

# Acetazolamide for patients with Acute Decompensated Heart Failure with Volume Overload

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The Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial showed that the addition of acetazolamide to loop diuretic therapy in patients with acute decompensated heart failure (ADHF) in a greater incidence of successful decongestion.[1,2]

### **Description**

The goal of the trial was to evaluate 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 ADHF with volume overload. [3]

### **Study Design**

- Randomization
- Parallel
- Double-blind
- Placebo-controlled
- Multicenter (nationwide)
- Outcome based on a congestion score (evaluated by a single observer)

Patients with ADHF, clinical signs of volume overload (i.e., oedema, 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 (BNP) level of more than 250 pg per milliliter were randomized to receive either intravenous acetazolamide (500 mg once daily) (n=259) or placebo (n=260) added to standardized intravenous loop diuretics (at a dose equivalent to twice the oral maintenance dose).[3] Randomization was stratified according to the left ventricular ejection fraction ( $\leq 40\%$  or  $>40\%$ ) and trial site.

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  $\geq 6$  hours) on each of the next 2 days. The bolus of acetazolamide or matching placebo was administered simultaneously with the first dose of loop diuretics each day. All patients received the same maintenance infusion with 500 mL dextrose 5% and 3 g MgSO<sub>4</sub> administered over 24 h until the end of the study treatment phase. Daily oral intake of fluids and sodium were restricted to 1500 mL and 1.5 g, respectively.

### **Patient population**

- Total number of trial participants: 519 subjects

- Duration of follow-up: 3 months
- Mean patient age: 78 years
- Percentage female: 37%

#### **Other salient features/characteristics**

- Left ventricular ejection fraction  $\leq 40\%$ : 43%
- Median congestion score at baseline (interquartile range [IQR]): 4 (3-6)
- Median NT-proBNP level (IQR): 6173 (3068-10,896) pg per milliliter
- Median home maintenance dose of furosemide equivalent (IQR): 60 (40-100) mg

#### **Inclusion criteria**

Patients with an elective or emergency hospital admission and clinical diagnosis of acute heart failure were eligible for the trial if:

- $\geq 1$  clinical sign of volume overload (i.e. oedema, ascites confirmed by abdominal ultrasound, or pleural effusion confirmed by a chest X-ray or chest ultrasound)
- Maintenance therapy with oral loop diuretics at a dose of  $\geq 1$  mg bumetanide or  $\geq 40$  mg furosemide or  $\geq 20$  mg torsemide for  $\geq 1$  month.
- Plasma NT-proBNP level  $> 1000$  pg/mL or BNP level  $> 250$  ng/mL at screening.

#### **Exclusion criteria**

- Systolic blood pressure  $< 90$  mmHg or mean arterial pressure  $< 65$  mmHg. [4]
- Expected use of intravenous inotropes, vasopressors, or sodium nitroprusside at any time point during the study. Nitrates only if systolic blood pressure is  $> 140$  mmHg.
- Estimated glomerular filtration rate  $< 20$  mL/min/1.73 m<sup>2</sup>.
- Treatment with intravenous loop diuretics  $> 2$  mg bumetanide or an equivalence of another loop diuretic during the index hospitalization and prior to randomization.
- Maintenance treatment with acetazolamide or sodium–glucose co-transporter-2 (SGLT2) inhibitors.
- Use of any non-protocol defined diuretic agent except for mineralocorticoid receptor antagonists.
- Concurrent diagnosis of an acute coronary syndrome defined as typical chest pain in addition to a troponin rise above the 99th percentile and/or electrocardiographic changes suggestive of cardiac ischaemia.

## Principal Findings

The primary outcome of successful decongestion (no more than trace oedema, no residual pleural effusion, and no residual ascites within 3 days after randomization without an indication for escalation of decongestive therapy) 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;  $p < 0.001$ ). [1] The primary end point of successful decongestion could not be assessed in 4 patients.

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. [1]

The key secondary end point of death from any cause or rehospitalization for heart failure during 3 months of follow-up 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). The duration of the index hospital admission (i.e., the number of days from randomization until the date of discharge) 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. [1]

## Interpretation

Expansion of extracellular fluid volume is critical to the pathophysiology of heart failure. [5] Increased extracellular fluid leads to elevated intracardiac filling pressures, resulting in a constellation of signs and symptoms of ADHF referred to as congestion. The evidence generated by the ADVOR trial confirms that the addition of acetazolamide to loop diuretics in patients with AHF with volume overload results in further successful decongestion compared to the standard of care. [5,6] The study showed convincing evidence in favor of the use of acetazolamide, since it found a higher-than-expected treatment effect (25% vs 46% relative difference), and a higher-than-expected event rate (15% vs 30.5% event rate in the control group). In absolute terms, the impact of the drug has massive implications (number needed to treat of 8.5, with an outcome difference between groups of ~12% of patients). We want to emphasize that the reported treatment effect was demonstrated in real world patients (mean age was 78 y.o., ~43% with heart failure with reduced ejection fraction) [7]. The most plausible explanation for this large treatment effect is the mechanism of the drug, which inhibits the absorption of sodium and bicarbonate ions in the renal proximal tubule, resulting in both natriuresis and diuresis. Whereas this 'old' and well-known drug can be used almost immediately, some challenges arise in the immediate future. [2] Patients receiving SGLT2 inhibitors were excluded from the ADVOR trial given the evidence and availability of the drug at the time. [1] Now, there is a huge body of evidence supporting the use of SGLT2 inhibitors in HF patients. [8] Unlike loop diuretics, both

acetazolamide and SGLT2 inhibitors has the mechanism of action in the proximal renal tubule, making harder to predict a potential cumulative effect.

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**Conflict of interest statement**

The authors declare that there is no conflict of interest.

**Data availability statement**

There is no original data in this editorial.

## References

1. Mullens W, Dauw J, Martens P *et al.* Acetazolamide in Acute Decompensated Heart Failure with Volume Overload. *N Engl J Med* 2022, DOI: 10.1056/NEJMOA2203094.
2. Felker GM. New Decongestion Strategies in an Evolving Heart Failure Landscape. *N Engl J Med* 2022, DOI: 10.1056/NEJMe2209997.
3. 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.
4. Rossello X, Bueno H, Gil V *et al.* Synergistic Impact of Systolic Blood Pressure and Perfusion Status on Mortality in Acute Heart Failure. *Circ Heart Fail* 2021;**14**:312–23.
5. 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.
6. 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.
7. 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, DOI: 10.1002/EJHF.2587.
8. Joshi SS, Singh T, Newby DE *et al.* Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure. *Heart* 2021;**107**:1032–8.