, and an estimated glomerular filtration rate (GFR) of less than 20 ml per minute per 1.73 $m^2$ of body-surface area. Treatment with intravenous loop diuretics at a dose of more than 80 mg of furosemide equivalent during the index hospitalization was not allowed before randomization. Details regarding the inclusion and exclusion criteria are provided in Section S2.

### TRIAL PROCEDURES

Patients were randomly assigned in a 1:1 ratio to receive an intravenous bolus of acetazolamide (500 mg once daily) or matching placebo, administered immediately after randomization and during the next 2 days or until the occurrence of complete decongestion, which was defined as the absence of any clinical sign of fluid overload other than trace edema. An automated, Web-based system was used for randomization with permuted blocks, with stratification according to the left ventricular ejection fraction (≤40% or >40%) and trial center.

At randomization, oral loop diuretics were stopped, and the patient received an intravenous loop diuretic at double the oral maintenance dose, administered as a single bolus immediately after randomization and split into two doses (separated by ≥6 hours) on each of the next 2 days (Fig. S2). The bolus of acetazolamide or matching placebo was administered simultaneously with the first dose of loop diuretics each day. All the patients received the same maintenance infusion with 500 ml of 5% dextrose and 3 g of magnesium sulfate administered over a period of 24 hours until the end of the treatment phase of the trial. It was recommended that treating physicians leave the doses of neurohumoral blockers unchanged during the treatment phase. Thereafter, it was strongly recommended that the doses of neurohumoral blockers be adjusted according to the European Society of Cardiology guidelines.[1,11]

According to the diuretic protocol, a timed urine collection was begun after the bladder had been emptied, which coincided with the first bolus of loop diuretics, and was continued until the second morning after randomization (time period ranged from 30 to 48 hours). If the cumulative urinary output over the period of 30 to 48 hours on that morning was less than 3.5 liters and signs of fluid overload were still present, an escalation of decongestive treatment was mandated by the protocol. At the time of enrollment and daily thereafter, the treating physician calculated the congestion score, on a scale from 0 to 10 on the basis of the sum of scores for the degree of edema (0 to 4), pleural effusion (0 to 3), and ascites (0 to 3), with higher scores indicating a worse condition on all scales (Fig. S3). This score was calculated before the administration of the morning dose of diuretics during the treatment phase, at discharge, and during 3 months of follow-up.

### END POINTS

The primary end point was successful decongestion, which was defined as the absence of signs of volume overload (i.e., no more than trace edema, no residual pleural effusion, and no residual ascites) as assessed by a cardiologist trained in the completion of the congestion score, within 3 days after randomization without an indication for escalation of decongestive therapy (Section S3 in the Supplementary Appendix). Key secondary end points were the composite end point of death from any cause or rehospitalization for heart failure during 3 months of follow-up and the duration of the index hospital admission (i.e., the number of days from randomization until the date of discharge). Exploratory tertiary end points were death from any cause and rehospitalization for heart failure during 3 months of follow-up.

Data regarding adverse events that resulted in the discontinuation of acetazolamide or placebo at the discretion of treating physician and on prespecified adverse events of interest (including severe metabolic acidosis, renal events, hypokalemia, and hypotension) were collected during the treatment phase. Severe metabolic acidosis was defined as a bicarbonate level of less than 12 mmol per liter. The combined renal safety end point was defined as the doubling of the serum creatinine level from baseline, a decrease of at least 50% in the estimated GFR, or receipt of renal-replacement therapy. Hypokalemia was defined as a potassium level of no more than 3 mmol per liter, and hypotension as a systolic blood pressure of less than 85 mm Hg.

### STATISTICAL ANALYSIS

Details regarding the analytic approach and power calculations have been published previously,[9] and the complete prespecified statistical analysis plan is available with the protocol. On the basis of the results of the DOSE trial,[4] we estimated that 15% of the patients in the placebo group would

have successful decongestion. No reliable data were available from large, randomized clinical trials to estimate the occurrence of the primary end point in the acetazolamide group. We estimated that 25% of the patients in the acetazolamide group would have successful decongestion within 3 days after randomization; 25% was chosen to represent a clear, meaningful absolute benefit of 10 percentage points as compared with placebo. Assuming a two-sided alpha of 0.05 and a statistical power of 80%, we calculated the targeted sample size for the trial to be 494, and to account for a potential withdrawal of 5% of the patients, we calculated that the trial would need to enroll 519 patients.

The analyses of the primary and secondary end points were based on the intention-to-treat principle and included data from all the patients who had undergone randomization and received at least one dose of acetazolamide or placebo; four patients were excluded because they did not receive either the trial drug or placebo. The safety population included all the patients who had undergone randomization, according to the treatment or placebo they actually received.

The baseline characteristics of the patients were summarized as means and standard deviations, medians and interquartile ranges, or numbers and percentages. The primary end point was evaluated by means of a generalized linear mixed model (log-link binomial model) that included a fixed treatment effect, a fixed effect for the stratification factor of the left ventricular ejection fraction, and a random center effect for the calculation of risk ratios and 95% confidence intervals. For the primary end point, prespecified subgroup analyses and a SARS-CoV-2 sensitivity analysis (described in the statistical analysis plan) as well as an exploratory analysis for patients who were discharged alive were also performed.

The composite end point of death from any cause and rehospitalization for heart failure after 3 months of follow-up was assessed in a time-to-event analysis with the use of a Cox proportional-hazards model that included trial group, the stratification factor of the left ventricular ejection fraction, and a random center effect (with the use of a log-normal frailty model) to calculate hazard ratios and 95% confidence intervals; results were summarized with the use of Kaplan–Meier survival curves. The duration of the index hospitalization was compared with the use of a linear mixed model (with fixed effects for treatment and the stratification factor of the left ventricular ejection fraction and a random center effect) after logarithmic transformation to calculate geometric means and the geometric mean ratio and 95% confidence interval.

Differences in diuresis and natriuresis were investigated by means of a linear mixed-effects model. Because the statistical analysis plan did not include a provision for correction for multiplicity when tests for secondary or other outcomes were conducted, results are reported as point estimates with 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used in place of a hypothesis test. Safety events were compared with the use of Fisher's exact test.

All the hypothesis testing was two-sided, and a P value of less than 0.05 was considered to indicate significance. All the statistical analyses were performed with the use of SAS software for Windows, version 9.4 (SAS Institute).

## RESULTS

### PATIENTS

Between November 11, 2018, and January 17, 2022, a total of 2915 patients underwent screening, of whom 519 were randomly assigned to receive either acetazolamide (259 patients) or placebo (260 patients) at 27 sites in Belgium. All patients were followed for 3 months for death from any cause and rehospitalization for heart failure. Details about the randomization and follow-up of the patients are provided in Figure S1. The characteristics of the patients at baseline were well balanced between the two groups (Tables 1, S1, and S2). Patients had clinically significant congestion, with a median NT-proBNP level of 6173 pg per milliliter (interquartile range, 3068 to 10,896) and a median congestion score of 4. Edema of the lower limb was the most prevalent sign of volume overload.

### PRIMARY END POINT

The primary end point of successful decongestion could not be assessed in 4 patients who underwent randomization because they did not receive the assigned acetazolamide (in 1 owing to the

**Table 1. Characteristics of the Patients at Baseline.***

| Characteristic | Placebo (N=260) | Acetazolamide (N=259) | Total (N=519) |
|---|---|---|---|
| Age — yr | 78.5±8.8 | 77.9 ±9.0 | 78.2±8.9 |
| Male sex — no. (%) | 155 (59.6) | 170 (65.6) | 325 (62.6) |
| White race — no. (%)† | 256 (98.5) | 258 (99.6) | 514 (99.0) |
| Heart rate — beats/min | 77±18 | 79±19 | 78±18 |
| Blood pressure — mm Hg | | | |
| Systolic | 127±22 | 126±20 | 127±21 |
| Diastolic | 73±13 | 72±13 | 72±13 |
| Weight — kg | 84.4±19.7 | 85.3±23.0 | 84.8±21.4 |
| Median congestion score at baseline (IQR)‡ | 4 (3–6) | 4 (3–5) | 4 (3–6) |
| Components of congestion score — no. (%) | | | |
| Edema§ | 241 (92.7) | 237 (91.5) | 478 (92.1) |
| Pleural effusion | 143 (55.0) | 130 (50.2) | 273 (52.6) |
| Ascites | 25 (9.6) | 21 (8.1) | 46 (8.9) |
| Median home maintenance dose of furosemide equivalent (IQR) — mg | 60 (40–100) | 80 (40–120) | 60 (40–100) |
| Left ventricular ejection fraction | | | |
| Mean — % | 43±15 | 43±15 | 43±15 |
| ≤40% — no. (%) | 111 (42.7) | 113 (43.6) | 224 (43.2) |
| Median NT-proBNP (IQR) — pg/ml | 6483 (3262–11,839) | 5600 (3034–10,100) | 6173 (3068–10,896) |
| NYHA functional class — no. (%) | | | |
| II | 35 (13.5) | 31 (12.0) | 66 (12.7) |
| III | 148 (56.9) | 148 (57.1) | 296 (57.0) |
| IV | 77 (29.6) | 80 (30.9) | 157 (30.3) |
| Ischemic cause — no. (%) | 113 (43.5) | 119 (45.9) | 232 (44.7) |
| Serum hemoglobin — g/dl | 11.9±2.0 | 11.9±2.0 | 11.9±2.0 |
| Sodium — mmol/liter | 140±4 | 139±4 | 139±4 |
| Median serum creatinine (IQR) — mg/dl | 1.5 (1.2–1.9) | 1.5 (1.2–2.0) | 1.5 (1.2–1.9) |
| Estimated GFR | | | |
| Median (IQR) — ml/min/1.73 $m^2$ | 38 (29–51) | 40 (30–52) | 39 (29–52) |
| <60 ml/min/1.73 $m^2$ — no. (%) | 215 (82.7) | 209 (80.7) | 424 (81.7) |
| Coexisting conditions — no. (%) | | | |
| History of atrial fibrillation | 189 (72.7) | 187 (72.2) | 376 (72.4) |
| Diabetes | 133 (51.2) | 112 (43.2) | 245 (47.2) |
| Hypertension | 207 (79.6) | 182 (70.3) | 389 (75.0) |
| Treatment — no. (%) | | | |
| ACE inhibitor, ARB, or ARNI | 140 (53.8) | 130 (50.2) | 270 (52.0) |
| Beta-blocker | 212 (81.5) | 207 (79.9) | 419 (80.7) |
| Mineralocorticoid receptor antagonist | 103 (39.6) | 113 (43.6) | 216 (41.6) |
| Loop diuretic | 260 (100.0) | 259 (100.0) | 519 (100.0) |
| Implantable cardioverter–defibrillator | 41 (15.8) | 38 (14.7) | 79 (15.2) |
| Cardiac-resynchronization therapy | 25 (9.6) | 36 (13.9) | 61 (11.8) |

* Plus–minus values are means ±SD. To convert values for creatinine to micromoles per liter, multiply by 88.4. ACE denotes angiotensin-converting enzyme, ARB angiotensin receptor blocker, ARNI angiotensin receptor–neprilysin inhibitor, GFR glomerular filtration rate, IQR interquartile range, NT-proBNP N-terminal pro–B-type natriuretic peptide, and NYHA New York Heart Association.
† Race was reported by the patient.
‡ Congestion scores range from 0 to 10 and are defined as the sum of scores for the degree of edema (0 to 4), pleural effusion (0 to 3), and ascites (0 to 3); on all scales, higher scores indicate a worse condition.
§ Edema was defined as a score of 1 or more (on a scale from 0 [no edema] to 4 [clear pitting edema above the knee]).

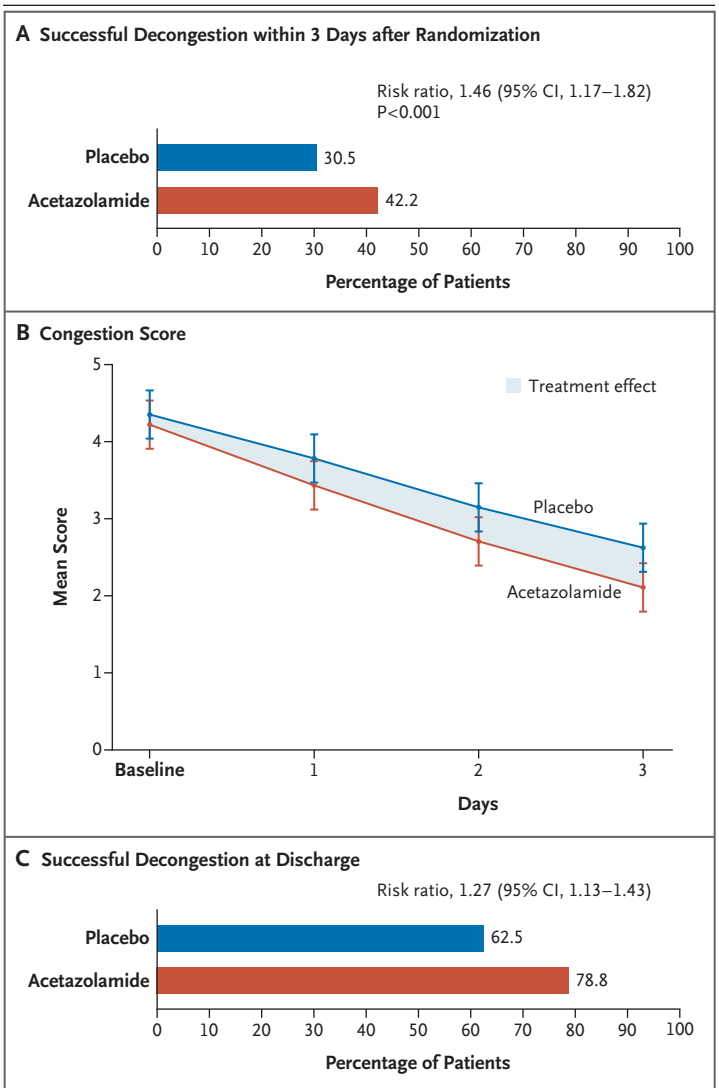


**Figure 1. Successful Decongestion and Evolution of Congestion Scores.**

The primary end point was successful decongestion, defined as the absence of signs of volume overload, within 3 days after randomization and without an indication for escalation of decongestive therapy. Congestion scores range from 0 to 10 and are defined as the sum of scores for the degree of edema (0 to 4), pleural effusion (0 to 3), and ascites (0 to 3); on all scales, higher scores indicate a worse condition. An exploratory analysis was conducted regarding successful decongestion at discharge among patients who were alive.

patient's decision, in 1 owing to the physician's decision, and in 1 who was withdrawn because the patient did not meet the inclusion criteria) or placebo (in 1 patient who withdrew informed consent). Successful decongestion occurred in 108 of 256 patients (42.2%) in the acetazolamide group and in 79 of 259 (30.5%) in the placebo group (risk ratio, 1.46; 95% confidence interval [CI], 1.17 to 1.82; P<0.001) (Fig. 1A and Table 2). Most of the patients who had been assigned to receive acetazolamide had a more pronounced reduction in congestion score over consecutive days than patients who had been assigned to receive placebo (Fig. 1B). A scenario that assumed no successful decongestion in the 3 patients in the acetazolamide group and successful decongestion in the 1 patient in the placebo group who could not be assessed for the primary end point was consistent with the results of the primary analysis (risk ratio, 1.44; 95% CI, 1.15 to 1.79) (Table S3). In a scenario that excluded the component of need for escalation therapy in the primary end point and only defined successful decongestion as the absence of a congestion score of greater than 1, more patients in the acetazolamide group than in the placebo group had successful decongestion (115 patients [44.9%] vs. 86 [33.2%]; risk ratio, 1.42; 95% CI, 1.15 to 1.76) (Table 2).

The effect of acetazolamide on the primary end point was generally consistent across prespecified subgroups, although the patients who were receiving a higher maintenance dose of loop diuretics appeared to have less benefit than those who were receiving a lower maintenance dose (Fig. 2). Among the patients who were alive at discharge, 190 of 241 (78.8%) in the acetazolamide group and 145 of 232 (62.5%) in the placebo group had successful decongestion (risk ratio, 1.27; 95% CI, 1.13 to 1.43) (Fig. 1C and Table 2). A sensitivity analysis for the primary end point that took into account the timing of cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Belgium (before or after the first case [February 2020]) showed no interaction between SARS-CoV-2 infection and the primary end point (Table S4).

### SECONDARY END POINTS

Death from any cause or rehospitalization for heart failure occurred in 76 of 256 patients (29.7%) in the acetazolamide group and in 72 of 259 patients (27.8%) in the placebo group (hazard ratio, 1.07; 95% CI, 0.78 to 1.48) (Table 2 and Fig. S4). The duration of the index hospitalization was a geometric mean of 8.8 days (95% CI, 8.0 to 9.5) in the acetazolamide group and 9.9 days (95% CI, 9.1 to 10.8) in the placebo group (Table 2). Additional data are provided in Tables S5 through S9.

**Table 2. Primary and Secondary End Points, Sensitivity and Exploratory Analyses, and Adverse Events.***

| Variable | Placebo (N=259) | Acetazolamide (N=256) | Treatment Effect (95% CI) | P Value |
|---|---|---|---|---|
| **Primary end point** | | | | |
| Successful decongestion within 3 days after randomization — no. (%)† | 79 (30.5) | 108 (42.2) | Risk ratio, 1.46 (1.17–1.82) | <0.001 |
| **Secondary end points** | | | | |
| Duration of hospital stay (95% CI) — days‡ | 9.9 (9.1–10.8) | 8.8 (8.0–9.5) | 0.89 (0.81–0.98) | |
| Death from any cause or rehospitalization for heart failure during 3 mo of follow-up — no. (%) | 72 (27.8) | 76 (29.7) | Hazard ratio, 1.07 (0.78–1.48) | |
| **Sensitivity analysis of primary end point** | | | | |
| Successful decongestion within 3 days after randomization, regardless of escalation of therapy — no. (%)§ | 86 (33.2) | 115 (44.9) | Risk ratio, 1.42 (1.15–1.76) | |
| **Exploratory analysis** | | | | |
| Successful decongestion at discharge among patients who were alive — no./total no. (%) | 145/232 (62.5) | 190/241 (78.8) | Risk ratio, 1.27 (1.13–1.43) | |
| Death from any cause at 3 mo — no. (%) | 31 (12.0) | 39 (15.2) | Hazard ratio, 1.28 (0.78–2.05) | |
| Rehospitalization for heart failure at 3 mo — no. (%) | 45 (17.4) | 47 (18.4) | Hazard ratio, 1.07 (0.71–1.59) | |
| **Adverse events** | | | | |
| During treatment phase — no. (%) | | | | |
| Combined renal safety end point | 2 (0.8) | 7 (2.7) | — | 0.10 |
| Doubling of serum creatinine level from baseline | 0 | 2 (0.8) | — | 0.24 |
| ≥50% sustained decrease in estimated GFR | 1 (0.4) | 4 (1.6) | — | 0.21 |
| Renal-replacement therapy during index hospitalization | 1 (0.4) | 4 (1.6) | — | 0.21 |
| Severe metabolic acidosis¶ | 0 | 0 | — | — |
| Hypokalemia‖ | 10 (3.9) | 14 (5.5) | — | 0.39 |
| Hypotension** | 9 (3.5) | 17 (6.6) | — | 0.11 |
| During 3 mo of follow-up — no. (%) | | | | |
| Serious adverse event | 124 (47.9) | 123 (48.0) | — | 1.00 |
| Adverse event related to placebo or acetazolamide | 3 (1.2) | 8 (3.1) | — | 0.14 |
| Cardiovascular adverse event | 122 (47.1) | 113 (44.1) | — | 0.53 |

* The primary end point could not be assessed in four patients (one in the placebo group and three in the acetazolamide group) because they did not receive the assigned intervention and the congestion score was not reported by the investigators. The secondary end points were assessed in the same intention-to-treat population that was used for the primary end-point analysis, as stipulated in the statistical analysis plan. Safety end points were assessed in patients according to the treatment they actually received. The determination of relatedness of an adverse event to acetazolamide or placebo was made by the investigator. The widths of confidence intervals have not been adjusted for multiplicity and cannot be used in place of a hypothesis test. Rehospitalization for heart failure after 3 months, which was an exploratory analysis, was assessed in a competing-risk survival analysis with the use of Fine and Gray's model, with death as the competing risk.

† The primary end point was successful decongestion, defined as the absence of signs of volume overload, within 3 days after randomization and with no indication for escalation of decongestive therapy.

‡ Values for duration of hospital stay are geometric means.

§ Escalation of decongestive treatment was mandatory if the patient's urinary output on the morning of the second day after randomization was less than 3.5 liters and the patient still had volume overload.

¶ Severe metabolic acidosis was defined as a bicarbonate level of less than 12 mmol per liter.

‖ Hypokalemia was defined as a potassium level of no more than 3 mmol per liter.

** Hypotension was defined as a systolic blood pressure of less than 85 mm Hg.

### DIURETIC EFFICACY

The total administered dose of intravenous loop diuretics was similar in the two trial groups (Table S10). On the second morning after randomization, the mean (±SD) urine output was 4.6±1.7 liters in the acetazolamide group and 4.1±1.8 liters in the placebo group, and natriuresis was 468±234 mmol and 369±231 mmol, respectively (Fig. 3).

### SAFETY AND ADVERSE EVENTS

Safety was assessed in the 515 patients (99%) who received acetazolamide or placebo. Severe metabolic acidosis did not occur in any patient during the treatment phase. The incidences of the combined renal safety end point, hypokalemia, and hypotension were similar in the two trial groups. The use of acetazolamide or placebo was stopped at the discretion of the physician because of hypotension (in 4 and 2 patients, respectively) or an increase in the serum creatinine level (in 1 patient in the acetazolamide group). The incidence of adverse events during 3 months of follow-up was similar in the two trial groups (Tables 2 and S11).

## DISCUSSION

In this multicenter, randomized, placebo-controlled trial involving patients with acute decompensated heart failure and volume overload, the addition of acetazolamide to standardized intravenous loop-diuretic therapy was associated with a higher incidence of successful decongestion within 3 days after randomization. Patients who

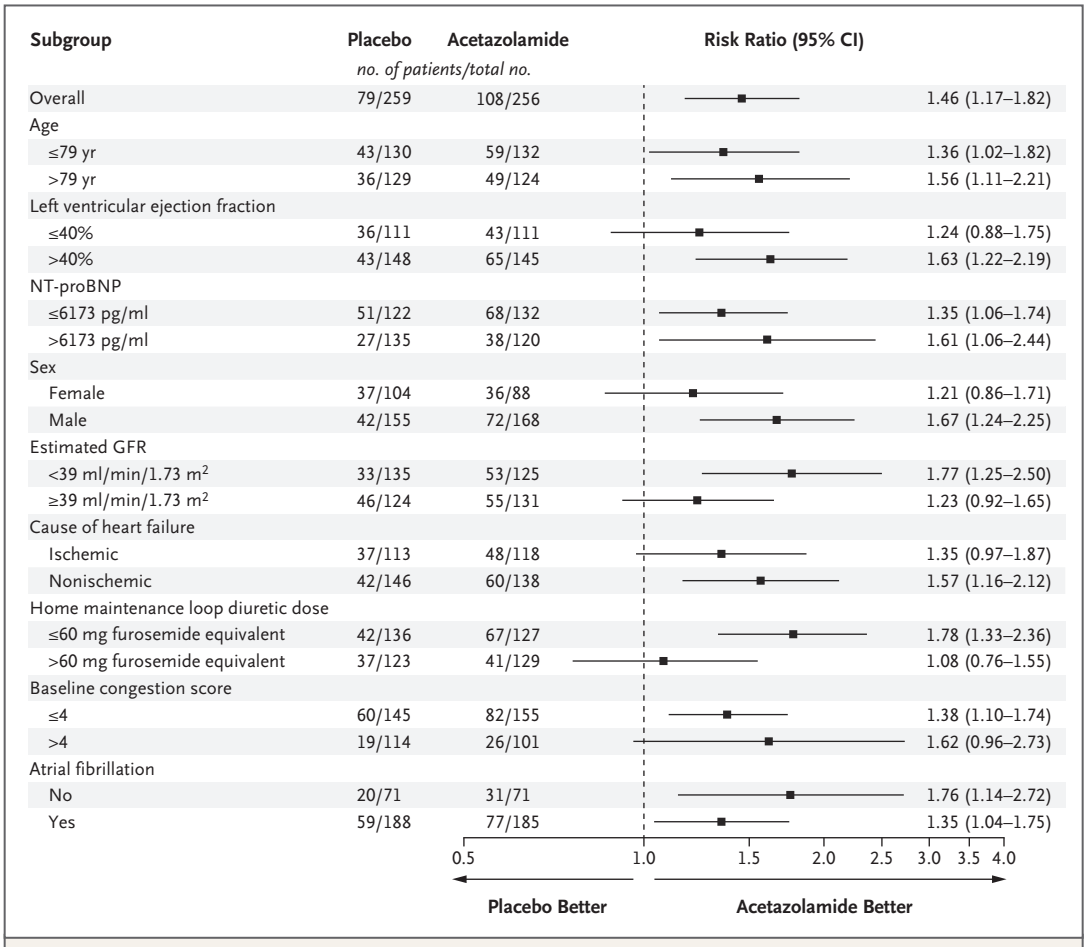


**Figure 2. Subgroup Analysis.**

Subgroups that were defined according to age, the N-terminal pro–B-type natriuretic peptide (NT-proBNP) level, the estimated glomerular filtration rate (GFR), the home maintenance dose of loop diuretic, and the baseline congestion score were based on observed median values at randomization.

had been treated with acetazolamide had more diuresis and natriuresis, had a shorter hospital stay, and were more likely to be discharged without residual signs of volume overload than those who had received placebo. There did not appear to be a higher incidence of adverse events with acetazolamide treatment.

Our trial involving patients with acute decompensated heart failure showed that acetazolamide, a diuretic agent blocking proximal tubular sodium reabsorption, added to loop-diuretic therapy led to more and faster decongestion and was associated with a shorter duration of hospital stay. The benefit with acetazolamide treatment with regard to decongestion was maintained at discharge, with a higher percentage of patients being discharged from the hospital without residual congestion (difference vs. placebo, 16.3 percentage points). The attainment of successful decongestion (euvolemia) has a class I recommendation from the European and American guidelines for the diagnosis and treatment of heart failure.[1,14] According to clinical trial and registry data, only a minority of patients with acute decompensated heart failure have decongestion at the end of the study period or are discharged without residual congestion.[4,5,12,13,15-19] Given that residual congestion is linked to adverse outcomes, the beneficial effects of acetazolamide therapy are important. The higher incidences of decongestion with acetazolamide treatment than with placebo were most probably related to the early and sustained increase in diuresis and natriuresis that were associated with the addition of acetazolamide. These findings highlight the importance of targeting congestion both early and aggressively and support the use of natriuresis as an indicator of diuretic response.[1,6,20]

The improvement with regard to successful decongestion with acetazolamide was generally consistent across all the prespecified subgroups, except for one comparison suggesting possible heterogeneity, which showed less treatment benefit among patients receiving a higher oral maintenance dose of loop-diuretic therapy. Other subgroups that were defined to reflect more congestion or more diuretic resistance (e.g., a higher congestion score, lower estimated GFR, or higher NT-proBNP level) did not show any heterogeneity in treatment effect.

The addition of acetazolamide to loop-diuretic therapy was not associated with an increased incidence of adverse events, and the higher incidence of successful decongestion was associated with a shorter duration of hospital stay. However, the risk of death from any cause or rehospitalization for heart failure (secondary composite end point) did not differ significantly between the two trial groups. In our trial, the risk of death or rehospitalization was considerably lower than that in the DOSE trial (50% at 60 days) and in the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF; 40% at 60 days).[4,12] The higher incidence of decongestion at discharge and the increase in the dose of neurohumoral blockers during the remainder of the hospital stay in our trial may account for the better outcomes, despite the fact that our trial patients had many coexisting conditions and ad-

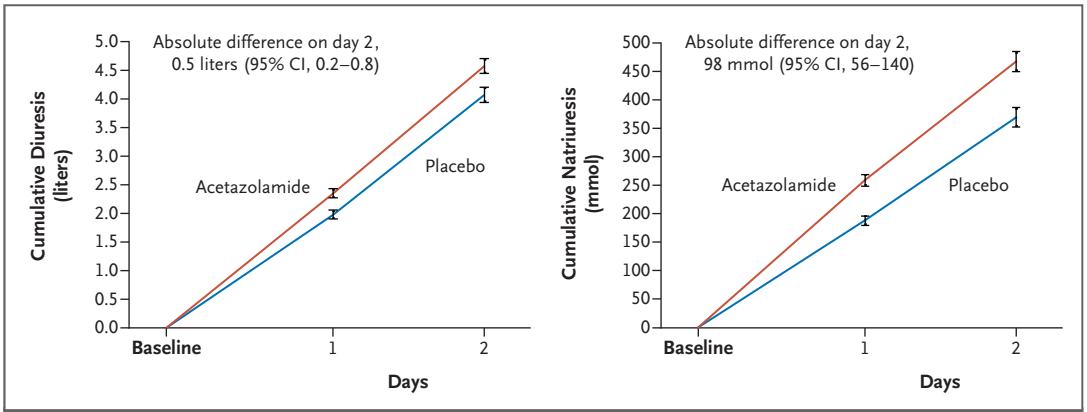


**Figure 3. Diuresis and Natriuresis According to Trial Group.**
I bars indicate standard errors.

vanced age. It was reassuring that acetazolamide treatment was not associated with higher incidences of hypokalemia, hypotension, or renal end points. To elucidate the complex relations among degree of decongestion, quality of life, and outcomes in patients with acute decompensated heart failure, more trials of diuretic agents with larger sample sizes are needed.

Our trial has certain limitations. Nearly all the patients who participated in the trial were White, given that the trial recruited exclusively in Belgium, which may limit the generalizability of our results to other racial or ethnic groups. Second, patients also had a history of chronic heart failure and had been receiving long-term outpatient treatment with at least 40 mg of furosemide equivalent. Therefore, results of the strategy we tested may not be applicable to patients with newly diagnosed heart failure. Third, patients in the two trial groups received similar standardized loop diuretics. It is unknown whether similar results may have been obtained with other dose regimens of loop diuretics or other diuretic agents. Fourth, the congestion score that was used for the assessment of the primary end point focused on the presence of edema in the lower limb, pleural effusion, and ascites — findings that are reflective of an assessment of mainly extracellular volume overload. Finally, during most of the trial period, SGLT2 inhibitors were not indicated and had not been approved as drugs to treat heart failure. To avoid confounding by any imbalance in their use between the trial groups, the trial design excluded their use. Although SGLT2 inhibitors and acetazolamide both exert natriuretic and diuretic effects on the proximal tubules, their mode of action and potency differ substantially.[6] Only 5% of proximal sodium uptake is mediated by SGLT2, whereas 60% is mediated by the apical sodium–hydrogen exchange that is inhibited by acetazolamide.[21-24]

In this placebo-controlled trial, we found that the addition of acetazolamide to standardized intravenous loop-diuretic therapy in patients with acute decompensated heart failure led to a higher incidence of successful decongestion.

The views expressed in this article are those of the authors and are not necessarily those of the Belgian Health Care Knowledge Center, which did not influence the analysis or reporting of the trial.

Supported by the Belgian Health Care Knowledge Center under the KCE Trials Program (KCE-17001).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

## APPENDIX

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## REFERENCES

1. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599-726.
2. Metra M, Davison B, Bettari L, et al. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. Circ Heart Fail 2012;5:54-62.
3. Arrigo M, Jessup M, Mullens W, et al. Acute heart failure. Nat Rev Dis Primers 2020;6:16.
4. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364:797-805.
5. Adams KF Jr, Fonarow GC, Emerman CL, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J 2005;149:209-16.
6. Mullens W, Damman K, Harjola VP, et al. The use of diuretics in heart failure with congestion — a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2019;21:137-55.
7. Verbrugge FH, Dupont M, Bertrand PB, et al. Determinants and impact of the

natriuretic response to diuretic therapy in heart failure with reduced ejection fraction and volume overload. Acta Cardiol 2015; 70:265-73.
**8.** Verbrugge FH, Martens P, Ameloot K, et al. Acetazolamide to increase natriuresis in congestive heart failure at high risk for diuretic resistance. Eur J Heart Fail 2019;21:1415-22.
**9.** Mullens W, Verbrugge FH, Nijst P, et al. Rationale and design of the ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload) trial. Eur J Heart Fail 2018;20:1591-600.
**10.** Mullens W, Dauw J, Martens P, et al. Acetazolamide in Decompensated Heart Failure with Volume Overload trial (ADVOR): baseline characteristics. Eur J Heart Fail 2022 June 22 (Epub ahead of print).
**11.** Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18: 891-975.
**12.** Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med 2012;367:2296-304.
**13.** Butler J, Anstrom KJ, Felker GM, et al. Efficacy and safety of spironolactone in acute heart failure: the ATHENA-HF randomized clinical trial. JAMA Cardiol 2017; 2:950-8.
**14.** Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145(18):e895-e1032.
**15.** Mebazaa A, Parissis J, Porcher R, et al. Short-term survival by treatment among patients hospitalized with acute heart failure: the global ALARM-HF registry using propensity scoring methods. Intensive Care Med 2011;37:290-301.
**16.** Fonarow GC, Abraham WT, Albert NM, et al. Age- and gender-related differences in quality of care and outcomes of patients hospitalized with heart failure (from OPTIMIZE-HF). Am J Cardiol 2009; 104:107-15.
**17.** Nieminen MS, Brutsaert D, Dickstein K, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J 2006;27:2725-36.
**18.** Crespo-Leiro MG, Anker SD, Maggioni AP, et al. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. Eur J Heart Fail 2016;18:613-25.
**19.** Arrigo M, Gayat E, Parenica J, et al. Precipitating factors and 90-day outcome of acute heart failure: a report from the intercontinental GREAT registry. Eur J Heart Fail 2017;19:201-8.
**20.** Tersalvi G, Dauw J, Gasperetti A, et al. The value of urinary sodium assessment in acute heart failure. Eur Heart J Acute Cardiovasc Care 2021;10:216-23.
**21.** Frömter E, Rumrich G, Ullrich KJ. Phenomenologic description of Na+, Cl- and HCO-3 absorption from proximal tubules of rat kidney. Pflugers Arch 1973; 343:189-220.
**22.** Aronson PS. Role of ion exchangers in mediating NaCl transport in the proximal tubule. Kidney Int 1996;49:1665-70.
**23.** Palmer LG, Schnermann J. Integrated control of Na transport along the nephron. Clin J Am Soc Nephrol 2015;10:676-87.
**24.** Beloto-Silva O, Machado UF, Oliveira-Souza M. Glucose-induced regulation of NHEs activity and SGLTs expression involves the PKA signaling pathway. J Membr Biol 2011;239:157-65.