Full Title: Effect of Empagliflozin on Kidney Biochemical and Imaging Outcomes in Patients with Type 2 Diabetes, or Prediabetes, and Heart Failure with Reduced Ejection Fraction (SUGAR-DM-HF)

Short title: Effect of empagliflozin on kidney perfusion in HFrEF

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Twitter handle: @MetaMedTeam; @UoGHeartFailure

Short tweet: Empagliflozin reduces kidney perfusion in patients with HFrEF

BACKGROUND

Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce risk of worsening kidney function in patients with heart failure and reduced ejection fraction (HFrEF).[1] Comparatively little is known about effects of these drugs on kidney perfusion in the setting of randomized controlled trials. We studied effects of these drugs using kidney magnetic resonance imaging (MRI).

METHODS

We conducted a randomized, double-blind, placebo-controlled trial investigating effects of empagliflozin in patients with NYHA functional class II to IV, left ventricular ejection fraction (LVEF) ≤40% and type 2 diabetes or prediabetes. Patients were randomized 1:1 to empagliflozin 10 milligrams daily or placebo. The study design, screening and consent process, ethical approvals, and main results are published.[2]

Prespecified outcomes included change from baseline to 36 weeks in kidney MRI biomarkers (kidney perfusion measured by both arterial spin labelling (ASL) and magnetic resonance renography (MRR), kidney pre-contrast longitudinal relaxation time (T1), kidney apparent extracellular volume (aECV) (post-contrast T1) and total kidney volume) and soluble biomarkers (eGFR CKD-EPI creatinine, urinary albumin creatinine ratio (ACR), urinary sodium concentration, fractional excretion of sodium (FENa), and urinary potassium concentration).

Integrated gadolinium contrast-enhanced cardio-kidney MRI (MAGNETOM Prisma 3T scanner, Siemens, Erlangen, Germany) was performed at baseline and week 36. Reproducibility kidney MRI analyses are published elsewhere.[3] Where both kidneys

could not be aligned within the same coronal oblique view, the right kidney was prioritized. For ASL, T1 and aECV, regions of interest (ROIs) were drawn manually around the whole kidney, cortex, and an area of user-defined representative cortex. For MRR and kidney volumes, ROIs were drawn around the whole kidney. Observers were blinded to subject ID, scan date, clinical data and randomization arm. The primary results analyses excluded patients in atrial fibrillation/flutter at week 36 to avoid cardiac image degradation.[2] For kidney analyses, we included patients in atrial fibrillation/flutter at week 36.

RESULTS

105 patients were randomized: mean age 68.7 [SD 11.1] years, 77 (73.3%) male, 82 (78.1%) diabetes and 23 (21.9%) prediabetes, mean LVEF 32.5% [9.8%], mean eGFR CKD-EPI creatinine 67.6 [22.1] mL/min/1.73 m^2, and median urinary ACR 11 (interquartile range 2-45) mg/g. Of 52 patients randomized to empagliflozin, 45 remained on randomized therapy and underwent baseline and 36-week MRI.[2] Of 53 patients randomized to placebo, 50 remained on randomized therapy and underwent baseline and 36-week MRI.

Compared with placebo, empagliflozin reduced right whole kidney perfusion (ASL) by 25 (95% CI, -47 to -4, *P*=0.021) mL/100mL/min (Figure 1), reduced right whole kidney aECV by 4.8 (-8.8 to -0.8; *P*=0.020) %, and reduced urinary sodium concentration by 14 (-25 to -3; *P*=0.012) mmol/L. Similar results were seen for right cortex, left whole kidney, left cortex kidney perfusion (ASL) and left whole kidney aECV. There were no between-group differences in MRR (although directionally concordant), kidney T1

(right whole kidney), total kidney volume, eGFR CKD-EPI creatinine, urinary ACR, FENa or urinary potassium concentration at 36 weeks.

Within each randomization group compared to baseline, for empagliflozin, ASL was unchanged: right whole kidney (p=0.55), left whole kidney (p=0.45), right cortex (p=0.69), left cortex (p=0.33). With placebo, ASL was unchanged in the right whole kidney (p=0.059), left whole kidney (p=0.07) and left cortex (p=0.14) but increased in the right cortex (p=0.038). In the empagliflozin group, right kidney (p=0.0094) and both kidney (p=0.013) MRR decreased but not left kidney MRR (p=0.058). In the placebo group, right kidney (p=0.24), left kidney (p=0.33) and both kidney (p=0.25) MRR was unchanged.

DISCUSSION

ASL was unchanged in the empagliflozin group. ASL of the right cortex increased in the placebo group, which is an unexpected, possibly chance finding. The placebo-corrected finding of ASL reduction with empagliflozin compared to placebo is hypothesis-generating. There were directionally concordant changes in kidney perfusion by MRR. These changes suggest possible protective effects against glomerular hyperfiltration with reduction in ASL as a surrogate of intraglomerular perfusion. Sustained reduction seen in kidney perfusion (ASL) over 36 weeks is consistent with trajectories of kidney function observed in SGLT2 inhibitor outcome trials in HFrEF, with eGFR in the SGLT2 inhibitor group initially lower than the placebo group until 76 weeks (EMPEROR-Reduced) and 86 weeks (DAPA-HF).[4,5] Empagliflozin reduced kidney aECV, which we speculate represents kidney ‘decongestion’ by reduction in renal interstitial fluid.

We know of few other trials examining effects of SGLT2 inhibition on kidney mechanisms in heart failure; these trials (NCT03027960, NCT03226457, NCT03198585,) had shorter follow-up duration of 14, 48 and 90 days respectively. To our knowledge, this is the first kidney MRI trial using SGLT2 inhibition in HFrEF. Other trials assess SGLT2 inhibition with kidney MRI, although are in patients without heart failure (NCT03093103, NCT04193566, ChiCTR2000037951).

CONCLUSIONS

Empagliflozin reduced kidney perfusion measured by ASL, with directionally concordant changes in MRR, and reduced aECV in patients with HFrEF and type 2 diabetes or prediabetes. Reduction in kidney perfusion and/or congestion may be mechanisms by which SGLT2 inhibitors affect kidney function in HFrEF.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT03485092.

Key Words: empagliflozin, SGLT2 inhibitors, heart failure, diabetes mellitus, prediabetes, mechanisms, clinical trial, MRI, hyperfiltration, randomized controlled trials, renal hemodynamics

Figure Legend

Figure 1. Change in Kidney Perfusion (ASL, MRR) and aECV from Baseline to Week 36. Data presented as mean and error bars represent 95% CIs. Treatment effect calculated using an analysis of covariance model adjusted for treatment group, age at baseline, diabetes status and baseline value. aECV indicates apparent extracellular

volume, ASL indicates arterial spin labelling, MRI indicates magnetic resonance imaging; and MRR, magnetic resonance renography.

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Disclosures

Dr Lee's employer, the University of Glasgow, has received grant support from Boehringer Ingelheim.

Dr Gillis reports personal fees from Napp, AstraZeneca and Vifor.

Dr Berry is employed by the University of Glasgow, which holds consultancy and research agreements with companies that have commercial interests in the diagnosis and treatment of ischemic heart disease, including Abbott Vascular, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, HeartFlow, Menarini Farmaceutica, Opsens, Philips, and Siemens Healthcare.

Dr Docherty's employer, the University of Glasgow, is paid by AstraZeneca for involvement in the DAPA-HF trial.

Dr Kuehn is an employee of Siemens Healthcare GmbH.

Dr Lang has received consultancy fees from AstraZeneca and Pharmacosmos and speaker's fees from Roche, Pfizer and Novartis. He receives grant support from Roche Diagnostics (paid to his employer, the University of Glasgow).

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Dr Jhund's employer, the University of Glasgow, is paid by AstraZeneca for involvement in the DAPA-HF and DELIVER trials. He has also received consulting, advisory board, and speaker's fees from Novartis and AstraZeneca, advisory board fees from Cytokinetics, and a grant from Boehringer Ingelheim.

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Dr Sattar has consulted for or received lecture fees from Afimmune, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceuticals, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, and Sanofi. He has received grant support from AstraZeneca, Boehringer Ingelheim, Novartis, and Roche Diagnostics through his institution, the University of Glasgow.

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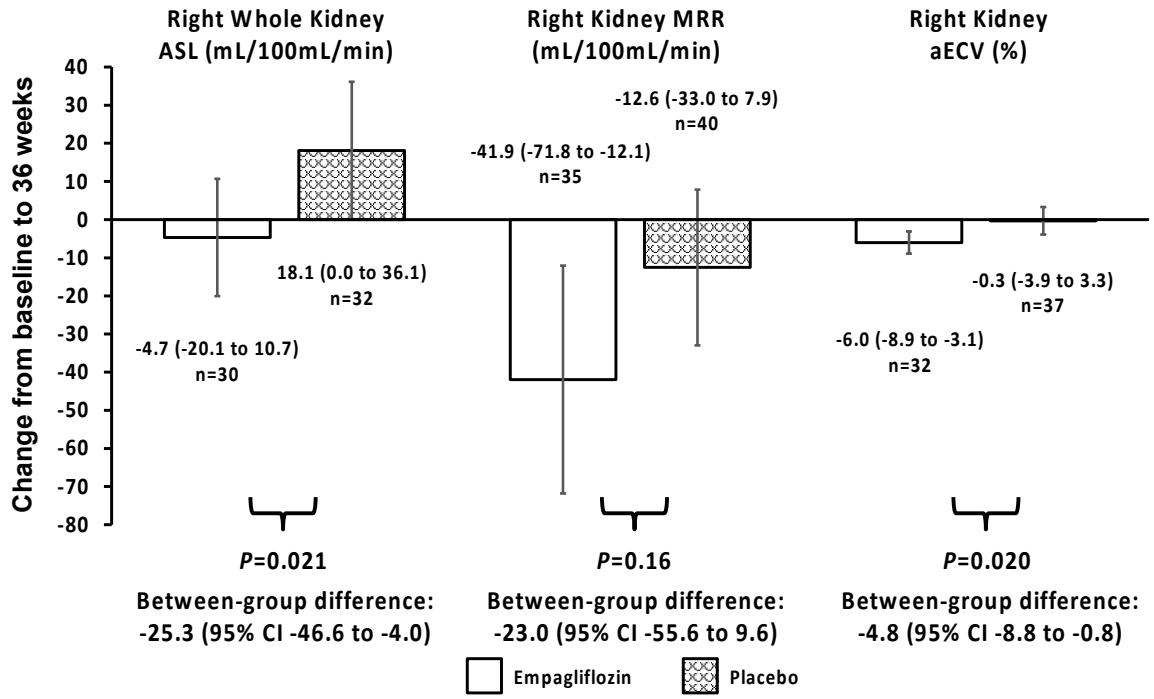

Figure 1.