Empagliflozin reduces markers of acute kidney injury in patients with acute decompensated heart failure

Kirsten Thiele1, Matthias Rau1, Niels-Ulrik Korbinian Hartmann1, Marcus Möller2, Julia Möllmann1, Joachim Jankowski3,4, András P. Keszei5, Michael Böhm6, Jürgen Floege2, Nikolaus Marx1* and Michael Lehrke1

1Department of Internal Medicine I, University Hospital Aachen, RWTH Aachen University, Aachen, Germany; 2Department of Internal Medicine II, University Hospital Aachen, RWTH Aachen University, Aachen, Germany; 3Institute for Molecular Cardiovascular Research, University Hospital Aachen, RWTH Aachen University, Aachen, Germany; 4Department of Pathology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre, Maastricht, The Netherlands; 5Center for Translational & Clinical Research Aachen (CTC-A), RWTH Aachen University, Aachen, Germany; and 6Department of Internal Medicine III, University Hospital Saarland, Saarland University, Homburg, Saar, Germany

Abstract

Aims In this prospective, placebo-controlled, double-blind, exploratory study, we examined early and more delayed effects of empagliflozin treatment on haemodynamic parameters (primary endpoint: cardiac output) and kidney function including parameters of acute kidney injury (AKI) in patients with acute decompensated heart failure (HF).

Methods and results Patients with acute decompensated HF with or without diabetes were randomized to empagliflozin 10 mg or placebo for 30 days. Haemodynamic, laboratory, and urinary parameters were assessed after 6 h, 1 day, 3 days, 7 days, and 30 days of treatment. Median time between hospital admission and randomization was 72 h. Baseline characteristics were not different in the empagliflozin (n = 10) and placebo (n = 9) groups. Empagliflozin led to a significant increase in urinary glucose excretion throughout the study (baseline: 37 ± 15 mg/24 h; Day 1: 14 565 ± 8663 mg/24 h; P = 0.001).

Empagliflozin did not affect the primary endpoint of cardiac index or on systemic vascular resistance index at any time point. However, empagliflozin significantly reduced parameters of AKI (urinary TIMP-2 and IGFBP7 by NephroCheck® as indicators of tubular kidney damage), which became significant after 3 days of treatment [placebo: 1.1 ± 1.1 (ng/mL)^2/1000; empagliflozin: 0.3 ± 0.2 (ng/mL)^2/1000; P = 0.02] and remained significant at the 7 day time point [placebo: 2.5 ± 3.8 (ng/mL)^2/1000; empagliflozin: 0.3 ± 0.2 (ng/mL)^2/1000; P = 0.003].

Conclusions In this study, empagliflozin treatment did not affect haemodynamic parameters but significantly reduced markers of tubular injury in patients with acute decompensated HF.

Keywords SGLT2 inhibitors; Empagliflozin; Acute decompensated heart failure; Acute kidney injury; Haemodynamic parameters

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*Correspondence to: Nikolaus Marx, MD, FESC, FAHA, Department of Internal Medicine I, University Hospital Aachen, RWTH Aachen University, Pauwelsstraße 30, D-52074 Aachen, Germany. Tel: +49 241 80-89300; Fax: +49 241 80-82545. Email: nmarx@ukaachen.de

Kirsten Thiele and Matthias Rau have equal contribution.

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Background

Sodium-glucose cotransporter-2 (SGLT2) inhibitors reduce heart failure (HF) hospitalization or cardiovascular (CV) death in patients with HF [HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF), respectively], type 2 diabetes mellitus (T2D), and/or chronic kidney disease (CKD). Inhibition of the SGLT2 transporter, which is expressed in the proximal tubule of the kidney, induces glucosuria and osmotic diuresis. Recent evidence suggests that SGLT2 inhibition also improves outcome in patients with acute decompensated HF—a situation often combined with impaired kidney function.

Aims

In this prospective, placebo-controlled, double-blind, exploratory pilot study, we randomized patients with acute...
dекомпенсированной КФС с и без Т2Д на эмпаглифлоzin или плацебо. Нами исследованы гемодинамические и почечные показатели включая маркеры почечного повреждения, свидетельствующие о хроническом почечном поражении (АКИ) в разные точки времени.

**Methods**

Это исследование было прервано из-за пандемии COVID-19. Конечные точки были проанализированы в наборе из 19 пациентов, принятых на исследование. В качестве основного показателя выбран объем крови (СО) как стабилизированный на протяжении времени. Рассчитывалось расстояние в 1 Л/мин в зависимости от структуры корреляции Бубенека-Туручони (Bubenek-Turconi correlation structure) во времени, с коэффициентом 0.5, стандартное отклонение, которое было рассмотрено: мощность 0.8, уровень значимости 0.05, автокорреляционный анализ для обнаружения различий в СО по сравнению с плацебо. Рассчитывалось базовое значение на протяжении лечения и группа диабета и различия во времени. Рассчитывалось общее количество пациентов 48. Базовые характеристики популяции представлены в таблице 1.

Таблица 1. Базовые характеристики населения

|               | Плацебо (N = 9) | Эмпаглифлоzin (N = 10) | P-значение |
|---------------|-----------------|------------------------|------------|
| Возраст, годы | 72.3 ± 9.9      | 71.8 ± 13.4            | 0.93       |
| Пол, %        | 3 (33.3)        | 6 (60)                 | 0.48       |
| Систолическое БП, ммРт.ст. | 126 ± 24 | 139 ± 23               | 0.19       |
| Диастолическое БП, ммРт.ст. | 67 ± 13  | 80 ± 24                | 0.46       |
| Скорость сердечного выброса, б.п.м. | 73 ± 10 | 75 ± 17                | 0.41       |
| LVEF, %       | 38 ± 11         | 34 ± 11                | 0.64       |
| 2-й диабет, % | 1 (11)          | 4 (40)                 | 0.36       |
| История сердечной недостаточности, % | 3 (33) | 5 (50)                 | 0.79       |
| Антитромбоциты | 5 (55.6)        | 3 (30)                 | 0.79       |
| Антитромбоагреганты | 6 (66.7) | 6 (60)                 | >0.999     |
| Диуретики     | 8 (88.9)        | 8 (80)                 | >0.999     |
| Кальций канал блокаторы | 3 (33.3) | 1 (10)                 | 0.66       |
| Бета-блокаторы | 8 (88.9)        | 8 (80)                 | >0.999     |
| RAAS ингибиторы | 7 (77.8) | 8 (80)                 | 0.66       |
| eGFR, ml/min/1.73 м² | 56 ± 16 | 63 ± 22               | 0.57       |
| NT-proBNP, пг/мл | 3996 ± 6293 | 3562 ± 2527           | 0.74       |

Примечание: Значения являются средними ± стандартное отклонение для нормально распределенных данных и медианы с интегралом квадратичного ранга для ненормально распределенных данных, или %; P-значения для непрерывных переменных рассчитывались с t-критерием; P-значения для категориальных переменных рассчитывались с помощью χ²-критерия; P-значения ≤ 0.05 идентифицировались как статистически значимые.

Сокращения: eGFR, оцененный глюмерулярный фильтрационный коэффициент; LVEF, коэффициент выброса; NT-proBNP, N-терминальный про-бради-наприурический пептид; RAAS, ренин-ангитенсин-альдостероновая система.
Table 2  Comparison of laboratory values, 24 h urine, haemodynamics, blood pressure, and echocardiography during the study

|                  | Baseline | 6 h         | Day 1          | Placebo | Empagliflozin | Placebo | Empagliflozin | P-value |
|------------------|----------|-------------|----------------|---------|---------------|---------|---------------|---------|
| Cardiac index (CI), L/min/m² | 2.4 ± 0.8| 3.0 ± 1.0   | 2.5 ± 1.0      | 3.0 ± 0.6| 0.70          | 2.6 ± 0.6| 3.1 ± 0.6     | 0.22    |
| Systemic vascular resistance index (SVRI), dyne*s*cm⁻⁵*m⁻² | 2588 ± 993| 2735 ± 780  | 2197 ± 651     | 2077 ± 716| 0.27          | 2806 ± 1084| 2221 ± 658    | 0.30    |
| Systolic blood pressure, mmHg | 123 ± 23 | 138 ± 19    | 114 ± 21       | 143 ± 23 | 0.04          | 126 ± 23| 126 ± 19      | 0.27    |
| Diastolic blood pressure, mmHg | 70 ± 11  | 74 ± 20     | 67 ± 11        | 77 ± 19 | 0.17          | 68 ± 13| 69 ± 7        | 1.00    |
| Heart rate, b.p.m. | 82 ± 16  | 77 ± 12     | 81 ± 21        | 68 ± 16 | 0.20          | 78 ± 17| 70 ± 13       | 0.36    |
| AKI risk markers (NephroCheck®), (ng/mL) | 0.6 ± 0.7| 0.9 ± 1.1   | -              | -       | 0.36          | 0.5 ± 1.1| 0.6 ± 0.6     | 0.07    |
| Oxygen saturation, % | 94.2 ± 2.6| 95 ± 1.7   | 94 ± 3.1       | 95 ± 1.6| 0.26          | 94 ± 3.4| 95 ± 1.5      | 0.04    |
| 24 h glucose excretion, mg/24 h | 1750 ± 1278| 1215 ± 640  | -              | -       | -             | 2037 ± 1386| 2794 ± 2223   | 0.27    |
| Cumulative doses of diuretics, mg/day furosemide equivalent | 56 ± 16  | 60 ± 20     | 54 ± 19        | 55 ± 19 | 0.50          | 55 ± 18| 52 ± 17       | 0.17    |
| eGFR, ml/min/1.73 m² | 100 ± 16 | 109 ± 26    | 117 ± 23       | 146 ± 53| 0.28          | 102 ± 11| 103 ± 33      | 0.26    |
| NT-proBNP, pg/mL | 3435 ± 5256| 3404 ± 3031| 3398 ± 4578    | 3703 ± 3454| -             | 2635 ± 4062| 2754 ± 2574   | -       |
| Glucose, mg/dL | 58 ± 0.5 | 60 ± 0.6    | 58 ± 0.5       | 60 ± 0.5| 0.03          | 1.8 ± 0.8| 1.7 ± 0.4     | 0.53    |
| HbA1c, % | 10.5 ± 5.6| 11.4 ± 9.1  | 51.9 ± 39.6    | 32.0 ± 28.2| 0.11          | 14.8 ± 9.3| 12.0 ± 10.1   | 0.78    |
| Haemoglobin, g/dL | 12 ± 2.3 | 12 ± 2.6    | 12 ± 2.4       | 12 ± 2.7| 0.39          | 12 ± 2.3| 12 ± 2.6      | 0.55    |
| Erythropoetin, mU/mL | 39 ± 5.2 | 37 ± 7.7    | 37 ± 6.3       | 37 ± 10| 0.52          | 36 ± 8.7| 36 ± 7.6      | 0.77    |
| Aldosterone, pg/mL | 12 ± 2.4 | 12 ± 2.6    | 12 ± 2.4       | 12 ± 2.7| 0.39          | 12 ± 2.3| 12 ± 2.6      | 0.55    |
| 24 h sodium excretion, mmol/24 h | 1750 ± 1278| 1215 ± 640  | -              | -       | -             | 2037 ± 1386| 2794 ± 2223   | 0.27    |
| Cumulative doses of diuretics, mg/day furosemide equivalent | 56 ± 16  | 60 ± 20     | 54 ± 19        | 55 ± 19 | 0.50          | 55 ± 18| 52 ± 17       | 0.17    |
| eGFR, ml/min/1.73 m² | 100 ± 16 | 109 ± 26    | 117 ± 23       | 146 ± 53| 0.28          | 102 ± 11| 103 ± 33      | 0.26    |
| NT-proBNP, pg/mL | 3435 ± 5256| 3404 ± 3031| 3398 ± 4578    | 3703 ± 3454| -             | 2635 ± 4062| 2754 ± 2574   | -       |
| Glucose, mg/dL | 58 ± 0.5 | 60 ± 0.6    | 58 ± 0.5       | 60 ± 0.5| 0.03          | 1.8 ± 0.8| 1.7 ± 0.4     | 0.53    |
| HbA1c, % | 10.5 ± 5.6| 11.4 ± 9.1  | 51.9 ± 39.6    | 32.0 ± 28.2| 0.11          | 14.8 ± 9.3| 12.0 ± 10.1   | 0.78    |
| Haemoglobin, g/dL | 12 ± 2.3 | 12 ± 2.6    | 12 ± 2.4       | 12 ± 2.7| 0.39          | 12 ± 2.3| 12 ± 2.6      | 0.55    |
| Erythropoetin, mU/mL | 39 ± 5.2 | 37 ± 7.7    | 37 ± 6.3       | 37 ± 10| 0.52          | 36 ± 8.7| 36 ± 7.6      | 0.77    |
| Aldosterone, pg/mL | 12 ± 2.4 | 12 ± 2.6    | 12 ± 2.4       | 12 ± 2.7| 0.39          | 12 ± 2.3| 12 ± 2.6      | 0.55    |
| 24 h sodium excretion, mmol/24 h | 1750 ± 1278| 1215 ± 640  | -              | -       | -             | 2037 ± 1386| 2794 ± 2223   | 0.27    |

(Continues)
Results

Baseline characteristics

From June 2018 to May 2020, a total of 19 patients underwent randomization. The median time between hospital admission and randomization was 72 h. Baseline characteristics were not different between empagliflozin and placebo-treated patients. The mean age of study participants was 72.1 ± 11.7 years, 47% were male, with a mean left ventricular ejection fraction (LVEF) of 36%, a history of CV disease in 42%, and diabetes in 26%. Mean NT-proBNP was 3420 pg/mL, mean eGFR was 58 mL/min/1.73 m², and patients had a baseline blood pressure of 114/70 mmHg with an HR of 80/min. No difference in baseline medication was present between treatment groups including renin-angiotensin-aldosterone system (RAAS) inhibition, beta-blockers, and oral diuretics (Table 1).

Effect of empagliflozin on haemodynamic parameters

Cardiac output was not significantly different between empagliflozin and placebo-treated patients at any time point (Table 2). No treatment-dependent difference in SVRI, SVI, HR, and blood pressure was observed between both groups (Table 2).

Effect of empagliflozin on metabolic parameters and kidney function

As expected, empagliflozin treatment significantly increased urinary glucose excretion throughout the study period (from 37 ± 15 mg/24 h at baseline to 14 565 ± 8663 mg/24 h at Day 1 (P = 0.001) and 8890 ± 10 872 mg/24 h at Day 30 (P = 0.06) (Figure 1, Table 2). In parallel with glucosuria, 24 h urinary volume increased in empagliflozin-treated patients without reaching statistical significance, most likely due to the small sample size. No difference in serum blood glucose, diuretic requirement, urinary sodium excretion, or body weight was found between both groups throughout the study (Table 2).

Empagliflozin had no significant effect on eGFR in comparison with placebo at any time point while serum cystatin C was transiently increased after 6 h but not at later time points in patients receiving empagliflozin (Table 2). TIMP-2 and IGFBP7 (by NephroCheck™) were significantly reduced with empagliflozin treatment [from 0.9 ± 1.1 (ng/mL)^2/1000 at baseline to 0.3 ± 0.2 (ng/mL)^2/1000 at Day 3 (P = 0.02) and 0.3 ± 0.2 (ng/mL)^2/1000 at Day 7 (P = 0.003)] suggesting nephroprotective effects of empagliflozin (Figure 1, Table 2).
Discussion/conclusions

Our study in acute decompensated HF patients demonstrates a significant reduction of risk markers of AKI by empagliflozin suggesting that SGLT2 inhibitor treatment may prevent AKI in patients with acute decompensated HF. Acute decompensated HF frequently causes kidney impairment and treatment of decompensated HF may lead to AKI.4 SGLT2 inhibitors have been shown to reduce both cardiac (CV death or HF hospitalization) and kidney endpoints in chronic HF patients,5–7 but concerns have been raised that the agents could lead to AKI in patients with acute decompensated HF. Recent data from the EMPULSE trial, enrolling patients with acute decompensated HF on average within 3.4 days after hospital admission, did not show an increased risk for AKI in empagliflozin-treated patients. Our data, enrolling patients within the same period, extend these results by demonstrating that empagliflozin significantly decreases the urinary AKI risk markers TIMP-2 and IGFBP7, previously established as a sensitive tool to assess AKI risk before a decrease of kidney function becomes evident.8,9 Renoprotective effects of SGLT2 inhibitors have been attributed to kidney tubular-glomerular feedback with subsequent reduction of glomerular filtration pressure as the driving mechanism. In our study, this was evidenced by a transient elevation of serum cystatin C and a trend towards a lower eGFR with empagliflozin. Beyond tubuloglomerular feedback, other mechanisms such as reduced tubular energy consumption may also contribute to the nephroprotective effects of SGLT2 inhibitors.

Taken together, our data in patients with acute decompensated HF suggest that empagliflozin treatment does not affect haemodynamic parameters but significantly reduces markers of AKI.

This study has certain limitations. The main limitation is that the reduction of important validated markers of acute kidney damage is an exploratory finding in a limited number of patients and warrants confirmation in a larger study with changes in renal function defined as primary outcome. Still, the present study was randomized, blinded, and placebo-controlled, and changes in renal function assessed by laboratory measurement and AKI Risk Score measured by NephroCheck® were predefined exploratory endpoints. Additional studies using larger populations will be required to investigate these effects of SGLT2 inhibition on structural changes of the kidney.

Conflict of interest

K.T., M.R., N.U.K.H., M.M., J.M., and A.K. report no potential conflict of interest. J.J. has given lectures for Bayer and Fresenius Medica Care. In addition, he holds four patents in the topic of the manuscript and is inventor of an additional, already sold patent to Baxter. M.B. received speaker honoraria from Astra-Zeneca and Boehringer Ingelheim and was national coordinator of DAPA-HF and EMPEROR-Reduced. J.F. has received consultancy fees from AstraZeneca, Bayer, Boehringer, and Vifor and is a member of the data safety monitoring committee in NovoNordisk trials. N.M. has received support for clinical trial leadership from Boehringer Ingelheim and Novo Nordisk and served as a consultant to Boehringer Ingelheim, Merck, Novo Nordisk, and AstraZeneca. B.M.S. received grant support from Boehringer Ingelheim, Merck, and Novo Nordisk and served as a speaker for Boehringer Ingelheim, Merck, Novo Nordisk, Lilly, BMS, and Astra Zeneca. M.L. received grants and personal fees from Boehringer Ingelheim, MSD, and Novo Nordisk and personal fees from Amgen, Sanofi, AstraZeneca, Bayer, and Lilly.
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References

1. Bubenek-Turconi SI, Craciun M, Miclea I, Perel A. Noninvasive continuous cardiac output by the Nexfin before and after preload-modifying maneuvers: a comparison with intermittent thermodilution cardiac output. Anesth Analg. 2013; 117: 366–372.
2. Broch O, Renner J, Gruenewald M, Meybohm P, Schöttler J, Caliebe A, Steinfath M, Malbrain M, Bein B. A comparison of the Nexfin® and transcardiopulmonary thermodilution to estimate cardiac output during coronary artery surgery. Anaesthesia. 2012; 67: 377–383.
3. Nalesso F, Cattarin L, Gobbi L, Fragasso A, Garzotto F, Calo LA. Evaluating Nephrocheck® as a predictive tool for acute kidney injury. Int J Nephrol Renovasc Dis. 2020; 13: 85–96.
4. Filippatos G, Farmakis D, Parissis J. Renal dysfunction and heart failure: things are seldom what they seem. Eur Heart J. 2014; 35: 416–418.
5. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Bruckmann M, Jamal W, Kimura K, Schnee JM, Gonzalez Juanaet J, Kaul S, Brunner-la Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020; 383: 1413–1424.
6. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-la Rocca HP, Choi DJ, Chopra V, Chuquiure-Valenzuela E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juanaet J, Merkely B, Nicholls SJ, Perrone SV, Piña IL, Ponikowski P, Senni M, Sim D, Spinar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Carson P, Lam CSP, Marx N, Zeller C, Sattar N, Jamal W, Schmidt S, Schnee JM, Bruckmann M, Pocock S, Zannad F, Packer M. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021; 385: 1451–1461.
7. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Bélohlavek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Hjund PS, Bengtsson O, Sjöstrand M, Langkilde AM. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019; 381: 1995–2008.
8. Kashani K, Al-Khafaji A, Arilles T, Artigas A, Bagshaw SM, Bell M, Bihorac A, Birkhahn R, Cely CM, Chawla LS, Davison DL, Feldkamp T, Forni LG, Gong M, Gunnesson KJ, Haase M, Hackett J, Honore PM, Hoste EAJ, Joannes-Boyau O, Joannidis M, Kim P, Koyner JL, Laskowitz DT, Lissauer ME, Marx G, McCullough PA, Mullaney S, Ostermann M, Rimmelé T, Shapiro NI, Shaw AD, Shi J, Sprague AM, Vincent JL, Vinsonneau C, Wagner L, Walker MG, Wilkerson RG, Zacharowski K, Kellum JA. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care. 2013; 17: R25.
9. Bihorac A, Chawla LS, Shaw AD, Al-Khafaji A, Davison DL, DeMuth GE, Fitzgerald R, Gong MN, Graham DD, Gunnesson K, Keung M, Jortani S, Kleerup E, Koyner JL, Krell K, LeTourneau J, Lissauer M, Minser J, Nguyen HB, Ortega LM, Safe WH, Sellman R, Shi J, Straszek J, Szlaidos JE, Wilber ST, Walker MG, Wilson J, Wunderink R, Zimmermann J, Kellum JA. Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication. Am J Respir Crit Care Med. 2014; 189: 932–939.