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RESEARCH ARTICLE

# Acetazolamide to increase natriuresis in congestive heart failure at high risk for diuretic resistance

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**Aims** To investigate the effects of acetazolamide on natriuresis, decongestion, kidney function and neurohumoral activation in acute heart failure (AHF).

**Methods and results** This prospective, two-centre study included 34 AHF patients on loop diuretics with volume overload. All had a serum sodium concentration < 135 mmol/L and/or serum urea/creatinine ratio > 50 and/or an admission serum creatinine increase of > 0.3 mg/dL compared to baseline. Patients were randomised towards acetazolamide 250–500 mg daily plus bumetanide 1–2 mg bid vs. high-dose loop diuretics (bumetanide bid with daily dose twice the oral maintenance dose). The primary endpoint was natriuresis after 24 h. Natriuresis after 24 h was similar in the combinational treatment vs. loop diuretic only arm (264 ± 126 vs. 234 ± 133 mmol; $P = 0.515$). Loop diuretic efficiency, defined as natriuresis corrected for loop diuretic dose, was higher in the group receiving acetazolamide (84 ± 46 vs. 52 ± 42 mmol/mg bumetanide; $P = 0.048$). More patients in the combinational treatment arm had an increase in serum creatinine levels > 0.3 mg/dL ($P = 0.046$). N-terminal pro-B-type natriuretic peptide reduction and peak neurohumoral activation within 72 h were comparable among treatment arms. There was a non-significant trend towards lower all-cause mortality or heart failure readmissions in the group receiving acetazolamide with low-dose loop diuretics vs. high-dose loop diuretic monotherapy ($P = 0.098$).

**Conclusion** Addition of acetazolamide increases the natriuretic response to loop diuretics compared to an increase in loop diuretic dose in AHF at high risk for diuretic resistance.
Trial registration: ClinicalTrials.gov NCT01973335.

**Keywords** Acetazolamide • Cardiorenal syndrome • Diuretics • Natriuresis • Systolic heart failure

## Introduction

Signs and symptoms of congestion are the predominant reason for hospital admission in acute heart failure (AHF).[1] Diuretics are mainstay treatment to alleviate volume overload and good diuretic efficiency with successful decongestion is associated with better outcomes.[2] However, there is a paucity of high-quality data from randomised clinical trials with diuretics in AHF. Consequently, their optimal type and dose regimen remain unclear. Loop diuretics are by far the most commonly used agents, which has led to a wealth of clinical experience and empirical knowledge regarding their use. In the Diuretic Optimization Strategies Evaluation (DOSE) trial, no

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difference was found between bolus vs. continuous administration or low dose (equal to the oral maintenance dose) vs. high dose (equal to 2.5 times the oral maintenance dose) with respect to any meaningful outcome.[3] Although randomisation towards higher dosing was associated with a trend towards faster and more pronounced decongestion, it came at the cost of an increased incidence of rising serum creatinine (Cr). More importantly, even with high dosing, only 18% of patients were completely free from signs and symptoms of congestion at the end of the study.[3] A rise in serum Cr during decongestive treatment in AHF is a common finding and associated with worse prognosis on a population level.[4,5] Yet, when accompanied by more effective decongestion in specific cases, a rising serum Cr might even be associated with a better prognosis in AHF.[2,6,7] The effects of loop diuretic dose increase vs. add-on combinational diuretic therapy in this setting have only been tested retrospectively in post-hoc, non-randomised analysis, predominantly with thiazide-type diuretics.[8]

The carbonic anhydrase inhibitor acetazolamide is infrequently used in AHF as it has poor diuretic and natriuretic capacity on its own, with rapidly emergent diuretic resistance in case of prolonged use.[9] However, an observational study in AHF has found that the addition of acetazolamide improves loop diuretic efficiency with approximately 100 mmol sodium excreted in surplus for every 40 mg furosemide-equivalent dose administered.[10] Other small studies, often before the era of evidence-based heart failure treatment, corroborate these findings and make acetazolamide an interesting agent to study *in combination* with loop diuretics for prevention or treatment of diuretic resistance.[11–14] Acetazolamide blocks sodium bicarbonate reabsorption in the renal proximal tubules, offering more sodium to Henle's loop, hence boosting the effect of loop diuretics, which might be especially useful in states of poor renal blood flow.[15] Additionally, acetazolamide has intrinsic renal vasodilatory effects, protecting the nephron against ischaemia–reperfusion damage.[16] Finally, it also blocks the pendrin system in the distal nephron, which might be a candidate mechanism of diuretic resistance.[17] The Diamox/Aldactone to Increase the Urinary Excretion of Sodium: an Investigational Study in Congestive Heart Failure (DIURESIS-CHF) was therefore set up as a pilot study to provide randomised data on the diuretic efficiency of acetazolamide combined with loop diuretic therapy in patients with AHF at high risk for diuretic resistance in the current era of heart failure treatment. In addition, potential consequences of acetazolamide use for decongestion, renal function, and neurohumoral activation were investigated.

# Methods

## Study design

DIURESIS-CHF is an investigator-driven, prospective, randomised study. In brief, patients with AHF at high risk for loop diuretic resistance were randomised in a 2x2 factorial design towards (i) single-blind combinational treatment with acetazolamide and low-dose loop diuretics vs. monotherapy with high-dose loop diuretics; and (ii) open-label oral spironolactone given upfront vs. at discharge. Here reported are the results of the acetazolamide arm of DIURESIS-CHF. Results of the spironolactone arm have been published previously.[18]

The study protocol was registered and released at ClinicalTrials.gov (NCT01973335) before inclusion of the first patient in November 2013. The original aim was to include 80 patients at a single tertiary care centre (Ziekenhuis Oost-Limburg, Genk, Belgium) over a time window of 2 years. However, the study was extended to another tertiary care centre (UZ Leuven, Leuven, Belgium) in October 2016, because of slow recruitment. In April 2017, after inclusion of the 34th patient, the investigators decided that it was not feasible to complete the study due to poor recruitment. The last patient was followed for 6 months, after which the study was terminated. The study complies with the Declaration of Helsinki and the locally appointed ethics committee has approved the research protocol. Written informed consent was obtained from every patient. All authors had full access to the data and contributed to the writing of the manuscript. Together, they take responsibility for the integrity of the data and agree to the report as written. The manuscript was drafted according to the CONSORT guidelines for randomised clinical trials.

## Study population

### Inclusion criteria

Patients included in DIURESIS-CHF were older than 18 years, able to give informed consent, and had a clinical diagnosis of AHF made within 8 h. All patients demonstrated $\geq 2$ clinical signs of congestion (oedema, ascites, jugular venous distention, or pulmonary congestion) and had a left ventricular ejection fraction $< 50\%$ as well as plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels $> 1000$ ng/L. Patients could only be included in DIURESIS-CHF if they were on maintenance therapy with oral loop diuretics at a $\geq 1$ mg equivalent dose of bumetanide for $\geq 1$ month prior to enrolment. To select a population at high risk for loop diuretic resistance, at least one out of three additional inclusion criteria had to be fulfilled: (i) serum sodium $\leq 135$ mmol/L; (ii) serum urea/Cr ratio $> 50$; or (iii) admission serum Cr increase of $> 0.3$ mg/dL compared to a previous measurement within 3 months.

### Exclusion criteria

Exclusion criteria were: (i) history of cardiac transplantation and/or a ventricular assist device; (ii) a concurrent diagnosis of acute coronary syndrome; (iii) mean arterial pressure $< 65$ mmHg or systolic blood pressure $< 90$ mmHg at inclusion; (iv) anticipated use of intravenous inotropes, vasopressors or nitroprusside; (v) baseline estimated glomerular filtration rate (eGFR) $< 15$ mL/min/1.73 m$^2$ according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; (vi) use of renal replacement therapy or ultrafiltration at any time before inclusion; (vii) treatment with acetazolamide within the previous month; (viii) treatment with $\geq 2$ mg bumetanide or an equivalent dose of loop diuretics during the index hospitalization; and (ix) exposure to nephrotoxic agents (i.e. contrast dye) anticipated within 3 days. Use of diuretics, vasopressin antagonists or mineralocorticoid receptor antagonists not specified by the study protocol was not allowed.

## Study protocol (*Figure 1*)

### Diuretic regimen

Every morning between 8:00 to 10:00 a.m., study participants were evaluated by the same investigator (M.D., W.D. or W.M.). If this investigator determined that the patient was strictly euvolemic, the study

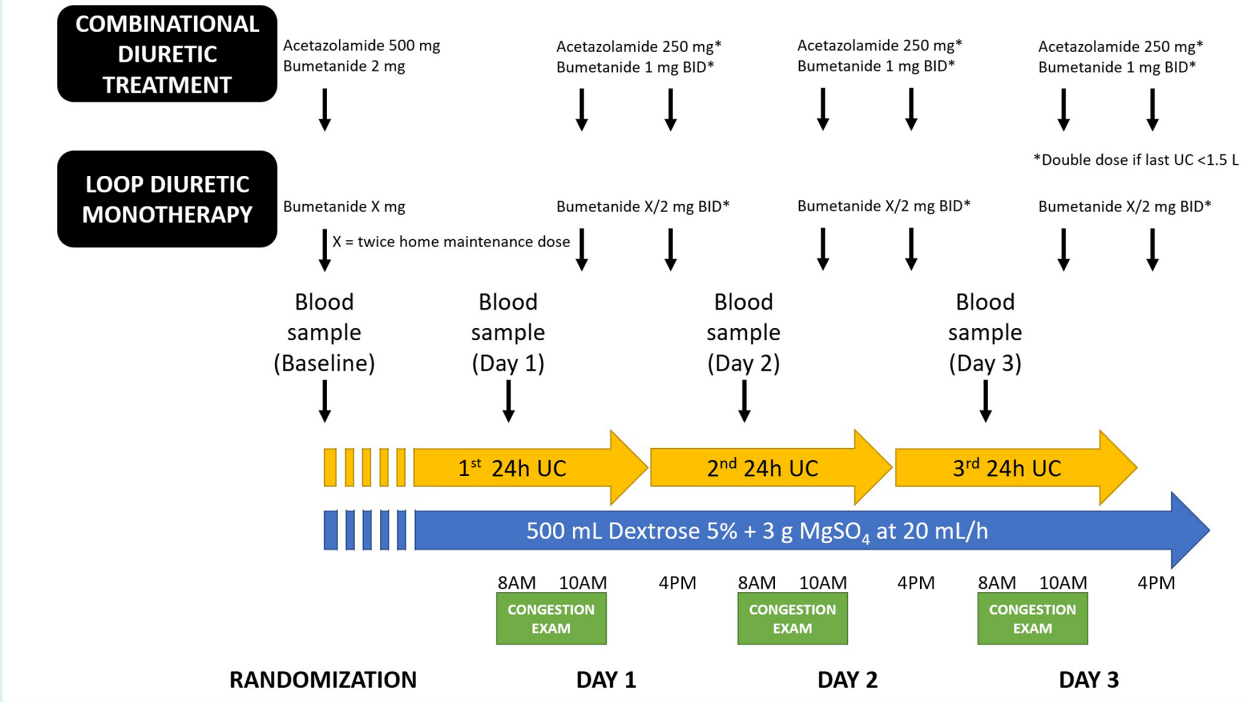


**Figure 1** Study flowchart. UC, urinary collection.

protocol was ended, and subsequent treatment was at the discretion of the treating physician. If volume overload was still present according to the investigator and urine output had been < 1.5 L within the last 12 h, subsequent doses of both acetazolamide and bumetanide were doubled for the remainder of the 72 h study period. In addition, according to the second randomisation arm, patients received open-label oral spironolactone 25 mg daily either upfront or from hospital discharge, unless serum potassium levels were > 5 mmol/L.

### Background fluid and salt intake

All patients received a maintenance infusion with 3 g $MgSO_4$ in 500 mL dextrose 5% solution at a rate of 20 mL/h. A low-salt diet (<3 g daily) was recommended to standardize sodium intake and participants were instructed to limit daily fluid intake < 1.5 L during the study period.

### Blood samples and urinary collections

A baseline venous blood sample was collected around the time of randomisation before the first administration of diuretic therapy and was repeated every morning at 8:00 a.m. on the next 3 days. If accurate 24 h urinary collections were not deemed possible, a bladder catheter was placed. Before the first administration of diuretic therapy, the patient was asked to void empty and any urine collected – including urine obtained from bladder catheterization – was discarded. Subsequently, three consecutive 24 h urinary collections were obtained after the moment of first diuretic administration according to the study protocol.

## Study outcomes

The primary study outcome was total natriuresis (mmol) after 24 h, calculated from the first 24 h urinary collection. Pre-specified secondary outcomes were the relative change in NT-proBNP levels after 72 h compared to baseline; incident worsening renal function (WRF) defined as a > 0.3 mg/dL rise in serum Cr within 72 h and peak plasma renin activity (PRA) as well as plasma aldosterone levels within 72 h.

## Statistical analysis

Continuous variables are expressed as mean ± standard deviation if normally distributed, or otherwise as median (interquartile range). Normality was assessed by the Shapiro–Wilk statistic. The independent Student's *t*-test and Mann–Whitney U test were used as indicated for comparisons between both intervention arms. Tukey's test was used to investigate the interaction of treatment effects according to both randomisation arms of the study. Categorical data are expressed as percentages and compared with Fisher's exact test. The Kaplan–Meier method was used to construct survival curves, with the log-rank test used for comparison among groups. Statistical significance was always set at a 2-tailed probability level of < 0.05. All statistics were performed using IBM SPSS® (version 24.0). With the originally aimed study population ($n = 80$), DIURESIS-CHF was expected to detect a 35% change in 24 h natriuresis with a statistical power of 80% at $\alpha = 0.05$. However, due to the early interruption of the study with inclusion of only 34 patients, the a posteriori calculated statistical power of the study was reduced to 44%.

# Results

## Study population

Thirty-four patients fulfilled all inclusion and no exclusion criteria and were included in DIURESIS-CHF. Eighteen were randomised towards combinational treatment with acetazolamide

**Table 1 Baseline characteristics of the study population**

| Characteristic | Overall population ($n = 34$) | A + LD ($n = 18$) | LD only ($n = 16$) |
|---|---|---|---|
| Age (years) | 80 ± 7 | 81 ± 6 | 78 ± 7 |
| Male sex | 65% | 61% | 69% |
| NYHA functional class (II/III/IV) | 9/56/35% | 11/67/22% | 6/44/50% |
| Diabetes | 29% | 28% | 31% |
| Heart rate (b.p.m.) | 74 ± 18 | 76 ± 18 | 72 ± 19 |
| Blood pressure (mmHg) | | | |
| Systolic | 128 ± 17 | 132 ± 18 | 123 ± 15 |
| Diastolic | 69 ± 13 | 69 ± 13 | 69 ± 12 |
| LV ejection fraction (%) | 43 ± 14 | 43 ± 16 | 42 ± 13 |
| eGFR (mL/min/1.73 $m^2$) | 31 (24–40) | 30 (24–40) | 33 (24–40) |
| NT-proBNP (ng/L) | 7849 (3816–15 352) | 8165 (4530–18 759) | 7339 (2967–14 402) |
| ACE-I/ARB use | 41% | 39% | 44% |
| Beta-blocker use | 91% | 89% | 94% |
| MRA use | 59% | 56% | 63% |

A, acetazolamide; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; LD, loop diuretic; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

and low-dose loop diuretics, while 16 received high-dose loop diuretic monotherapy. Baseline characteristics of the study population are summarized in *Table 1*. As a consequence of the inclusion criteria, an advanced heart failure population was recruited with 26% of patients presenting with hyponatremia (≤ 135 mmol/L), 35% with an increased serum Cr ≥ 0.3 mg/L above an outpatient measurement within 3 months, and 76% with a urea/Cr ratio > 50. Plasma NT-proBNP levels were 7849 ng/L (3816–15 352 ng/L), which was similar among treatment arms ($P = 0.581$).

## Clinical decongestion

In 6 out of 16 patients randomised towards high-dose loop diuretics (38%) and 4 patients out of 18 randomised towards acetazolamide plus low-dose loop diuretics (22%), the study investigator decided to stop intravenous diuretics before the end of the 72 h study period as the patient was considered euvolemic ($P = 0.457$). At the end of the study period, five patients in the former (31%) and six patients in the latter group (33%) had no residual clinical signs of congestion ($P = 1.000$). *Table 2* provides an overview of clinical congestion signs at baseline vs. the end of the 72 h study period.

**Table 2 Clinical congestion signs at baseline vs. 72 h according to diuretic treatment**

| Clinical congestion sign | A + LD ($n = 18$) | LD only ($n = 16$) | *P*-value |
|---|---|---|---|
| Elevated jugular venous pressure | | | |
| Baseline | 94% | 94% | 1.000 |
| 72 h | 39% | 50% | 0.730 |
| Hepatosplenomegaly or ascites | | | |
| Baseline | 61% | 69% | 0.729 |
| 72 h | 22% | 38% | 0.457 |
| More than trace oedema | | | |
| Baseline | 89% | 88% | 1.000 |
| 72 h | 56% | 38% | 0.327 |
| Rales | | | |
| Baseline | 89% | 88% | 1.000 |
| 72 h | 39% | 31% | 0.729 |

A, acetazolamide; LD, loop diuretic.

## Primary study outcome

Total natriuresis after 24 h was not significantly different in the combinational treatment (264 ± 126 mmol) vs. loop diuretic monotherapy group (234 ± 133 mmol; $P = 0.515$). There was no significant treatment interaction with randomisation according to the spironolactone arm of the study ($P = 0.962$). In an exploratory analysis within the subgroup of patients presenting with an increased serum Cr ≥ 0.3 mg/L above an outpatient measurement within 3 months ($n = 11$), total natriuresis after 24 h was borderline significantly higher in the combinational treatment (391 ± 64 mmol) vs. loop diuretic monotherapy group (239 ± 137 mmol; $P = 0.050$). By protocol design, the combinational treatment group received a lower dose of loop diuretics. During the first 24 h in the combinational treatment group, 11 patients received 3 mg of bumetanide, while the other 7 received 4 mg. In the loop diuretic monotherapy group, the median dose of bumetanide during the first 24 h was 6 mg (3–8 mg). Loop diuretic efficiency, defined as natriuresis corrected for loop diuretic dose, was significantly higher in patients who received acetazolamide vs. not (84 ± 46 vs. 52 ± 42 mmol/mg bumetanide; $P = 0.048$) (*Figure 2*).

## Pre-specified secondary outcomes

### Natriuretic peptide change after 72 h

Plasma NT-proBNP levels decreased from 8165 ng/L (4242–20 719 ng/L) to 6341 ng/L (3377–14 034 ng/L) after 72 h

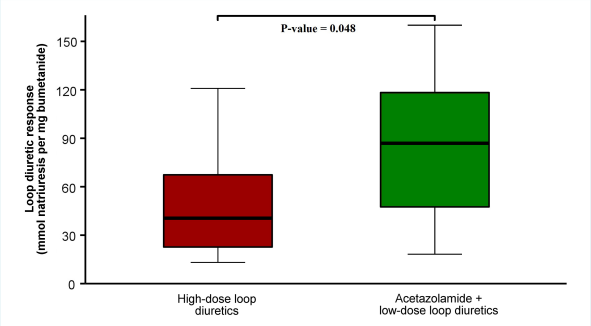


**Figure 2** Loop diuretic efficacy after 24 h, defined as natriuresis corrected for loop diuretic dose, according to treatment arm.

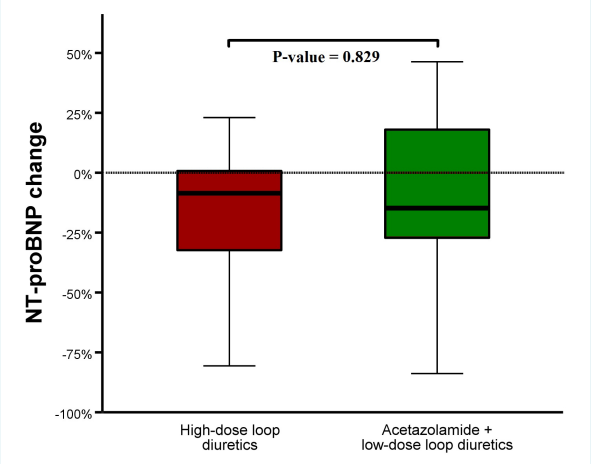


**Figure 3** Relative change in N-terminal pro-B-type natriuretic peptide (NT-proBNP) plasma levels after 72 h, according to treatment arm.

in the combinational treatment arm ($P = 0.001$). In the high-dose loop diuretic only arm, plasma NT-proBNP levels decreased from 7339 ng/L (2542–14 877 ng/L) to 5746 ng/L (1850–17 231 ng/L) ($P = 0.035$). The relative change in NT-proBNP levels was similar among treatment arms at $-12 \pm 38\%$ vs. $-9 \pm 40\%$ ($P = 0.829$) (*Figure 3*).

### Worsening renal function

Five patients in the combinational treatment arm with acetazolamide (28%) vs. none in the high-dose loop diuretic monotherapy arm demonstrated WRF, defined as a > 0.3 mg/dL rise in serum Cr within 72 h ($P = 0.046$). Conversely, six patients in the high-dose loop diuretic monotherapy (38%) vs. one patient in the combinational treatment arm (6%) had improved renal function, defined as a > 0.3 mg/dL decrease in serum Cr within 72 h ($P = 0.035$).

### Neurohumoral activation

Both peak PRA [4.8 μg/L/h (0.8–21.8 μg/L/h) vs. 4.9 μg/L/h (1.7–14.7 μg/L/h); $P = 0.904$] and peak plasma aldosterone levels within 72 h [260 ng/L (140–355 ng/L) vs. 212 ng/L (151–522 ng/L); $P = 0.756$] did not differ significantly among patients with combinational treatment vs. high-dose loop diuretic monotherapy.

## Exploratory tertiary outcomes

### Serum sodium levels

In the combinational treatment arm with acetazolamide, serum sodium levels were 138 mmol/L (135–140 mmol/L) at baseline, which remained practically unchanged after 72 h at 138 mmol/L (136–140 mmol/L). In the high-dose loop diuretic monotherapy arm, serum sodium levels were 138 mmol/L (132–139 mmol/L) and 138 mmol/L (132–141 mmol/L) at the same time-points, respectively.

### Serum potassium levels and potassium excretion

In the combinational treatment arm with acetazolamide, serum potassium levels decreased from $4.73 \pm 0.62$ mmol/L at baseline to $4.02 \pm 0.48$ mmol/L after 72 h. In the high-dose loop diuretic monotherapy arm, corresponding serum potassium levels were $4.52 \pm 0.65$ mmol/L and $4.05 \pm 0.52$ mmol/L, respectively. The change in serum potassium levels was similar among both intervention arms ($P = 0.298$). Total kaliuresis after 24 h was not significantly different in the combinational treatment ($65 \pm 23$ mmol) vs. loop diuretic monotherapy group ($59 \pm 22$ mmol; $P = 0.516$).

## Clinical outcome

During 34 months (22–38 months) of follow-up, 21 patients died (62%) and 13 were readmitted for heart failure (38%). Follow-up time was similar in both treatment arms ($P = 0.408$). There was no difference in the time to all-cause mortality ($P = 0.786$) (*Figure 4*). Median time to all-cause mortality or readmission with heart failure was 273 days in the high-dose loop diuretic group vs. 803 days in the combinational treatment group, a difference that favoured the combinational treatment group but was not statistically significant ($P = 0.098$) (*Figure 4*).

# Discussion

DIURESIS-CHF provides unique data from a randomised study design with acetazolamide used as an adjunct to loop diuretic therapy for AHF with volume overload in the current era of treatment with neurohumoral blockers. Key findings of the study are: (i) acetazolamide 250–500 mg daily in addition to low-dose loop diuretics (bumetanide 1–2 mg bid) produces similar natriuresis when compared to high-dose loop diuretics and might even increase natriuresis in patients presenting with elevated serum Cr; (ii) loop diuretic efficiency, defined as natriuresis per loop diuretic dose administered, increased by 62% with the addition of acetazolamide; (iii) WRF, defined as a > 0.3 mg/dL rise in serum Cr was more frequent in patients receiving combinational treatment with acetazolamide, although without adverse impact on clinical outcome; and (iv) even though a very sick population of AHF patients was targeted and recruited, most patients demonstrated good diuretic

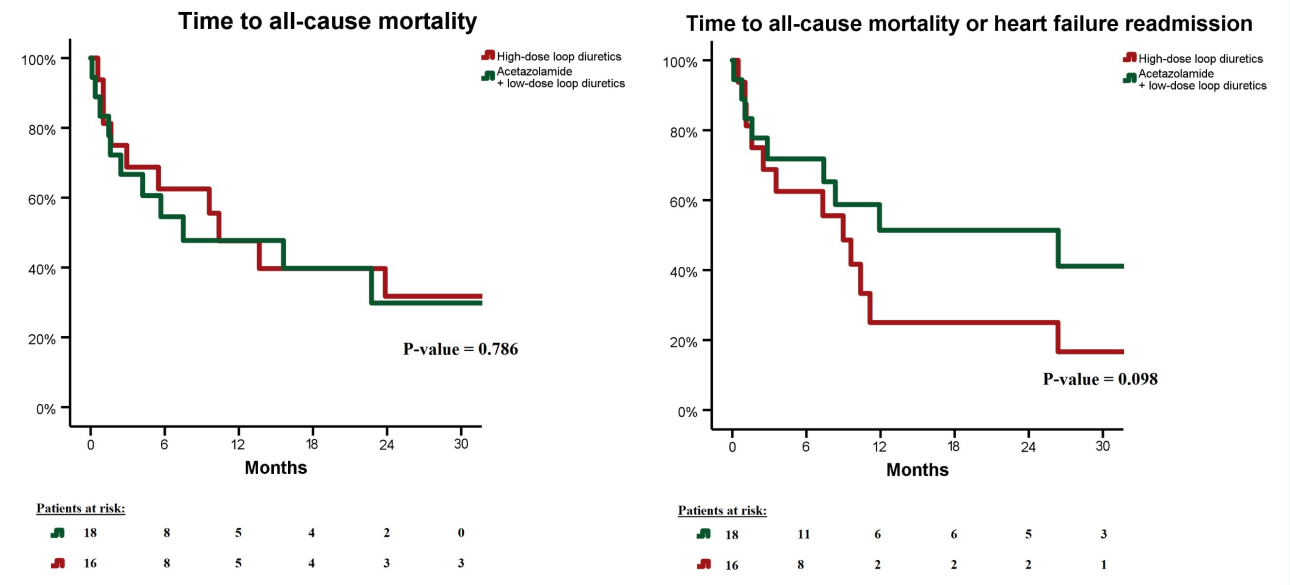


**Figure 4** Time to all-cause mortality (*left panel*) and time to all-cause mortality or heart failure readmission (*right panel*), according to treatment arm.

efficiency with the excretion of approximately 250 mmol of sodium during the first 24 h.

Acetazolamide is an old and largely forgotten diuretic, although recent interest has sparked renewed attention to its use in AHF.[15] It is a carbonic anhydrase inhibitor, hence impeding the catalysation of the chemical reaction that converts carbonic acid to carbon dioxide and water. In the proximal convoluted tubules of the nephron, this reaction is essential to drive sodium reuptake by the sodium–proton exchanger located at the apical membrane of tubular cells. Importantly, the proximal convoluted tubules are responsible for approximately 65% of total tubular sodium reabsorption in normal circumstances, a number which may increase up to 85% in AHF.[15,19] Yet, the net natriuretic effect of acetazolamide depends heavily on subsequent tubular segments of the nephron regulated by the renin–angiotensin–aldosterone system. As the loop of Henle and distal tubules have a high capacity for sodium reabsorption, they can easily compensate for an increased delivery of sodium and prevent a negative sodium balance, especially when the neurohumoral system is activated. Therefore, to achieve a powerful natriuretic response, acetazolamide should be used *together* with a more distally working diuretic (i.e. loop or thiazide-like diuretic).[2,17]

From a pathophysiological perspective, there are several reasons to use acetazolamide as an *adjunct* diuretic in AHF to support loop diuretic therapy.[15] First, increased substrate delivery with acetazolamide (i.e. sodium offered to Henle's loop) enhances the natriuretic effect of loop diuretics.[10] The current study clearly supports this, as loop diuretic efficiency was significantly higher in patients treated with acetazolamide. Importantly, loop diuretic efficiency has emerged as a very strong and independent predictor of clinical outcome in AHF, although it remains to be proven that this relationship is causal.[2] Secondly, inhibition of proximal renal sodium reabsorption causes increased sodium and chloride delivery to macula densa cells at the end of Henle's loop (sodium *and* chloride because of solvent drag as well as electroneutral coupling of chloride to sodium transport in the renal tubules). This activates tubulo–glomerular feedback in a way that is very similar to the effect of sodium–glucose co-transporter 2 (SGLT2) inhibitors.[20] Presumably through this mechanism, SGLT2 inhibitors have been demonstrated to reduce plasma volume effectively, in contrast to ordinary diuretics that mainly reduce interstitial fluid.[21,22] Thirdly, activation of tubulo–glomerular feedback prevents renin release by the afferent arteriole and subsequent activation of the neurohumoral axis. This was not supported by the findings of the current study as both peak PRA and peak plasma aldosterone levels were similar in patients receiving acetazolamide vs. not. However, it could be possible that because of the very sick population studied with substantial neurohumoral activation, this signal was too difficult to pick up in the small sample size. Indeed, peak PRA and plasma aldosterone levels demonstrated high inter-individual variability. Finally, acetazolamide might possess some intrinsic reno-protective effects. In rodent models, ischaemia–reperfusion injury is prevented by acetazolamide, presumably through stimulation of nitric oxide-dependent vasodilatation.[16] Moreover, one small study has suggested that acetazolamide might be effective to prevent contrast-induced acute kidney injury.[23]

In the current study, acetazolamide use was associated with a trend towards more WRF during decongestive treatment in AHF. However, the clinical implications of this finding are unsure as it is now well-known that WRF during decongestive treatment in AHF poorly predicts persistent renal impairment and might even be associated with improved outcomes when reflecting better decongestion.[24] It is reassuring that in the current study there is no hint of increased mortality with acetazolamide. However, this

should be investigated further in adequately powered randomised clinical trials. In addition, our results suggest that acetazolamide is particularly effective to increase natriuresis in patients already presenting with WRF. Importantly, achieving a net negative sodium balance is more consistently associated with favourable outcome in AHF when compared to changes in glomerular filtration rate.[25] Furthermore, the vasodilatory properties of acetazolamide, especially at the level of the efferent arteriole, might explain a transient drop in intraglomerular pressure and hence glomerular filtration rate although being protective on the long term. Similar observations have already been observed with SGLT2 inhibitors that decrease intraglomerular pressure through afferent arteriolar vasoconstriction in cases of glomerular hyperfiltration.[26–28] Eventually, more mechanistic and long-term studies are needed to fully comprehend the effects of acetazolamide on kidney function.

Acetazolamide has been tested in other small prospective studies in AHF. A recent open-label study randomised 20 AHF patients with ejection fraction < 50% and clinical signs of volume overload to acetazolamide or nothing in addition to usual care.[13] Diuresis, natriuresis, net fluid balance and subjective improvement of dyspnoea were significantly greater in patients receiving acetazolamide. In addition, several studies outdating the current era of heart failure treatment with neurohumoral blockers used acetazolamide as an effective agent to break loop diuretic resistance.[11,12,14] The current study extrapolates these findings to contemporary treated AHF patients with advanced cardiorenal disease and confirms that acetazolamide is a safe and effective drug to use in this context. A potential trend towards less heart failure readmissions was observed in the current study, yet only after 7–8 months Kaplan–Meier curves seemed to diverge clearly. Such late divergence might argue against a drug-related effect on congestion. Anyhow, results of this small pilot study can only be considered hypothesis-generating and warrant confirmation by larger independent studies with adequate statistical power. The Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR, NCT03505788) is currently recruiting and aims to randomise a population of 519 AHF patients with clinical signs of volume overload to acetazolamide or matching placebo in addition to standard of care with high-dose loop diuretics.[29] This trial – constituting the largest randomised diuretic study in AHF if successfully performed – is powered for achievement of complete clinical decongestion without the need for diuretic therapy escalation because of poor diuretic response. The results of the ADVOR trial will undoubtedly provide more insight in the value of acetazolamide as an upfront addition to loop diuretic therapy in AHF.

## Study limitations

DIURESIS-CHF was halted due to slow recruitment before the target population of 80 patients was achieved. This limits the statistical power of the study and warrants a conservative interpretation of statistically significant results. Secondly, a mixed model of General Linear Model repeated measures would have been more correct to assess repeated measures in this study. However, due to the nature of this study being a small pilot project, the use of simple descriptive statistics did not influence the study results. Thirdly, the study design instigated a population of very sick patients with a median NT-proBNP level of 7849 ng/L and 62% all-cause mortality risk within 34 months. Study findings therefore do not necessarily apply for the general AHF population with less advanced disease. In particular, patients in DIURESIS-CHF had poor renal function with a median estimated glomerular filtration rate of 31 mL/min/1.73 $m^2$. This explains the low uptake of renin–angiotensin system blockers in the study, which could have influenced PRA and aldosterone assessments. Fourthly, despite a study protocol encouraging treating physicians to pursue complete decongestion, only about a third of the patients were completely free from clinical signs of volume overload after 72 h. This may be due to the fact that this population that was at high risk for developing diuretic resistance may require more time for complete decongestion. However, this number compares favourably with results from large randomised clinical trials in AHF, illustrating how difficult the goal of strict euvolemia is to achieve, even when ultrafiltration is used.[3,30] Finally, the upfront dosing of acetazolamide at 250 mg and bumetanide at 1 mg in the current study might have been too low in some patients with advanced kidney disease at low glomerular filtration rate, which had potential implications for the primary endpoint.

# Conclusions

In an AHF population with advanced disease at high risk for diuretic resistance, acetazolamide with low-dose loop diuretics produced similar natriuresis when compared to raising loop diuretic dosing as monotherapy.

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