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ORIGINAL SCIENTIFIC PAPER

Acetazolamide, residual congestion and clinical outcomes in acute heart failure – a prespecified analysis of the ADVOR trial

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ABSTRACT

Aims: Acetazolamide, an inhibitor of proximal tubular sodium reabsorption, improves decongestion in acute heart failure (AHF). The aim of the current subanalysis is to evaluate which factors influence decongestion success and the impact of acetazolamide on 3-month clinical outcomes.

Methods: This analysis of the Acetazolamide in Decompensated heart failure with Volume OveRload (ADVOR) trial, that randomised 519 patients with AHF to intravenous acetazolamide or matching placebo, assessed the relationship between acetazolamide treatment, residual congestion, and all-cause mortality and/or heart failure hospitalisation (HFH).

Results: After 90 days, 148 patients (28.7%) experienced the combined endpoint of all-cause mortality and HFH. Predictors of the occurrence of this endpoint were higher baseline doses of loop diuretics (HR = 1.60; 95% CI = [1.26–2.03]; $p < 0.001$) and higher natriuretic peptide levels (HR = 1.34; 95% CI = [1.09–1.65]; $p = 0.006$). Acetazolamide lowered the risk of residual congestion (OR = 0.54, 95% CI = [0.36–0.82]), and residual congestion at day 4 (HR = 1.70, 95% CI = [1.18–2.43], $p = 0.004$) and at discharge (HR = 2.43, 95% CI = [1.76–3.36], $p < 0.001$) were associated with a worse clinical outcome. The presence of residual congestion despite use of acetazolamide was associated with the highest event rate for all-cause mortality or HFH ($p = 0.019$).

Conclusions: Residual congestion after decongestive treatment for AHF is associated with an increased risk of all-cause mortality and HFH. The upfront addition of acetazolamide reduced the incidence of residual congestion. However, patients with residual congestion despite acetazolamide use are at excessive risk for mortality and HFH, identifying a subset of patients requiring specialised heart failure care.

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Introduction

Heart failure is a global problem with increasing incidence and prevalence worldwide. Signs and symptoms of congestion are the main reason for patients with heart failure to seek medical attention. Despite implementation of disease-modifying agents, hospitalisation rates have been reported to exceed 20% within 1 year in ambulatory patients with heart failure [1–3]. After an acute heart failure (AHF) event, the risk for rehospitalisation or all-cause mortality is even higher, mounting to 25% within 3 months and 50% within one year [4–7]. Residual congestion at discharge has been associated with adverse outcomes in observational studies [8,9]. Therefore, current guidelines recommend to pursue complete decongestion at discharge [9,10]. The Acetazolamide in Decompensated heart failure with Volume OveRload (ADVOR) trial has demonstrated that adding upfront intravenous acetazolamide to standardised intravenous loop diuretic therapy in patients with AHF and volume overload improves the chance of successful decongestion within three days and at discharge, increases diuretic response and reduces length of stay [11]. The current prespecified analysis of the ADVOR trial aims to determine (a) which factors were associated with reaching effective decongestion and (b) the relationship between acetazolamide, successful decongestion and 3-month clinical outcome.

Methods

Study design

The methods and results of the ADVOR trial (NCT03505788) have been published previously [11,12]. Briefly, patients enrolled were adults who were admitted for AHF. Patients were required to have an N-terminal pro-B-type natriuretic peptide (NT-proBNP) level >1000 pg/mL or B-type natriuretic peptide level >250 pg/mL, with at least one clinical sign of volume overload (i.e. ascites, pleural effusion, or oedema), despite oral maintenance therapy with at least 40 mg of furosemide (or an equivalent dose) for at least one month. Main exclusion criteria comprised acetazolamide maintenance therapy before randomisation, treatment with sodium-glucose-linked transporter-2 inhibitors, systolic blood pressure <90 mmHg, or an estimated glomerular filtration rate <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 standardised intravenous loop diuretic therapy (twice oral maintenance dose daily) upon randomisation and during the next two days. The study complied with principles outlined in the Declaration of Helsinki, was approved by all local ethic committees of participating centres and all participants provided written informed consent.

End points

The primary end point of the ADVOR trial was defined as successful decongestion on the third morning after randomisation (i.e. day four) 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 morning of day three). Successful decongestion was defined as the absence of pleural effusion and ascites and not more than trace oedema. Secondary end points were the length of index hospital stay and the first occurrence of the composite end point of death from any cause or rehospitalisation for heart failure during a 3-month follow-up period. Heart failure hospitalisations (HFHs) were adjudicated and defined as either a hospital admission or an unscheduled contact at the emergency department for worsening heart failure with the administration of intravenous loop diuretics.

Statistical analysis

Baseline characteristics are summarised as means and standard deviations, medians and 25–75th percentile, or numbers and percentages and evaluated using chi-square, ANOVA and Kruskal–Wallis tests as appropriate. Predictors of residual congestion were assessed using binomial logistic regression models, with variables with a p value below 0.05 introduced into multivariable models. The combined and individual end points of HFHs and all-cause mortality were assessed in a time-to-event analysis using a Cox proportional hazard model including the decongestion state and treatment arm to calculate hazard ratio (HR) and 95% confidence interval (CI). The model was adjusted for known heart failure prognosticators, i.e. sex, diabetes, mean arterial blood pressure, heart rate, home maintenance dose loop diuretics, serum sodium, serum creatinine, serum troponin T levels and natriuretic peptide levels. Logarithmic transformation was performed for skewed variables. All the hypotheses testing was two-sided with a significance level of $\alpha = 0.05$. All statistical analyses were done using SPSS version 28 (SPSS Inc., Chicago, IL).

Results

Baseline features of patients with or without heart failure hospitalisation and all-cause mortality

In the ADVOR-trial, 519 patients were randomised towards either acetazolamide (259/519) or matching placebo (260/519). Four patients lacked the assessment of the combined end point of HFHs and all-cause mortality and were excluded from this analysis. Therefore, the final patient population for this analysis consisted of 515 patients. Table 1 illustrates baseline features of patients with or without HFHs and/or all-cause mortality during follow-up. Of the 515 patients, 92 (18%) patients experienced a HFH and 70 (14%) patients died during the 90-day follow-up period. Patients who died or were hospitalised due to heart failure were more likely to receive a higher maintenance loop diuretic dose, have a lower systolic blood pressure and higher congestion score (mainly driven by oedema) at the moment of admission. Their blood analyses showed lower levels of sodium, chloride and albumin, higher natriuretic peptide levels, a higher level of troponin and a more pronounced kidney impairment. Multivariable regression analysis indicated that a higher dose of maintenance loop diuretic therapy (HR, 1.60; 95% CI, 1.26–2.03; $p < 0.001$) and higher levels of natriuretic peptides (HR, 1.34; 95% CI, 1.09–1.65; $p = 0.006$) were independently associated with a higher risk for the combined endpoint of HFHs and all-cause mortality.

Residual congestion

Residual congestion was apparent in 57.8% versus 69.5% (odds ratio (OR), 0.60; 95% CI, 0.42–0.86; $p = 0.006$) at three days and 21.2% versus 37.5% (OR; 0.45; 95% CI, 0.30–0.67; $p < 0.001$) at discharge in the acetazolamide and placebo group, respectively. A multivariate analysis of the factors associated with the residual congestion at day 4 and at the moment of discharge is represented in Table 2. Randomisation towards acetazolamide treatment, lower baseline bicarbonate and natriuretic peptides levels and a lower loop diuretic maintenance dose were independent predictors of successful decongestion. In a multivariable regression model, randomisation to acetazolamide was independently associated with a lower risk for residual congestion at day 4 (OR 0.54; 95% CI, 0.36–0.82; $p = 0.004$) and at the moment of discharge (OR 0.45; 95% CI, 0.30–0.69; $p < 0.001$) (Table 2).

The combined end point occurred in 40 out of 187 patients (21.4%) who were appropriately decongested at day 4 and in 108 out of 328 patients (32.9%) with residual congestion upon the same moment (HR 1.70, 95% CI, 1.18–2.45, $p = 0.004$) (Supplemental Figure S1). Residual congestion at discharge was also associated with a higher risk for the combined end point of all-cause mortality and HFHs (HR 2.43, 95% CI, 1.76–3.37, $p < 0.001$).

Relationship between acetazolamide, residual congestion and outcome

The incidence of the combined end point did not differ between the treatment groups (placebo $n = 72$, acetazolamide $n = 76$, HR 1.07, 95% CI, 0.78–1.48; $p = 0.667$). With regard to the individual end points, 31 (12.0%) patients in the placebo group and 39 (15.2%) patients in the acetazolamide group died during 3-month follow-up (HR 1.28; 95% CI, 0.80–2.04; $p = 0.313$). With regard to HFHs, 45 (17.4%) patients in the placebo group and 47 (18.4%) patients in the acetazolamide group were rehospitalised during 3-month follow-up (HR 1.07; 95% CI, 0.71–1.59; $p = 0.751$). There was a trend towards a higher in-hospital mortality in the placebo group (18/259 patients, 6.9%) compared to the acetazolamide arm (11/256 patients, 4.3%) (OR, 0.60; 95% CI, 0.28–1.30). Figure 1 illustrates the relation between randomisation towards acetazolamide, residual congestion and outcome for the combined endpoint of HFH and all-cause mortality. Event rate per 100 patient years (PY) was the lowest in the patients who received acetazolamide and were assessed as decongested at day 4 (81 events per 100 PY) and highest for patients with residual congestion despite treatment with acetazolamide (146 events per 100 PY). Kaplan–Meier's curves are presented in Figure 1. Randomisation towards acetazolamide was associated with an increase of 11.7% more patients being decongested and having a better outcome (Figure 1). The interaction term between acetazolamide and decongestion on mortality/heart failure rehospitalisation was not significant (p for interaction = 0.704).

Guideline-directed medical therapy

Except for a clear increase in the prescription of mineralocorticoid receptor antagonists, guideline-directed medical therapy (GDMT) prescription rate declined in both treatment arms after the AHF hospitalisation (Table 3 and Supplemental Table 1). Although all patients were treated with loop diuretics at the

Table 1. Baseline characteristics based on clinical outcome at 3 months.

	Total (*N* = 515)	Alive, non-rehospitalised (*N* = 367)	Dead or rehospitalised (*N* = 148)	*p* Value
Acetazolamide	256 (49.7%)	180 (49.0%)	76 (51.4%)	0.697
Age	78.2 (±8.9)	78.4 (±8.9)	77.9 (±8.7)	0.525
Male sex	323 (62.7%)	225 (61.3%)	98 (66.2%)	0.315
HR	78.0 (±18.3)	77.7 (±18.8)	78.9 (±16.9)	0.478
Blood pressure				
Systolic	126.5 (±20.7)	127.9 (±20.3)	123 (±21.4)	**0.017**
Diastolic	72.1 (±13.0)	72.8 (±13.2)	70.4 (±12.3)	0.059
Weight	84.5 (±20.6)	84.1 (±19.8)	84.4 (±22.6)	0.520
Components of congestion				
Edema				**0.005**
0	25 (4.9%)	21 (5.7%)	4 (2.7%)	
1	16 (3.0%)	14 (3.8%)	2 (1.4%)	
2	72 (14.0%)	59 (16.1%)	13 (8.8%)	
3	227 (44.1%)	164 (44.7%)	63 (42.6%)	
4	175 (34.0%)	109 (29.7%)	66 (44.6%)	
Pleural effusion				0.859
0	243 (47.2%)	174 (47.4%)	69 (46.6%)	
2	200 (38.8%)	140 (38.1%)	60 (40.5%)	
3	71 (13.8%)	52 (14.2%)	19 (12.8%)	
Ascites				0.344
0	469 (91.1%)	337 (91.8%)	132 (89.2%)	
2	25 (4.9%)	18 (4.9%)	7 (4.7%)	
3	21 (4.0%)	12 (3.3%)	9 (6.1%)	
Home maintenance dose of furosemide equivalents	60.0 (40.0–100.0)	60.0 (40.0–100.0)	80.0 (40.0–200.0)	**<0.001**
LVEF (%)	43.2 (±15.1)	43.5 (±15.2)	42.4 (±14.9)	0.470
NT-proBNP	6137 (3038–10,896)	5459 (2962–9828)	7532 (3502–13,998)	**0.003**
NYHA functional class				0.473
II	65 (12.6%)	46 (12.5%)	19 (12.8%)	
III	295 (57.3%)	216 (59.9%)	79 (53.4%)	
IV	155 (30.1%)	105 (28.6%)	50 (33.8%)	
Ischemic cause (%)	231 (44.9%)	170 (46.3%)	61 (41.2%)	0.328
Serum haemoglobin	11.9 (±2.0)	11.9 (±2.0)	11.8 (±1.9)	0.403
Serum haematocrit	36.5 (±5.9)	36.6 (±5.9)	36.3 (±5.8)	0.596
Sodium	139.5 (±4.3)	139.7 (±4.4)	138.8 (±4.1)	**0.024**
Potassium	4.2 (±0.6)	4.2 (±0.6)	4.3 (±0.6)	0.111
Chloride	100.6 (±5.3)	101.0 (±5.5)	99.6 (±4.9)	**0.006**
Bicarbonate	26.3 (±4.1)	26.1 (±4.0)	26.6 (±4.3)	0.230
Serum osmolality	299 (290–305)	298 (290–304)	300 (290–308)	0.146
Serum urea	72.0 (52.0–100.0)	67.7 (49.0–92.0)	85.5 (59.0–112.5)	**<0.001**
Serum creatinine	1.49 (1.18–1.94)	1.43 (1.13–1.88)	1.59 (1.33–2.05)	**<0.001**
Estimated GFR	39.9 (29.3–52.0)	42.0 (30.0–56.0)	34.5 (29.3–45.5)	**<0.001**
<60 mL/min/1.73 m^2	421 (81.7%)	288 (78.5%)	133 (89.9%)	**0.002**
Total protein	68.5 (±7.2)	68.7 (±7.2)	68.0 (±7.4)	0.325
Albumin	38.6 (±4.8)	38.9 (±4.8)	37.7 (±4.8)	**0.017**
LDH	272 (228–358)	268 (220–350)	287 (238–365)	0.081
Troponin T	40.0 (24.7–63.8)	39.0 (23.9–59.0)	45.7 (31.3–76.1)	**0.005**
Coexisting conditions				
History of atrial fibrillation	373 (72.4%)	261 (71.1%)	112 (75.7%)	0.328
Stroke	62 (12.0%)	48 (13.1%)	14 (9.5%)	0.296
Diabetes	243 (47.2%)	167 (45.5%)	76 (51.4%)	0.243
Hypertension	385 (74.8%)	282 (76.8%)	103 (69.6%)	0.093
Valve surgery	90 (17.5%)	63 (17.2%)	27 (18.2%)	0.798
PAD	101 (19.6%)	82 (22.3%)	19 (12.8%)	**0.014**
COPD	101 19.6%)	71 (19.3%)	30 (20.3%)	0.807
Treatment – no. % at baseline				
ACEi, ARB, or ARNI	267 (51.8%)	197 (53.7%)	70 (47.3%)	0.206
Beta-blocker	415 (80.6%)	302 (82.3%)	113 (76.4%)	0.140
MRA	214 (41.6%)	138 (37.6%)	76 (51.4%)	**0.006**

Bold values indicate a statistically significant result with a *p* value < 0.05.
ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; GFR: glomerular filtration rate; HR: heart rate; LDH: lactate dehydrogenase; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PAD: peripheral arterial disease.

moment inclusion, this was reduced by approximately 25% at 3-month follow-up. With regard to 3-month outcome of all-cause death and heart failure rehospitalisation, there was no difference in the prescription of GDMT, neither in the change over time between both groups (Supplemental Tables S1 and S2).

Discussion

The ADVOR trial demonstrated that the addition of acetazolamide to loop diuretic therapy led to a higher incidence of decongestion in patients with acute decompensated heart failure with volume overload and this additional analysis evaluated the relationship

Table 2. Factors associated with the residual congestion at day 4 and at the moment of discharge (unadjusted and adjusted).

	Univariate (OR, 95% CI)	*p* Value	Multivariate (OR, 95% CI)	*p* Value
Residual congestion at day 4				
Age	1.016 (0.996–1.037)	0.121		
Gender	0.889 (0.614–1.287)	0.534		
Ischemic cause	0.963 (0.671–1.381)	0.836		
Diabetes	0.881 (0.615–1.262)	0.490		
Acetazolamide	0.601 (0.419–0.864)	**0.006**	0.543 (0.360–0.819)	**0.004**
Mean arterial pressure	0.987 (0.973–1.000)	0.058		
Home maintenance dose of furosemide equivalents[a]	1.425 (1.078–1.884)	**0.013**	1.411 (1.028–1.937)	**0.033**
Serum sodium	0.974 (0.933–1.017)	0.233		
Serum chloride	0.956 (0.922–0.990)	0.013		
Serum bicarbonate	1.056 (1.009–1.105)	0.019	1.063 (1.009–1.118)	**0.022**
Serum creatinine	1.420 (0.993–2.029)	0.055		
Troponin T[a]	1.283 (1.022–1.610)	**0.032**		
NT-proBNP[a]	1.722 (1.394–2.127)	**<0.001**	1.534 (1.209–1.945)	**<0.001**
Median congestion score at baseline[a]	7.248 (4.245–12.374)	**<0.001**	5.223 (2.961–9.214)	**<0.001**
Residual congestion at discharge				
Age	1.008 (0.987–1.029)	0.477		
Gender	0.955 (0.650–1.403)	0.813		
Ischemic cause	1.295 (0.892–1.879)	0.174		
Diabetes	1.204 (0.830–1.746)	0.328		
Acetazolamide	0.451 (0.308–0.660)	**<0.001**	0.450 (0.295–0.687)	**<0.001**
Mean arterial pressure	0.993 (0.979–1.008)	0.347		
Home maintenance dose of furosemide equivalents[a]	1.202 (0.914–1.582)	0.188		
Serum sodium	0.965 (0.926–1.007)	0.101		
Serum chloride	0.979 (0.946–1.013)	0.215		
Serum bicarbonate	1.001 (0.956–1.048)	0.980		
Serum creatinine	1.130 (0.789–1.618)	0.506		
Troponin T[a]	1.560 (1.216–2.001)	**<0.001**	1.460 (1.124–1.897)	**0.005**
NT-proBNP[a]	1.460 (1.186–1.796)	**<0.001**		
Median congestion score at baseline[a]	5.201 (3.041–8.898)	**<0.001**	5.264 (2.962–9.355)	**<0.001**

Bold values indicate a statistically significant result with a p value < 0.05.
[a]Log transformation.

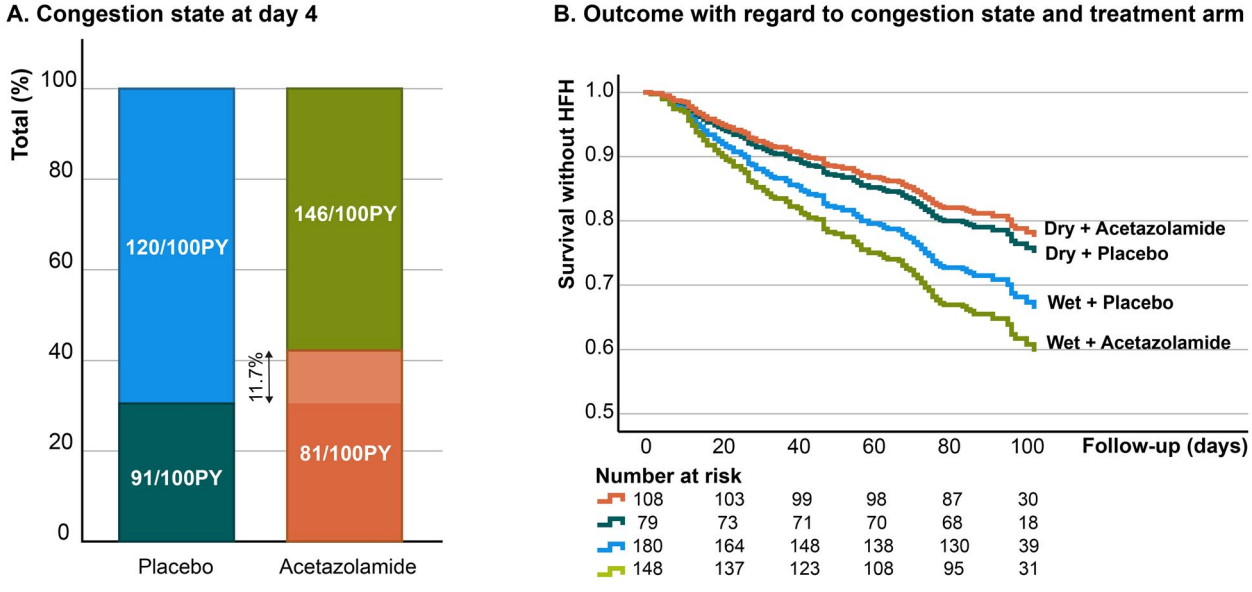

Figure 1. Congestion state at day 4 based on treatment arm and event rate per 100 patient years per category (A) and Kaplan–Meier's curves (B).

between acetazolamide, residual decongestion and clinical outcome. The main messages of this analysis are: (1) randomisation towards acetazolamide is independently associated with a lower risk for residual congestion on day 4 and at discharge, with those patients experiencing successful decongestion demonstrating subsequently better clinical outcomes, (2) residual congestion after three days regardless of method of decongestion identifies a phenotype of patients with a higher risk of rehospitalisation for heart

Table 3. Guideline-directed medical therapy prescription over time.

	Placebo	Acetazolamide	*p* Value
Beta-blockers			0.480*
Screening	208 (80.9)	203 (79.6)	0.740
Day 4	180 (70.6)	193 (74.5)	0.325
Discharge	192 (74.4)	200 (77.2)	0.474
3 months follow-up	167 (64.5)	170 (66.1)	0.712
ACE/ARB			0.486*
Screening	96 (37.2)	92 (35.8)	0.784
Day 4	77 (29.8)	88 (34.1)	0.345
Discharge	89 (34.6)	89 (34.6)	1.000
3 months follow-up	68 (26.5)	74 (28.7)	0.622
ARNI			0.676*
Screening	39 (15.0)	38 (14.7)	1.000
Day 4	40 (15.4)	39 (15.1)	1.000
Discharge	55 (21.2)	48 (18.5)	0.509
3 months follow-up	49 (18.8)	40 (15.4)	0.352
MRA			0.330*
Screening	110 (43.0)	100 (38.8)	0.370
Day 4	113 (44.3)	110 (43.3)	0.858
Discharge	152 (60.1)	155 (61.5)	0.785
3 months follow-up	122 (48.2)	138 (54.1)	0.214
Loop diuretics			0.311*
Screening	260 (100)	259 (100)	
Dose	77.5 (40–120)	60 (40–100)	0.357
Discharge	233 (89.6)	244 (94.2)	0.076
Dose	80 (40–100)	80 (40–100)	0.479
3 months follow-up	196 (75.4)	203 (78.4)	0.466
Dose	40 (5–100)	50 (30–100)	0.289

*p value for interaction term.

failure; however, the effect is more pronounced with residual congestion despite therapy with acetazolamide allowing for patient identification for potential intensification of care; (3) there was no signal towards harm with treatment with acetazolamide, and a trend towards lower in-hospital mortality in these patients was noted, and (4) HFH is associated with a more advanced disease stage with overall a lower prescription rate of GDMT after hospitalisation.

Signs and symptoms of volume overload are the main reason to seek medical attention in patients with AHF. Judicious titration of diuretic therapy has a class I recommendation to relieve congestion and prevent worsening heart failure [10,13,14], considering that residual congestion is associated with an increased risk for rehospitalisation and mortality which was clearly also the case in the ADVOR trial [8,9]. Patients with an adverse outcome were more likely to have a higher dose of maintenance loop diuretic therapy and higher levels of natriuretic peptides, suggesting more advanced stage of heart failure and an increased vulnerability to subsequent events. Despite the benefit of acetazolamide on reaching euvolemia, it failed to demonstrate a benefit in the long-term outcome on HFH. Interestingly, the same observation has been made in other diuretic trials. Despite the beneficial effect on dyspnoea relieve and higher fluid loss in the high-dose compared to the low-dose arm, there was no difference on the 60-day composite endpoint of mortality and heart failure rehospitalisations (63 events and 67 events, respectively; HR with high dose, 0.83; 95% CI, 0.60–1.16; p = 0.28) [15]. The safety and efficacy of the combination of loop with thiazide-type diuretics in patients with decompensated heart failure (CLOROTIC) trial demonstrated the beneficial effect on weight loss and diuresis of a thiazide on top of loop diuretics without a benefit on 90-day mortality and rehospitalisation risk (HR 1.25; 95% CI: 0.81–1.92; p = 0.32) [16]. Lastly, the aldosterone targeted neurohormonal combined with natriuresis therapy in heart failure (ATHENA-HF) trial demonstrated that the addition of MRA in AHF was well tolerated; however, did not influence 30-day mortality or readmission rate (adjusted HR, 1.22; 95% CI, 0.68–2.19; p = .50) [17]. While treating patients with AHF, it is important to realise that the main goal of the therapy is to improve signs and symptoms of congestion, which are the drivers for patients to seek medical attention, despite being treated with GDMT. While acetazolamide on top of loop diuretics very effectively improved decongestion rates in safe, effective manner at low cost, it might not be realistic to expect that a therapy given in hospital for a couple of days will influence long-term outcome. The current subanalysis also confirms the association between congestion state and long-term outcome. These findings are also in line with recent contemporary work emphasising the prognostic importance of residual congestion and the need for more individualised decongestive strategies in AHF [18–20]. This corroborates previous findings of observational and other post hoc analysis of randomised controlled trials, which demonstrated that an increased risk for adverse outcome was primarily seen in patients with residual congestion at discharge [9,15,21–23]. Acetazolamide has a strong effect on decongestion both at day 4 and at discharge, reducing the chance of residual congestion. Importantly, patients who remained congested despite treatment with acetazolamide had the highest observed risk for adverse outcomes. However, this finding should be interpreted cautiously, as persistent congestion may reflect both incomplete decongestion and a more advanced heart failure phenotype with intrinsically higher risk. Therefore, residual congestion likely represents both a clinically relevant therapeutic target and a marker of disease severity.

During AHF, achieving fully decongestion while optimising GDMT should be the main focus of the treatment and patients being discharged with

residual congestion should receive closer follow-up as they have an increased risk for adverse events [10]. Despite the proven benefits on hard outcomes of GDMT, the current study demonstrated a non-significant, however, gradual decrease in the prescription of these agents during hospitalisation and follow-up, which likely reflects the advanced disease stage and limited treatment tolerability of this elderly and multimorbid population. Importantly, this downtitration occurred despite that uptitration of GDMT was warranted by the ADVOR protocol and the fact that these patients were followed in dedicated HF centres. Episodes of AHF mandate the addition of intravenous diuretic agents, which often lead to temporarily downtitration of GDMT because of hypotension or worsening glomerular filtration [21,22]. These changes in GDMT during follow-up may also have influenced subsequent clinical outcomes and should therefore be considered when interpreting the prognostic analyses. More importantly, the hospitalisation for AHF represents an additional physiological insult, signifying progression to a more advanced stage of disease, with reduced tolerability to GDMT.

Compared with other aforementioned diuretic trials in AHF, patients enrolled in ADVOR were considerably older with higher NT-proBNP levels, reflecting the real-world clinical situation [11]. Nevertheless, the overall event size for adverse outcome in the ADVOR trial was lower (14% for all-cause mortality and 18% for readmissions at 90-days follow-up) in comparison to other trials such as the DOSE trial (11% for all-cause mortality and 29% for readmissions at 60-days follow-up) and the CLOROTIC trial (18% for all-cause mortality and 36% for readmissions at 3 months). This may be related to the fact that better decongestion and follow-up probably improved overall outcome in the trial. Despite a reduction in HFH, mortality rate has remained relatively stable. This can be attributed to the older multimorbid trial population, in which all-cause mortality is largely driven by non-cardiovascular events, which are less impacted by heart failure management. Moreover, the overall rate of non-cardiovascular hospitalisations remains high, likely due to the presence of multiple comorbidities in this patient population [2]. These comorbidities often lead to some level of congestion, necessitating IV diuretics. As a result, hospitalisations are typically due to a combination of factors, making it challenging to determine whether congestion is the primary cause or a secondary effect, especially when the degree of congestion is not carefully considered. Despite this, every hospitalisation for heart failure should be viewed as an opportunity not only for complete decongestion prior to discharge but also for the optimisation of GDMT, which is critical for improving long-term prognosis [23].

Limitations

While this study is a predefined post hoc analysis of the ADVOR-trial, the results should be interpreted as hypothesis-generating, 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 HR more. Therefore, the current study was not powered for an evaluation of all-cause mortality and HFH. In addition, the follow-up period might have been too small to detect meaningful differences between treatment groups.

Conclusions

The upfront addition of acetazolamide on top of standardised intravenous loop diuretics has demonstrated to improve the rate of successful decongestion in the ADVOR trial. In addition, the current analysis confirms that residual congestion is associated with adverse outcomes. Especially, residual congestion after use of thorough decongestive strategies with high dose loop diuretics in combination with acetazolamide identifies a subgroup of patients at particularly high clinical risk who may benefit from closer monitoring, optimisation of guideline-directed therapy and specialised heart failure follow-up. The current analysis further reassures that use of acetazolamide is safe and not associated with a higher risk of all-cause mortality.

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