Acute over-additive natriuretic effects by a combination of finerenone and SGLT2 inhibition in rats with an activated renin–angiotensin–aldosterone system: A mechanistic basis for clinical outcomes?

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Background

- Recent preclinical studies suggested an independent benefit of non-steroidal mineralocorticoid receptor (MR) antagonism by finerenone and sodium-glucose co-transporter-2 (SGLT2) inhibition in cardiorenal diseases, with a potential for combination therapy
- Chronic low-dose combination of finerenone and empagliflozin in hypertensive rats revealed an early, sustained and over-additive reduction in proteinuria, but the underlying mechanism(s) are not fully understood

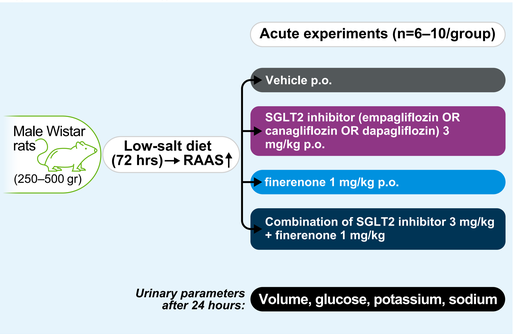
Purpose

- To compare the acute glucosuric, natriuretic, kaliuretic and diuretic efficacy of individual dosages of finerenone and SGLT2 inhibitors (empagliflozin, canagliflozin or dapagliflozin) with the combined administration of both drug classes in conscious rats with an activated renin–angiotensin–aldosterone system (RAAS)

Methods

- The RAAS was activated in male Wistar rats (body mass 250 to 500 g) by placing them on a low-salt diet containing 0.02% sodium chloride for 72 hours
- In a series of three independent experiments, finerenone (1 mg/kg), SGLT2 inhibitor (3 mg/kg; either empagliflozin, canagliflozin or dapagliflozin) alone and the respective combinations were administered in 2–3 ml/kg of solvent (PEG400) by oral gavage, and the animals (n=6–10/group) were individually placed in metabolic cages on water ad libitum
- Individual urine samples were collected for 24 hours and the concentrations of glucose, sodium and potassium excreted in the urine were measured by a clinical chemical analyser system (ADVIA 2400, Siemens)

Figure 1. Study design



p.o., per os (medication taken by mouth or orally)

Results

- Administration of 1 mg/kg finerenone had no influence on urinary volume, urinary glucose and urinary potassium, but a trend of increased urinary sodium excretion was observed
- At a dose of 3 mg/kg, all SGLT2 inhibitors induced a strong increase in urinary glucose excretion but had no significant influence on urinary potassium and urinary sodium, while only dapagliflozin caused an increase in urinary volume at the tested dose
- Administration of a combination of 1 mg/kg finerenone and 3 mg/kg SGLT2 inhibitor did not significantly modify urinary glucose and urinary potassium in comparison to the respective individual finerenone and SGLT2 inhibitor dosages, and only the combination with empagliflozin increased urinary volume vs the respective monotherapies
- Surprisingly, combination of finerenone with SGLT2 inhibition over-additively induced sodium excretion consistently in all three experiments:
  - This was in comparison to the calculated sum (set to 100%) of the respective individual finerenone and SGLT2 inhibitor groups
    - **finerenone + dapagliflozin: 133.9%**
    - **finerenone + canagliflozin: 139.6%**
    - **finerenone + empagliflozin: 171.4%**

Figure 2. dapagliflozin + finerenone

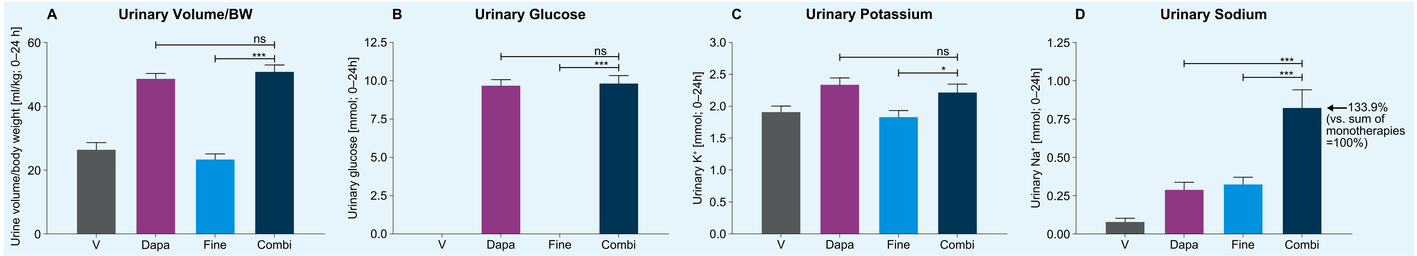


Figure 3. canagliflozin + finerenone

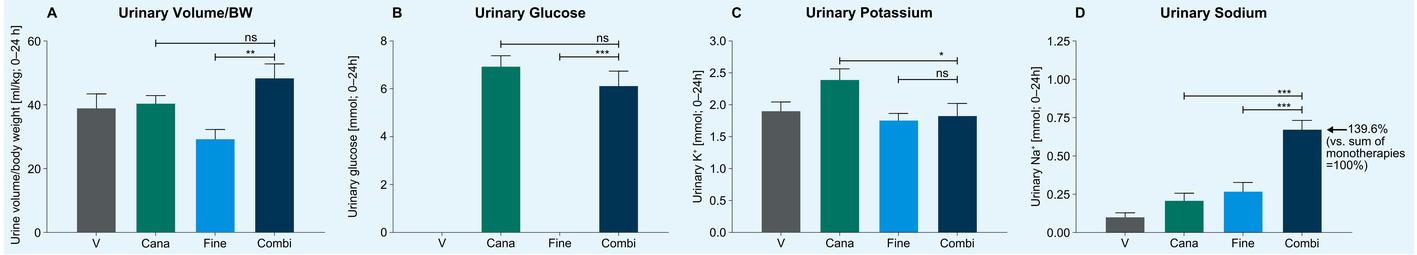
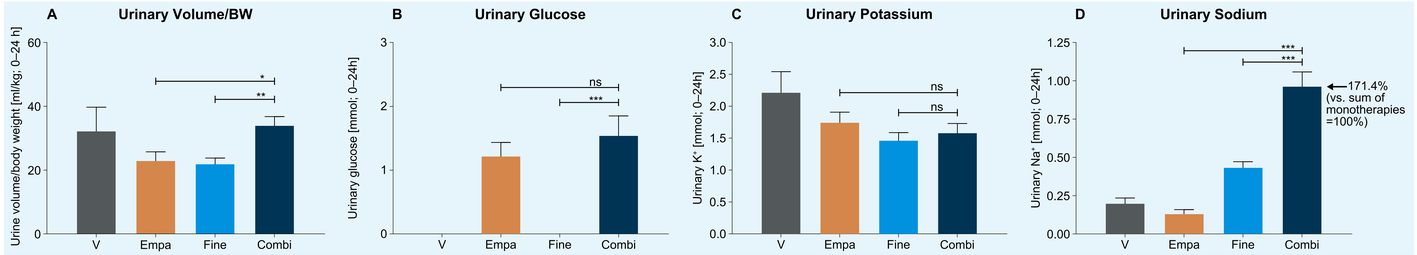


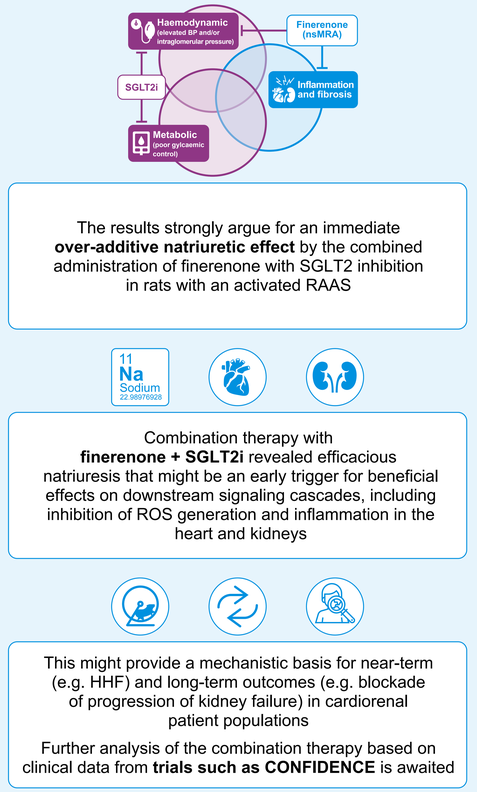
Figure 4. empagliflozin + finerenone



BW, body weight; ns, not significant

Summary

Figure 5. Summary



HHF, hospitalisation for heart failure; ROS, reactive oxygen species

Conclusions

- Combination of MR antagonism by finerenone and SGLT2 inhibition revealed an acute over-additive natriuresis in a rat diuresis model
- This might provide an additional mechanistic basis for near-term (e.g. hospitalisation for heart failure) and long-term outcomes (e.g. blockade of the progression of kidney failure) in cardiorenal patient populations