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STUDY DESIGN

Rationale and design of the ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload) trial

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Aims Decisive evidence on the optimal diuretic agent, dosing schedule, and administration route is lacking in acute heart failure (AHF) with congestion. The Acetazolamide in Decompensated heart failure with Volume OveRload (ADVOR) trial is designed to test the hypothesis that the carbonic anhydrase inhibitor acetazolamide, a potent inhibitor of proximal tubular sodium reabsorption, improves decongestion when combined with loop diuretic therapy in AHF, potentially leading to better clinical outcomes.

Methods The ADVOR trial is set up as a multicentre, randomized, double-blind, placebo-controlled study, aiming to recruit 519 patients with AHF and clinically evident volume overload. All study participants receive high-dose intravenous loop diuretics as background therapy and are randomized towards intravenous acetazolamide at a dose of 500 mg once daily vs. placebo, stratified according to including study centre and ejection fraction ($< 40\%$ vs. $\geq 40\%$). The primary endpoint is successful decongestion with no more than trace oedema assessed on the third morning after hospital admission, with good diuretic efficacy defined as a urine output > 3.5 L during the first 30–48 h of decongestive treatment. Secondary endpoints include all-cause mortality or heart failure readmission after 3 months, length of hospital stay for the index admission, and longitudinal changes in the EuroQol-5 dimensions questionnaire.

Conclusion ADVOR will investigate if acetazolamide combined with loop diuretic therapy improves decongestion in AHF with volume overload.

Keywords Acetazolamide • Congestion • Heart failure • Diuretic

Introduction

Acute heart failure (AHF) frequently complicates the disease trajectory of patients with heart failure.[1] AHF episodes are associated with increased morbidity as well as mortality and pose an economic burden on our society.[2] Signs and symptoms of congestion are the main reason why patients with AHF seek urgent care.[3,4] Indeed, increased neurohumoral activation in heart failure induces a state of increased sodium and water avidity, resulting in an increased plasma volume.[5,6] Current AHF guidelines recommend the use of loop diuretics to alleviate signs and symptoms of fluid overload.[7] However, contemporary data suggest that many patients are discharged with residual clinical congestion.[8–10] For example, only about 15% of patients included in the Diuretic Optimization Strategies Evaluation (DOSE) study were free from clinical signs of congestion after 72 h of treatment.[11] In addition, approximately 20% of patients in the Acute Decompensated Heart Failure National Registry (ADHERE) were discharged with

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an increased body weight compared to admission.[12] Importantly, clinical congestion at discharge, especially in the setting of worsening renal function (WRF), is a strong predictor of poor outcome and early readmissions.[13] Acetazolamide, a diuretic agent inhibiting sodium reabsorption in the proximal tubules of the nephron, may facilitate decongestion and boost loop diuretic efficacy, which in itself is an established prognostic marker in AHF.[14–17] Intriguingly, it has been shown that inhibition of proximal renal sodium reabsorption decreases the set-point of plasma volume by stimulating tubulo–glomerular feedback, an effect not observed with more distally working diuretics.[18,19] Finally, acetazolamide also blocks renal sodium reabsorption in distal parts of the nephron through inhibition of pendrin and has renal vasodilatory properties that improve renal blood flow.[20,21] These unique properties make it an interesting agent to test in AHF. The Acetazolamide in Decompensated heart failure with Volume OveRload (ADVOR) trial is therefore set up as a multicentre, randomized, double-blind, placebo-controlled study to test the hypothesis that acetazolamide improves decongestion when combined with loop diuretic therapy in AHF, potentially leading to better clinical outcomes. This article discusses the rationale for and detailed methodology of the trial.

The ADVOR trial

Study design

The ADVOR trial is a multicentre, randomized, double-blind, placebo-controlled trial on the diuretic and decongestive effects of acetazolamide in patients with AHF and clear signs of volume overload (*Figure 1*). The study flowchart is presented in *Figure 2*. In brief, patients are randomized towards daily use of acetazolamide administered as a single intravenous bolus of 500 mg vs. matching placebo on a background therapy of high-dose loop diuretics on three consecutive days.

Study objectives

The first objective of the ADVOR trial is to determine whether combination therapy with acetazolamide on top of loop diuretics improves the success rate of achieving complete decongestion in AHF with volume overload. It is hypothesized that because acetazolamide may improve loop diuretic efficacy, thereby facilitating natriuresis and diuresis, better and faster decongestion can be achieved which could potentially result in improved clinical outcomes, a shorter length of stay and increased quality of life. In addition, the specific design of the ADVOR trial incorporates a continuous assessment of loop diuretic efficacy as an objective way to escalate decongestive strategies. As urinary collections with sodium levels are systematically acquired, comparison of different metrics of loop diuretic efficacy will be possible and their role in guiding diuretic treatment may be more clear from the results.

Eligibility

Eligibility criteria are listed in *Table 1*. Patients with an elective or emergency hospital admission and clinical diagnosis of AHF with at least one clinical sign of volume overload (i.e. oedema, ascites, or pleural effusion), an N-terminal pro-B-type natriuretic peptide (NT-proBNP) level > 1000 pg/mL or B-type natriuretic petptide (BNP) level > 250 ng/mL at screening, and maintenance therapy with oral loop diuretics at a daily dose of at least 1 mg bumetanide or 40 mg furosemide or 20 mg torsemide for at least 1 month are eligible. If patients are included based on pleural effusion and/or ascites, a chest X-ray or chest ultrasound and/or abdominal ultrasound is needed to confirm its presence. Patients on acetazolamide maintenance therapy, those with a systolic blood pressure < 90 mmHg, and those with an estimated glomerular filtration rate < 20 mL/min/1.73 m^2 are excluded.

Study intervention

At the moment of randomization, oral loop diuretics are stopped and the patient receives an intravenous bolus at a dose equal to the double of his or her oral daily maintenance dose, with a maximal dose of 5 mg bumetanide (conversion factor 20 mg torsemide = 40 mg furosemide = 1 mg bumetanide). Together with this initial dose of loop diuretics, patients receive an intravenous bolus of 500 mg acetazolamide or matching placebo. Between administering the starting dose and next treatment dose, a minimum of 6 h is required.

During the remaining part of the treatment phase on the next 2 days, the patient will continue to receive two loop diuretic treatment doses every day, provided that the treating physician has concluded during the morning rounds that the patient is still volume overloaded (*Figures 3* and *4*). These doses are half the starting dose given at randomization (equal to the patient's daily maintenance dose) and are administered between 8:00 and 12:00 a.m., with the second dose administered 6 h later. Together with the first loop diuretic dose, an intravenous bolus of 500 mg acetazolamide or matching placebo is repeated. Any patient with more than trace oedema, residual pleural effusion (to be confirmed by chest X-ray, only if present at study inclusion), or residual ascites (to be confirmed by ultrasound, only if present at study inclusion) is considered still to be volume overloaded. Only when the patient has no residual signs of volume overload, diuretic treatment can be stopped according to the study protocol with a switch towards an oral regimen at the discretion of the treating physician. The investigator (= cardiologist) determining the degree of volume overload will be blinded to study assignment. He/she has to complete the clinical congestion assessment (*Figure 4*) every day as illustrated in *Figure 1*. Training will be provided for the investigators how to score the congestion assessment (*Figure 4*) in order to minimize inter-individual variability. Blinding of patients and physicians should avoid any bias towards the IMP-stratified group. To standardize fluid input, daily oral intake of fluids and sodium is restricted to 1500 mL and 1.5 g, respectively. All patients receive the same maintenance infusion with 500 mL dextrose 5% and 3 g $MgSO_4$ administered over 24 h until complete decongestion or the end of the study treatment phase. All non-protocol fluids administered (including those for administration of intravenous medication) are prospectively registered.

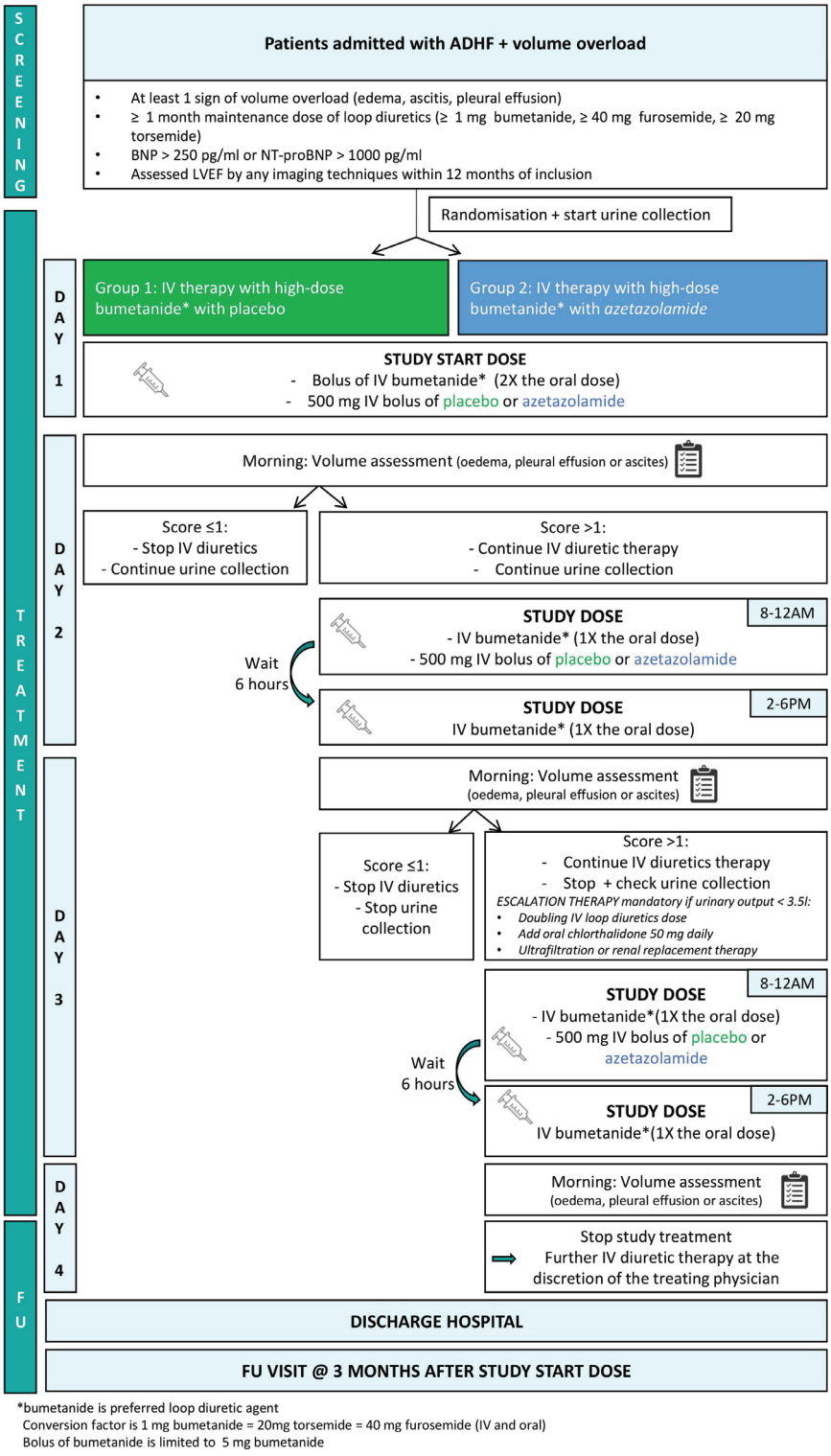

Figure 1 Central illustration. ADHF, acute decompensated heart failure; BNP, B-type natriuretic peptide; FU, follow-up; IV, intravenous; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

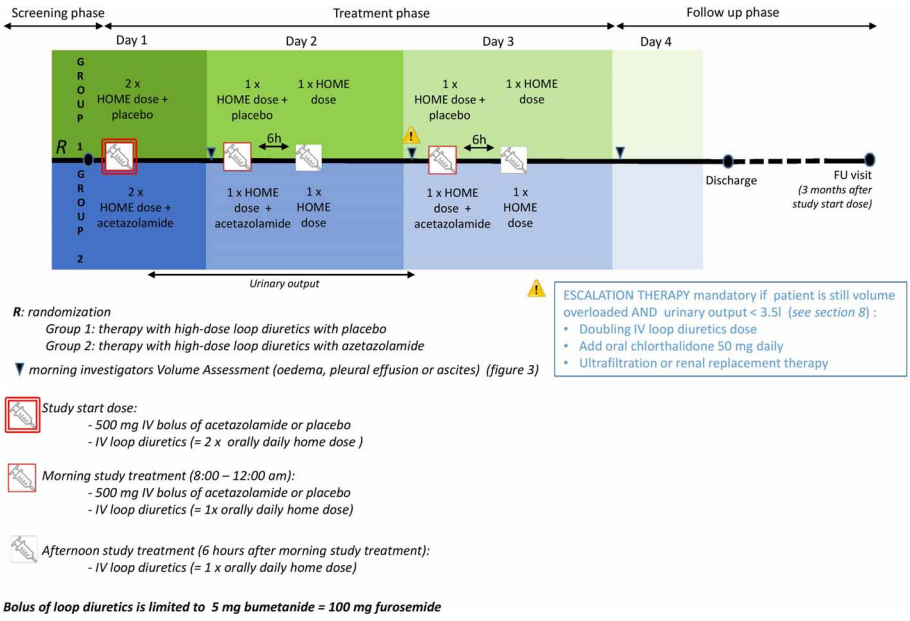

Figure 2 Study flowchart. FU, follow-up; IV, intravenous.

Table 1 Eligibility criteria for the ADVOR trial

Inclusion criteria

1 An elective or emergency hospital admission with clinical diagnosis of acute heart failure and ≥ 1 clinical sign of volume overload (i.e. oedema, ascites, or pleural effusion).
2 Maintenance therapy with oral loop diuretics at a dose of ≥ 1 mg bumetanide or ≥ 40 mg furosemide or ≥ 20 mg torsemide for ≥ 1 month.
3 Plasma NT-proBNP level > 1000 pg/mL or BNP level > 250 ng/mL at screening.

Exclusion criteria

1 Systolic blood pressure < 90 mmHg or mean arterial pressure < 65 mmHg.
2 Expected use of intravenous inotropes, vasopressors or sodium nitroprusside at any time point during the study. Nitrates are allowed only if systolic blood pressure is > 140 mmHg.
3 Estimated glomerular filtration rate < 20 mL/min/1.73 m^2.
4 Use of renal replacement therapy or ultrafiltration at any time before study inclusion.
5 Exposure to nephrotoxic agents (i.e. contrast dye) anticipated within the next 3 days.
6 Treatment with intravenous loop diuretics > 2 mg bumetanide or an equivalence of another loop diuretic during the index hospitalization and prior to randomization.
7 Maintenance treatment with acetazolamide or sodium–glucose co-transporter-2 inhibitors.
8 Use of any non-protocol defined diuretic agent except for mineralocorticoid receptor antagonists. Thiazides, metolazone, indapamide and amiloride should be stopped upon study inclusion. If the patient was taking a combination drug including a thiazide-like diuretic, the thiazide-like diuretic should be stopped upon study inclusion.
9 Concurrent diagnosis of an acute coronary syndrome defined as typical chest pain in addition to a troponin rise above the 99th percentile and/or electrocardiographic changes suggestive of cardiac ischaemia.
10 A previous or current diagnosis of hypertrophic, restrictive, or constrictive cardiomyopathy as documented in the medical record.
11 History of congenital heart disease requiring surgical correction.
12 History of cardiac transplantation and/or ventricular assist device.
13 Subjects who are pregnant or breastfeeding.

BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

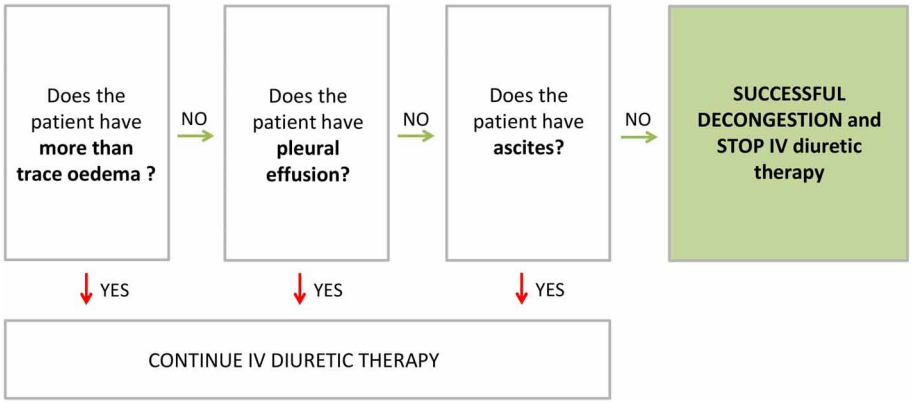

Figure 3 Decongestion flowchart. IV, intravenous.

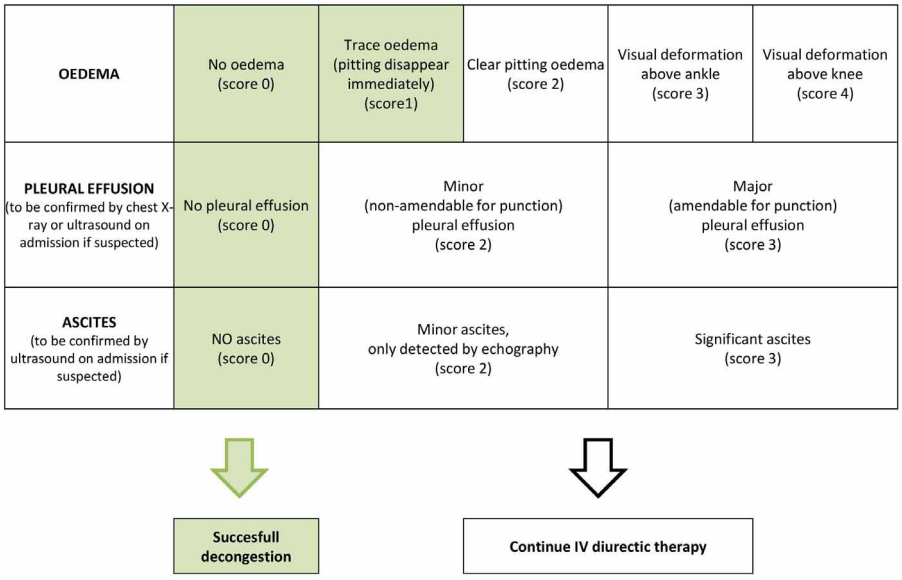

Figure 4 Clinical congestion assessment. IV, intravenous.

Urinary collection and treatment escalation

Patients need to empty their bladder before administration of the first dose of loop diuretics according to the study protocol. The urinary collection starts immediately after the first bolus of loop diuretics together with acetazolamide or placebo. The collection ends at 8:00 a.m. on the second morning after randomization, which is day 3 of study treatment. Insertion of a bladder catheter is strongly recommended but not mandatory to achieve an optimal urine collection. In case of urinary incontinence, placement is mandatory according to the study protocol. Special care should be taken to ensure that all urine is collected.

If urinary output (*Figure 1*) on morning of day 3 is < 3.5 L and the patient is still volume overloaded, an escalation of decongestive treatment is mandatory. Three options can be chosen at the discretion of the treating physician: (i) doubling of the intravenous dose of loop diuretics (equal to the study starting dose bid); (ii) addition of oral chlorthalidone 50 mg once daily; or (iii) ultrafiltration or renal replacement therapy. The decision to proceed with escalation therapy needs to be collected in the case report form as patients needing escalation are considered not to have reached the primary endpoint of complete decongestion with good loop diuretic efficacy.

The cut-off of 3.5 L urine output to define good loop diuretic efficacy may warrant some further explanation. First of all, it is important to notice that because of the variable times expected at study inclusion, the urinary collection is slightly longer than 24 h, approximately after 36 h. The 3.5 L cut-off is therefore expected to reflect the minimal urine output that ensures a net negative fluid balance in every possible scenario acknowledging the fact that patients are administered 500 mL maintenance infusion and

oral intake may be up to 1.5 L over 24 h. In addition, 3.5 L closely resembles the urine output goal of 3 L per day in the stepped pharmacological care arm in the CArdio-Renal REScue Study in acute decompensated Heart Failure (CARRESS-HF) trial.[22]

Study endpoints

The primary endpoint of the ADVOR trial is treatment success (decongestion achieved) on the third morning after randomization, which means on day 4 after three consecutive days of diuretic treatment, without the need for escalating treatment for poor loop diuretic efficacy on the morning of day 3. Secondary endpoints are: (i) the combined endpoint of all-cause mortality and heart failure readmissions during 3 months of follow-up; (ii) length of index hospital admission; and (iii) longitudinal changes in the EuroQol-5 dimensions (EQ-5D) questionnaire assessed at baseline, on the morning of day 4, during any readmission, and after 3 months. Exploratory endpoints include: (i) body weight changes; (ii) natriuresis; (iii) BNP or NT-proBNP changes; (iv) total dose of loop diuretics administered; (v) changes in dosing of neurohumoral blockers during the 3 months of follow-up; as well as (vi) plasma volume changes.

Safety monitoring

The treating physician is allowed to stop the study treatment, which counts as treatment failure in case of persistent volume overload in the following cases: (i) symptomatic hypotension with a systolic blood pressure < 100 mmHg; (ii) asymptomatic hypotension with a systolic blood pressure < 90 mmHg; (iii) a 150% relative increase in serum creatinine levels compared to baseline; (iv) occurrence of metabolic acidosis (pH < 7.2). Serum electrolyte levels and creatinine are checked daily during the treatment phase of the trial. In case of serum potassium levels < 4 mmol/L, 40 mmol of KCl is added to the maintenance infusion. Oral potassium supplements may be used at the discretion of the treating physician with their use prospectively registered. In case of metabolic acidosis with serum bicarbonate levels < 20 mmol/L, it is recommended to administer 100 mL of $NaHCO_3$ 8.4% intravenously. The steering committee of ADVOR will assess mortality events throughout the trial and in case of an unexpectedly high event rate may decide to unblind the trial.

Statistical plan

Sample size and power calculation

The ADVOR study is powered for its primary endpoint, which is the most relevant endpoint with respect to the study hypothesis and reliable data from large randomized clinical trials are available to make a formal power calculation. In the DOSE trial, which recruited a similar study population as targeted in the ADVOR study, successful decongestion with a similar definition was approximately 11% vs. 18% after 72 h in the low vs. high-dose loop diuretic arm.[11] The high-dose loop diuretic arm of the DOSE trial is quite comparable to the standard of care group in the ADVOR trial as the loop diuretic dose used is only slightly lower (2 x instead of 2.5 x the oral maintenance outpatient dose) and non-loop diuretics, which were infrequently used in the DOSE trial, are not allowed. Because of these slight differences, 15% is chosen as an estimate for occurrence of the primary endpoint in the monotherapy with high-dose loop diuretics group. No reliable data are available from large clinical trials to estimate occurrence of the primary endpoint in the acetazolamide arm of the ADVOR study. Therefore, after thorough discussion with the advisory board, a success rate of 25% was chosen, which represents a clear meaningful benefit of 10% more patients with appropriate decongestion after 72 h. Using both estimates, considering a type I error rate $\alpha = 0.05$ and type II error rate $\beta = 0.20$ (yielding a statistical power of 80%), the targeted sample size for the ADVOR study is calculated at $n = 494$. Anticipating a 5% drop-out, the total number of patients to be enrolled in the study is 519.

Randomization

An automated web-based system is used to randomly assign patients in a 1:1 ratio with variable block sizes, stratified for left ventricular ejection fraction according to study centre. To ensure an equal proportion of patients with heart failure with preserved (HFpEF) vs. reduced ejection fraction (HFrEF) in both study arms, the population will be stratified at inclusion according to a left ventricular ejection fraction $< 40\%$ vs. $\geq 40\%$. Permuted block randomization according to centre and LVEF stratum will be used to achieve this.

Statistical analysis

The primary statistical analysis in ADVOR will be a modified intention-to-treat analysis including all patients in whom the primary endpoint could be reliably assessed. This encompasses that urine output could have been measured reliably until morning of day 3 as diuretic resistance in patients with persistent volume overload is defined according to that metric. The treatment effect for the primary endpoint will be evaluated by means of a generalized linear mixed model. The statistical model will include a fixed treatment effect and random centre effect. For the first secondary endpoint (occurrence of the combined endpoint of all-cause mortality and heart failure readmission during 3 months of follow-up), a generalized linear mixed model for a binary outcome will be used. The model will incorporate a fixed treatment effect and random centre effect. If the treatment effect on the composite endpoint of all-cause mortality and heart failure readmission turns out to be statistically significant, both components will be evaluated separately in a hierarchical fashion with heart failure readmissions first and all-cause mortality second. For this analysis, heart failure readmission will include patients dying from heart failure during the 3 months of follow-up. As a sensitivity analysis the worst-case scenario, assuming a heart failure readmission for all patients dying due to non-heart failure related causes during the 3-month follow-up, will be executed. Length of index hospitalization and change in quality of life scores are compared among treatment arms with a linear mixed model (fixed treatment effect and random centre effect). Transformation will be employed when the model assumptions (such as normality) are violated. All hypotheses are 2-sided

and will be tested with a significance level of $\alpha = 0.05$. The proposed statistical models all assume the missing data mechanism to be missing at random. To investigate the sensitivity of the conclusions with respect to this assumption, a sensitivity analysis by means of multiple imputation technique will be performed. For the primary and secondary endpoint, subgroup analyses, with subgroups based on left ventricular ejection fraction (HFpEF vs. HFrEF), are also performed. In case of relevant protocol violations, sensitivity analyses will be carried out whenever appropriate.

Discussion

Current decongestive treatment with diuretic therapy in acute heart failure

Signs and symptoms of volume overload are the predominant reason for hospital admissions with AHF.[23] Over time, heart failure patients may build up a large volume of excess sodium and water in both their intravascular and interstitial compartment.[24] Urinary excretion, mechanical removal from third-space compartments (i.e. paracentesis), and mechanical removal from the intravascular compartment through ultrafiltration are the only ways to correct this volume overload. Diuretic therapy is the primary intervention in AHF to achieve this by stimulating natriuresis and diuresis. Importantly, patients presenting with AHF have a similar profile of congestion, irrespective of their ejection fraction.[25] Consequently, the decongestion treatment goal and guidelines are similar in patients with HFrEF and HFpEF.[7]

Loop diuretics

Loop diuretics are used in approximately 90% of patients with AHF, in more than half of cases as the sole therapy applied. They are protein-bound (> 90%), preventing them to be filtrated by the glomerulus. To reach their target of action, which is the $Na^+/K^+/2Cl^-$ symporter at the luminal side of the thick ascending limb of Henle's loop, they need to be secreted in the proximal tubules by organic anion transporters and the multidrug resistance-associated protein 4.[26] As 25% of sodium is reabsorbed at this level in the nephron, loop diuretics are the most potent diuretics, promoting excretion of sodium, potassium and chloride.[27] Importantly, loop diuretics directly stimulate renin release by inhibiting the $Na^+/K^+/2Cl^-$ symporter at the level of the macula densa. Impaired chloride flux into macula densa cells causes increased cyclo-oxygenase-2 and nitric oxide synthase I activity, leading to paracrine prostaglandin E2 and nitric oxide secretion.[15,28] Both prostaglandin E2 and nitric oxide work in concert to stimulate renin release by granulosa cells of the afferent arteriole and further activates the renin–angiotensin–aldosterone axis. Furthermore, chronic use of loop diuretics promotes compensatory distal tubular sodium reabsorption, preventing excessive natriuresis.[29] Other reasons for loop diuretic resistance are poor bioavailability in case of abdominal congestion; impaired secretion of loop diuretic agents in the proximal tubules because of competition with anions in chronic kidney disease or metabolic acidosis; low plasma protein levels; or significant proteinuria. Loop diuretics exhibit a steep dose–response curve, necessitating a minimal threshold dose to induce natriuresis that is increased in AHF, especially when concomitant kidney dysfunction is present.[30,31]

Current guidelines make the following recommendations for loop diuretic therapy in AHF: (i) diuretic naïve patients should receive intravenous furosemide at a dose of 20-40 mg[30,31]; (ii) patients on a maintenance oral loop diuretic regimen should receive at least this dose administered intravenously. Furthermore, results from the DOSE trial suggest that high-dose (2.5 times the maintenance dose) compared to low-dose (equal to the maintenance dose) loop diuretics may be associated with faster dyspnoea relief, more pronounced weight loss and a higher net fluid loss.[11] WRF, defined as a ≥ 0.3 mg/dL rise in serum creatinine, occurred more frequently in the high-dose group, yet did not reflect worse outcome.[32] Remarkably, the proportion of patients with clear persistent clinical signs of congestion after 72 h was 82% in the high-dose and 89% in the low-dose group. This indicates that persistent congestion is actually quite common after loop diuretic therapy in AHF.

Thiazide-like diuretics

Thiazide-like diuretics target the sodium–chloride co-transporter in the distal convoluted tubules.[14] Therefore, they are very effective to break diuretic resistance caused by distal nephron hypertrophy. Most clinical evidence to support the use of thiazide-like together with loop diuretics in AHF comes from small observational studies. Those studies indicate a probable class effect and 75–90% response rate in patients considered loop diuretic resistant.[24,33] Moreover, in CARRESS-HF, a stepped pharmacological care plan with early assessment of urinary output and adjustment of loop diuretic dosing, and addition of metolazone accordingly, produced similar decongestion success as ultrafiltration, yet with less adverse events.[22] Despite this, freedom from clinical signs of volume overload after 96 h was only 10% in CARRESS-HF. Thus, especially in a population like that recruited in CARRESS-HF, at high risk for WRF, there is an unmet need to improve current decongestive strategies beyond thiazide-like diuretics. Moreover, the latter are frequently associated with exaggerated potassium losses as well as hyponatraemia.[24,34] Indeed, in a propensity-matched analysis of real-world use of thiazide-like in addition to high-dose loop diuretics in AHF, thiazide use was an independent predictor of hyponatraemia and hypokalaemia with a trend towards a higher risk for all-cause mortality.[35]

Mineralocorticoid receptor antagonists

Mineralocorticoid receptor antagonists (MRA) have a class I recommendation as a disease-modifying therapeutic agent in symptomatic HFrEF.[36] In addition, the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial suggests that selected HFpEF patients with elevated natriuretic peptide levels may benefit as well.[37] Recently, the incremental diuretic effect of high-dose MRA therapy in adjunct to standard loop diuretic therapy in AHF has been evaluated

in the Aldosterone Targeted NeuroHormonal CombinEd with Natriuresis TherApy in Heart Failure (ATHENA-HF) trial.[38] However, therapy with 100 mg of spironolactone was not superior to 0–25 mg per day in reducing NT-proBNP levels after 96 h. Moreover, there was neither a significant effect on urine output.

Loop diuretic efficacy

The concept of loop diuretic efficacy is emerging as an important parameter in AHF. Different definitions are used based on urine output, net fluid balance, weight loss, natriuresis, or fractional sodium excretion normalized for the loop diuretic dose administered (typically 40 mg of furosemide equivalents). With remarkable consistency in observational studies and post-hoc analyses from randomized clinical trials, loop diuretic efficacy metrics have been found to predict clinical outcome in AHF. The exact mechanistic underpinning of this robust association is less obvious than at first sight. A logical explanation might be that AHF patients who present with loop diuretic resistance have a lower chance of achieving appropriate decongestion. Yet, similar congestion signs were reported in some cohorts at discharge in patients with vs. without diuretic resistance and still there was a difference in outcomes.[17] Alternatively, loop diuretic efficacy might be interpreted as a *renal stress test*, indicating the reserve function of the kidneys to excrete sodium and water in analogy to the maximal aerobic capacity being reflective of the cardiac reserve during exercise. Finally, poor diuretic response might indicate as well that volume overload is not present and sodium levels are possibly depleted.[39,40] In the latter scenario, diuretic therapy is unlikely to target the underlying pathophysiological culprit of AHF and may be harmful instead. Although diuretic resistance clearly is a risk marker in AHF, it remains an open question whether interventions that increase loop diuretic efficacy also lead to improved outcomes in AHF. This would make it a *causal factor* and hence an attractive endpoint in future clinical trials.

Acetazolamide

The proximal tubules of the nephron reabsorb the largest fraction of filtered sodium and chloride (75–85%). Importantly, as the epithelium lining the proximal tubular lumen is very leaky to water and small ions like sodium and chloride, Starling forces across the peritubular capillaries ultimately determine their fractional reabsorption.[41] The proximal tubules immediately receive the ultrafiltrate produced in the glomerulus. When renal blood flow is low, the filtration fraction or ratio of the glomerular filtration rate over renal blood flow increases, which is further exacerbated by activation of the renin–angiotensin system that causes predominantly efferent arteriolar vasoconstriction and increases the hydrostatic pressure inside the glomerulus. Filtering more plasma towards the tubular system raises the peritubular capillary oncotic pressure, hence promoting sodium and chloride reabsorption in the proximal tubules. Secondly, renal venous hypertension substantially increases the hydrostatic pressure in both the renal interstitium and peritubular capillaries, but also in the tubular lumen, since the kidney is an encapsulated organ. The consequence is an increased renal lymph flow, washing out interstitial proteins and decreasing colloid osmotic pressure in the renal interstitium, further promoting sodium reabsorption. From a pathophysiological point of view, targeting sodium reabsorption in the proximal tubules has therefore several potential benefits in heart failure. In addition, chloride not absorbed in the proximal tubules will reach the macula densa cells at the end of Henle's loop, ceasing renin release and neurohumoral activation. Finally, endogenous natriuretic peptides (acting predominantly in the distal nephron) will possibly regain their effects.[14]

The carbonic anhydrase inhibitor acetazolamide, which is approved for the treatment of mountain sickness and glaucoma treatment, inhibits sodium reabsorption in the proximal tubules. On its own, acetazolamide increases natrium and bicarbonate excretion, urine alkalosis, and blood acidosis.[42] Acetazolamide was used alone or in combination with mercurial diuretics in the 1950s and 1960s to treat volume overload in AHF.[43] With the discovery of potent loop diuretics, their use has been largely abandoned, despite the pathophysiological rationale for inhibition of proximal sodium reabsorption. One observational study in patients with AHF and marked volume overload found that the addition of acetazolamide (500 mg administered as intravenous bolus on top of loop diuretic therapy) improved loop diuretic efficacy with approximately 100 mmol sodium excreted per 40 mg of furosemide equivalent dose.[16] Thus, although the diuretic and natriuretic capacity of acetazolamide is poor on its own, it might well be a very efficient booster of diuretic efficacy in combination diuretic therapy with loop diuretics. This concept is further supported by two other small randomized trials including patients with volume overload refractory to loop diuretic therapy.[14,44] All these AHF patients demonstrated a reduced fractional sodium excretion, which improved by the addition of acetazolamide. Furthermore, acetazolamide also improves thiazide-like diuretic efficacy, as it potently downregulates pendrin expression in the distal nephron.[21] Pendrin, also known as the sodium-independent chloride/iodide transporter, compensates for sodium and chloride loss in the distal convoluted tubules and might be an unrecognized source of diuretic resistance.[45,46] Finally, acetazolamide use is associated with renal vasodilatation and improved renal blood flow with a potential protection against ischaemia–reperfusion damage, which might suggest nefroprotective effects.

Conclusions

There is a pressing need to find novel interventions that effectively and safely promote diuresis and improve decongestion success in AHF with volume overload. From a pathophysiological perspective, there are sound reasons to expect that acetazolamide improves loop diuretic efficacy of loop diuretics to achieve this goal. If the ADVOR trial shows promising results, it might change the treatment for congestion and volume overload worldwide as the drug is off-patent and very cheap. It will also lay the groundwork for a more definite outcome trial in AHF.

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