DOI:
10.1002/ejhf.2634

Document Version
Peer reviewed version

Combination diuretic therapy for acute heart failure: “Alone we can do so little; together we can do so much”.

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Acute heart failure (AHF) is associated with high in-hospital and post-discharge 1-year mortality, with rates up to 9% and 31%, respectively (1, 2). Evidence-based treatments for AHF are limited. So far, intravenous loop diuretics have one of the strongest (class I) recommendations for its treatment (3). They are effective at reducing the signs and/or symptoms of volume overload and, are recommended therapies across the entire spectrum of left ventricular ejection fraction (EF) (3). However, the level of evidence is C, given the lack of large randomised controlled trials (RCTs) investigating the prognostic benefit of diuretic therapy compared to placebo. Their effects on mortality can only be extrapolated from small RCTs or meta-analyses. However, many of these studies did not specifically investigate patients with AHF, and used evidence being derived from trials using surrogate endpoints (4). In addition, large RCTs of prognostic therapy for heart failure with reduced ejection fraction (HFrEF) recruited patients with high background rates of loop diuretic prescription, which adds indirect evidence for their use alongside guideline-directed therapy.

Sequential nephron blockade is used as a second line regimen to treat diuretic resistance, defined as an impaired sensitivity to diuretics resulting in reduced natriuresis and diuresis, and persistent congestion (3, 5). However, few studies have specifically examined combination therapy (**Fig 1**). In this issue of the European Journal of Heart Failure, Mullens *et al.* describe the baseline characteristics of patients enrolled to the Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial and compare these to other contemporary trials in AHF [REF MULLENS ET AL]. ADVOR is a multicentre, randomised, double blind, placebo-controlled trial of acetazolamide in combination with intravenous loop diuretic therapy in admitted patients with AHF. The primary endpoint of the ADVOR trial is the rate of successful decongestion, measured using a clinical congestion score, on day 3 after randomisation, without the need for additional diuretics. In addition, the authors should be commended for including quality of life, using the EuroQol-5 dimensions (EQ-5D) questionnaire, as an imperative secondary endpoint, along with all-cause mortality, or heart failure readmission after 3 months and length of hospital stay.

Acetazolamide is a carbonic anhydrase inhibitor that inhibits sodium reabsorption from the proximal convoluted tubule (PCT) of the nephron and is therefore a suitable candidate for sequential nephron blockade in addition to loop diuretics. It was first shown to synergistically improve natriuresis in a small randomized study of patients with resistant volume overload (n=24) (albeit including only 6 patients with HF) (6), which has since been confirmed elsewhere.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors can also be used for sequential nephron blockade. These are one of the four pillars of medical treatment in HFrEF (3), and have pleiotropic actions that include a diuretic effect at the PCT that is like acetazolamide. They have been shown to improve

diuresis in AHF without worsening renal function in the randomised EMPAG-HF trial (7). SGLT2 inhibitors also resulted in clinically meaningful and sustained decongestion in stabilised hospitalised patients with background intravenous loop diuretic therapy enrolled in the EMPULSE trial (8).

Other studies have investigated the combination of loop diuretics with the stepped use of agents acting on the distal nephron that may be useful to reduce the sodium avidity of the distal convoluted tubule (DCT) and increase natriuresis. Metolazone is a sodium-chloride transporter blocker diuretic that acts on the early DCT. There are no RCTs evaluating the effect of metolazone in AHF, and the results of MELT-HF, a phase 4 study comparing metolazone to placebo with respect to decongestion in AHF, are not yet available (clinicaltrials.gov/NCT02620384). However, a large, propensity-matched observational analysis of patients with AHF in the US compared high-dose loop diuretics (median peak furosemide equivalent dose 120 mg) to standard-dose loop diuretics (median peak furosemide equivalent dose 80mg) plus metolazone (9). The study found that combination therapy with standard-dose loop diuretic and metolazone, but not high-dose loop diuretics alone, was an independent predictor of hyponatraemia, hypokalaemia, and all-cause mortality. Finally, the results of CLOROTIC (clinicaltrials.gov/NCT02620384), a phase 4 study comparing hydrochlorothiazide to placebo in addition to loop diuretics, are also awaited.

The addition of a high-dose mineralocorticoid receptor antagonist (MRA), which acts at the late DCT, to standard loop-diuretic therapy has been investigated in the double-blind randomised Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure (ATHENA-HF) trial (10). Here, 100 mg of spironolactone did not improve NT-proBNP concentrations, a clinical congestion score, dyspnoea, urine output, or net weight change at 96 hrs compared to placebo or standard-dose spironolactone (25 mg).

ADVOR is the largest trial of diuretics in AHF, to date. Importantly, it investigates “up-front“ combination diuretic therapy for AHF, distinguishing it from studies of combination therapy for diuretic resistance. The study enrolled a population that is relevant to contemporary HF practice. Patients were elderly with mean age 78±9 years, had a high NT-proBNP concentration (median 6173 pg/mL), significant comorbidities, and poor quality of life. All patients had demonstrable congestion, including 78% with >grade 2 oedema and 53% with a pleural effusion. The authors compare this to other diuretic trials, including the Diuretic Optimization Strategies Evaluation (DOSE) trial, ATHENA-HF, and CARRESS-HF [REF MULLENS ET AL]. This comparison demonstrated that ADVOR had a more elderly population (mean age 78 compared to 65 years), with higher NT-proBNP, and similar rates of comorbidities. This makes the patients in ADVOR more akin to AHF patients enrolled into large registries, which report a median age between 69 and 79 years with comparable rates of comorbidities

(11-13). Data from registries highlight how often the populations enrolled into clinical trials differ from those encountered in clinical practice, making some results only partially generalisable. Once available, the results of the ADVOR are expected to be highly relevant, which is one of its main strengths.

A more aggressive, combination diuretic strategy may be more effective in decongesting AHF patients. In clinical trials and registries of diuretics in AHF, many patients are discharged with residual clinical congestion [REF MULLENS ET AL]. This has been associated with poor outcomes in an observational study (14), but only in the presence of worsening renal function (WRF; defined by an absolute increase in serum creatinine of ≥0.3 mg/dL from values measured at the time of admission). Congestion alone was not an independent predictor of mortality or transplant. Even in combination with WRF, the association with poor outcomes disappeared when HF hospitalization was added to the composite endpoint. Therefore, it is vital that ADVOR includes all-cause mortality as an (albeit secondary) endpoint.

One of the caveats of the ADVOR trial relates to the exclusion of patients on SGLT2 inhibitors. It is increasingly apparent that contemporary disease-modifying therapies for HFrEF also have either diuretic properties or synergistic effects with diuretics (5, 7). Previous trials of diuretic therapy pre-date much guideline-directed therapy, especially angiotensin receptor-neprilysin inhibitors (ARNIs) and SGLT2 inhibitors. Therefore, assessment of diuretic therapy over and above the diuretic effect conferred by these therapies is now necessary. ADVOR describes high prescription rates of guideline-directed therapy, which is commendable, but a limitation is that patients were excluded if they were on other agents acting at the PCT, including SGLT2 inhibitors. While ADVOR recruited 225 patients with HFrEF, the number of eligible patients would be expected to reduce as guidelines are adopted into routine clinical practice. Furthermore, there is now evidence for their potential use in patients with HF with preserved ejection fraction (HFpEF), which might further restrict the direct relevance of ADVOR. Therefore, sequential nephron blockade should be evaluated in addition to optimal medical therapy, including ARNIs and SGLT2 inhibitors, to address the best strategy to optimise diuresis and improve clinical outcomes.

Overall, ADVOR is a welcome study of “up-front” combination diuretic therapy, with a loop diuretic and acetazolamide, that will add important information to the treatment of AHF, the role of acetazolamide, and the utility of sequential nephron blockade. The ADVOR baseline characteristics reveal that it is a clinically relevant population, and the results are expected to be widely generalizable to contemporary heart failure patients. Helen Keller recognised the importance of working together when she said: *“Alone we can do so little. Together we can do so much”*. When the results of ADVOR

are announced as a late-breaking clinical trial at the European Society of Cardiology 2022, it is hoped combination diuretic therapy with acetazolamide will, indeed, justify that saying for patients with AHF.

Figure legend

Fig 1: Research evidence for sequential nephron blockade.

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