Effects of Empagliflozin on Kidney and Cardiac Magnetic Resonance Imaging Measures in Patients With CKD: An EMPA-KIDNEY Mechanistic Substudy

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The EMPA-KIDNEY trial demonstrated that, compared with placebo, empagliflozin 10 mg once daily reduced the risk of its primary composite outcome of kidney disease progression or cardiovascular death by 28% (95% CI, 18%-36%) in 6,609 patients with chronic kidney disease (CKD) at risk of progression.[1,2] The primary aim of this embedded mechanistic substudy was to use multiparametric magnetic resonance imaging (MRI) to assess the effects of empagliflozin versus placebo on an MRI-based measure indicative of kidney fibrosis and inflammation (cortical longitudinal relaxation time [T_1] mapping) at around 18 months after randomization. The effects of empagliflozin on other kidney and cardiac MRI measures were also assessed (Table S1).

A total of 6,609 adults with a race-adjusted estimated glomerular filtration rate (eGFR) ≥20 to <45 mL/min/1.73 m^2, or an eGFR ≥45 to <90 mL/min/1.73 m^2 with a urinary albumin-creatinine ratio (UACR) ≥200 mg/g, were randomized as previously described.[1] All randomized participants from 8 trial centers in the United Kingdom and Germany without a contraindication to an MRI scan were invited to participate in this optional MRI substudy. Initially designed to include baseline and follow-up scans, the protocol was amended during the COVID-19 pandemic to a single scan at approximately 18 months post-randomization with an increased sample size of 172 participants. The scan protocol included 3-Tesla multiparametric kidney MRI and cardiac MRI measures.[3] Analyses followed the intention-to-treat principle, using linear regression adjusted for age, sex, diabetes, eGFR, and albuminuria, with multiple imputation for missing data.[4] The MRI and statistical methods are provided in Items S2-S3; the substudy protocols, justification for the redesign, and prespecified data analysis plan are provided in Supplementary Files 2-4.

Between February 4, 2020, and December 5, 2022, 172 participants were recruited. Mean age was 60 years, 26% were female, 23% self-reported diabetes, mean eGFR was 37 mL/min/1.73 m^2, and geometric mean UACR was 242 mg/g at randomization (Table 1). All participants had an MRI scan at around 18 months postrandomization and 21 participants also had a baseline MRI scan prior to randomization (Fig S1). Over 96% reported taking at least 80% of allocated study treatment at 12 months postrandomization.

At around 18 months postrandomization, the adjusted mean (SE) marker of kidney fibrosis and inflammation measured by cortical T_1 mapping was 1,622 (10) ms in participants allocated empagliflozin versus 1,634 (11) ms in those allocated placebo (absolute difference in means of −12 ms, 95% CI −42 to 17 ms; P = 0.4) (Table 2). In addition, allocation to empagliflozin, compared with placebo, did not significantly modify any of the other prespecified secondary kidney MRI measures and the absence of significant effects was consistent across subgroups defined by age, sex, presence of diabetes, eGFR, or albuminuria (Fig S2). At around 18 months of follow-up, empagliflozin also had no significant effect on the cardiac MRI measures of left ventricular mass index, ejection fraction, cardiac fibrosis, or diastolic dysfunction (Table 2). Sensitivity analyses excluding participants with missing data or adjusting for baseline scans yielded similar results (Tables S2 and S3).

These analyses represent the largest MRI study to date to examine the cardiorenal effects of sodium/glucose cotransporter-2 (SGLT2) inhibition in patients with CKD. Previous kidney MRI studies were predominantly conducted in patients with diabetes and/or heart failure and focused on assessing kidney oxygenation or perfusion, with inconsistent results.[5-10] Kidney cortical T_1 was positively correlated with UACR and 5-year estimated kidney failure risk and inversely correlated with eGFR at randomization (Fig S3). This suggests the absence of a significant effect on the primary outcome may not be explained by a lack of correlation between this novel MRI parameter and clinically important markers of kidney disease progression.

This substudy has several strengths, including its randomized double-blind design, larger sample size and longer duration of treatment compared with previous studies, and standardized MRI image and data acquisition and processing. Limitations include the absence of baseline

Table 1. Baseline Characteristics of the EMPA-KIDNEY MRI Substudy Participants by Treatment Allocation

Characteristics	Empagliflozin (N = 93)	Placebo (N = 79)	Total (N = 172)
Demographic details			
Age at randomization (y)	59.7 ± 15.5	61.0 ± 15.2	60.3 ± 15.3
Sex			
Male	67 (72%)	60 (76%)	127 (74%)
Female	26 (28%)	19 (24%)	45 (26%)
Race			
White	86 (92%)	74 (94%)	160 (93%)
Black	1 (1%)	1 (1%)	2 (1%)
Asian	5 (5%)	2 (3%)	7 (4%)
Other (eg, mixed race)	1 (1%)	2 (3%)	3 (2%)
Country			
United Kingdom	61 (66%)	47 (59%)	108 (63%)
Germany	32 (34%)	32 (41%)	64 (37%)
Prior diabetes[a]			
Yes	22 (24%)	18 (23%)	40 (23%)
No	71 (76%)	61 (77%)	132 (77%)
History of cardiovascular disease[b]			
Yes	13 (14%)	20 (25%)	33 (19%)
No	80 (86%)	59 (75%)	139 (81%)
History of patient-reported heart failure			
Yes	5 (5%)	8 (10%)	13 (8%)
No	88 (95%)	71 (90%)	159 (92%)
Clinical measurements			
Systolic blood pressure (mm Hg)	139 ± 18	138 ± 19	138 ± 19
Diastolic blood pressure (mm Hg)	80 ± 11	82 ± 12	81 ± 12
Body mass index (kg/m^2)	29.4 ± 5.7	28.4 ± 5.3	28.9 ± 5.5
Laboratory measurements			
Estimated glomerular filtration rate (mL/min/1.73 m^2)[c]			
Mean (SD)	36.1 ± 14.2	37.3 ± 10.9	36.6 ± 12.8
<30	32 (34%)	20 (25%)	52 (30%)
≥30 to <45	45 (48%)	43 (54%)	88 (51%)
≥45	16 (17%)	16 (20%)	32 (19%)
Urinary albumin- creatinine ratio (mg/g)[c]			
Geometric mean (95% CI)	285 (195-417)	200 (131-304)	242 (182-321)
Median (Q1-Q3)	555 (1,172)	409 (692)	442 (967)
<30	17 (18%)	15 (19%)	32 (19%)
≥30 to <300	20 (22%)	21 (27%)	41 (24%)
≥300	56 (60%)	43 (54%)	99 (58%)
Median NT-proBNP (ng/L) (IQR)	134 (188)	128 (242)	132 (200)
Median urine biomarker (pg/mL) (IQR)			
DKK-3	1,156 (2,699)	1,557 (3,153)	1,338 (3,118)
EGF	1,465 (1,162)	1,476 (1,200)	1,465 (1,176)
IL-18	91 (116)	92 (123)	91 (117)
KIM-1	1,119 (1,186)	1,226 (1,163)	1,129 (1,185)
MCP-1	331 (315)	316 (329)	326 (333)
NGAL	42,149 (71,297)	50,219 (93,798)	47,114 (89,425)
Uromodulin	1.88×10^7 (1.31×10^7)	1.66×10^7 (1.7×10^7)	1.73×10^7 (1.45×10^7)
YKL-40	264 (849)	261 (1094)	263 (937)
Concomitant medication use			
RAS inhibitor	84 (90%)	69 (87%)	153 (89%)
Any diuretic	29 (31%)	31 (39%)	60 (35%)
Any lipid-lowering medication	58 (62%)	44 (56%)	102 (59%)

(Continued)

Table 1 (Cont'd). Baseline Characteristics of the EMPA-KIDNEY MRI Substudy Participants by Treatment Allocation

Characteristics	Empagliflozin (N = 93)	Placebo (N = 79)	Total (N = 172)
Any MRA	4 (4%)	3 (4%)	7 (4%)
Any GLP-1RA	1 (1%)	2 (3%)	3 (2%)
Cause of kidney disease			
Diabetic kidney disease	14 (15%)	7 (9%)	21 (12%)
Hypertensive/renovascular disease	15 (16%)	15 (19%)	30 (17%)
Glomerular disease	38 (41%)	35 (44%)	73 (42%)
Other/unknown	26 (28%)	22 (28%)	48 (28%)

Plus/minus values are means ± SD. Percentages may not total 100 because of rounding. Abbreviations: DKK-3, dickkopf-3; EGF, epidermal growth factor; GLP-1RA, glucagon-like peptide-1 receptor agonist; IL-18, interleukin-18; IQR, interquartile range; KIM-1, kidney injury molecule-1; MCP-1, monocyte chemoattractant protein-1; MRA, mineralocorticoid receptor antagonist; NGAL, neutrophil gelatinase–associated lipocalin; NT-proBNP, N-terminal pro–B-type natriuretic peptide; RAS, renin-angiotensin system; YKL-40, human cartilage glycoprotein-40.
[a]Prior diabetes was defined as a patient-reported history of diabetes of any type, use of glucose-lowering medication, or a glycated hemoglobin level of at least 48 mmol per mole (6.5%) at the randomization visit.
[b]History of cardiovascular disease was defined as a patient-reported history of myocardial infarction, heart failure, stroke, transient ischemic attack, or peripheral arterial disease.
[c]The values represent the measurement recorded at the randomization visit or the most recent local laboratory result recorded before randomization.

MRI measurements in most patients that prevented us from adjusting for these, and therefore undetected baseline imbalances in the MRI measures may have biased our results. However, the substudy sample size was increased (from 64 to 172 participants) to compensate for the lack of baseline measurements, ensuring that there was a very low probability (<1%) of having a baseline imbalance that could have obscured a real difference in the primary MRI-based outcome between treatment groups by chance (Item S3). Participants were predominantly White, and it remains unclear whether 18 months is a sufficient duration to observe structural changes detectable by MRI.

Table 2. Effect of Allocation to Empagliflozin Versus Placebo on MRI Parameters at About 18 Months

Outcome (Units)	No. With Measured Values	No. With Imputed Values[a]	Adjusted Mean (SE) Values of MRI Parameter[b]		Difference in Means (95% CI)[c]	*P* Value
			Empagliflozin (N = 93)	Placebo (N = 79)		
Primary assessment at about 18 months						
Kidney cortical T_1 using MOLLI (ms)	167	5	1,622 (10)	1,634 (11)	−12 (−42, 17)	0.4
Secondary assessments at about 18 months						
Kidney						
Kidney size (mL)	167	5	192 (7)	204 (8)	−12 (−33, 9)	0.3
Kidney arterial flow (mL/s)	96	76	4.5 (0.4)	3.5 (0.4)	1.0 (−0.2, 2.1)	0.1
Kidney global perfusion (mL/100 g/min)	89	83	295 (46)	246 (38)	20% (−22%, 84%)	0.4
Kidney diffusion (× 10^{-3} mm^2/s)	134	38	2.10 (0.03)	2.05 (0.03)	0.05 (−0.04, 0.14)	0.3
Kidney oxygenation (ms)	166	6	49.1 (1.3)	48.6 (1.4)	0.6 (−3.3, 4.4)	0.8
Kidney fat content mapping (%)	172	0	3.7 (0.1)	3.6 (0.1)	0.1 (−0.1, 0.3)	0.3
Cardiac						
Left ventricular mass index (g/m^2)	166	6	45 (1)	47 (1)	−3 (−5, 0)	0.05
Left ventricular ejection fraction (%)	166	6	52 (1)	50 (1)	2 (−1, 4)	0.2
Cardiac fibrosis (ms)	166	6	1275 (5)	1278 (5)	−4 (−17, 10)	0.6
Left ventricular global circumferential strain (%)	166	6	−17.6 (0.3)	−17.4 (0.3)	−0.2 (−1.0, 0.6)	0.6
Left ventricular global longitudinal strain (%)	166	6	−16.8 (0.3)	−16.6 (0.3)	−0.1 (−1.0, 0.7)	0.8
Left ventricular diastolic strain rate (1/s)	153	19	0.76 (0.03)	0.73 (0.03)	0.04 (−0.04, 0.11)	0.3
Left ventricular stroke volume (mL)	166	6	65 (2)	68 (2)	−3 (−9, 2)	0.2

Abbreviations: MOLLI, Modified Look-Locker inversion recovery; MRI, magnetic resonance imaging; SE, standard error.
[a]Missing MRI parameter values at 18 months were imputed with the use of multiple imputation.
[b]Arithmetic mean values presented for all outcomes with the exception of kidney global perfusion for which geometric means are presented (owing to use of log transformed values).
[c]Values are absolute differences in arithmetic means (95% CI) with the exception of kidney global perfusion, for which a relative difference is presented owing to use of log transformed values in the analyses. The estimates and *P* values were derived from linear regression with adjustment for factors included in the minimization algorithm, which determined treatment allocation (age, sex, prior diabetes, estimated glomerular filtration rate, and urinary albumin-creatinine ratio (but not region, as the MRI substudy was only conducted in Europe).

This EMPA-KIDNEY MRI substudy did not demonstrate any detectable effects of 18 months of empagliflozin on an MRI-based measure of kidney fibrosis and inflammation nor any other MRI-based measures of kidney and cardiac structure and function, despite clear cardiorenal benefits of SGLT2 inhibitors. These findings encourage ongoing mechanistic investigations into exact mechanisms of action of this important class of drug.

Supplementary Material

Supplementary File (PDF) 1

Figures S1-S3; Items S1-S3; Tables S1-S3.

Supplementary File (PDF) 2

Substudy Protocol.

Supplementary File (PDF) 3

Substudy Justification for Re-design.

Supplementary File (PDF) 4

Substudy Data Analysis Plan.

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References

1. Herrington WG, Wanner C, Green JB, et al. Design, recruitment, and baseline characteristics of the EMPA-KIDNEY trial. *Nephrol Dial Transpl*. 2022;37(7):1317-1329. doi:10.1093/ndt/gfac040
2. Herrington WG, Staplin N, Wanner C, et al. Empagliflozin in patients with chronic kidney disease. *New Engl J Med*. 2023;388(2):117-127. doi:10.1056/NEJMoa2204233
3. Cox EF, Buchanan CE, Bradley C, et al. Multiparametric renal magnetic resonance imaging: validation, interventions, and alterations in chronic kidney disease. *Front Physiol*. 2017;8:696. doi:10.3389/fphys.2017.00696
4. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. Wiley; 1987.
5. Laursen JC, Sondergaard-Heinrich N, de Melo JML, et al. Acute effects of dapagliflozin on renal oxygenation and perfusion in type 1 diabetes with albuminuria: a randomised, double-blind, placebo-controlled crossover trial. *EClinicalMedicine*. 2021;37:100895. doi:10.1016/j.eclinm.2021.100895
6. Zhou S, Zhang Y, Wang T, et al. Canagliflozin could improve the levels of renal oxygenation in newly diagnosed type 2 diabetes patients with normal renal function. *Diabetes Metab*. 2021;47(5):101274. doi:10.1016/j.diabet.2021.101274
7. Mori K, Inoue T, Machiba Y, et al. Effects of canagliflozin on kidney oxygenation evaluated using blood oxygenation level-dependent MRI in patients with type 2 diabetes. *Front Endocrinol (Lausanne)*. 2024;15:1451671. doi:10.3389/fendo.2024.1451671
8. Zhang C, Zhu B, Feng Y, et al. Assessing early tubular protective effects of SGLT2 inhibitor empagliflozin against type 2 diabetes mellitus using functional magnetic resonance imaging. *Acta Diabetol*. 2024;61(4):473-483. doi:10.1007/s00592-023-02220-x
9. Lee MMY, Gillis KA, Brooksbank KJM, et al. 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). *Circulation*. 2022;146(4):364-367. doi:10.1161/CIRCULATIONAHA.122.059851
10. Gullaksen S, Vernstrom L, Sorensen SS, et al. Separate and combined effects of semaglutide and empagliflozin on kidney oxygenation and perfusion in people with type 2 diabetes: a randomised trial. *Diabetologia*. 2023;66(5):813-825. doi:10.1007/s00125-023-05876-w