Official Title: Diamox/Aldactone to Increase the URinary Excretion of Sodium: an Investigational Study in Congestive Heart Failure

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1. Background

Aging of the population and prolongation of the lives of cardiac patients by modern therapeutic innovations have led to an increased incidence of congestive heart failure (CHF).[1] During the last two decades, important progress has been made in the treatment of ambulatory CHF patients with reduced ejection fraction. Renin-angiotensin system blockers, β-blockers, mineralocorticoid receptor antagonists (MRA), ivabradine and cardiac resynchronization therapy have all demonstrated to reduce morbidity and/or mortality in ambulatory CHF patients.[2-17] Despite these important advances, many patients are still hospitalized frequently with signs and symptoms of systemic congestion, which is associated with worse outcome.[18] Treatment in these cases mainly focuses on symptomatic relief through administration of diuretics, although clear evidence on the optimal agent, dosing schedule, and administration route is lacking.

Coexisting renal dysfunction often complicates decongestive treatment and worsening renal function (WRF), often defined as a 0.3 mg/dL rise in serum creatinine (Cr), is a common finding in this context.[19] However, the prognostic impact of WRF, defined as Cr change is unsure as it might be associated with worse, neutral or even better outcome.[20-22] In contrast, persistent congestion, as a reflection of the inability of the kidneys to preserve sodium homeostasis, has been more consistently associated with higher mortality and more frequent readmissions in CHF.[23] This suggests that achieving a negative sodium balance might be an attractive treatment target in heart failure.

Loop diuretics are by far the most commonly used diuretic agents to achieve a negative sodium balance in acute decompensated heart failure (ADHF). Especially in diuretic-naïve patients, they are often very effective to relief dyspnea and congestive symptoms. However, in the recent Diuretic Optimization Strategies Evaluation (DOSE) trial, no differences in patients' global assessment of symptoms or change in renal function were observed when loop diuretics were administered by bolus as compared with continuous

infusion or at high versus low dose during a hospitalization for ADHF, with high dose therapy currently considered as usual care by most clinicians.[24] Importantly, there are several reasons why loop diuretics might be less effective or even harmful in CHF. First, loop diuretics directly stimulate renin production by inhibiting the $Na^+/K^+/2Cl^-$-cotransporter on the luminal side of the macula densa, which depletes intracellular chloride levels in the macula densa. The consequence is an increased COX-2 and NOS I activity in macula densa cells, leading to paracrine PGE_2 and NO secretion.[25] Both PGE_2 and NO work in concert to stimulate renin release by granulosa cells of the afferent arteriole and further detrimental activation of the renin-angiotensin-aldosterone axis. Second, impaired secretion of loop diuretics in the proximal tubules of CHF patients, especially when there is concomitant renal dysfunction, results in lower concentrations at the place where these agents act – the luminal side of the thick ascending limb of Henle's loop (TAL). Third, increased sodium reabsorption in the proximal tubules might result in less sodium offered to the TAL, especially if glomerular filtration is concomitantly impaired, hampering the efficacy of loop diuretics. As a result, physicians often use combination therapies of different acting diuretic agents in order to increase the overall diuretic effect.

From a pathophysiological point of view, targeting sodium reabsorption in the proximal tubules has several potential benefits in CHF. First, it is the place where most sodium is reabsorbed, especially in ADHF. Second, greater delivery of chloride to macula densa cells will decrease renin production, ceasing neurohumoral activation. Third, endogenous natriuretic peptides (acting in the distal nephron) will possibly regain their effects. The carbonic anhydrase inhibitor acetazolamide (Diamox®), which is approved for the treatment of mountain sickness and is used to increase the diuretic efficacy of loop diuretics in patients with therapy-refractory congestion, inhibits sodium reabsorption in the proximal tubules. Remarkably, in a small study of 9 patients with advanced CHF and diuretic resistance, therapy with acetazolamide was able to elicit potent diuresis.[26] Despite this

promising case series and the pathophysiological rationale for inhibition of proximal sodium reabsorption in ADHF, acetazolamide is now a largely forgotten diuretic.

MRA have an established role in the treatment of chronic CHF.[11, 12] However there are remarkable few data on their use in patients who present with ADHF. Nevertheless, in this context with frequent use of potassium wasting diuretics, they might be of particular interest to prevent occurrence of hypokalemia, which has been associated with a worse prognosis.[27] Moreover, by inhibiting distal tubular sodium reabsorption and counteracting aldosterone breakthrough, MRA might improve the natriuretic efficiency of loop diuretics.

2. Study Hypotheses

1. Combination therapy with acetazolamide improves loop diuretic efficacy to induce natriuresis in ADHF patients, allowing for a lower dose of the latter medication and potentially less adverse events such as worsening renal function.
2. Combination therapy with acetazolamide and low-dose loop diuretics leads to less pronounced neurohumoral activation compared to treatment with high-dose loop diuretics in ADHF patients.
3. Upfront therapy with MRA is safe in patients presenting with ADHF and lowers the incidence of hypokalemia and the need for potassium supplementation, without causing a higher incidence of hyperkalemia.
4. Combination diuretic therapy with acetazolamide and/or upfront spironolactone will lead to improved clinical outcome (less heart failure rehospitalizations and lower all-cause mortality).

3. Study Protocol

3.1. Study design

Randomized clinical trial with factorial 2x2 design, 2 treatment arms, and 4 groups (n=20 each):

- Arm 1: Acetazolamide + low-dose loop diuretics versus high-dose loop diuretics (=standard of care)

  ➔ Triple blinded to treatment allocation (patient, treating physician and investigator blinded)

- Arm 2: Upfront versus discharge spironolactone

  ➔ Treating physician and investigator blinded to treatment allocation. Patient not blinded to treatment allocation because no matching placebo will be provided due to logistic constraints.

Consecutive patients, presenting with ADHF at different Belgian hospitals will be screened by staff members, cardiology fellows, a study nurse and the cardiology Ph.D. fellows. All those people will be able to login via the website www.hartcentrumlimburg.be, where they can print the case report form and informed consent of the study and will receive the randomization number by a computer algorithm with blocks of 4.

3.2. Study population

3.2.1. Inclusion criteria

- Older than 18 years of age and able to give informed consent
- Clinical diagnosis of ADHF within the previous 8 h
- At least two clinical signs of congestion (e.g. edema, ascites, jugular venous distension or pulmonary vascular congestion on chest radiography)
- Maintenance therapy with oral loop diuretics at a dose of at least 1 mg bumetanide or an equivalent dose for at least 1 month before hospital admission

  Conversion: 1 mg bumetanide = 40 mg furosemide = 20 mg torsemide
- Plasma NT-proBNP >1,000 pg/mL
- Left ventricular ejection fraction <50% (on examination ≤3 months)
- One out of three of the following criteria:
  - Serum sodium <136 meq/L

- Urea/creatinine ratio >50
- WRF defined as a >0.3 mg/dL increase in Cr compared to a previous value within 3 months before admission

3.2.2. Exclusion criteria

- History of a cardiac transplantation and/or ventricular assist device
- Concurrent diagnosis of an acute coronary syndrome defined as typical chest pain and/or electrocardiographic changes in addition to a troponine rise >99th percentile
- Systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg at the moment of admission
- Use of intravenous inotropes, vasopressors or nitroprusside at any time point during the study
- A baseline estimated glomerular filtration rate <15 mL/min/1.73m² according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula
- Use of renal replacement therapy or ultrafiltration before study inclusion
- Treatment with acetazolamide during the previous month
- Treatment with ≥2 mg bumetanide or an equivalent dose of loop diuretics during the index hospitalization before randomization
- Use of diuretics or MRA not specified by the protocol
- Exposure to nephrotoxic agents (i.e. contrast dye) anticipated within 3 days

3.3. Interventions (See Addendum 1 for therapy schedules)

3.3.1. Arm 1, control group: High-dose loop diuretics

- At the moment of randomization the patient receives an intravenous bolus of loop diuretics at a dose equal to the double of his normal daily oral dose (e.g. a patient who takes 1x1 mg bumetanide will receive 2x1x1 mg = 2mg; or a patient who takes 2x1 mg bumetanide will receive 2x2x1 mg = 4mg).
- The next three days, the patient will receive the same dose equally divided between two administrations at 10u00 and 16u00 provided that the treating physician has concluded during the morning rounds that the patient is still volume overloaded.
- If diuresis since administration of the previous dose of loop diuretics is <1,500 mL and the patient is still volume overload, subsequent bolus doses are doubled.
- If after doubling of the dose, the patient is considered therapy-refractory. The treating physician is recommended to add chlorthalidone 50mg once daily and consider ultrafiltration or renal replacement therapy after which results of the patient will be censored.
- Switch to treatment at the discretion of the treating physician if any of the following criteria is fulfilled
    - After 3 days
    - The patient had no longer clinical signs or symptoms of congestion
    - Doubling of the serum creatinine value

3.3.2. Arm 1, treatment group: Acetazolamide + low-dose loop diuretics

- At the moment of randomization, the patient receives 500 mg of intravenous acetazolamide and 2 mg of intravenous bumetanide in bolus.
- The next three days, the patient will receive 250 mg of intravenous acetazolamide and 1 mg of intravenous bumetanide in bolus at 10u00 provided that the treating physician has concluded during the morning rounds that the patient is still volume overloaded.

- If diuresis since administration of the previous dose of loop diuretics is <1,500 mL and the patient is still volume overloaded, the patient continues to receive 500 mg of acetazolamide and 2 mg of bumetanide.
- If after doubling of the dose, the patient is considered therapy-refractory. The treating physician is recommended to add chlorthalidone 50mg once daily and consider ultrafiltration or renal replacement therapy after which results of the patient will be censored.
- Switch to treatment at the discretion of the treating physician if any of the following criteria is fulfilled
    - After 3 days
    - The patient had no longer clinical signs or symptoms of congestion
    - Doubling of the serum creatinine value

3.3.3. Arm 2, control group: Discharge spironolactone

This group will receive no active treatment. No placebo will be provided either due to logistic constraints. As instructed by the guidelines, addition of a MRA to maintenance therapy will be recommended upon discharge from the hospital.

3.3.4. Arm 2, treatment group: Upfront spironolactone

This group will receive oral spironolactone 25 mg immediately after randomization and subsequently each day in the morning (10u00) provided serum potassium levels are <5.0 mmol/L. If no contraindications emerge during hospitalization, spironolactone will be added to the maintenance therapy of the patient upon hospital discharge.

3.3.5. All groups

All groups will receive the same maintenance intravenous therapy with 500 mL Glucose 5% and 3g MgSO4 administered over a 24enin-angiotensin system blockers and β-blockers) will be continued at the discretion of the treating physician, but they are recommended to keep maintenance dosages unchanged.

3.4. Collected data

- Baseline at the moment of randomization
    - Demographics, medical history, current medical therapy, baseline body weight, blood pressure, heart rhythm (sinus or not), heart rate, Visual-analogue scale (VAS) score for dyspnea and 4-point Likert scale for edema will be assessed upon study inclusion
    - Blood sample: hematocrit, electrolytes, serum osmolality, serum urea, serum creatinine, serum Cystatin C, serum urate, plasma renin activity (PRA), plasma aldosterone, plasma adrenaline, plasma noradrenaline, total protein, plasma NT-proBNP
- Day 1-3:
    - VAS score for dyspnea
    - 4-point Likert scale for edema
    - Body weight and fluid balance
    - Blood pressure, heart rate, heart rhythm
    - Blood sample: hematocrit, electrolytes, serum osmolality, serum urea, serum creatinine, serum Cystatin C, serum urate, PRA, plasma aldosterone, plasma adrenaline, plasma noradrenaline, total protein, plasma NT-proBNP
- Three consecutive 24h urinary collections will be performed; the first one started with the first bolus administration of loop diuretics; urinary assessment of creatinine, protein, sodium, potassium, chloride, ureum, urate, microalbuminura
- At an outpatient follow-up appointment 2-6 weeks after hospital discharge, a final blood sample with hematocrit, electrolytes, serum osmolality serum urea, serum creatinine, serum Cystatin C, serum urate and plasma NT-proBNP will be collected.
- All-cause mortality and hospital readmissions will be collected prospectively for the study cohort. The patient will receive a telephone call from a study nurse after 3, 6, 9 and 12 months

3.5. Study end-points

3.5.1. Primary study end-point acetazolamide arm

Total urinary sodium excretion (mmol) after 24 h

3.5.2. Pimary study end-point for spironolactone arm

Incidence of hypo- (serum potassium <3.5mmol/L or need for oral/intravenous potassium supplements) or hyperkalemia (serum potassium >5.0mmol/L) during the entire 72 h interval after randomization.

3.5.3. Secondary end-points

- Relative plasma NT-proBNP change (%) after 72 h compared to admission
- Worsening renal function defined as a >0.3 mg/dL increase in serum creatinine or a >20% decrease in estimated glomerular filtration rate by the CKD-EPI formula compared to baseline at any time point before 72 h
- Persistent renal impairment, defined as persistently elevated serum creatinine levels >0.3 mg/dL or a >20% decrease in estimated glomerular filtration rate by the CKD-EPI formula compared to baseline at the moment of outpatient follow-up 2-6 weeks after hospital discharge.
- Peak plasma aldosterone concentration (ng/L) after 72 h
- Peak plasma renin activity (ng/mL/h) after 72 h

3.5.4. Other pre-specified outcome measures

- Total urinary sodium excretion (mmol) after 48 h and 72 h
- Total urine output after 24 h, 48 h and 72 h
- Change in VAS score for dyspnea at 24 h, 48 h and 72 h
- Change in 4-point Likert scale for edema at 24 h, 48 h and 72 h
- Body weight change upon hospital discharge compared to admission
- Incidence of therapy-refractory congestion defined as the need for combinational diuretic therapy with chlorthalidone, bail-out ultrafiltration or renal replacement therapy

- Incidence of all-cause mortality and readmissions after 1 year

3.6. Statistical analysis

Continuous variables will be expressed as mean ± standard deviation when normally distributed and as median (interquartile range) in case of a non-normal distribution. Normality will be assessed by the Shapiro-Wilk statistic. The independent-samples Student's *t*-test and Mann-Whitney *U* test will be used as indicated to compare between groups. Categorical variables will be expressed as percentages and compared using Fisher's exact test or Pearson's χ^2-test in case of a non-binary response. Statistical significance will always be set at a 2-tailed probability level of <0.05. All statistics will be performed using IBM SPSS® (Chicago, Illinois, USA) (version 22.0 for Mac).

4. Potential adverse events

- Metabolic acidosis is the only agent-specific adverse event that might be expected from treatment with acetazolamide. Serum bicarbonate is monitored daily. If serum bicarbonate <22 meq/L, substitution with oral $NaHCO_3$ will be provided.
- Hyperkalemia might be expected as a potential adverse event of spironolactone, but this medication will be withheld when serum potassium levels are >5.0 mmol/L and serum potassium levels are monitored daily throughout the study.

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