Acetazolamide in Acute Decompensated Heart Failure with Volume Overload (ADVOR)

Reviewer: Caleb Shelton, PharmD
PGY-1 Resident
CHI St. Vincent Infirmary

Background
The researchers of this trial sought to determine whether acetazolamide, a carbonic anhydrase inhibitor, could improve the efficiency of loop diuretics in patients with acute decompensated heart failure with volume overload. Patients with acute decompensated heart failure are often discharged from the hospital with residual signs of volume overload, many times requiring rehospitalization.[1] The search for medications that improve the signs and symptoms as well as the overall mortality of patients with heart failure is ongoing.

Inclusion Criteria	Exclusion Criteria

• Age ≥ 18 years
• Admitted for acute decompensated heart failure and at least 1 clinical signs of volume overload
  • 2+ or worse edema
  • Pleural effusion verified by chest X-ray
  • Ascites
• Elevated natriuretic peptide
  • NT-proBNP > 1,000 pg/mL
  • BNP > 250 pg/mL
• Receipt of oral maintenance diuretics for ≥ 1 month
  • Furosemide 40 mg/day
  • Bumetanide 1 mg/day
  • Torsemide 20 mg/day
	• Receipt of acetazolamide maintenance therapy in the prior month
	• Receipt of a different proximal tubular diuretic (e.g. SGLT2 inhibitors)
	• SBP < 90
	• eGFR < 20 mL/min/1.73m^2
	• Treatment with IV loop diuretics in doses > 80mg of furosemide, > 2mg bumetanide, or > 20mg torsemide
	• Patients requiring vasopressor support
	• Admission for ACS
	• Prior heart transplant or LVAD
	• On RRT
	• Breastfeeding

Study Design	Notable Baseline Characteristics
• Multicenter • Double-blind • Randomized • Placebo-controlled • N = 519 • Conducted at 27 sites in Belgium • Trail Enrollment Period: 2018-2022 • Follow-Up: 3 months • Analysis: intention-to-treat	• 99% white • 57% NYHA Functional Class II

Intervention	
Treatment Group (N= 259)	**Control Group (260)**
All patients maintenance loop diuretics were stopped. The patients were placed on IV loop diuretics at double the maintenance dose divided into two doses at least 6 hours apart. All patients received 500 mL of D5W with 3g of Magnesium Sulfate given over 24 hours.	
Acetazolamide 500 mg IV daily given with the first loop diuretic dose and for two days or until decongestion.	Placebo given daily with the first loop diuretic dose.

Primary Endpoint	Secondary Endpoints
• Successful decongestion, defined as the absence of volume overload signs (no more than trace edema, no residual pleural effusion or ascites) within 3 days of randomization.	• Composite Endpoint: Death from any cause or rehospitalization for heart failure within 3 months of randomization and the the number of days from randomization until discharge.

Statistical Analysis
The analyses of the primary and secondary endpoints were conducted with the intention-to-treat principle. Data from patients that had received at least one dose of acetazolamide or placebo were included. Four patients were excluded because they did not receive either acetazolamide or placebo. The primary endpoint was evaluated using a log-link binomial model with 95% confidence intervals. The composite endpoint of death from any cause and rehospitalization for heart failure after 3 months was evaluated using a COX proportional-hazards model. Results were summarized using Kaplan-Meier survival curves. Safety events were evaluated by using Fisher's exact test. For all hypothesis testing, a P value < 0.05 was considered indicative of significance.

Results[1]
Successful decongestion occurred in 42.2% of the acetazolamide group versus 30.5% in the placebo group ([CI]: 1.17 -1.82). Death from any cause or rehospitalization for heart failure occurred in 29.7% of the acetazolamide group versus 27.8% in the placebo group ([CI]: 0.78-1.48).

Variable	Placebo (N=260)	Acetazolamide (N=259)	Treatment Effect (95% CI)	P Value
Successful decongestion three days after randomization	79 (30.5%)	108 (42.2%)	Risk Ratio: 1.46 (1.17-1.82)	< 0.001
Death from any cause or rehospitalization for heart failure during 3 month follow-up	72 (27.8%)	76 (29.7%)	Hazard ratio: 1.07 (0.78-1.48)	

Adverse Events
Adverse events occurred in similar rates in both groups. The researchers focused on metabolic acidosis and renal safety in both groups throughout the trial. Other adverse events of note included hypokalemia and hypotension.

Discussion
The authors concluded that the addition of acetazolamide to loop diuretics successfully improved congestion, decreased hospital admission length, and did not increase adverse events versus placebo. The risk of death from any cause or rehospitalization for heart failure was not found to be significantly improved by the addition of acetazolamide.

Strengths	Weaknesses
Randomized trial	Not generalizable due to the predominance of white participants
Double-blinded	May not be applicable to patients newly diagnosed with heart failure
	Unknown if other dosing regimens of loop diuretics would have yielded the same results
	Congestion score used may have been reflective of volume overload only
	SGLT2 inhibitors were excluded to avoid confusion

Reviewer's Conclusions
While the ADVOR trial showed acetazolamide successfully relieved congestion, questions still remain on its utility in treating acute decompensated heart failure. The benefit of acetazolamide may not be generalizable to the greater public given the predominance of Caucasian participants in the trial. The trial excluded patients on SGLT2 inhibitors, which have become guideline recommended therapy for HFrEF as of 2022. This trial was unable to show that acetazolamide reduced mortality for patients with acute decompensated heart failure. SGLT2 inhibitors, however, have been shown to reduce cardiovascular death and rehospitalization due to heart failure. Acetazolamide may be considered as an add-on therapy, but lacks the clinical evidence of other guideline directed medication therapies (GDMT) for heart failure. Furthermore, it is unclear based on this study whether acetazolamide would be more beneficial to patients with acute decompensated heart failure than dose optimization of loop diuretics. Because acetazolamide doesn't provide unique benefits over GDMT medications, it is unlikely that it will find a place in therapy for acute decompensated heart failure without further clinical trials with more robust results.

References

1. Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E, Tartaglia K, Chenot F, Moubayed S, Dierckx R, Blouard P, Troisfontaines P, Derthoo D, Smolders W, Bruckers L, Droogne W, Ter Maaten JM, Damman K, Lassus J, Mebazaa A, Filippatos G, Ruschitzka F, Dupont M; ADVOR Study Group. Acetazolamide in Acute Decompensated Heart Failure with Volume Overload. N Engl J Med. 2022 Sep 29;387(13):1185-1195. doi: 10.1056/NEJMoa2203094. Epub 2022 Aug 27. PMID: 36027559.