Critical Review Form
Therapy

HYPERLINK "http://pmid.us/36335479"Martens P, Dauw J, Verbrugge FH, et al. Decongestion With Acetazolamide in Acute Decompensated Heart Failure Across the Spectrum of Left Ventricular Ejection Fraction: A Prespecified Analysis From the ADVOR Trial. Circulation. 2023 Jan 17;147(3):201-211.

Objectives: **"The current work is a prespecified analysis of the ADVOR trial, assessing the decongestive response of acetazolamide across the enrolled LVEF spectrum." (p. 202)**

Methods: **Please see the PGY-1 appraisal form the details of the ADVOR trial. In addition to the outcomes assessed in the original trial, this secondary analysis also assessed changes in weight, creatinine patterns, and NTproBNP. The authors attempted to evaluate outcomes stratified by baseline ejection fraction (≤ 40% and > 40%) as well as heart failure categories (HFrEF with LVEF ≤40%, HFmrEF with LVEF 41% to 49%, and HFpEF (LVEF >50%).**

Among 519 patients in the analysis, the median LVEF was 45%. There were 224 patients (43%) with a LVEF ≤ 40%, 75 patients (5%) with a LVEF 41 to 49% (HFmrEF), and 220 patients (42%) with HFpEF.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	Yes. "Patients were randomly assigned to receive an intravenous bolus of acetazolamide (500 mg once daily) or 1:1 matching placebo upon randomization and during the next 2 days or until successful decongestion was achieved (ie, the treatment phase)." (p. 203) Additionally, randomization was stratified according to a LVEF ≤40% or > 40%.
2.	Was allocation concealed? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	Presumably yes. While authors report in the initial paper that a Web-based system was used for randomization, they do not mention how allocation occurred following randomization or how medications were dispensed (allocation concealment).
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "All analyses were performed according to the intention-to-treat principle." (p. 203)

4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Uncertain. While the two groups appeared to be similar in the original study, the authors do not break down risk factors by treatment group based upon stratification by LVEF.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	Presumably no. The authors report that this was "double blind" study and that a matching placebo was used, but do not specify who prepared the placebo, if the appearance and volume of the placebo was identical to that of the acetazolamide, or what additional barriers were in place to prevent treatment allocation from becoming known to patients, nurse, or physicians.
2.	Were clinicians aware of group allocation?	See above.
3.	Were outcome assessors aware of group allocation?	Uncertain. The authors do not mention whether the cardiologist assessing the primary outcome—which was quite subjective—was blinded to group allocation. While all other outcomes were fairly objective, the authors do not mention who adjudicated those outcomes and whether they were blinded (observer bias).
4.	Was follow-up complete?	Yes. The primary outcome was assessed in all but 4 patients who did not receive the assigned treatment. The authors do not mention loss to follow-up for any of the remaining outcomes.
II.	**What are the results ?**	
1.	How large was the treatment effect?	● The primary endpoint occurred more frequently in the acetazolamide group across all subgroups of LVEF, but this difference did not achieve statistical significance for LVEF ≤ 40% or those with HFrEF or HFmrEF: ○ EF ≤ 40%, OR 1.36 (95% CI 0.74-2.50) ○ EF > 40%, OR 1.98 (95% CI 1.22-3.21) ○ HFrEF, OR 1.36 (95% CI 0.74-2.50) ○ HFmrEF, OR 2.70 (95% CI 0.91-8.03) ○ HFpEF, OR 2.15 (95% CI 1.16-4.00) ● Successful decongestion at discharge occurred more frequently in the acetazolamide group across all subgroups of LVEF; this difference achieved statistical significance in all groups but the HFmrEF group.

		• There was no statistically significant difference in risk of call-cause mortality and heart failure readmission for any of the subgroups.
2.	How precise was the estimate of the treatment effect?	See above.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Somewhat. While the study was conducted in Belgium, the patients overall had a high incidence of medical comorbidities (atrial fibrillation, diabetes, hypertension) and are likely similar to patients admitted to our institution with decompensated heart failure. Unfortunately, delivery of medical care, specifically outpatient follow-up, is quite difference from our healthcare system in the US (external validity).
2.	Were all clinically important outcomes considered?	Yes. The authors considered successful diuresis, length of hospital stay, death, need for hospital readmission, and incidence of major renal safety events (including need for renal replacement therapy).
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. This was a secondary analysis of previously collected data, stratifying patients according to degree/type of heart failure. While there was a trend toward improvement in the primary outcome across all subgroups, due to a smaller sample size in these subgroups the results did not achieve statistical significance for those with lower ejections fractions. The significance of this is very uncertain.

Limitations:

1. **The authors do not specify how group allocation occurred following random sequence generation or how blinding of patients and clinicians was achieved.**
2. **The authors used a congestion score which was not validated and for which the interrater reliability has not been assessed.**
3. **This was a secondary analysis of previously collected data. While thought provoking, the utility of this information is uncertain. Smaller sample sizes in each subgroup led to many of the results not achieving statistical significance.**

Bottom Line:

This secondary analysis of a multicenter, randomized controlled trial from Belgium found that the addition of acetazolamide to diuresis with a loop diuretic for patients admitted with decompensated heart failure sought to evaluate clinical effect for various degrees of heart failure. While addition of acetazolamide led to increased

rates of successful diuresis at 3 days in all groups, this difference did not achieve statistical significant in those subgroups of more severe heart failure (LVEF ≤ 40%) and only achieved statistical significance in those with preserved ejection fraction. While interesting, the clinical significance of these findings is very uncertain.