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FASTTRACK CLINICAL RESEARCH
Heart failure and cardiomyopathies

Renal function and decongestion with acetazolamide in acute decompensated heart failure: the ADVOR trial

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See the editorial comment for this article 'Acetazolamide for acute heart failure: is ADVOR a riddle wrapped in a mystery inside an enigma?', by H. Bueno and M. Packer, https://doi.org/10.1093/eurheartj/ehad560.

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Abstract

Background and Aims In the ADVOR trial, acetazolamide improved decongestion in acute decompensated heart failure (ADHF). Whether the beneficial effects of acetazolamide are consistent across the entire range of renal function remains unclear.

Methods This is a pre-specified analysis of the ADVOR trial that randomized 519 patients with ADHF to intravenous acetazolamide or matching placebo on top of intravenous loop diuretics. The main endpoints of decongestion, diuresis, natriuresis, and clinical outcomes are assessed according to baseline renal function. Changes in renal function are evaluated between treatment arms.

Results On admission, median estimated glomerular filtration rate (eGFR) was 40 (30–52) mL/min/1.73 m^2. Acetazolamide consistently increased the likelihood of decongestion across the entire spectrum of eGFR (*P*-interaction = .977). Overall, natriuresis and diuresis were higher with acetazolamide, with a higher treatment effect for patients with low eGFR (both *P*-interaction < .007). Acetazolamide was associated with a higher incidence of worsening renal function (WRF; rise in creatinine ≥ 0.3 mg/dL) during the treatment period (40.5% vs. 18.9%; *P* < .001), but there was no difference in creatinine after 3 months (*P* = .565). This was not associated with a higher incidence of heart failure hospitalizations and mortality (*P*-interaction = .467). However, decongestion at discharge was associated with a lower incidence of adverse clinical outcomes irrespective of the onset of WRF (*P*-interaction = .805).

Conclusions Acetazolamide is associated with a higher rate of successful decongestion across the entire range of renal function with more pronounced effects regarding natriuresis and diuresis in patients with a lower eGFR. While WRF occurred more frequently with acetazolamide, this was not associated with adverse clinical outcomes.

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Structured Graphical Abstract

Key Question

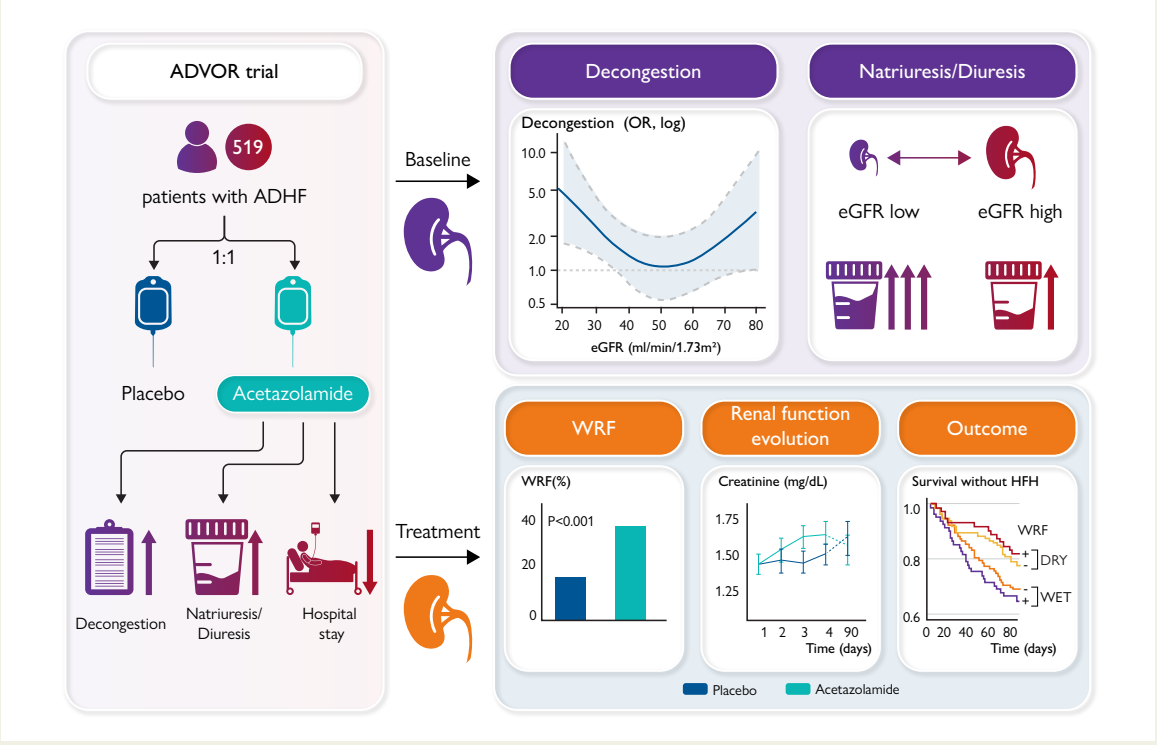
The ADVOR trial demonstrated that intravenous acetazolamide in addition to standardized intravenous loop diuretics increased the incidence of successful decongestion in patients with acute decompensated heart failure (ADHF). This prespecified subanalysis evaluated the clinical effects of acetazolamide on renal function and potential clinical benefit across the spectrum of renal function.

Key Finding

The beneficial effects of acetazolamide on decongestion remained consistent across the entire renal function spectrum. The effects on natriuresis and diuresis were even more pronounced in patients with lower renal function. While patients treated with acetazolamide experienced a modest but statistically significant higher rise in serum creatinine during decongestion, this difference disappeared within 3 months and was not associated with worse outcome if decongestion was achieved.

Take Home Message

- Acetazolamide is safe and effective to treat congestion across the entire range of renal function, with more pronounced beneficial effects in patients with a lower estimated glomerular filtration rate.
- Treatment with acetazolamide increases the risk of worsening renal function during the treatment phase, which does not portend adverse outcomes as long as decongestion is achieved.



ADHF, acute decompensated heart failure; eGFR, estimated glomerular filtration rate; HFH, heart failure hospitalization; OR, odds ratio; WRF, worsening renal function.

Keywords Acute heart failure • acetazolamide • decongestion • kidney function • worsening renal function

Introduction

Almost 50% of patients with heart failure have chronic kidney disease (CKD) defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2, which is associated with an impaired diuretic response. Consequently, achieving decongestion in such patients becomes a more arduous task.[1,2] In addition, worsening renal function (WRF), assessed by an increase in serum creatinine, is reported in up to 20%–40% of the patients with acute decompensated heart failure (ADHF).[2,3] Although highly prevalent, few trials have investigated diuretic strategies in patients with impaired renal function.[4]

In the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial, a stepped diuretic protocol was as effective as ultrafiltration in achieving decongestion in patients with WRF and persistent congestion.[5] The stepped diuretic protocol used high doses of loop diuretics with association of thiazides in case of insufficient diuretic response. Recent trials such as the Combining Loop with Thiazide Diuretics for Decompensated Heart Failure (CLOROTIC) and the Acetazolamide in Decompensated heart failure with Volume OveRload (ADVOR) have focused on an upfront strategy of combinational diuretics assessing the impact on decongestive response in comparison with a loop diuretic only strategy.[6,7]

In the ADVOR trial, in which 82% of the patients had CKD,[8] the addition of intravenous acetazolamide to standardized intravenous loop diuretics improved diuretic efficacy in patients with ADHF and volume overload, resulting in a higher incidence of successful decongestion and shorter hospital stay.[7] Whether the effects of acetazolamide observed in the ADVOR trial are consistent across the entire range of baseline renal function remains unclear. In addition, limited information is available about the impact of acetazolamide on renal function and the potential prognostic meaning of these treatment-induced alterations. Therefore, a prespecified subanalysis addressing these questions was conducted.

Methods

Study design

The methods and results of the ADVOR trial (NCT03505788) have been published previously.[8,9] Patients admitted for ADHF were eligible for inclusion if they had at least one clinical sign of volume overload (i.e. ascites, pleural effusion, or oedema), elevated natriuretic peptides (NT-proBNP > 1000 pg/mL or BNP > 250 pg/mL), and oral maintenance therapy with at least 40 mg of furosemide (or equivalent dose) for at least 1 month. Main exclusion criteria were acetazolamide maintenance therapy before randomization, treatment with sodium-glucose cotransporter 2 inhibitors (SGLT2i), a systolic blood pressure <90 mmHg, or an eGFR <20 mL/min/1.73 m^2. Participants were randomly assigned in a 1:1 fashion to treatment with an intravenous bolus of acetazolamide (500 mg once daily) or matching placebo in addition to standardized intravenous loop diuretic therapy (twice oral home dose daily) upon randomization and during the next 2 days. The study complied with principles outlined in the Declaration of Helsinki and was approved by all local ethics committees from participating centres. All participants provided written informed consent.

Endpoints

The primary endpoint of the ADVOR trial was defined as successful decongestion on the third morning after randomization without the need for escalation of decongestive therapies due to poor loop diuretic efficacy (defined as total urinary output below 3.5 L on the second morning after randomization). Successful decongestion was defined as the absence of signs of volume overload (no pleural effusion, no ascites, and not more than trace oedema). Key secondary endpoints were the length of index hospital stay, cumulative diuresis (mL), and natriuresis (mmol) during the first 2 days after randomization and the composite endpoint of first occurrence of death from any cause or rehospitalization for heart failure during a 3-month follow-up period.

Renal function assessment

Serum creatinine was measured by the local hospital's laboratories and reported through the clinical report forms. Blood samples including creatinine levels were collected per protocol at randomization (baseline = Day), Day 2, Day 3, Day 4, and after 3 months. The eGFR (according to the CKD-EPI formula, expressed as mL/min/1.73 m^2) reported by local laboratories at the sites was used in this analysis.[10]

Statistical analysis

Baseline characteristics are summarized as means and standard deviations, medians and 25–75th percentile, or numbers and percentages and evaluated using analysis of variance, Kruskal–Wallis, and χ^2 tests as appropriate. The primary and secondary (binary) endpoints were evaluated using a generalized linear mixed model (logit binomial model) which included a fixed treatment effect and random intercept to calculate odds ratios (ORs) and 95% confidence intervals (CIs). For interaction analysis with baseline eGFR, eGFR was entered into the model as a fixed effect interaction term with treatment allocation. This was done with eGFR both as a categorical variable (eGFR above and below the median) and according to the KDIGO classification[11] and on a continuous scale, using restricted cubic splines. Continuous endpoints (urine output, natriuresis, and length of stay) were assessed using a similar generalized linear mixed regression model. The models were performed unadjusted and adjusted for baseline differences with *P*-value <.05 between patients with an eGFR ≤40 and >40 mL/min/1.73 m^2, i.e. age, heart rate, diastolic blood pressure, oedema score, home maintenance dose of furosemide (ln transformed), NT-proBNP (ln transformed), serum haemoglobin, potassium, troponin T (ln transformed). Longitudinal changes in serum creatinine level according to treatment allocation were assessed using a linear mixed-effects model with repeated measurements over time including fixed treatment effect, time, and its interaction and including also a random intercept. No imputation for missing data was performed as this was generally low (below 5%) for the in-hospital treatment period. Worsening renal function was defined as an increase in serum creatinine of at least 0.3 mg/dL at any point during the treatment phase (i.e. first 4 days). A sensitivity analysis with a relative increase in serum creatinine of 25% was performed as comparison.[12] Predictors of WRF were assessed using binomial logistic regression models. Variables with a *P*-value <.05 were included in a multivariable model. The combined endpoint of all-cause mortality and heart failure rehospitalization after 3 months was assessed in a time-to-event analysis using a Cox proportional hazard model including the occurrence of WRF and the occurrence of WRF in relation to clinical congestion state. Interaction between WRF and congestion state was evaluated with a generalized linear mixed model. No adjustments for multiplicity were performed, so all reported *P*-values are exploratory. All the hypotheses testing was 2-sided with a significance level of $\alpha = 0.05$. All statistical analyses were done using SPSS version 28.

Results

Baseline characteristics

In total, 519 patients were included in the ADVOR trial and renal function was available in all patients at baseline. The median serum creatinine was 1.49 (1.17–1.94) mg/dL with a median eGFR of 40 (30–52; range 13–118) mL/min/1.73 m^2. The distribution of renal function, including the proportion of patients with eGFR ≤40 and >40 mL/min/1.73 m^2 or KDIGO class, was well balanced between the two treatment groups (*Figure 1*). *Table 1* illustrates the baseline features of patients with eGFR ≤40 and >40 mL/min/1.73 m^2. Of note, patients with an eGFR ≤ 40 mL/min/1.73 m^2 were more likely to be older, had a higher home maintenance dose of loop diuretics, and a higher baseline level of natriuretic peptides. Overall, the ejection fraction, NYHA class, total congestion score, and prescription rate of guideline-directed medical therapy did not differ between patients with an eGFR ≤40 and >40 mL/min/1.73 m^2.

Treatment effect of acetazolamide according to baseline renal function

The treatment effect of acetazolamide for the different endpoints according to the baseline eGFR is shown in *Table 2*. The primary endpoint of successful decongestion after 3 days was higher in patients treated with acetazolamide (OR 1.97; 95% CI 1.29–3.02; *P*-value = .002) when adjusted for baseline differences between patients with low vs. high baseline eGFR. Baseline eGFR did not modify the treatment effect of acetazolamide on the primary endpoint for high vs. low eGFR (*P*-interaction = .672) or over the entire range of eGFR as a continuous variable (*P*-interaction = .977; *Figure 2*). There was also no difference in the treatment effect when baseline eGFR was evaluated according to the KDIGO categories (*P*-interaction = .852; see Supplementary data online, *Table S1*). The secondary combined endpoint of all-cause mortality and heart failure hospitalizations after 90 days did not differ between the placebo and the acetazolamide group. In an analysis adjusted for baseline differences, there was no significant treatment interaction between patients with a high vs. low baseline eGFR (*P*-interaction

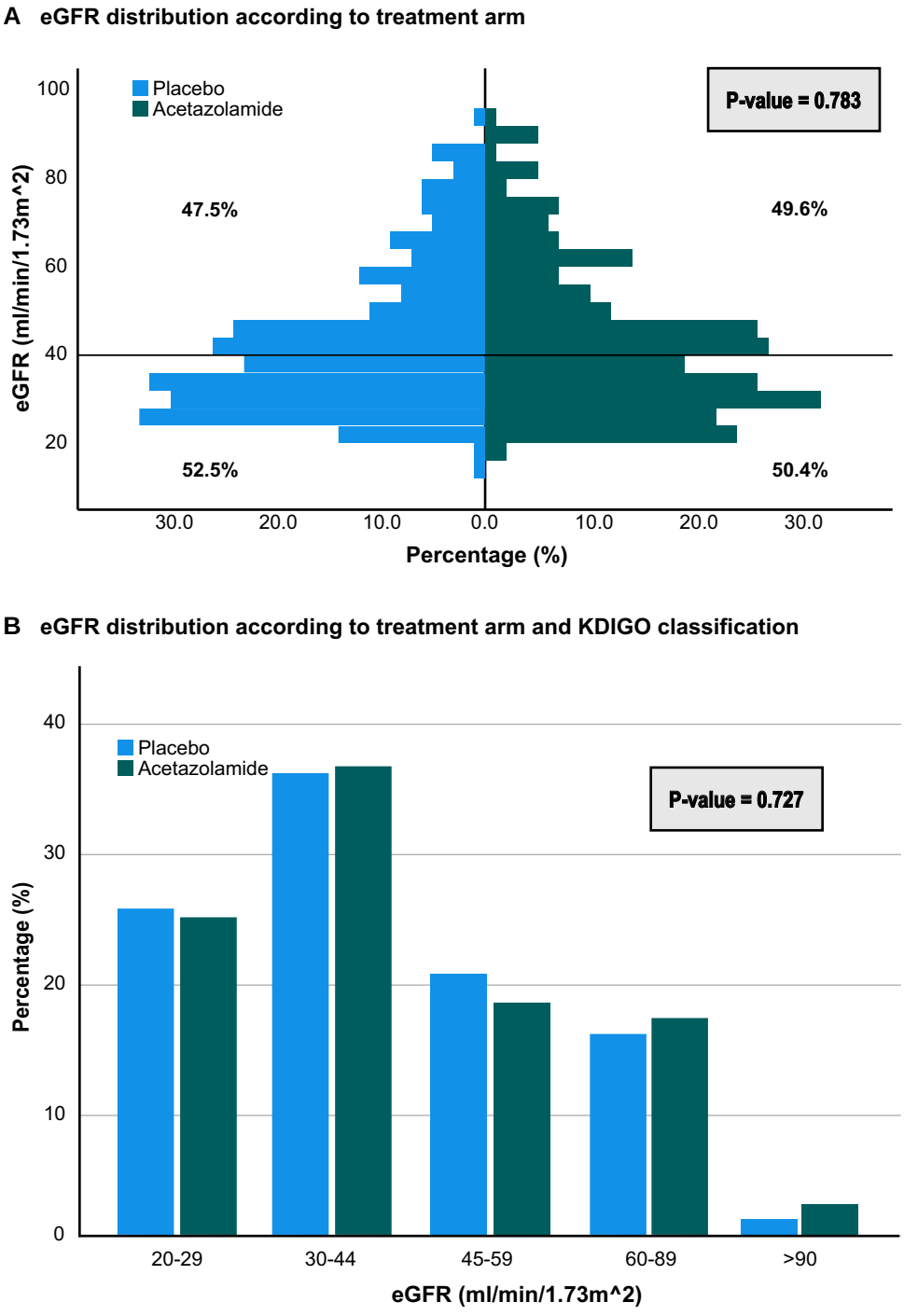


Figure 1 Distribution estimated glomerular filtration rate per treatment category: (*A*) continuous and (*B*) KDIGO classification

= .636, *Table 2*). There was also no treatment interaction for the individual endpoints of all-cause mortality (*P*-interaction = .553) or heart failure hospitalizations (*P*-interaction = .439, *Table 2*). Treatment with acetazolamide reduced length of hospital stay compared with the placebo group (geometric mean: 8.7 ± 1.7 days vs. 9.8 ± 1.8 days; geometric mean ratio = 1.14; 95% CI 1.03–1.26; *P* = .009), and this effect was not modified by low vs. high baseline eGFR (*P*-interaction = .684).

When assessed according to baseline KDIGO categories, there was no significant treatment interaction with regard to the combined (*P*-interaction = .613, Supplementary data online, *Table S1*) or individual endpoints of all-cause mortality and heart failure hospitalizations (*P*-interaction = .474 and .296, respectively; Supplementary data online, *Table S1*). All aforementioned results were similar in unadjusted analyses (see Supplementary data online, *Table S2*).

Table 1 Baseline characteristics of patients with an estimated glomerular filtration rate (estimated glomerular filtration rate) ≤40 and >40 mL/min/1.73 m²

	Total (*n* = 519)	eGFR ≤ 40 mL/min/1.73 m² (*n* = 265)	eGFR > 40 mL/min/1.73 m² (*n* = 254)	*P*-value
Acetazolamide	259 (49.9%)	129 (48.7%)	130 (51.2%)	.599
Age (years)	78 ± 9	80 ± 8	77 ± 10	**<.001**
Female	194 (37.4%)	109 (41.1%)	85 (33.5%)	.085
Heart rate (b.p.m.)	78 ± 18	76 ± 19	80 ± 18	**.036**
Systolic BP (mmHg)	127 ± 21	126 ± 21	127 ± 20	.617
Diastolic BP (mmHg)	72 ± 13	70 ± 13	74 ± 13	**.001**
Weight (kg)	84.8 ± 21.4	83.3 ± 20.6	86.4 ± 22.1	.099
Congestion score	4 (3–6)	4 (3–6)	4 (3–6)	.630
Components of congestion				
Oedema				**.019**
0	25 (4.8%)	16 (6.0%)	9 (3.5%)	
1	16 (3.1%)	2 (0.8%)	14 (5.5%)	
2	73 (14.1%)	35 (13.2%)	38 (15.0%)	
3	228 (43.9%)	119 (44.9%)	109 (42.9%)	
4	117 (34.1%)	93 (35.1%)	84 (33.1%)	
Pleural effusion				.442
0	246 (47.5%)	124 (47.0%)	122 (48.0%)	
2	201 (38.8%)	108 (40.9%)	93 (36.6%)	
3	71 (13.7%)	32 (12.1%)	39 (15.4%)	
Ascites				.841
0	473 (91.1%)	241 (90.9%)	232 (91.3%)	
2	25 (4.8%)	14 (5.3%)	11 (4.3%)	
3	21 (4.0%)	10 (3.8%)	11 (4.3%)	
Home maintenance dose of furosemide (mg)	60 (40–100)	80 (40–132.2)	40 (40–100)	**<.001**
LVEF (%)	43 ± 18	42 ± 17	44 ± 15	.129
NT-proBNP (pg/mL)	6134 (3034–10 765)	7386 (3883–14 417)	4435 (2517–8907)	**<.001**
NYHA class				.233
II	66 (12.7%)	40 (15.1%)	26 (10.2%)	
III	296 (57.0%)	145 (54.7%)	151 (59.5%)	
IV	157 (30.3%)	80 (30.2%)	77 (30.3%)	
Ischaemic cause	232 (44.7%)	123 (46.4%)	109 (42.9%)	.428
Haemoglobin (g/dL)	11.9 ± 2.0	11.7 ± 1.9	12.1 ± 2.1	**.015**
Sodium (mmol/L)	139.5 ± 4.3	139.7 ± 4.0	139.2 ± 4.6	.265
Potassium (mmol/L)	4.2 ± 0.6	4.3 ± 0.6	4.1 ± 0.6	**<.001**
Serum creatinine (mg/dL)	1.49 (1.17–1.94)	1.92 (1.64–2.215)	1.17 (1.00–1.40)	**<.001**
eGFR (mL/min/1.73 m²)	40 (30–52)	30 (25–34)	54 (45–67)	**<.001**
Troponin T	40.0 (24.6–63.3)	45.0 (28.5–71.9)	35.3 (22.0–54.5)	**<.001**
Coexisting conditions				
Atrial fibrillation	376 (72.4%)	193 (72.8%)	183 (72.0%)	.845
Diabetes	245 (47.2%)	134 (50.6%)	111 (43.7%)	.135

Continued

Table 1 *Continued*

	Total ($n = 519$)	eGFR ≤ 40 mL/min/1.73 m² ($n = 265$)	eGFR > 40 mL/min/1.73 m² ($n = 254$)	*P*-value
Hypertension	389 (75.0%)	199 (75.1%)	190 (74.8%)	1.000
Peripheral artery disease	101 (19.5%)	55 (20.8%)	46 (18.1%)	.506
Treatment				
ACEi, ARB, or ARNI	269 (51.8%)	136 (51.3%)	133 (52.4%)	.861
Beta-blocker	419 (80.7%)	221 (83.4%)	198 (78.0%)	.121
MRA	216 (41.6%)	115 (43.4%)	101 (39.8%)	.423

Significance of bold values represents $P < .05$.
ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction.

Table 2 Treatment effect of acetazolamide according to median estimated glomerular filtration rate

Parameter	Placebo, *n* (%)	Acetazolamide, *n* (%)	Adjusted OR/HR (95% CI)	*P*-value	*P*-interaction
Primary endpoint (OR)					
Overall	79/259 (30.5%)	108/256 (42.2%)	1.97 (1.29–3.02)	.002	.672
eGFR ≤40 mL/min/1.73 m²	34/136 (25.0%)	54/129 (41.9%)	2.32 (1.27–4.24)		
eGFR >40 mL/min/1.73 m²	45/123 (36.6%)	54/127 (42.5%)	1.79 (0.97–3.30)		
Primary endpoint with or without need for escalation (OR)					
Overall	86/259 (33.2%)	115/256 (44.9%)	2.01 (1.31–3.08)	.001	.994
eGFR ≤40 mL/min/1.73 m²	41/136 (30.1%)	57/129 (44.2%)	2.04 (1.12–3.73)		
eGFR > 40 mL/min/1.73 m²	45/123 (36.6%)	58/127 (45.7%)	2.08 (1.11–3.89)		
Complete decongestion at discharge (OR)					
Overall	145/250 (58.0%)	190/252 (75.4%)	2.37 (1.54–3.65)	<.001	.467
eGFR ≤40 mL/min/1.73 m²	77/132 (58.3%)	91/127 (71.7%)	1.88 (1.02–3.45)		
eGFR > 40 mL/min/1.73 m²	68/118 (57.6%)	99/125 (79.2%)	3.00 (1.56–5.77)		
All-cause mortality and heart failure hospitalization (HR)					
Overall	72/259 (27.8%)	76/256 (29.7%)	1.09 (0.78–1.54)	.618	.636
eGFR ≤40 mL/min/1.73 m²	43/136 (31.6%)	47/129 (36.4%)	1.17 (0.75–1.83)		
eGFR >40 mL/min/1.73 m²	29/123 (23.6%)	29/127 (22.8%)	0.99 (0.96–1.02)		
All-cause mortality (HR)					
Overall	31/259 (12.0%)	39/256 (15.2%)	1.36 (0.82–2.24)	.230	.553
eGFR ≤40 mL/min/1.73 m²	18/136 (13.2%)	24/129 (18.6%)	1.45 (0.74–2.83)		
eGFR > 40 mL/min/1.73 m²	13/123 (10.6%)	15/127 (11.8%)	1.51 (0.67–3.40)		
Heart failure hospitalization (HR)					
Overall	45/259 (17.4%)	47/256 (18.4%)	1.09 (0.71–1.69)	.684	.439
eGFR ≤40 mL/min/1.73 m²	25/136 (18.4%)	29/129 (22.5%)	0.98 (0.95–1.02)		
eGFR > 40 mL/min/1.73 m²	20/123 (16.3%)	18/127 (14.2%)	1.00 (0.50–2.00)		

Adjusted for age, HR, diastolic BP, oedema, home maintenance dose of furosemide (LN), NT-proBNP (LN), serum haemoglobin, potassium, and troponin T (LN).

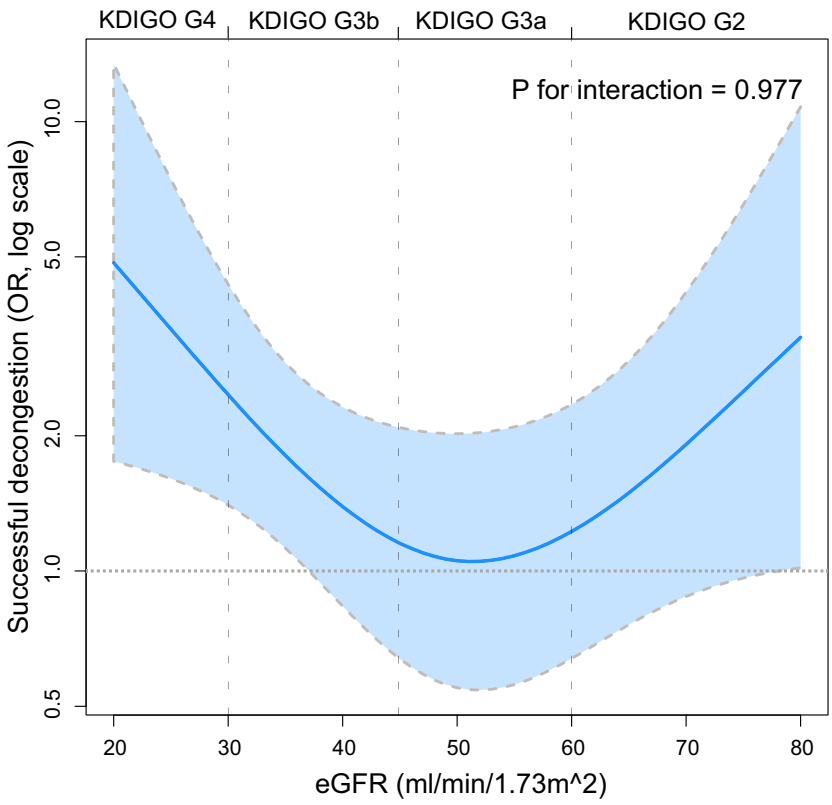


Figure 2 Splines reflecting the treatment effect of acetazolamide on decongestion (within 3 days after randomization) across estimated glomerular filtration rate (continuous)

Effect of the renal function on treatment effect for natriuresis and diuresis

Overall, acetazolamide resulted in more diuresis (4572 ± 1725 vs. 4069 ± 1806 mL; $P = .001$) and natriuresis (468 ± 234 vs. 369 ± 231 mmol; $P < .001$) after 2 days compared with placebo. Although acetazolamide was associated with a higher natriuresis and diuresis in both low and high baseline eGFR, the treatment effect of acetazolamide was more pronounced in patients with low baseline eGFR for both diuresis (P-interaction = .006) and natriuresis (P-interaction < .001) (*Figure 3* and Supplementary data online, *Table S3*).

Change in renal function over time according to treatment arm

In total, 153 patients (out of 516 patients, 29.7%) experienced WRF during the treatment phase. *Figure 4A* shows the evolution of serum creatinine during the treatment phase (Day 1 to Day 4). Patients in the acetazolamide arm showed a modestly higher increase in creatinine in comparison with patients in the placebo arm (mean difference = 0.11 mg/dL, 95% CI 0.02–0.20; $P = .009$). Acetazolamide was associated with a higher incidence of WRF [104 out of 257 patients (40.5%) vs. 49 out of 259 patients (18.9%); OR 2.91; 95% CI 1.96–4.33; $P < .001$; *Figure 4B*]. A sensitivity analysis accounting for a 25% increase in serum creatinine demonstrated similar findings [75 out of 257 patients treated with acetazolamide (29.2%) and 40 out of 259 patients in the control arm (15.4%); OR 2.26; 95% CI 1.47–3.47; $P < .001$]. After 3 months, there was no longer a difference in serum creatinine between the acetazolamide arm [1.62 (1.19–2.04) mg/dL] and placebo arm [1.69 (1.24–2.11) mg/dL; $P = .565$]. One patient in the placebo group and four patients in the acetazolamide group received renal replacement therapy during hospitalization ($P = .21$).

Relationship between worsening renal function and outcomes

Patients with WRF had a higher baseline weight, higher incidence of ischaemic cardiomyopathy and diabetes, higher levels of serum potassium and creatinine, and lower baseline levels of natriuretic peptides (see Supplementary data online, *Table S4*). Patients with WRF were more likely to be treated with acetazolamide and had a higher incidence of successful decongestion within 3 days (47.1% vs. 31.6%; OR 1.93; 95% CI 1.31–2.74; $P < .001$). *Table 3* shows the independent predictors from a multivariable model associated with the development of WRF. Both decongestion (OR 1.78; 95% CI 1.17–2.70, $P = .007$) and randomization towards acetazolamide (OR 2.88; 95% CI 1.88–4.40; $P < .001$) were associated with higher odds of WRF. There was no difference with regard to heart failure hospitalizations and all-cause mortality between patients with or without WRF during hospitalization (HR 0.99; 95% CI 0.70–1.41; $P = .964$). The occurrence of WRF did not modify the treatment effect of acetazolamide on the combined endpoint of heart failure hospitalizations and all-cause mortality (P-interaction = .467; see Supplementary data online, *Figure S1*). *Figure 5* shows the relationship between WRF, decongestion, and clinical outcome. Supplementary data online, *Figure S2* demonstrates the separate curves for decongestion and WRF on the clinical outcome. Decongestion at discharge was associated with a lower rate of the composite endpoint

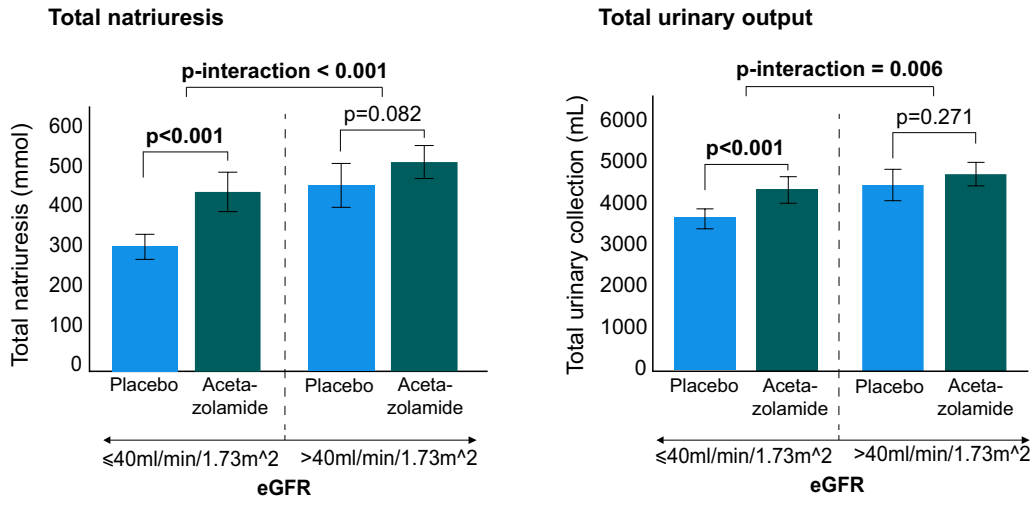


Figure 3 Relationship between baseline estimated glomerular filtration rates—natriuresis/urinary output and treatment arm after 2 days

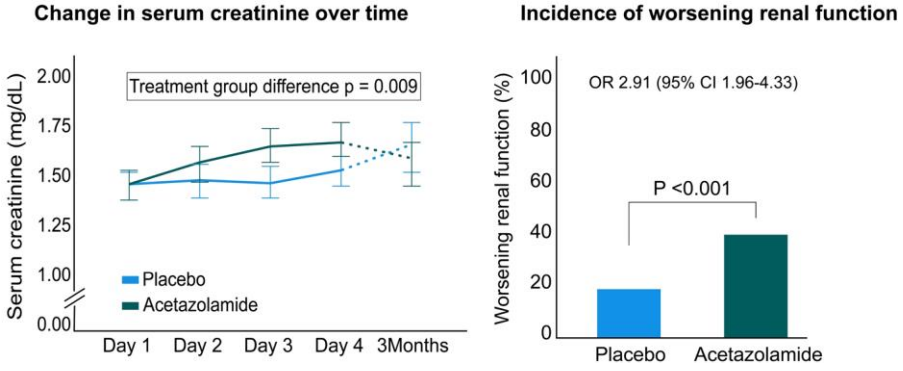


Figure 4 Change in serum creatinine over time and proportion of patients with worsening renal function (defined as a rise of at least 0.3 mg/dL in serum creatinine)

of heart failure hospitalization or all-cause mortality in both patients with WRF (HR 0.51; 95% CI 0.27–0.94; $P = .032$) or without WRF (HR 0.63, 95% CI 0.40–0.99, $P = .046$) (P-interaction = .805).

Discussion

The main findings of this pre-specified analysis of the ADVOR trial are that acetazolamide on top of loop diuretics increased the rate of successful decongestion, irrespectively of baseline renal function. Importantly, the positive effects of acetazolamide on natriuresis and diuresis are larger in patients with a lower baseline eGFR. While acetazolamide increases the risk of WRF during decongestive therapy, there is no difference in renal function or clinical outcome after 3-month follow-up. Importantly, decongestion remains to be associated with improved outcomes irrespectively of WRF (*Structured Graphical Abstract*).

In the ADVOR trial, the use of acetazolamide on top of standardized intravenous loop diuretics was associated with more successful decongestion within 3 days and at discharge. Due to haemodynamic and neurohormonal alterations, proximal tubular sodium and water reabsorption is increased in patients with chronic heart failure.[3] Acetazolamide is a diuretic agent that specifically targets the proximal tubules to address these alterations.

In patients with an impaired renal function, higher doses of intravenous loop diuretics are often needed to reach a sufficient diuretic response as delivery of loop diuretics depends on renal perfusion. Indeed, loop diuretics are protein bound and need to be actively secreted in the proximal tubules to reach their acting site in the tubular lumen in the more distal part of the ascending loop of Henle.[13,14] In patients with lower eGFR and ADHF, it is particularly difficult to attain successful decongestion. Therefore, there is an urgent need for agents that can enhance the response to loop diuretics. This is illustrated by the fact that in the ADVOR trial, patients with an eGFR < 40 mL/min/1.73 m^2 required higher maintenance doses of loop diuretics as an indicator of more diuretic resistance at home. It is reassuring and important that this pre-defined analysis confirmed that the combination therapy with acetazolamide did enhance decongestive response independent of baseline renal function. Moreover, a proportionally higher natriuresis and diuresis was observed in patients with lower renal function, suggesting a higher benefit in inhibiting proximal sodium

Table 3 Multivariable analysis for covariates associated with worsening renal function

	Univariable, OR (95% CI)	*P*-value	Multivariable, OR (95% CI)	*P*-value
Acetazolamide	2.91 (1.96–4.34)	**<.001**	2.88 (1.88–4.40)	**<.001**
Male sex	0.59 (0.39–0.88)	**.010**		
Weight (kg)	1.02 (1.01–1.02)	**.001**	1.02 (1.01–1.03)	**.002**
Ischaemic cause (%)	1.66 (1.13–2.43)	**.009**	1.56 (1.03–2.37)	**.035**
Potassium (mmol/L)	1.38 (1.00–1.89)	.050		
Serum creatinine[a]	2.04 (1.15–3.64)	**.015**		
NT-proBNP[a]	0.83 (0.67–1.02)	.072		
Diabetes	1.87 (1.27–2.74)	**.001**	1.63 (1.06–2.50)	**.025**
ACEi, ARB, or ARNI	1.49 (1.01–2.18)	**.043**		
Successful decongestion	1.93 (1.31–2.84)	**.001**	1.78 (1.17–2.70)	**.007**

Significance of bold values represents $P < .05$.
[a]LN transformed.

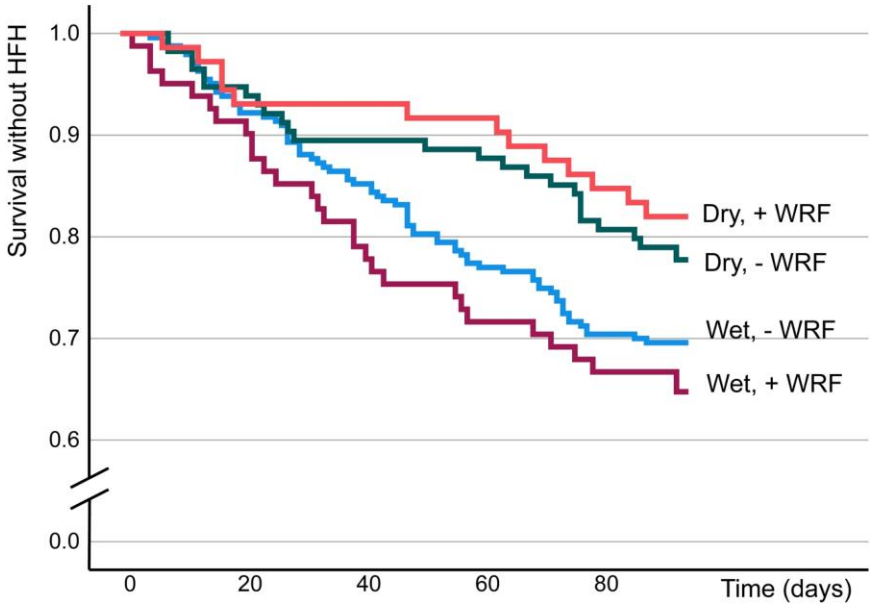


Figure 5 Relationship between the composite outcome of heart failure hospitalizations and all-cause mortality, congestion state, and worsening renal function

reabsorption in these patients, which probably relates to treatment and further prevention of loop diuretic resistance.[15] Importantly, this is in contrast with hydrochlorothiazide (which works distal in the nephron) as the recently reported subanalysis of CLOROTIC indicated a better decongestive response with hydrochlorothiazide on top of loop diuretics mostly in patients with higher eGFR.[16] Since SGLT2i were excluded, the interaction with acetazolamide, baseline renal function and SGLT2i could not be evaluated. Of note, SGLT2i were excluded in ADVOR given the lack of evidence for its use in this patient population at the time. They exhibit their mode of action at the level of the proximal tubules by enhancing glucosuria by blocking sodium-glucose reabsorption resulting in an osmotic diuresis, mainly in diabetic patients with significant glucosuria.[17–19] However, their natriuretic effect is limited in extent and time and their glucosuric effect is dose dependent and diminishes with a lower renal function.[20] Both the Empagliflozin in Patients Hospitalized With Acute Heart Failure Who Have Been Stabilized (EMPULSE) trial and the Dapagliflozin vs. Metolazone in Heart Failure Resistant to Loop Diuretics (DAPA-RESIST) trial have evaluated the use of SGLT2i in patients with ADHF. However, diuresis and weight change were used as a metric for diuretic efficiency instead of urinary collections and SGLT2i were mostly only added days after admission.[21,22] In contrast to patients with a lower renal function, most of the patients with a higher eGFR already exhibit a good diuretic response on loop diuretics. Thus, the presented data once again

provide further evidence that the combination of acetazolamide with loop diuretics is a crucial strategy to enhance decongestion by inhibiting proximal sodium reabsorption. Moreover, the additional natriuretic and diuretic effect of acetazolamide is more pronounced in patients with a lower eGFR.

With regard to the combined endpoint of all-cause mortality and heart failure rehospitalizations, there was numerically a slightly higher event rate in patients treated with acetazolamide. However, this was non-significant and there was even a trend towards lower in-hospital mortality in patients treated with acetazolamide.[7] In addition, it is also important to emphasize that the overall event rate for the ADVOR trial was only 28.7% at 3 months with 17.7% being admitted for heart failure hospitalizations. This was considerably lower compared with previous ADHF trials, such as the DOSE trial[23] (42% already at 2 months) and the CLOROTIC trial (18.3% for all-cause mortality and 36.1% for readmissions at 3 months). This probably relates to the fact that better decongestion was achieved at discharge (71% overall) and the good implementation of HFA-ESC guidelines with frequent outpatient visits and implementation of guideline-directed medical therapy in participating centres in Belgium. The lower event rate is important as in those settings a few extra events in one arm due to the play of chance affect the hazard ratio more. Importantly, the occurrence of WRF did not modify the treatment effect of acetazolamide on this clinical outcome.

During the acute treatment phase, the incidence of WRF was higher in the acetazolamide arm. Main predictors for the onset of WRF were treatment with acetazolamide, successful decongestion, diabetes, and a higher baseline weight. Diabetes and obesity are known risk factors for reduced glomerular reserve and CKD.[1,24] Worsening renal function often accompanies decongestion, as a result of multifactorial haemodynamic alterations including intravascular volume contraction and neurohormonal activation, and is not necessarily associated with worse outcomes.[25] In the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial, patients with a greater reduction in filling pressures were at higher risk of WRF, but this was not associated with an increased hazard of all-cause mortality among patients successfully decongested at discharge.[26,27] In contrast, WRF with persisting signs of congestion is associated with worse outcomes.[28] Therefore, WRF is usually not a sign of renal injury in case of successful decongestion.[29–32] As acetazolamide was associated with a higher diuresis and natriuresis, the higher incidence of WRF is probably merely a reflection of more effective decongestion as significantly more patients were decongested in the WRF group. Therefore, these data corroborate previous findings that WRF during the decongestive phase should not immediately be a reason to cease diuretic therapy (pseudo-WRF).[25] The lack of true renal injury in these patients is supported by the fact that there was no longer a difference in renal function between both treatment groups after 3 months, no increase in the need for renal replacement therapy, an increase in diuresis instead of oliguria, and the absolute difference in creatinine between two groups was at most modest (mean difference = 0.11 mg/dL, 95% CI 0.02–0.20). More importantly, this analysis confirmed that WRF during ADHF always needs to be interpreted in the context of decongestion. Especially as there was no difference in the incidence of the combined endpoint of all-cause mortality and heart failure hospitalizations or in the separate endpoints of all-cause mortality or heart failure hospitalizations between patients with or without WRF. A better clinical outcome was mostly driven by successful decongestion irrespective of the occurrence of WRF. Therefore, pursuing complete decongestion at discharge should remain the most important treatment goal irrespective of changes in renal function during the treatment phase. Modest increases in creatinine can be expected in parallel with the improved decongestive response of acetazolamide.

Limitations

Several limitations should be mentioned. First, although this is a prespecified analysis of the ADVOR trial, the results are exploratory to provide a better understanding of the results of the main trial, but should be considered hypothesis generating. Second, as a baseline renal function with an eGFR <20 mL/min/1.73 m^2 was an exclusion criterium, no information is available regarding the effects of acetazolamide in this subpopulation.

Conclusion

Acetazolamide increases the likelihood of successful decongestion in patients with ADHF with volume overload and this effect is independent of baseline renal function. The effects of acetazolamide on natriuresis and diuresis were larger in patients with low eGFR. Treatment with acetazolamide was associated with a higher incidence of WRF during treatment, but without a difference in renal function after 3 months. Worsening renal function did not modify the beneficial effect of successful decongestion on heart failure hospitalization and mortality.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

Nothing to declare.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Ethical Approval

The study was approved by all local ethic committees from participating centres.

Pre-registered Clinical Trial Number

The pre-registered clinical trial number is NCT03505788.

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