Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF)

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Aims

Inhibition of sodium–glucose co-transporter 2 (SGLT2) reduces the risk of death and heart failure (HF) admissions in patients with chronic HF. However, safety and clinical efficacy of SGLT2 inhibitors in patients with acute decompensated HF are unknown.

Methods and results

In this randomized, placebo-controlled, double-blind, parallel group, multicentre pilot study, we randomized 80 acute HF patients with and without diabetes to either empagliflozin 10 mg/day or placebo for 30 days. The primary outcomes were change in visual analogue scale (VAS) dyspnoea score, diuretic response (weight change per 40 mg furosemide), change in N-terminal pro brain natriuretic peptide (NT-proBNP), and length of stay. Secondary outcomes included safety and clinical endpoints. Mean age was 76 years, 33% were female, 47% had de novo HF and median NT-proBNP was 5236 pg/mL. No difference was observed in VAS dyspnoea score, diuretic response, length of stay, or change in NT-proBNP between empagliflozin and placebo. Empagliflozin reduced a combined endpoint of in-hospital worsening HF, rehospitalization for HF or death at 60 days compared with placebo \(4 (10\%) \text{ vs. } 13 (33\%); P = 0.014\). Urinary output up until day 4 was significantly greater with empagliflozin vs. placebo \[\text{difference} 3449 (95\% \text{ confidence interval} 578–6321) \text{mL}; P < 0.01\]. Empagliflozin was safe, well tolerated, and had no adverse effects on blood pressure or renal function.

Conclusions

In patients with acute HF, treatment with empagliflozin had no effect on change in VAS dyspnoea, diuretic response, NT-proBNP, and length of hospital stay, but was safe, increased urinary output and reduced a combined endpoint of worsening HF, rehospitalization for HF or death at 60 days.

Keywords

Acute heart failure • Empagliflozin • Sodium–glucose co-transporter 2 • Hospital readmission • Dyspnoea • Diuresis • Renal function • Blood pressure

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Introduction

Multiple randomized clinical trials indicated that sodium–glucose co-transporter 2 (SGLT2) inhibitors reduce the risk for heart failure (HF) hospitalization in patients with type 2 diabetes.1–4 Although only a minority of patients included in these trials had pre-existing HF, the results showed the potential to also improve outcomes in patients with established HF.5–8 Beneficial effects in patients with established chronic HF were shown in a recent trial where the SGLT2 inhibitor dapagliflozin reduced the risk of death and HF admissions in patients with established chronic HF with a reduced ejection fraction (HFrEF), either with or without diabetes.9 These beneficial effects are at least partly explained by the diuretic/natriuretic effects of SGLT2 inhibitors, although other mechanisms such as direct cardiometabolic and renal enhancing effects have been proposed as well.10–12

Acute (decompensated) HF is one of the leading causes of hospital admissions worldwide with a post-discharge mortality and rehospitalization risk as high as 20–30% within the first 3 to 6 months. Unlike chronic HF, there is no established therapy available that improves clinical outcome in acute HF.13 Despite treatment with loop diuretics, many are discharged with residual congestion, which is related to an even higher risk of early rehospitalization and death.14 Renal failure and worsening renal function in patients with acute HF are common and related to an impaired outcome when diuretic response is poor.15,16 Based on both the promising pharmacological profile of the SGLT2 inhibitor empagliflozin and the demonstrated benefits on HF and renal outcomes, we hypothesized that empagliflozin exerts positive effects in patients admitted with acute HF, with or without diabetes mellitus.

Methods

Study design

EMPA-RESPONSE-AHF was an investigator-initiated randomized, placebo-controlled, double-blind, parallel group, multicentre pilot study in subjects admitted for acute (decompensated) HF. Patients with and without type 2 diabetes mellitus could participate. A total of 80 eligible subjects were randomized in a 1:1 ratio to receive either empagliflozin 10 mg/day or matched placebo. A blocked randomization was used (size 4), with stratification by study site. Investigators used a web-based randomization system to determine treatment assignment. The trial was executed in five cardiology centres in the Netherlands (online supplementary Appendix S1). The trial was approved by the ethics committee at each study centre and the study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. All participating patients provided written informed consent. This trial was registered with ClinicalTrials.gov, number NCT03200860.

Patient population

Eligible patients were male or female aged >18 years who were hospitalized for acute HF, defined as all of the following; (i) dyspnoea at rest or with minimal exertion, (ii) signs of congestion, such as oedema, rales, and/or congestion on chest radiograph, (iii) brain natriuretic peptide (BNP) ≥350 pg/mL or N-terminal pro BNP (NT-proBNP) ≥1400 pg/mL (for patients with atrial fibrillation; BNP ≥500 pg/mL or NT-proBNP ≥2000 pg/mL), and (iv) treated with loop diuretics at screening. Patients needed to have an estimated glomerular filtration rate (based on the Chronic Kidney Disease Epidemiology Collaboration formula17) ≥30 mL/min/1.73 m² between presentation and randomization. Exclusion criteria were: (i) type 1 diabetes mellitus, (ii) dyspnoea primarily due to non-cardiac causes, (iii) cardiogenic shock, (iv) acute coronary syndrome within 30 days prior to randomization, (v) planned or recent percutaneous or surgical coronary intervention within 30 days prior to randomization, (vi) signs of ketoacidosis and/or hyperosmolar hyperglycaemic syndrome (pH < 7.30 and glucose > 15 mmol/L and HCO₃ > 18 mmol/L), (vii) pregnant or nursing (lactating) women, (viii) current participation in any interventional study, (ix) inability to follow instructions or comply with follow-up procedures, (x) any other medical conditions that would put the patient at risk or influence study results in the investigator’s opinion, or that the investigator deemed unsuitable for the study.

Patients were randomized within 24 h of presentation to the hospital. After informed consent, patients were randomly assigned to one of the treatment groups and received the assigned (blinded) therapy after baseline assessment, which included assessment of HF signs and symptoms, visual analogue scale (VAS) dyspnoea score, vital signs, demographics, and urine and plasma sampling. During 4 days following randomization, patients were evaluated daily per protocol and included evaluation of HF signs and symptoms, vital signs, weight, laboratory assessments (including NT-proBNP at day 4), plasma and urine sampling and assessment of adverse events (AE). Three of four primary outcome measures (VAS dyspnoea score, NT-proBNP, diuretic response) were assessed at day 4. If a patient was discharged before day 4, assessment took place outside the hospital at day 4. Randomized treatment was continued through day 30, when a study visit was carried out and assessments were repeated. Patients were followed until day 60 for AE, and the study was concluded by a telephone call at day 60 to assess AE and vital status.

Study endpoints

The primary endpoints of this study were (i) change in dyspnoea VAS from baseline to day 4, (ii) diuretic response (defined as Δ weight kg/[(total intravenous dose)/40 mg] + [(total oral dose)/80 mg]) furosemide or equivalent loop diuretic dose) through day 4,18 (iii) length of initial hospital stay; and (iv) percentage change in NT-proBNP from baseline to day 4. Secondary endpoints of the study included worsening HF (defined as worsening signs and/or symptoms of HF that require an intensification of intravenous therapy for HF or mechanical ventilatory, renal or circulatory support), all-cause death and/or HF readmission through day 30 and through day 60 as part of AE assessment. Safety endpoints included (i) AE (general), (ii) AE that lead to treatment discontinuation, (iii) serious AE (which could include a secondary endpoint), (iv) AE of special interest (AESI), including hepatic injury, worsening renal function, metabolic acidosis, ketoacidosis and diabetic ketoacidosis (online supplementary Methods S1).

Randomized treatment was required to be discontinued per protocol if systolic blood pressure dropped below 90 mmHg or decreased below 100 mmHg with signs/symptoms of hypotension, or signs of ketoacidosis and/or hyperosmolar hyperglycaemic syndrome, or...
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any increase in serum creatinine >50%. Treating physicians were encouraged to initiate randomized treatment after resolution of the above mentioned criteria.

Statistical analysis

Normally distributed continuous variables are presented as mean ± standard deviation (SD), non-normally distributed variables as median and 25th–75th percentile. Categorical variables are presented as numbers (percentage).

Power calculation was based on capturing the primary outcome measures in the placebo group with a degree of certainty. With 40 patients in the control group, a given mean continuous response can be estimated within ±0.2 SD with 80% confidence intervals (CI). We estimated the following mean responses for the primary outcome measures (in the placebo group):

1. Change in VAS dyspnoea score: 1756 ± 2353 mm x h at day 4.
2. Diuretic response [of 0.56 ± 0.78 kg/40 mg furosemide (or equivalent)] at day 4.
3. Length of stay 9.6 to 10.5 days (±9.1).
4. Percentage change in NT-proBNP 24 (−1.0–88.7)% (SD 67%) at day 4.

Consequently, 40 patients per group would provide approximately 80% power to detect standardized mean treatment differences of approximately 0.48 SDs at the two-sided 20% significance level for this pilot study. The difference in change in dyspnoea VAS from baseline to day 4 was assessed by comparing the area under the curve (AUC) of change in VAS dyspnoea score by Student’s t-test. To do so, individual changes in VAS score were visualized (virtually) as a curve where the x-axis shows study baseline to day 4, and y-axis shows VAS score. Using this approach, AUC for each study day (trapezoids) can be calculated, and added together, resulting in an overall VAS AUC score (mm x h) that can be compared across treatment groups.9 Difference in diuretic response and percentage change in NT-proBNP at day 4 was assessed by Student’s t-test. Difference in length of stay was assessed by Wilcoxon rank-sum test. All analyses were carried out in the full analysis set based on the intention-to-treat principle where all randomized patients were analysed. As this was an exploratory study with limited power, all four individual primary endpoints were tested separately, with no formal correction for multiplicity. Only as a sensitivity analysis, if at least two out of four primary endpoints showed significant difference in the same direction (favouring either investigational drug or placebo), a Bonferroni correction would be applied (P < 0.05).

As an exploratory analysis, and for graphical presentation, individual responses to the above-mentioned endpoints were standardized. This was done by dividing the difference from the overall mean (or log transformed mean if non-normally distributed) of each endpoint by the overall SD of that variable, which generates a z-score. The treatment effect can then be measured by the mean difference of standardized z-scores, which was visually presented on a forest plot by mean ± 80% CI (given P < 0.2).

Then, all four standardized scores for each individual endpoints were averaged, and mean treatment difference and associated 95% CI for this overall treatment effect visually presented. Statistical analysis for the treatment difference was carried out by Student’s t-test. Two-tailed P-values <0.2 were considered statistically significant for the (exploratory) primary endpoints with 80% CI. Statistical analyses were performed using STATA SE 12.0 (Stata Corp., College Station, TX, USA).

Results

Patients

From December 2017 through July 2019 patients were enrolled at five centres in the Netherlands. The CONSORT diagram of this study is presented in Figure 1. A total of 80 patients were randomized (41 to empagliflozin and 39 to placebo). One patient randomized to empagliflozin withdrew informed consent, leaving 40 empagliflozin and 39 placebo patients for our analyses. Table 1 shows the baseline characteristics in the two groups. Mean age of the patients was 76 years, 33% were female, 47% had de novo acute HF, mean left ventricular ejection fraction was 36%, and median NT-proBNP was 5236 pg/mL. One third of patients had type 2 diabetes mellitus. Groups were reasonably well-balanced, although patients in the empagliflozin group were older, more often female and had lower NT-proBNP levels.

Primary outcome

Results of the primary endpoints are presented in Figure 2. The AUC of the change in dyspnoea VAS over the first 4 days was 1264 ± 1211 mm x h) in the empagliflozin group vs. 1650 ± 1240 mm x h in the placebo group (P = 0.18). Diuretic response through day 4 was −0.35 ± 0.44 kg/40 mg furosemide equivalents in the empagliflozin group vs. −0.12 ± 1.52 kg/40 mg furosemide equivalents in the placebo group (P = 0.37). Percentage change in NT-proBNP through day 4 was −46 ± 32% in the empagliflozin group vs. −42 ± 31% in the placebo group (P = 0.63).

Length of hospital stay was 8 (6–10) days in the empagliflozin group vs. 8 (6–9) days in the placebo group (P = 0.58). There were no differences in the primary outcome measures in subgroups of de novo vs. decompensated HF.

A summary of the four endpoints, standardized by z-scores, are presented in Figure 3. The overall combined z-score was not significantly different between empagliflozin and placebo (mean difference −0.019, 95% CI −0.306 to 0.269; P = 0.90).

Secondary and exploratory analyses

Figure 4 shows the incidence of in-hospital worsening HF, death, and/or HF hospital readmission. A combined endpoint of in-hospital worsening HF, rehospitalization for HF or all-cause death at 60 days occurred in 4 patients (10%) in the empagliflozin group vs. 13 patients (33%) in the placebo group (P = 0.014). Online supplementary Table S1 provides the data for the individual components. There was a greater, but not statistically different, drop in diastolic blood pressure in the empagliflozin treated patients, similar reductions in systolic blood pressure and heart rate, and no differences in renal function were demonstrated up until day 4 (online supplementary Figure S1). Patients randomized to empagliflozin more often had a diuretic response better than...
0.4 kg decrease/40 mg furosemide equivalent compared with placebo (42% vs. 24%, \( P = 0.14 \)).

In a subset of patients, urinary output and net fluid loss were available. The effects of empagliflozin on urinary output and net fluid balance are presented in Figure 5. At day 1, there was a significantly greater urine output with empagliflozin (3442 ± 1922 mL) compared with placebo (2400 ± 993 mL) (\( P = 0.013 \); \( n = 58 \)). Net fluid loss at day 1 was also greater with empagliflozin (−2163 ± 1896 mL) compared with placebo (−1007 ± 1049 mL) (\( P = 0.009 \); \( n = 53 \)). After 4 days, the difference in cumulative urine output (3449, 95% CI 578–6321 mL; \( n = 28 \)) was significantly greater (\( P = 0.02 \)), whereas net fluid loss with empagliflozin was greater (2701, 95% CI −586 to 8988 mL; \( n = 25 \); \( P = 0.10 \)). Weight change after 4 days was −2.83 ± 3.15 kg in the empagliflozin group vs. −2.30 ± 3.26 kg in the placebo group (\( P = 0.48 \)). Median loop diuretic dose (re-calculated to furosemide) through day 4 was 320 (194–466) mg furosemide in the empagliflozin group and 300 (200–500) mg furosemide in the placebo group (\( P = 0.94 \)).

Safety

Safety data are presented in Table 2. The incidence rates of AE were similar in subjects treated with placebo or empagliflozin. Patients randomized to empagliflozin had significantly lower number of cardiovascular AE compared with placebo (9 vs. 17 events, \( P = 0.046 \)). This was mostly due to more frequent worsening HF events in the placebo group. We did not find an excess in urinary tract infections or other adverse effects with the use of empagliflozin.

There were 8 serious adverse events in the empagliflozin group vs. 11 in the placebo group (\( P = 0.54 \)). The causes of these events are listed in online supplementary Table S2. Overall seven patients in the empagliflozin group and five patients in the placebo group discontinued study medication due to AE (\( P = 0.36 \)) (online supplementary Table S3). There was no difference in the occurrence of AESI. Four patients (10%) in the empagliflozin and three patients (8%) in the placebo group developed a worsening renal function AESI (\( P = 0.74 \)), while one patient with type 2 diabetes due to weight loss.
## Table 1  Baseline characteristics

| Variable                              | Randomized treatment | Placebo | P-value |
|---------------------------------------|----------------------|---------|---------|
|                                      | Empagliflozin        | Placebo |         |
| Patients (n)                          | 40                   | 39      | 0.14    |
| Age (years)                           | 79 (73–83)           | 73 (61–83) | 0.17    |
| Female sex, n (%)                     | 16 (40)              | 10 (26) | 0.15    |
| Caucasian race (%)                    | 100                  | 95      | 0.42    |
| Body weight at baseline (kg)          | 87 ± 23              | 83 ± 20 | 0.25    |
| SBP (mmHg)                            | 127 ± 22             | 121 ± 25| 0.27    |
| DBP (mmHg)                            | 76 ± 15              | 72 ± 15 | 0.50    |
| HR (bpm)                              | 83 ± 19              | 80 ± 23 | 0.60    |
| Respiratory rate (breaths/min)        | 19 ± 4               | 20 ± 5  | 0.90    |
| NYHA class III/IV (%)                 | 92                   | 97      | 0.57    |
| LVEF if known (%) (n = 46)            | 36 ± 17              | 37 ± 14 | 0.87    |
| De novo acute HF (%)                  | 48                   | 46      | 0.89    |
| Ischaemic aetiology (%)               | 28                   | 29      | 0.012   |
| Medical history (%)                   |                      |         |         |
| Myocardial infarction                 | 30                   | 38      | 0.43    |
| Hypertension                          | 68                   | 56      | 0.31    |
| Atrial fibrillation/flutter           | 78                   | 64      | 0.19    |
| Diabetes mellitus type 2              | 38                   | 28      | 0.38    |
| Cerebrovascular accident              | 5                    | 5       | 0.98    |
| COPD                                  | 28                   | 26      | 0.85    |
| Cancer                                | 38                   | 13      | 0.012   |
| Medical therapy (%)                   |                      |         |         |
| ACEi                                  | 40                   | 47      | 0.51    |
| ARB                                   | 5                    | 3       | 0.45    |
| ARNI                                  | 5                    | 3       | 0.52    |
| Beta-blocker                          | 70                   | 66      | 0.69    |
| MRA                                   | 48                   | 45      | 0.81    |
| Loop diuretic                         | 100                  | 100     | NA      |
| Intravenous vasodilator               | 10                   | 3       | 0.36    |
| ICD                                   | 8                    | 23      | 0.054   |
| CRT                                   | 15                   | 13      | 0.78    |
| Laboratory at baseline                |                      |         |         |
| NT-proBNP (pg/mL)                     | 4406 (2873–6979)     | 6168 (3180–10,489) | 0.14   |
| Serum creatinine (μmol/L)             | 114 ± 34             | 116 ± 33| 0.72    |
| eGFR (mL/min/1.73 m²)                 | 55 ± 18              | 55 ± 18 | 0.97    |
| Sodium (mmol/L)                       | 135 ± 17             | 135 ± 5 | 0.99    |

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NA, not applicable; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.

in the placebo group experienced diabetic ketoacidosis (online supplementary Table S4). There was no sign that empagliflozin was associated with more renal events as the renal/urinary AE rate was similar, and the occurrence of worsening renal function or acute kidney injury was also not different between treatment groups. Online supplementary Table S5 lists all individual AEs.

### Discussion

In this randomized, double-blind, placebo-controlled, multicentre pilot study on the safety and efficacy of empagliflozin in patients with acute (decompensated) HF, change in VAS dyspnoea, reduction in NT-proBNP, diuretic response (weight loss per 40 mg furosemide) and length of hospital stay were similar with empagliflozin and placebo. Empagliflozin increased cumulative urinary volume and net fluid balance in a subset of patients. Importantly, empagliflozin appeared to be safe and well tolerated, without major effects on heart rate and blood pressure. Finally, we observed significantly fewer deaths, in-hospital worsening of HF and/or HF readmissions through day 60.

As far as we know, this is the first randomized, double-blind, placebo-controlled trial on the effects of a SGLT2 inhibitor in patients with acute HF. SGLT2 inhibitors were originally designed as glucose-lowering agents for glycaemic control. In four large
randomized controlled trials in patients with diabetes, SGLT2 inhibitors consistently reduced cardiovascular events, and HF hospitalizations in particular. These data prompted the design of large phase III clinical trials on the effects of SGLT2 inhibitors in patients with established chronic HF, irrespective of whether they had diabetes or not. Recently, main results of the first trial, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF), were presented and published. In 4474 patients with HFrEF with and without diabetes, dapagliflozin reduced the risk of a composite endpoint of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or cardiovascular death. These effects were accompanied by an improvement of quality of life. These beneficial effects of dapagliflozin in patients with HFrEF on quality of life were recently confirmed in a smaller study. Until now, no data on the effects of SGLT2 inhibitors in patients admitted with acute HF, irrespective of left ventricular ejection fraction and diabetes status, have been available.

In the present study, we could not show any significant differences for the primary endpoints between empagliflozin and placebo. First, despite both a significantly greater urinary output and a more negative net fluid balance, there was no reduction in dyspnoea, as recorded by a VAS. Second, we did not observe an improvement in diuretic response, defined as weight change per 40 mg of furosemide (or equivalent dose of another loop diuretic). This endpoint was chosen to correct for a decreased use of loop diuretic when symptoms had recovered more quickly in the empagliflozin treated patients. However, symptoms in hospital did not recover more quickly and diuretic use during the first 4 days were similar in both groups. Thirdly, although we observed an expected large drop in NT-proBNP in the first days of hospital admission in all patients, we did not demonstrate a greater drop in patients treated with empagliflozin. These findings are similar to a recent study with dapagliflozin in patients with chronic HFrEF. Finally, length of hospital stay was not shortened by empagliflozin.

**Figure 2** Primary endpoints. (A) Change in visual analogue scale (VAS) dyspnoea. (B) Diuretic response. (C) Percentage change in N-terminal pro brain natriuretic peptide (NT-proBNP). (D) Length of stay. Error bars represent 80% confidence intervals for (B) and (C). AUC, area under the curve; SD, standard deviation.
probably since it may be determined by multiple factors other than those specifically related to improvement in HF, particularly in an elderly, fragile, high-risk patient cohort such as included in this study. We observed a significant reduction of a combined endpoint of in-hospital worsening HF, death and/or hospital readmission through day 60. However, these data should be interpreted with caution for two major reasons. Firstly, this study was not powered and not designed to show an effect on clinical endpoints, and the number of events is very low. Secondly, there was no significant reduction in the pre-defined secondary endpoint of death and/or hospital readmission within 30 days. Nevertheless, the reduction in clinical endpoints is consistent with previous morbidity and mortality benefits for SGLT2 inhibitors in diabetes and in line with results of the DAPA-HF trial in patients with chronic HFrEF. If anything, our results suggest this novel HF treatment can safely be initiated in a high-risk population of acute HF patients and should pave the way for larger studies.

Although loop diuretics and nitrates (in selected patients) remain the mainstay of the treatment of acute HF, several drugs have been...

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investigated but failed to improve clinical outcomes in patients with acute HF. Most of these investigational drugs had significant effects on blood pressure and/or renal function.23–25 However, in our small pilot study, we did not find any clinically relevant effect on blood pressure, heart rate, or renal function. In addition, empagliflozin drug was safe and well tolerated with less AE than in placebo treated patients. Specifically, empagliflozin therapy was not associated with more frequent worsening of renal function or renal AE.

Finally, we found a remarkable effect on urinary output and net fluid balance. These findings strongly support an incremental diuretic effect with empagliflozin treatment, which has not been previously shown in patients with HF. The disconnect between this increase in diuresis, without an effect on symptoms or markers of volume overload is probably related to the limited correlation between these variables in clinical practice. Whether the beneficial effects of SGLT2 inhibitors on clinical outcomes in patients with HFrEF are related to their diuretic effect or whether they are mediated via other pathways where SGLT2 inhibitors exert their actions remains to be established.

Limitations

This study has several limitations. First and foremost, this study is limited by the number of patients and should be considered as a pilot study. The results of this study should therefore be interpreted with caution. Secondly, we screened many more patients than were included in the study due to different reasons. Although for this reason the generalizability of the finding to the average acute HF patient can be questioned, the characteristics of our patients included suggest it represents the phenotype of acute HF patients currently admitted. Thirdly, the number of missing urinary collections and fluid intake limits the interpretability of the data on urinary output and net fluid loss, although an effect was already observed after 24 h. Finally, there was no standardized protocol for in-hospital treatment of acute HF and no protocol for diuretic therapy, which means individual differences in the treatment of these patients may have impacted the results.

Conclusion

In this randomized, double-blind, placebo-controlled pilot study in patients with acute (decompensated) HF, empagliflozin was safe and well tolerated, but did not improve dyspnea, NT-proBNP, diuretic response and length of hospital stay. However, empagliflozin was associated with greater urinary output and a reduction in a combined endpoint of worsening HF, rehospitalization for HF or death at 60 days. Larger randomized clinical trials with SGLT2 inhibitors are greatly needed to further study the possible beneficial role of SGLT2 inhibitors in patients with acute HF.
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Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. EMPA-RESPONSE-AHF site list and investigators.

Methods S1. Adverse events of special interest definitions.

Figure S1. Changes in vitals and serum creatinine.

Table S1. Cardiovascular outcome.

Table S2. Serious adverse events.

Table S3. Adverse events leading to treatment discontinuation.

Table S4. Adverse events of special interest.

Table S5. List of all adverse events according to treatment.

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