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ORIGINAL RESEARCH ARTICLE

Decongestion With Acetazolamide in Acute Decompensated Heart Failure Across the Spectrum of Left Ventricular Ejection Fraction: A Prespecified Analysis From the ADVOR Trial

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BACKGROUND: Acetazolamide inhibits proximal tubular sodium reabsorption and improved decongestion in the ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload) trial. It remains unclear whether the decongestive effects of acetazolamide differ across the spectrum of left ventricular ejection fraction (LVEF).

METHODS: This is a prespecified analysis of the randomized, double-blind, placebo-controlled ADVOR trial that enrolled 519 patients with acute heart failure (HF), clinical signs of volume overload (eg, edema, pleural effusion, or ascites), NTproBNP (N-terminal pro-B-type natriuretic peptide) >1000 ng/L, or BNP (B-type natriuretic peptide) >250 ng/mL to receive intravenous acetazolamide (500 mg once daily) or placebo in addition to standardized intravenous loop diuretics (twice that of the oral home maintenance dose). Randomization was stratified according to LVEF (≤40% or >40%). The primary end point was successful decongestion, defined as the absence of signs of volume overload within 3 days from randomization without the need for mandatory escalation of decongestive therapy because of poor urine output.

RESULTS: Median LVEF was 45% (25th to 75th percentile; 30% to 55%), and 43% had an LVEF ≤40%. Patients with lower LVEF were younger and more likely to be male with a higher prevalence of ischemic heart disease, higher NTproBNP, less atrial fibrillation, and lower estimated glomerular filtration rate. No interaction on the overall beneficial treatment effect of acetazolamide to the primary end point of successful decongestion (OR, 1.77 [95% CI, 1.18-2.63]; P=0.005; all P values for interaction >0.401) was found when LVEF was assessed per randomization stratum (≤40% or >40%), or as HF with reduced ejection fraction, HF with mildly reduced ejection fraction, and HF with preserved ejection fraction, or on a continuous scale. Acetazolamide resulted in improved diuretic response measured by higher cumulative diuresis and natriuresis and shortened length of stay without treatment effect modification by baseline LVEF (all P values for interaction >0.160).

CONCLUSIONS: When added to treatment with loop diuretics in patients with acute decompensated HF, acetazolamide improves the incidence of successful decongestion and diuretic response, and shortens length of stay without treatment effect modification by baseline LVEF.

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Key Words: acetazolamide ■ heart failure ■ diuresis ■ natriuresis

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Clinical Perspective

What Is New?

- Results from the present analyses demonstrate that the treatment effects of acetazolamide in patients hospitalized with acute heart failure (HF) are not modified by the left ventricular ejection fraction.
- Acetazolamide is associated with a modest increase in creatinine during decongestion which is more pronounced in patients with HF with reduced ejection fraction.

What Are the Clinical Implications?

- Despite profound pathophysiologic differences in HF with reduced ejection fraction, HF with mildly reduced ejection fraction, and HF with preserved ejection fraction, acetazolamide leads to significant improvement in decongestive and diuretic response, as well as shorter lengths of stay, in HF with reduced ejection fraction, HF with mildly reduced ejection fraction, and HF with preserved ejection fraction, without clear statistical treatment effect modification.
- Acetazolamide should be considered in addition to loop diuretics in acute decompensated HF to improve decongestive responses and shorten lengths of stay, irrespective of left ventricular ejection fraction.

Nonstandard Abbreviations and Acronyms

ADHF	acute decompensated heart failure
ADVOR	Acetazolamide in Decompensated Heart Failure with Volume Overload
ATII	angiotensin II
HF	heart failure
HFmrEF	heart failure with mildly reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
LVEF	left ventricular ejection fraction
NHE3	natrium-hydrogen exchanger 3
NTproBNP	N-terminal pro-B-type natriuretic peptide
SGLT2i	sodium-glucose cotransporter 2 inhibitor

The ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload) trial investigated the effect of adding acetazolamide on top of standardized high-dose intravenous loop diuretics in patients with acute decompensated heart failure (ADHF). Acetazolamide improved decongestion, reflected by the increased likelihood that clinical signs of volume overload were absent after 3 days of decongestive therapy (ie, the primary end point) as well as at discharge.[1] Acetazolamide resulted in an improved diuretic response measured by increased diuresis and natriuresis, resulting in a shorter length of stay for the index ADHF admission. Acetazolamide inhibits carbonic anhydrase, resulting in diminished NHE3 (natrium-hydrogen exchanger 3)–mediated proximal tubular sodium reabsorption.[2,3] In both healthy conditions and in heart failure (HF), the proximal nephron is responsible for the largest proportion of glomerular filtered sodium reabsorption.[4] Whereas this is ≈60% to 65% in healthy individuals, proximal sodium reabsorption in HF may rise to ≈75% to 85%.[4,5] Although several mechanisms contribute to enhanced proximal nephron sodium reabsorption in HF, these mechanisms are partially influenced by neurohormonal activation. For instance, elevated levels of ATII (angiotensin II) can enhance the vasoconstrictive tonus of the efferent arteriole, thereby reducing glomerular blood flow associated with elevated filtration fraction (which drives proximal nephron sodium reabsorption).[6] Additionally, the expression and activity of the NHE3 transporter is regulated by ATII.[7] Because neurohormonal activation is more clearly implicated in HF with lower left ventricular ejection fraction (LVEF), it is important to determine whether the decongestive effects of acetazolamide are different according to the patients' baseline ejection fraction. The current work is a prespecified analysis of the ADVOR trial, assessing the decongestive response of acetazolamide across the enrolled LVEF spectrum.

METHODS

Trial Design and Population

ADVOR was an investigator-initiated, academic, multicenter, randomized, parallel-group, double-blind, placebo-controlled trial. The details and results of the trial have been published previously.[1,8,9] Briefly, patients ≥18 years of age with an ADHF admission and clinical signs of volume overload (peripheral edema, pleural effusion, and ascites) were eligible for participation. Patients were required to have an NT-proBNP (N-terminal pro-B-type natriuretic peptide) or BNP (B-type natriuretic peptide) level >1000 pg/mL or >250 pg/mL, respectively, with ≥1 clinical sign of volume overload (eg, ascites, pleural effusion, or edema). In addition, oral maintenance therapy with ≥40 mg of furosemide or an equivalent dose (1 mg of bumetanide or 20 mg of torasemide) for ≥1 month was required for randomization.[8] The clinically suspected presence of pleural effusion and/or ascites needed to be confirmed with chest X-ray or chest and/or abdominal ultrasound at baseline before randomization and at every time point a volume assessment was done (Figure S1).[8] The main exclusion criteria were acetazolamide maintenance therapy or treatment with another proximal tubular diuretic, including SGLT2i (sodium-glucose cotransporter 2 inhibitor), a systolic blood pressure <90 mmHg, or an estimated glomerular filtration rate <20 mL/(min·1.73 m^2). During

the index admission, treatment with intravenous loop diuretics at a dose of >80 mg of furosemide equivalents before randomization (eg, in the emergency department) was an additional exclusion criteria. A full list of inclusion and exclusion criteria are provided in the Supplemental Appendix. Ziekenhuis Oost Limburg AV sponsored the trial, which was supported by a grant from the Belgian Health Care Knowledge Centre under the Kenniscentrum Trials Program. The trial protocol was approved by all local ethics committees and the competent authority of Belgium (Federal Agency for Medicines and Health Products). All participants provided written informed consent. An independent clinical end point committee adjudicated predefined events (Supplemental Appendix). The data and analytic methods will be made available for reproducing the results upon reasonable request to the corresponding author.

Trial Intervention

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). Successful decongestion was defined as the absence of any clinical sign of fluid overload (other than trace edema) graded by a volume assessment score (Figure S1; volume score 0 to 1), as previously published.[8] At randomization, oral loop diuretics were stopped, and the patient received intravenous loop diuretic administration at a dosage double that of the oral maintenance dose. If, on the second morning after randomization, urine output was <3.5 L, physicians were required to use escalating diuretic therapies, which could consist of increasing the loop diuretic dose or adding a thiazide-type diuretic (Figure S2).[8]

Primary End Point Collection

The primary end point of the ADVOR trial was successful decongestion, defined as the absence of any signs of volume overload (ie, no more than trace edema, no residual pleural effusion, and no residual ascites) as assessed by a cardiologist trained in the completion of the volume score, at 3 days from randomization in the absence of open-label diuretic therapy escalation for low urine output. Urine collection was started, after voiding empty, at the time of randomization. Placement of a bladder catheter was mandatory in enrolled patients if complete and reliable urine collection could not be collected correctly without. If cumulative urinary output on the second morning after randomization (time frame, 36 to 48 hours) was <3.5 L and signs of fluid overload were still present, escalation of decongestive treatment was mandated by the study protocol (Figure S2), which would also constitute treatment failure in the binary primary end point. As a result, the primary end point incorporates both successful decongestion and diuretic response. A volume score (Figure S1) was completed upon inclusion and thereafter daily before the morning dose of diuretics for the duration of the entire treatment phase and then again at discharge.

Auxiliary End Points

Other predefined congestion/volume end points, similar to the original report of the ADVOR trial, included successful decongestion on the morning of day 3 (without taking the need of escalation therapy into account); and successful decongestion at the day of discharge. Auxiliary end points included cumulative diuresis (mL) and natriuresis (mmol) until the second morning after randomization, diuretic efficacy (urine output per 40-mg furosemide equivalent), length of stay, evolution of the volume score during the treatment phase, and the combined end point of all-cause mortality and rehospitalization for HF during 3 months of follow-up. Additionally, we assessed other end points, including changes in weight, creatinine patterns during decongestion, and NTproBNP. While weight change during the treatment phase was not a predefined end point, it was collected daily in the electronic case record form; however, no standardization of the weight scale was mandated.

Left Ventricular Ejection Fraction

At the time of randomization, site investigators entered the last available (ie, ≤12 months old) LVEF into an automated, web-based system. Randomization was stratified according to an LVEF ≤40% or >40%. Interaction analysis were performed for this stratification and additionally for the HF categories: HF with reduced ejection fraction ([HFrEF] LVEF ≤40%), HF with mildly reduced ejection fraction ([HFmrEF] LVEF, 41% to 49%) and HF with preserved ejection fraction ([HFpEF] LVEF >50%). In addition to the aforementioned categoric approaches, analyses were also performed with LVEF on a continuous scale.

Statistical Analysis

The analytic approach and statistical analysis plan have been published previously.[1,8,9] All analyses were performed according to the intention-to-treat principle. Baseline characteristics are summarized as mean±SD, median (25th to 75th percentile), or n (%), and evaluated using χ^2, ANOVA, and Kruskal–Wallis, as appropriate. The primary end point (binary) was evaluated using a generalized linear-mixed model (logit link function), which included a fixed-treatment effect and random intercept to calculate odds ratios (ORs) and 95% CI. For interaction analysis with baseline LVEF, LVEF was entered into the model as a fixed-effect interaction term with treatment allocation. LVEF was used either categorically when presenting results on category analysis (eg, LVEF strata or HF categories) and continuous when reporting a treatment effect over the entire LVEF range. When using LVEF as a continuous variable, restricted cubic splines based on 3 LVEF knots (25th, 50th, and 75th) were used to visualize the relationship with the outcome variable on the *y* axis. Continuous end points (urine output and natriuresis) were assessed using a similar generalized linear-mixed model, but for continuous end points. Changes in volume score on consecutive days were assessed using a linear mixed-effect model for repeated measurements with a fixed treatment effect, its interaction by treatment day and the interaction with LVEF and a random intercept. The combined end point of all-cause mortality and HF rehospitalization after 3 months was assessed in a time-to-event analysis using a Cox proportional hazard model, including the treatment arm and interaction of LVEF × treatment to calculate hazard ratios (HRs) and 95% CI. The assumptions of the Cox proportional hazard model were checked. Length of index hospitalization was compared with a linear-mixed model after logarithmic transformation to calculate a geometric mean, geometric mean ratio, and 95% CI. No multiplicity adjustments were done for any secondary analysis, so all reported values are exploratory, and a *P* value for interaction <0.05 was deemed significant. Although overall

analyses were not covariate-adjusted, sensitivity analyses for all aforementioned linear models were repeated after correcting for covariates reaching significant differences in baseline (Table 1). Hypotheses testing is 2-sided, and a significance level of α=0.05 was used. All statistical analyses were done using SPSS v25 or STATA v12.

RESULTS

Patient Population

A total of 519 patients were enrolled in the ADVOR trial. The mean age of the patient population was 78 years, and 63% were male. A total of 72% of patients had a history of atrial fibrillation, and 42% of patients had a history of diabetes. All 519 patients randomized in the ADVOR trial had an LVEF available at baseline. In 516 patients (99.4%) LVEF was measured by transthoracic echocardiography, in 2 patients (0.4%) by magnetic resonance imaging, and in one patient by scintigraphy (0.2%). Median LVEF was 45% (25th to 75th percentile; 30% to 55%). A total of 224 (43%) had an LVEF ≤40%, and 42% had an LVEF >50%. Figure S3 illustrates the distribution of baseline LVEF in both the placebo and acetazolamide arms. Baseline LVEF was well balanced in both treatment groups (placebo, 43±15% versus acetazolamide, 43±15%; *P*=0.688). At randomization, 17 patients were treated with a thiazide diuretic as antihypertensive agent (which was stopped as part of the diuretic protocol). Baseline characteristics after classification in HFrEF (n=224), HFmrEF (n=75), and HFpEF (n=220) are provided in Table 1. Patients with HFrEF were more often male and younger, with lower systolic blood pressure and LVEF, higher NTproBNP, less atrial fibrillation or hypertension, and more often, they had ischemic heart disease. Additionally, they were more often treated with renin–angiotensin–aldosterone system inhibitors, cardiac resynchronization therapy, or implantable cardioverter defibrillators.

Event Rate According to Baseline LVEF

The overall event rate, not accounting for treatment allocation, for the primary end point, primary end point excluding the need for therapy escalation, successful decongestion at discharge, combined end point of mortality and HF readmission, cumulative diuresis, cumulative natriuresis, and length of stay were similar in patients with HFrEF, HFmrEF, and HFpEF (Table S1).

Effect of LVEF on Treatment Effect to Decongestion End Points

In the overall trial, assignment towards acetazolamide was associated with a 1.77 higher odds ratio of successful decongestion (*P*=0.005). Table 2 shows the proportion of patients meeting the different decongestion end points according to treatment allocation for the overall population (indicated by overall), and for the subgroups used in LVEF strata randomization (≤40% and >40%) and the HF categories of HFrEF, HFmrEF, and HFpEF. Table 2 also reports the treatment effect and 95% CI first for the overall group and then for the subgroups. As illustrated by the *P* value for interaction, no statistical treatment effect modification was found using LVEF categories as LVEF randomization strata or as HF categories. Similarly, Figure 1 illustrates the treatment effect of acetazolamide visualized as a restricted cubic spline across the entire LVEF range. Approaching LVEF as a continuous variable in the interaction analysis confirmed the absence of statistical treatment effect modification by baseline LVEF (*P* for interaction=0.462). Table S2 shows similar analyses in a sensitivity analysis that adjusts for baseline differences among HF categories, showing a consistent absence of statistical interaction between HF categories and the treatment effect of acetazolamide on decongestive end points in the covariate-adjusted analyses. Similarly, in the 17 patients who underwent discontinuation of the thiazide at baseline as stipulated by the protocol, no difference in the response to acetazolamide was seen for the primary end point (*P* for interaction=0.776).

Acetazolamide was associated with a lower volume score on consecutive days (overall treatment *P*<0.001), with increasing treatment effect over time (time*treatment interaction *P*<0.001; Figure 2). Figure 2A through 2C illustrates the changes in volume score according to HFrEF, HFmrEF, and HFpEF. No interaction between LVEF and the treatment effect of acetazolamide was present on the changes in volume score (*P* for interaction=0.969). Figure S3 shows the individual components (peripheral edema, pleural effusion, and ascites) of the volume score from baseline to day 3 and at discharge per treatment allocation and HF type. Changes in volume score were predominantly driven by changes in peripheral edema and pleural effusion and less so by ascites.

Treatment with acetazolamide resulted in a more pronounced reduction in weight from baseline to the morning of day 3 (absolute difference, −2.9 [−0.1 to −5.7] kg; *P*=0.04), with similar effects in HFrEF, HFmrEF, and HFpEF (*P* for interaction=0.309). Table S3 shows changes in weight from baseline to day 3 for HFrEF, HFmrEF, and HFpEF, in addition to changes in systolic blood pressure and NTproBNP. In both the placebo arm and the acetazolamide arm, NTproBNP significantly dropped from baseline to day 3; however, the difference among treatment arms did not reach statistical significance (*P*=0.155; Figure S4), a finding consistent in HFrEF, HFmrEF, and HFpEF (*P* for interaction= 0.805)

Effect of LVEF on Treatment Effect to Kidney Function

Figure 3 shows the treatment effect of acetazolamide on diuresis (left) and natriuresis (right) according to the

Table 1. Baseline Characteristics in HFrEF, HFmrEF, and HFpEF

Parameter	HFrEF (N=224)	HFmrEF (N=75)	HFpEF (N=220)	*P* value
Age, y*	76±10	80±8	80±8	<0.001
Male sex, n (%)	175 (78)	47 (63)	103 (47)	<0.001
White race, n (%)	223 (99.6)	73 (97.3)	218 (99.1)	0.233
Heart rate, beats/min*	77±17	80±20	79±19	0.359
Systolic blood pressure, mmHg*	122±19	129±21	130±22	<0.001
Diastolic blood pressure, mmHg*	72±12	74±15	72±13	0.453
Weight, kg*	85±20	85±20	85±23	0.970
Volume score at baseline*†	4.4±1.7	4.2±1.6	4.4±1.7	0.588
Composite of volume assessment score, n (%)†				
Edema (>1+)	201 (90)	67 (89)	210 (96)	0.558
Pleural effusion	125 (56)	38 (51)	109 (50)	0.262
Ascites	21 (9)	5 (7)	20 (9)	0.617
Maintenance dose furosemide equivalents, mg‡	65 (40–100)	40 (40–80)	80 (40–130)	0.143
LVEF, %*	29±8	45±8	58±7	<0.001
NT-proBNP, pg/mL‡				
Overall	9137 (4990–18505)	5766 (2663–9469)	4099 (2269–7386)	<0.001
If sinus rhythm	8824 (3831–20417)	6493 (3743–9641)	6281 (2297–10362)	0.091
If AF	9175 (5614–17745)	5506 (2575–8360)	3814 (2268–6955)	<0.001
NYHA, n (%)				0.266
II	33 (15)	11 (15)	22 (10)	
III	128 (57)	36 (48)	132 (60)	
IV	63 (28)	28 (37)	66 (30)	
Ischemic etiology, n (%)	136 (61)	32 (43)	64 (29)	<0.001
Sodium, mmol/L*	140±4	140±4	139±4.8	0.265
Bicarbonate, mmol/L*	25.6±3.9	26.9±3.7	26.8±4.3	0.005
Albumin, g/L*	38.7±4.6	38.5±4.4	38.6±4.1	0.943
eGFR, mL/(min·1.73 m^2)‡	37 (28–51)	43 (31–54)	42 (32–54)	0.049
eGFR <60 mL/(min·1.73 m^2), n (%)	182 (81)	61 (81)	179 (81)	0.976
Comorbidities, n (%)				
History of AF	144 (64)	53 (71)	179 (81)	<0.001
Diabetes	110 (49)	35 (47)	100 (46)	0.739
Hypertension	155 (69)	60 (80)	174 (79)	0.031
Baseline medication				
ACEi/ARB/ARNI	137 (61)	40 (53)	92 (42)	<0.001
Beta-blocker	193 (86)	60 (80)	166 (76)	0.017
MRA	113 (50)	24 (32)	79 (36)	0.002
ICD	70 (31)	2 (3)	7 (3)	<0.001
CRT	46 (21)	6 (8)	9 (4)	<0.001

ACEi indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator, LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.

*Mean±SD

†Congestion score: see Figure S1.

‡Medium (25th-75th percentile).

LVEF strata (A and B), HF categories (C and D), and LVEF as a continuous variable using a restricted cubic spline (E and F). Acetazolamide induced significant diuresis and natriuresis without overall treatment effect modification (*P* for interaction >0.160 in all models) by LVEF. Similarly, Table 2 shows the OR for poor diuretic response defined as a cumulative urine output <3.5 L during the first 2 days. Randomization toward

Table 2. Treatment Effect for Different End Points for 2 Categorical Left Ventricular Ejection Fraction Classifications

Parameter	Placebo	Acetazolamide	OR/HR/Absolute Difference	95% CI	*P* for Interaction*
Primary end point, n (%)†					
Overall	79 (30.5)	108 (42.2)	1.77	1.18–2.63	*P*=0.005
EF strata ≤40%	36 (32.4)	43 (38.7)	1.36	0.74-2.50	0.508*
EF strata >40%	43 (291)	65 (44.8)	1.98	1.22–3.21	
HFrEF	36 (32.4)	38.7 (43)	1.36	0.74–2.50	0.401*
HFmrEF	16 (34.8)	16 (55.2)	2.70	0.91–8.03	
HFpEF	27 (26.5)	49 (42.2)	2.15	1.16–4.00	
Primary end point, excluding need for escalation, n (%)†					
Overall	83 (33.2)	115 (44.9)	1.77	1.19–2.64	*P*=0.005
EF strata ≤40%	39 (35.1)	45 (40.5)	1.30	0.71–2.40	0.401*
EF strata >40%	47 (31.8)	70 (48.3)	2.00	1.24–3.22	
HFrEF	39 (35.1)	45 (40.5)	1.30	0.71–2.40	0.172*
HFmrEF	19 (41.3)	17 (58.6)	2.32	0.78–6.91	
HFpEF	28 (27.5)	43 (45.7)	2.43	1.31–4.50	
Successful decongestion at discharge, n (%)†					
Overall	152 (65.5)	193 (80.1)	2.03	1.34–3.08	*P*=0.001
EF strata ≤40%	61 (61.6)	78 (75.7)	2.03	1.34–3.08	0.263*
EF strata >40%	91 (68.4)	115 (83.3)	2.07	1.19–3.59	
HFrEF	61 (61.6)	78 (75.7)	1.99	1.05–3.77	0.338*
HFmrEF	30 (73)	25 (92.6)	2.57	0.82–8.06	
HFpEF	61 (66.3)	90 (81.1)	2.05	1.08–3.90	
Diuresis <3.5 L, n (%)†					
Overall	98 (38.9)	68 (27)	0.56	0.37–0.84	*P*=0.005
EF strata ≤40%	39 (36.4)	31 (28.2)	0.67	0.36–1.24	0.735*
EF strata >40%	59 (40.7)	37 (26.1)	0.51	0.31–0.85	
HFrEF	39 (36.4)	31 (28.2)	0.67	0.36–1.24	0.511*
HFmrEF	14 (31.0)	7 (25.0)	0.74	0.25–2.25	
HFpEF	45 (45.0)	30 (26.3)	0.40	0.22–0.75	
Diuretic efficacy (L/40 mg furosemide equivalents)‡§					
Overall	1.3±0.8	1.5±0.9	0.148	0.01–0.31	*P*=0.003
EF strata ≤40%	1.3±0.8	1.5±1.0	0.219	−0.03 to 0.47	0.664
EF strata >40%	1.3±0.8	1.4±1.0	0.095	−0.11 to 0.30	
HFrEF	1.3±0.8	1.5±1.0	0.219	−0.03 to 0.47	0.446
HFmrEF	1.5±1.0	1.5±1.0	0.05	−0.45 to 0.35	
HFpEF	1.3±0.8	1.4±1.0	0.17	−0.07 to 0.41	
Risk for all-cause mortality and heart failure admission, n (%)‖					
Overall	72 (27.7)	76 (29.3)	1.07	0.77–1.48	*P*=0.667
EF strata ≤40%	30 (27.5)	33 (29.7)	1.11	0.68–1.82	0.944*
EF strata >40%	42 (28.4)	43 (29.7)	1.03	0.67–1.57	
HFrEF	30 (27.5)	33 (29.7)	1.11	0.67–1.82	0.700*
HFmrEF	15 (32.6)	10 (34.5)	0.92	0.42–2.06	
HFpEF	27 (26.5)	33 (28.4)	1.11	0.67–1.84	

EF indicates ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; and OR, odds ratio.

*Indicates the *P* value for interaction.

†Treatment estimate = OR.

‡Treatment estimate = absolute difference.

§Expressed as mean±SD.

‖Treatment estimate = HR.

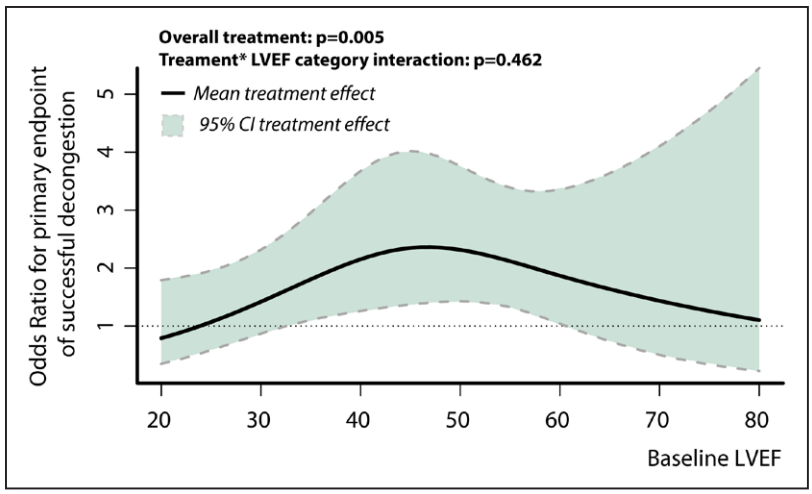

Figure 1. Odds for primary end points across the LVEF spectrum.
Restricted cubic spline of (3-spline knot) spline of LVEF on the *x* axis and the result of generalized linear mixed-effect model outcome expressed as odds ratios (95% CI) on the *y* axis. LVEF indicates left ventricular ejection fraction.

acetazolamide was associated with decreased risk for poor diuretic response without treatment effect modification per HF type. Additionally, Table 2 illustrates the impact of acetazolamide on diuretic efficacy (urine output per 40-mg furosemide equivalent), showing that assignment to acetazolamide resulted in an incremental 148-mL (95% CI, 1 to 310) diuresis per 40 mg of furosemide administered, without significant treatment effect modification by HF types (*P* for interaction=0.446). Table S3 shows similar results in a covariate-adjusted analysis accounting for differences among HFrEF, HFmrEF, and HFpEF. Figure 4 shows the change in creatinine during the treatment phase for the overall population and for patients with HFrEF, HFmrEF, and HFpEF. Randomization toward acetazolamide was associated with a modestly higher creatinine level during decongestion in the overall cohort. In the HFrEF cohort—but not the HFmrEF and HFpEF cohorts—creatinine was also significantly higher during the treatment phase compared with the placebo group. Patients in the HFrEF cohort had, in general, more pronounced increases in creatinine (*P* for interaction treatment × HF types = 0.031).

Effect of LVEF on Treatment Effect to Length of Stay

Patients randomized to acetazolamide had shorter lengths of stay versus patients in the placebo group (geometric mean, 8.8 [8.0 to 9.5] days versus 9.9 [9.1 to 10.8] days, respectively; geometric mean ratio, 0.89 [0.81 to 0.98]; *P*=0.016). No statistical treatment effect modification was found on the beneficial treatment effect of acetazolamide to length of stay for LVEF strata (*P* for interaction=0.341), HF categories (*P* for interaction=0.705), or LVEF on a continuous scale (*P* for interaction=0.239).

Effect of LVEF on Treatment Effect to Mortality and HF Admission

Table 2 illustrates the HR for the combined end point of all-cause mortality and HF readmission from randomization to the 3-month follow-up. Overall acetazolamide was not associated with a higher or lower risk (HR, 1.11 [95% CI, 0.67 to 1.84]; *P*=0.639) for the combined end point. No treatment interaction

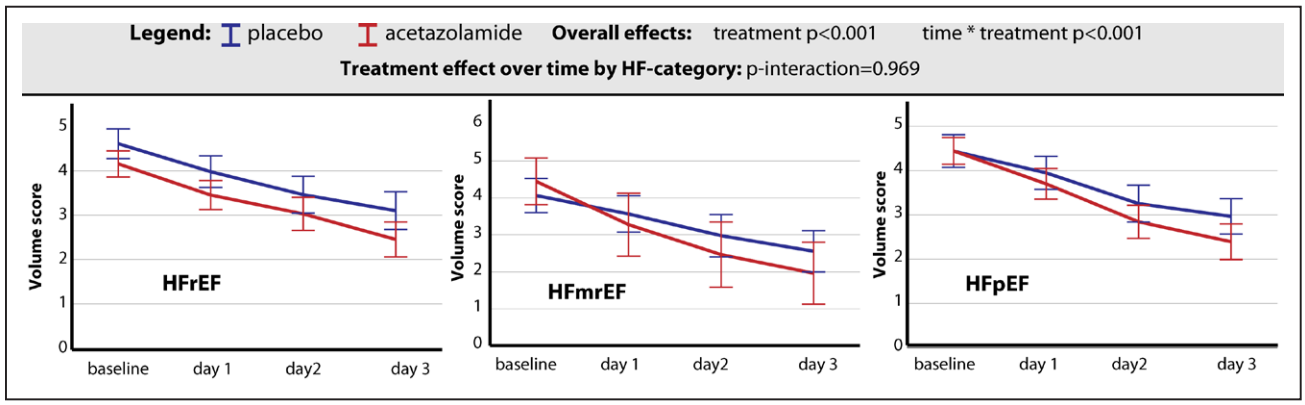

Figure 2. Evolution of volume assessment scores per LVEF quartile.
Results linear mixed-effect model. The overall effects indicate the change in volume score in the overall treatment group and its interaction by time. Changes in volume scores of HFrEF, HFmrEF, and HFpEF are shown. No treatment interactions were observed for the effect of change in volume score of the treatment over time for HFrEF, HFmrEF, and HFpEF (*P*=0.969). HFmrEF indicates heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and LVEF, left ventricular ejection fraction.

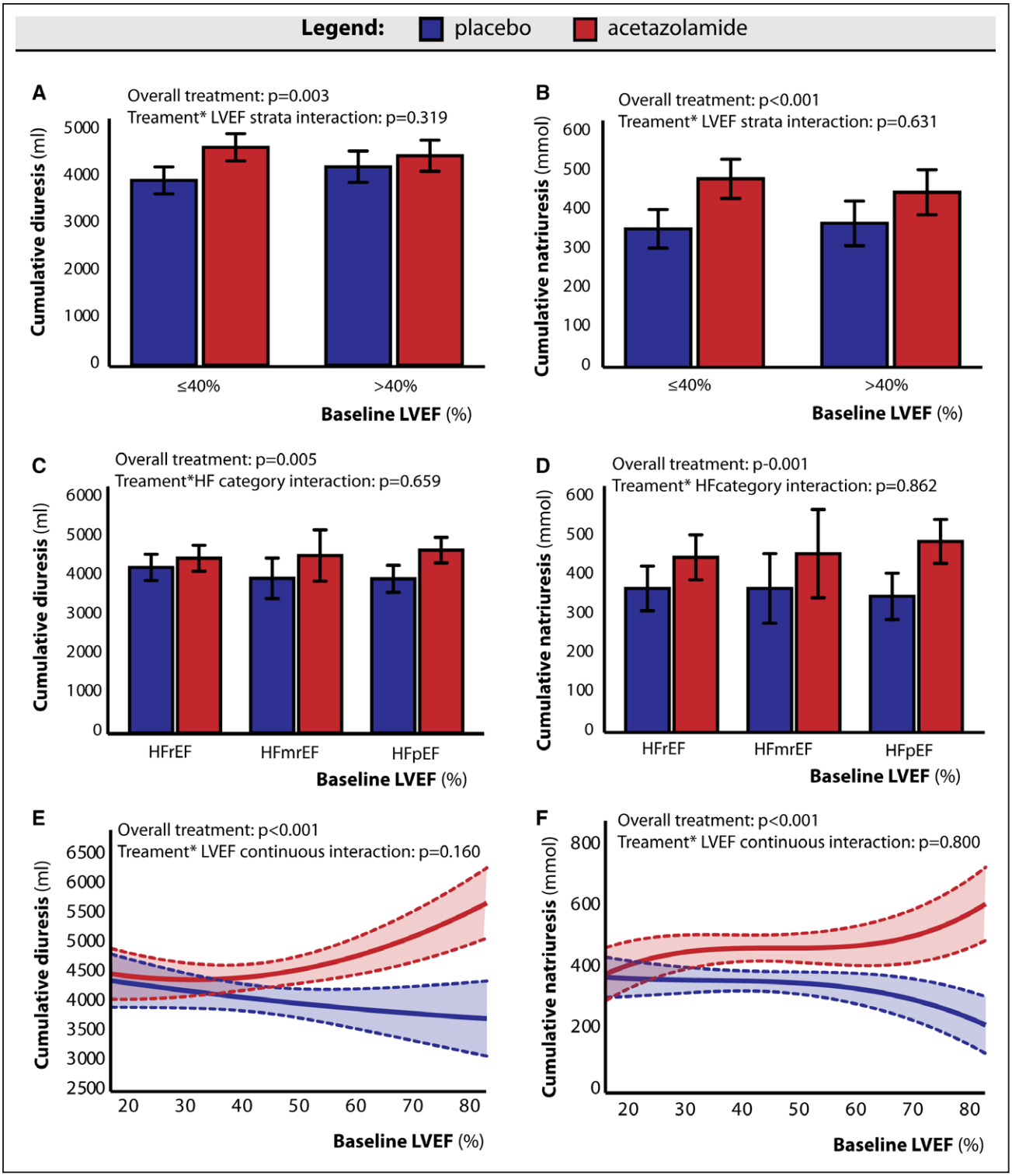

Figure 3. Diuresis and natriuresis across LVEF quartiles and LVEF continuously.
The effect of acetazolamide on diuresis (left, **A**, **C**, **E**) and natriuresis (right, **B**, **D**, **F**) is shown. **A** and **B** use LVEF strata, **C** and **D** use heart failure categories, and **E** and **F** model LVEF continuously as a 3-knot spline. Error bars and splines indicate mean (95% CI). HFmrEF indicates heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and LVEF, left ventricular ejection fraction.

was found across the different, LVEF strata (*P* for interaction=0.700), HF categories (*P* for interaction=0.700) or LVEF on a continuous scale (*P* for interaction=0.208). Similar results were found in a covariate adjusted analysis (Table S3), but the hazard for the combined end point of all-cause mortality and

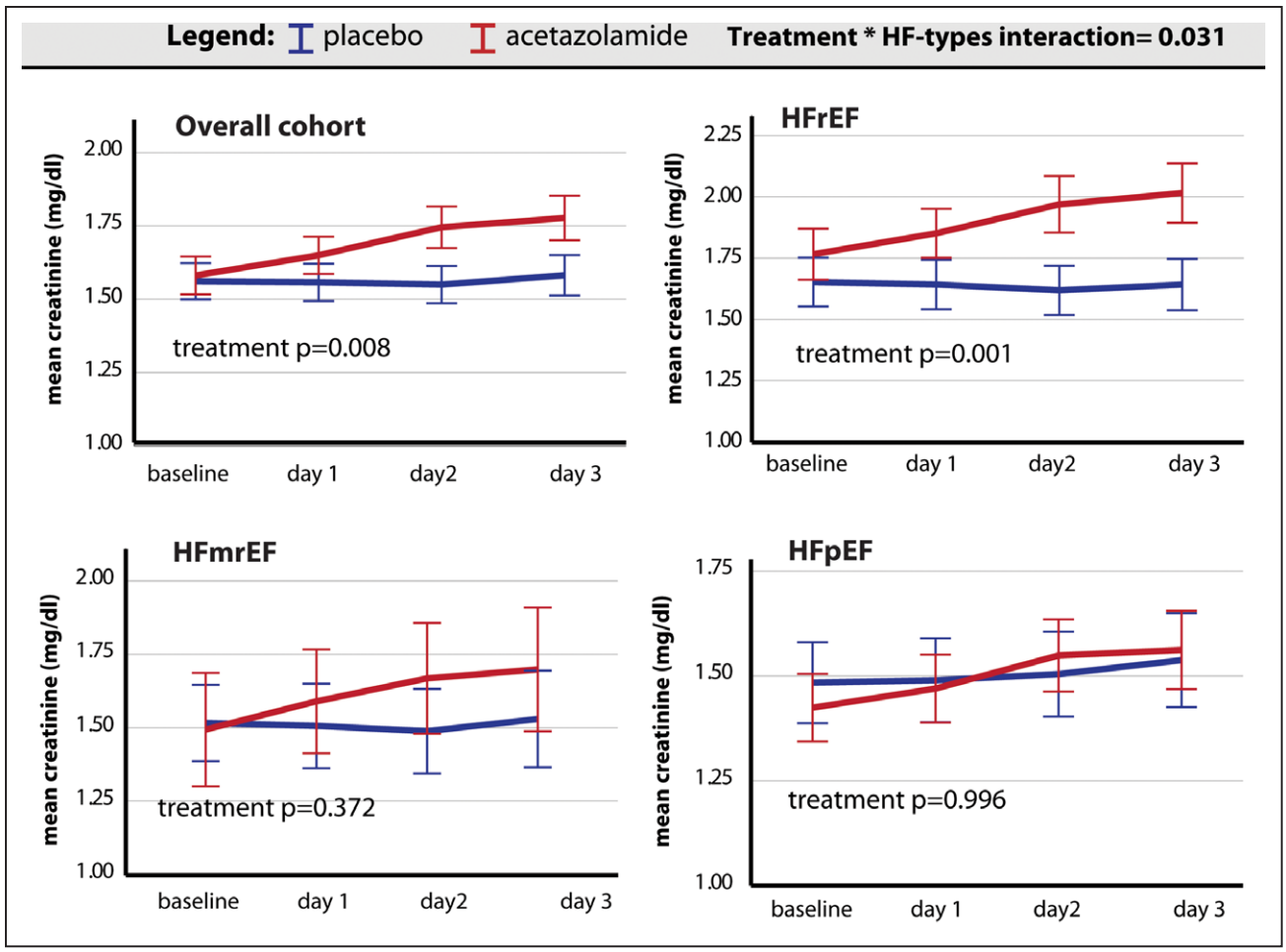

Figure 4. Changes in creatinine during decongestion in the overall cohort and in HFrEF, HFmrEF, and HFpEF.
Results derived from linear mixed-effect model for repeated measurements (creatinine). Changes in creatinine in the overall cohort and in HFrEF, HFmrEF, and HFpEF are shown. Interaction terms assess differences in creatinine changes among heart failure types. HFmrEF indicates heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

HF readmission from randomization to 3 months was lower (HR, 1.05 [95% CI, 0.75 to 1.47]; *P*=0.750), indicating that the numerical nonsignificantly higher HR in unadjusted analyses was predominantly attributable to an imbalance in key prognosticating factors.

DISCUSSION

This prespecified subanalysis of the ADVOR trial assesses the decongestive effect of acetazolamide across the entire range of LVEF. The primary conclusions of this study are that acetazolamide use increases decongestive effectiveness (assessed by the proportion of patients who achieve successful decongestion), enhances diuretic efficacy (measured by natriuresis and diuresis), and decreases lengths of stay without statistical treatment effect modification by baseline LVEF. However, acetazolamide use was associated with a moderate increase in creatinine during decongestion—an observation that may be more pronounced in patients with HFrEF.

Both the European Society of Cardiology and the American Heart Association/American College of Cardiology guidelines give class-I recommendations for the use of diuretics to congestion relief in HF.[10,11] Despite the fact that congestion is the predominant reason of an ADHF admission, and diuretics are used almost ubiquitously in ADHF, there are few clinical trials that test the use of different diuretic agents or diuretic strata, especially combinations of diuretic agents added to loop diuretics.[12,13] Observations from the ADVOR trial showed that acetazolamide, when added to a standardized high dose of intravenous loop diuretics (twice the home maintenance dose), was associated with a greater proportion of patients without residual signs of congestion after 3 days of treatment and without a greater risk of adverse events compared with high-dose intravenous loop diuretics alone. Subjects treated with acetazolamide had greater diuretic efficacy highlighted by a greater amount of diuresis and natriuresis, shorter hospital stays, and were more likely to be discharged without residual signs of volume overload.[1]

Congestion is a universal phenomenon occurring in HFrEF, HFmrEF, and HFpEF, and is characterized by elevated cardiac filling pressures and a variable degree of extravascular volume overload. The ADVOR trial included patients with ADHF and clear signs of volume overload. The development of extravascular volume overload in ADHF is closely related water and sodium retention by the kidneys and interstitial space.[14] In particular, kidney sodium avidity is partially driven by neurohormonal activation. For instance, ATII can modulate the activity and expression of proximal nephron sodium transporters such as NHE3, which is an indirect target for acetazolamide through tubular retention of sodium bicarbonate via carbonic anhydrase inhibition.[7] Additionally, aldosterone levels can modulate distal nephron sodium reabsorption through the epithelial sodium channel.[5] Therefore, because of the role of neurohormonal activation in HF and that therapies targeting different neurohormonal pathways are only effective in HFrEF, we sought to determine the possibility of treatment effect modification by baseline LVEF for patients enrolled in the ADVOR trial. As such, the current study is reassuring, as we did not observe any statistical treatment effect modification by baseline LVEF on the treatment effect of acetazolamide to different decongestion end points, including the proportion of patients reaching euvolemia (volume score ≤1) on day 3, at discharge, or for weight change. As illustrated by Table S3, most changes in the volume score occurred either because of peripheral edema resolution or pleural effusion.

In this study, LVEF was assessed categorically, as well as on a continuous scale. The continuous LVEF scale was utilized in order to avoid misclassification by HFrEF, HFmrEF, and HFpEF related to interobserver measurement variability. However, despite this, we found comparable results when adjusting for typical confounding that commonly differs among patients with HFrEF, HfmrEF, and HFpEF. Furthermore, the adjusted models for the end point of all-cause mortality and HF readmission illustrate that the numerically higher HR for the combined end point may be driven by an imbalance of prognostic characteristics.

The doubling of creatinine was a predefined safety end point in the ADVOR trial and was not more frequent in patients randomized to acetazolamide.[1] However, in the current analyses, we observed that patients treated with acetazolamide had statistically significant but modest increases in creatinine during the treatment phase; this was more pronounced in patients with HFrEF. Although the reasons for which patients with HFrEF may have greater increases in creatinine remain speculative, it may be a function of a worse baseline estimated glomerular filtration rate, different pathophysiology in maintaining the glomerular filtration rate, or a type I error. For instance, estimated glomerular filtration rates in patients with HFrEF might be more dependent on the vasoconstrictive tone of the efferent arteriole in the glomerulus. As acetazolamide use increases chloride delivery to the macula densa (inhibition of proximal sodium chloride absorption), renin release may decrease, resulting in diminished vasoconstrictive tone of the efferent arteriole.[5] Whether this influences long-term adverse events is less clear: a modest increase in creatinine during decongestion in patients who demonstrate clinical improvement (better decongestion and good diuretic response) has also been associated with better clinical outcomes compared with patients having slightly increased creatinine and no clinical improvement.[15] Indeed, a recent position statement from the cardiorenal working group of the European Heart Failure Association stated that modest increases in creatinine should not lead to automatic down-titration of the decongestive therapy in ADHF if patients are generally improving because residual congestion at discharge is associated with worse outcome.[16]

As expected, marked differences were observed in baseline features of patients with lower versus higher LVEF, as previously alluded to in the baseline characteristics paper of the ADVOR trial.[9] Similar to other cohorts, patients in the lower LVEF range were often male, had more ischemic heart disease, and a higher NTproBNP, whereas patients in the higher LVEF range were more likely to be female with higher prevalence rates of atrial fibrillation or hypertension.[17,18] Despite these baseline differences, the overall event rates of successful decongestion and degree of diuretic response were relatively similar in the different LVEF categories and consistently improved if patients were randomized toward acetazolamide in both covariate-adjusted and -unadjusted analyses. Accordingly, we conclude that the universal feature of congestion in HFrEF, HFmrEF, and HFpEF may be beneficially influenced by acetazolamide, despite known pathophysiologic and baseline differences in these subtypes of HF.

Limitations

Several limitations of this study should be acknowledged. First, this was a prespecified analysis of the ADVOR trial, which was only powered to test the treatment effect in the overall study cohort. Second, the echocardiographic assessment of LVEF is subject to interobserver and temporal variability, particularly when performed locally by the study sites. Third, the use of SGLT2i was excluded, because at the time of trial initiation, no data were available on the use of SGLT2i in HF. Nevertheless, SGLT2, as a different proximal nephron sodium reabsorption channel, is only responsible for ≈5% of proximal nephron reabsorption, while the apical sodium–hydrogen exchange mediated by NHE3 is the most important reabsorption mechanism, responsible for 60% of proximal sodium reabsorption.[4] Therefore, although the pharmacologic interaction between SGLT2i and acetazolamide

is unknown, we would not expect a significantly different effect when using SGLT2i simultaneously. Finally, LVEF was reported by site investigators and not by a core laboratory. However, the approach of using LVEF on a continuous scale would lessen potential misclassification of LVEF compared with using a categoric classification approach alone.

Conclusions

Acetazolamide, when added to treatment with loop diuretics, improves decongestive effectiveness and diuretic response, and shortens length of stay without treatment effect modification by underlying LVEF.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Methods

Figures S1–S4

Tables S1–S3

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