Empagliflozin Leads to a Rapid and Sustained Improvement of Left Ventricular Filling Pressure in Patients With Type 2 Diabetes: a Randomized Controlled Study

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Abstract

Background

In the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial) treatment with the sodium-glucose cotransporter-2 (SGLT2) inhibitor empagliflozin significantly reduced heart failure hospitalization (HHF) in patients with type 2 diabetes mellitus (T2D) and established cardiovascular disease. The early separation of the HHF event curves within the first 3 months of the trial suggest that early hemodynamic effects may play a role, potentially mediated by direct diuretic effects of the drug. In this study we examined immediate and more delayed effects of empagliflozin on urinary volume excretion, left ventricular filling pressure and function in addition to hemodynamic parameters.

Methods

In this placebo-controlled, randomized, double blind, exploratory study patients with T2D were randomized to empagliflozin 10 mg or placebo for a period of 3 months. Urinary volume excretion, echocardiographic and hemodynamic parameters were assessed after 1 day, 3 days and 3 months of treatment.

Results

Baseline characteristics were comparable in the empagliflozin (n = 20) and placebo (n = 22) group. Empagliflozin led to a significant increase of urinary glucose excretion (baseline: 7.3 ± 22.7 g/24 hrs; day 1: 48.4 ± 34.7 g/24 hrs; $p < 0.001$) as well as urinary volume (1740 ± 601 mL/24 hrs to 2112 ± 837 mL/24 hrs; $p = 0.011$) at day one of treatment which remained significant after 3 months. In addition empagliflozin significantly improved left ventricular filling pressure as assessed by a reduction of early mitral inflow velocity relative to early diastolic left ventricular relaxation (E/e') which became significant at day 1 of treatment (baseline: 9.2 ± 2.6; day 1: 8.5 ± 2.2; $p = 0.005$) and remained apparent throughout the study. This was primarily attributable to reduced early mitral inflow velocity E (baseline: 0.8 ± 0.2 m/sec; day 1: 0.73 ± 0.2 m/sec; $p = 0.003$). No difference in left ventricular function or hemodynamic parameters was observed.

Conclusion

Empagliflozin treatment of patients with T2D led to a significant rapid and sustained improvement of left ventricular filling pressure.

Trial Registration: EudraCT Number: 2016-000172-19; date of registration: 2017-02-20 (clinicaltrialregister.eu)

Background

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are glucose-lowering drugs currently used to treat patients with type 2 diabetes mellitus (T2D). These agents act by inhibiting SGLT2 in the proximal tubule of the kidney with a subsequent increase in urinary glucose excretion thus lowering blood glucose levels. Several placebo-controlled cardiovascular outcome trials (CVOTs) with SGLT2 inhibitors (EMPA-REG OUTCOME with empagliflozin [1], the CANVAS program [2] and CREDENCE [3] with canaglifozin, DECLARE with dapagliflozin [4]) demonstrated a reduction in CV events as well as a reduction in hospitalisation for heart failure (HHF) in patients with T2D and atherosclerotic CV disease (ASCVD), multiple CV risk factors, or diabetic nephropathy. Moreover, favourable effects of SGLT2 inhibitors on HHF and CV death in these trials were present in patients with or without HF at baseline [5], suggesting that these agents could prevent the development of HF in patients with T2D. In addition, data from the DAPA-HF trial suggest that SGLT2 inhibitors may reduce HF related endpoints and CV death independent of the presence of diabetes. The underlying mechanisms of these beneficial effects of SGLT2 inhibitors on HF-related events remain unclear but changes in blood pressure, blood glucose, or body weight are unlikely to solely explain the observed results. The early separation of HHF event curves in the CVOTs suggested SGLT2 inhibition to provide immediate effects on volume status and/or modulation of hemodynamic parameters potentially mediated by early diuretic effects [6–8]. Therefore, we conducted a prospective, placebo-controlled, double blind, randomized, exploratory pilot study in patients with T2D to assess the effect of empagliflozin on urinary volume, left ventricular filling pressure and function in addition to hemodynamic parameters after 1 day, 3 days and 3 months of treatment.

Methods

Study population and study design

In this single center, prospective, placebo-controlled, double blind, randomized, 2-arm parallel, interventional and exploratory pilot study 44 patients with T2D were randomized into 2 groups. The randomisation list was computer generated using a permuted block randomisation with block size of 4. The sequence generation method and the block size was concealed from the investigators. An independent pharmacist labelled the study medications according to the randomisation list. Study participants received empagliflozin 10 mg or placebo for a period of 3 months in addition to their concomitant medication. Non-invasive hemodynamic measurement, transthoracic echocardiography, blood pressure, blood- and urine-chemistry were performed at baseline (day 0), day 1, day 3 and after 3 months. Participants were recruited from the Department of Internal Medicine I at University Hospital Aachen, RWTH Aachen University, Germany. Inclusion criteria were as follows: type 2 diabetes, HbA1c ≥ 6.5% and age ≥ 18 years. The study protocol was approved by the local ethic committee and all subjects gave written informed consent. The trial was registered: EudraCT Number: 2016-000172-19.

Laboratory Measurement

Serum chemistry including haematology, lipid profile, glucose metabolism, eGFR (CKD-EPI formula), cystatin C, NT-proBNP, aldosterone were performed at every visit of the clinical trial. We collected 24 hrs urine at baseline, day 1, day 3 and after 3 months to measure renal excretion of glucose and sodium.

Hemodynamics

We used ClearSight System® (Edwards Lifesciences, Irvine, USA) as a validated [9] non-invasive tool to explore effects of empagliflozin on hemodynamic parameters including cardiac index (CI), stroke volume index (SVI), heart rate (HR), and systemic vascular resistance index (SVRI) at baseline, day 1, day 3 and after 3 months. ClearSight System® uses finger arterial pressure measurement based on the volume clamp method in combination with Physiocal calibration. Dividing the systolic area of the time integral of the pressure curve above the diastolic pressure by the estimated arterial impedance gives a beat-to-beat stroke volume which is multiplied with the heart rate to reach cardiac output, as has been described previously [9].

Transthoracic Echocardiography

Transthoracic and Doppler echocardiography were performed by technicians blinded to clinical information and treatment assignment with commercially available ultrasound systems (GE Healthcare, Chicago, USA). Standardized echocardiographic measurements were obtained in accordance with the guidelines of the EACI (European Association of Cardiovascular Imaging) and ASE (American Society of Echocardiography). Left ventricular systolic function (EF) was measured in 4 chamber and 2 chamber views by Simpson's Biplane Method. Additionally we performed myocardial deformation analysis of the left ventricle to assess peak global longitudinal strain (GLS) of the endocardial layer by speckle-tracking echocardiography in 4 chamber, 2 chamber and apical 3 chamber views. For diastolic function we determined early (E) and late (A) diastolic mitral inflow velocities, deceleration time (DT), septal early diastolic mitral annular tissue velocity (septal e') and lateral early diastolic mitral annular tissue velocity (lateral e') by mitral pulse wave Doppler and tissue Doppler. We calculated E/e' ratio and E/A ratio by dividing E peak by average e' calculated from septal e' and lateral e' respectively E peak by A. Additionally we performed myocardial deformation imaging as determined by 2D and 3D parameter global strain rate. Images were stored digitally for subsequent offline analysis. Interpretation of the echocardiograms was performed by two independent blinded investigators. Interobserver variability of the key echocardiographic endpoints E and e' was 0.8 for E and 0.77 for e'.

Endpoints

The study was powered for primary study outcome of empagliflozin on systemic vascular resistance index (SVRI) in comparison to placebo after 1 day, 3 days and 3 months of treatment. Secondary endpoints included changes in the following parameters after 1 day, 3 days and 3 months: cardiac index (CI), stroke volume index (SVI), blood pressure, sodium excretion in 24 hrs urine collection, body weight, heart rate, serum levels of NT-proBNP, cystatin C, glucose, HbA1c and aldosterone.

Further secondary analysis included changes in left ventricular systolic function as determined by EF and GLS, and in left ventricular diastolic function as determined by standardized parameters.

Statistical analysis

Descriptive statistics of baseline characteristics were calculated as relative (%) and absolute frequencies for categorical variables. Quantitative variables were described as means and standard deviations, in case of non-normally distributed data, as median with 1st and 3rd quartiles. Data distributions were visualized using box-plots.

Outcome variables were analysed using linear mixed models with fixed effects for treatment, visits (day 1, day 3 and 3 months) and baseline measurement of the variable. For the primary endpoint analysis, randomisation blocks were also included as fixed effect. The random part of the models consisted of intercepts grouped by individuals. Restricted maximum likelihood estimation was used. For NT-proBNP the log transformed variable was used in the analyses. Treatment effects were estimated at each visit along with Wald type 95% confidence intervals. For the primary endpoint the null hypothesis that all treatment-visit interactions are zero was tested against the alternative that at least one of them is not zero using an F test. Kenward-Roger approximation of the degrees of freedom was used. As additional analyses, correlation between changes from baseline to 3 months were calculated for selected variables using the Pearson correlation coefficient, and changes from baseline were compared between treatment groups separately at each visit. Results were not adjusted for multiple comparison.

Four data points (2%) of the primary outcome measurements were missing. All observed data at each visit were used in the linear mixed models allowing inference under the assumption of missing at random missingness mechanism.

Results

Baseline characteristics

From May 2017 to January 2019 a total of 44 patients underwent randomization. Data analysis was performed on 42 patients with 2 patients in the empagliflozin group being excluded because of protocol violations (concomitant intake of SGLT2 inhibitors at baseline and throughout study). Comparable baseline characteristics were observed between empagliflozin and placebo treated patients. Mean age of study participants was 62 ± 6.8 years, 81% were male, with a mean glycated hemoglobin of 7.7 ± 1.1%, a mean BMI of 31.3 ± 4.6 kg/m², a mean eGFR of 83 ± 19 mL/min/1.73 m², a history of CVD in 71%, and

presence of chronic heart failure in 43% of all patients. Patients had a baseline blood pressure of 135/81 mmHg (SD 16.9/13.2) and a mean LDL cholesterol of 99 ± 36.9 mg/dL. Baseline medication was comparable in both groups including anti-diabetic drugs, RAAS-inhibition, beta blockers and statins (Table 1).

Table 1
Baseline characteristics of the study population

	Placebo (N = 22)	Empagliflozin (N = 20)
Age - years	61.2 ± 7.9	62.8 ± 5.4
Male - no. (%)	18 (81.8)	16 (80)
BMI - kg/m²	31.2 ± 4.0	31.4 ± 5.3
Systolic blood pressure - mmHg	136 ± 18	135 ± 16
Diastolic blood pressure - mmHg	81 ± 14	82 ± 13
Heart rate - bpm	69 ± 15	71 ± 12
Type 2 diabetes		
Glycated hemoglobin - %	7.9 ± 1.3	7.5 ± 0.9
Diabetes duration - years	9 (6–18)	10 (4–14)
Insulin treated - no. (%)	8 (36)	11 (55)
Metformin - no. (%)	18 (82)	13 (65)
DPP-4 inhibitors - no. (%)	6 (27)	8 (40)
Others - no. (%)	1 (5)	3 (15)
History of CVD - no. (%)		
Coronary heart disease	15 (68.2)	15 (75)
Myocardial infarction	10 (45.5)	5 (25)
CABG	4 (18.2)	4 (20)
PCI	12 (54.5)	10 (50)
Peripheral artery disease	2 (9.1)	4 (20)
Chronic heart failure - no. (%)	11 (50)	7 (35)
Medication - no. (%)		
Antiplatelets	16 (73)	11 (55)
Oral anticoagulants	5 (23)	6 (30)
Diuretics	10 (45)	10 (50)
Statins	15 (68)	15 (75)
Calcium channel blockers	5 (23)	4 (20)
Beta blockers	16 (73)	16 (80)
RAAS inhibitors	20 (91)	15 (75)
eGFR - mL/min/1.73 m²	88 ± 16	77 ± 21
Total cholesterol - mg/dL	155 ± 39	169 ± 41
LDL-C - mg/dL	95 ± 38	103 ± 36
HDL-C - mg/dL	44 ± 9	43 ± 9
Triglycerides - mg/dL	156 ± 71	245 ± 150
Values are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, or no. (%)		
BMI = body mass index, CABG = coronary artery bypass graft, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, PCI = percutaneous coronary intervention, RAAS = renin-angiotensin-aldosterone system		

Effect Of Empagliflozin On Metabolic Parameters And Renal Function

As expected, empagliflozin treatment significantly increased urinary glucose excretion already after one day from 7.3 ± 22.7 g/24 hrs to 48.4 ± 34.7 g/24 hrs ($p < 0.001$) (Fig. 1a and Table 2) which led to an early decrease of fasting blood glucose levels from 181 ± 75 mg/dL to 152 ± 38 mg/dL ($p = 0.049$) (Table 2). Urinary volume significantly expanded in parallel with glucosuria after day 1 from 1740 ± 601 mL/24 hrs to 2112 ± 837 mL/24 hrs ($p = 0.011$) and remained significantly increased after 12 weeks of treatment (2319 ± 873 mL/24 hrs; $p = 0.001$) compared to placebo (Fig. 1b and Table 2).

Table 2
Comparison of laboratory values, 24 hrs urine, hemodynamics, blood pressure and echocardiography during the study

	Baseline			Day 1			Day 3			Month 3	
	Placebo	Empagliflozin	p	Placebo	Empagliflozin	p	Placebo	Empagliflozin	p	Placebo	Empagliflo
Laboratory											
Glucose - mg/dL	175 ± 52	181 ± 75	0.742	171 ± 48	152 ± 38	0.049	166 ± 52	146 ± 35	0.037	156 ± 52	151 ± 42
HbA1c - %	7.9 ± 1.3	7.5 ± 0.9	0.228	7.9 ± 1.3	7.4 ± 0.9	0.722	7.9 ± 1.2	7.4 ± 0.9	0.690	7.8 ± 1.5	7.1 ± 0.7
Total cholesterol - mg/dL	155 ± 39	169 ± 41	0.257	155 ± 37	174 ± 43	0.178	152 ± 40	168 ± 39	0.824	152 ± 42	185 ± 48
LDL-C - mg/dL	95 ± 38	103 ± 36	0.522	94 ± 36	102 ± 36	0.915	93 ± 39	102 ± 40	0.477	89 ± 39	112 ± 47
HDL-C - mg/dL	44 ± 9	43 ± 9	0.530	44 ± 9	42 ± 10	0.947	44 ± 9	43 ± 9	0.900	46 ± 11	46 ± 10
eGFR - mL/min/1.73 m^2	88 ± 16	77 ± 21	0.076	85 ± 16	70 ± 19	0.014	85 ± 17	70 ± 21	0.039	85 ± 16	68 ± 20
Cystatin C - mg/L	1.0 ± 0.2	1.2 ± 0.4	0.148	1.0 ± 0.2	1.3 ± 0.4	< 0.001	1.0 ± 0.2	1.3 ± 0.4	0.001	1.0 ± 0.2	1.3 ± 0.4
Hemoglobin - g/dL	14.3 ± 1.3	13.7 ± 1.8	0.299	14.1 ± 1.2	13.7 ± 1.9	0.487	14.0 ± 1.4	13.2 ± 1.8	0.685	14.2 ± 1.7	14.2 ± 2.4
Hematocrit - %	42.4 ± 3.4	41.0 ± 4.5	0.284	42.1 ± 3.5	40.9 ± 4.6	0.761	41.5 ± 3.7	39.9 ± 4.5	0.930	42.3 ± 4.6	43.3 ± 5.6
NT-proBNP - pg/mL	166 (73–238)	239 (91–463)	0.481	168 (67–252)	192 (63–385)	0.224	147 (58–226)	173 (57–402)	0.408	158 (42–262)	133 (32–500)
Aldosterone - pg/mL	83 ± 33	104 ± 65	0.213	88 ± 32	111 ± 67	0.825	96 ± 50	108 ± 59	0.635	108 ± 71	137 ± 104
24 hrs urine											
Urinary volume – mL/24 hrs	1788 ± 756	1740 ± 601	0.829	1626 ± 681	2112 ± 837	0.011	2007 ± 913	2111 ± 758	0.429	1664 ± 594	2319 ± 873
Glucose excretion - g/24 hrs	10.9 ± 22.7	7.3 ± 22.7	0.617	6.9 ± 14.1	48.4 ± 34.7	< 0.001	7.5 ± 14.5	65.7 ± 43.3	< 0.001	10.2 ± 18.7	67.6 ± 50.9
Sodium excretion - mmol/24 hrs	196 ± 84	164 ± 88	0.255	181 ± 76	185 ± 111	0.223	203 ± 107	181 ± 126	0.970	175 ± 55	201 ± 145
Electrolyte-free water clearance - mL/24 hrs	-15 ± 721	166 ± 830	0.467	-124 ± 654	417 ± 802	0.011	90 ± 874	461 ± 551	0.070	-91 ± 597	380 ± 765
Hemodynamics											
CI - L/min/m^2	3.2 ± 0.6	3.2 ± 0.6	0.682	3.1 ± 0.5	3.1 ± 0.5	0.771	3.1 ± 0.5	3.0 ± 0.6	0.293	3.1 ± 0.5	3.1 ± 0.5
SVI - mL/b/m^2	50 ± 7	47 ± 7	0.266	48 ± 8	45 ± 8	0.344	48 ± 8	44 ± 8	0.131	47 ± 7	47 ± 7
SVRI - dyne*sec*cm-5*m-2	1836 ± 361	1841 ± 379	0.967	1942 ± 355	1864 ± 373	0.411	1831 ± 310	1837 ± 376	0.991	1909 ± 428	1908 ± 451
HR - bpm	66 ± 13	68 ± 12	0.665	65 ± 11	69 ± 13	0.122	66 ± 11	68 ± 14	0.717	66 ± 11	67 ± 10
Blood pressure											
Systolic – mmHg	136 ± 18	135 ± 16	0.934	134 ± 16	128 ± 16	0.279	133 ± 19	125 ± 16	0.115	132 ± 20	128 ± 15
Diastolic - mmHg	81 ± 14	82 ± 13	0.964	80 ± 13	80 ± 11	0.876	80 ± 12	80 ± 9	0.925	82 ± 11	79 ± 11

Values are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, p-values were calculated for the int effect at each visit using the Wald method, e' mean is the mean of e' septal and e' lateral

bpm = beats per min, CI = cardiac index, CVP = central venous pressure, DT = deceleration time, eGFR = estimated glomerular filtration rate, GLS = global longit strain, HDL-C = high density lipoprotein cholesterol, HR = heart rate, IVSd = interventricular septum in diastole, LA = left atrial, LDL-C = low density lipoprotein ch LV = left ventricular, LVEDD = left ventricular enddiastolic diameter, LV-EF = left ventricular ejection fraction, LVESD = left ventricular endsystolic diameter, RVS ventricular systolic pressure, SVI = stroke volume index, SVRI = systemic vascular resistance index

	Baseline			Day 1			Day 3			Month 3	
	Placebo	Empagliflozin	p	Placebo	Empagliflozin	p	Placebo	Empagliflozin	p	Placebo	Empagliflo
Echocardiography											
LV-EF - %	48 ± 6.8	51 ± 5.0	0.183	48 ± 6.2	51 ± 4.6	0.852	48 ± 6.1	51 ± 4.7	0.333	48 ± 6.4	51 ± 4.4
LVEDD - mm	50 ± 5	49 ± 5	0.365	50 ± 6	49 ± 5	0.864	49 ± 5	48 ± 5	0.449	50 ± 6	48 ± 6
LVESD - mm	36 ± 8	34 ± 6	0.386	36 ± 9	35 ± 5	0.595	35 ± 8	34 ± 5	0.187	37 ± 8	33 ± 6
IVSd - mm	10 ± 2	10 ± 1	0.940	10 ± 2	11 ± 2	0.764	10 ± 2	11 ± 2	0.630	10 ± 2	10 ± 1
LV mass index - g/m²	91 ± 21	86 ± 19	0.474	94 ± 24	87 ± 19	0.448	90 ± 21	84 ± 19	0.701	89 ± 23	84 ± 17
LA area - cm²	20 ± 4.2	20 ± 3.7	0.484	20 ± 5.3	18 ± 4.3	0.082	20 ± 5.7	19 ± 4.8	0.691	20 ± 4.1	18 ± 4.0
LA volume index - mL/m²	31 ± 11	28 ± 9	0.414	30 ± 13	26 ± 10	0.300	30 ± 13	28 ± 10	0.840	31 ± 12	26 ± 9
E - m/sec	0.78 ± 0.14	0.80 ± 0.20	0.686	0.80 ± 0.12	0.73 ± 0.20	0.003	0.78 ± 0.11	0.72 ± 0.18	0.005	0.78 ± 0.13	0.72 ± 0.21
A - m/sec	0.73 ± 0.17	0.82 ± 0.17	0.095	0.74 ± 0.20	0.81 ± 0.15	0.786	0.75 ± 0.19	0.80 ± 0.15	0.550	0.73 ± 0.20	0.83 ± 0.15
E/A	1.18 ± 0.53	0.97 ± 0.22	0.121	1.20 ± 0.55	0.88 ± 0.20	0.042	1.16 ± 0.58	0.89 ± 0.23	0.181	1.21 ± 0.52	0.85 ± 0.23
e' septal - cm/sec	7.2 ± 1.7	7.5 ± 1.9	0.603	6.6 ± 2.0	7.8 ± 2.1	0.077	7.2 ± 1.6	7.5 ± 2.0	0.785	7.2 ± 1.6	7.8 ± 2.1
e' lateral - cm/sec	9.8 ± 2.0	10.4 ± 1.8	0.319	9.6 ± 2.4	10.1 ± 2.4	0.970	9.5 ± 1.9	9.8 ± 2.3	0.840	9.3 ± 2.0	10.4 ± 2.9
e' mean	8.5 ± 1.5	8.9 ± 1.6	0.361	8.1 ± 1.8	8.9 ± 2.1	0.352	8.4 ± 1.3	8.7 ± 2.0	0.968	8.3 ± 1.5	9.1 ± 2.3
E/e' mean	9.3 ± 2.2	9.2 ± 2.6	0.898	10.1 ± 1.4	8.5 ± 2.2	0.005	9.5 ± 1.5	8.5 ± 2.4	0.079	9.7 ± 1.9	8.3 ± 2.9
DT - msec	198 ± 54	206 ± 45	0.610	189 ± 45	212 ± 35	0.234	202 ± 54	215 ± 43	0.624	196 ± 59	218 ± 59
RVSP - mmHg + CVP	28 ± 6	29 ± 4	0.515	26 ± 5	26 ± 6	0.827	25 ± 4	29 ± 10	0.261	27 ± 8	26 ± 11
GLS (endocardial layer)	-17 ± 5.3	-19 ± 4.1	0.107	-17 ± 4.8	-19 ± 3.4	0.877	-17 ± 4.4	-19 ± 3.7	0.735	-17 ± 4.6	-19 ± 2.7

Values are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, p-values were calculated for the int effect at each visit using the Wald method, e' mean is the mean of e' septal and e' lateral

bpm = beats per min, CI = cardiac index, CVP = central venous pressure, DT = deceleration time, eGFR = estimated glomerular filtration rate, GLS = global longit strain, HDL-C = high density lipoprotein cholesterol, HR = heart rate, IVSd = interventricular septum in diastole, LA = left atrial, LDL-C = low density lipoprotein ch LV = left ventricular, LVEDD = left ventricular enddiastolic diameter, LV-EF = left ventricular ejection fraction, LVESD = left ventricular endsystolic diameter, RVS ventricular systolic pressure, SVI = stroke volume index, SVRI = systemic vascular resistance index

Consistent with the initiation of renal tubule-glomerular feedback, empagliflozin significantly decreased eGFR from 77 ± 21 mL/min/1.73 m^2 at baseline to 70 ± 19 mL/min/1.73 m^2 (p = 0.014) after 1 day of treatment (Fig. 1c and Table 2) and increased serum cystatin C compared to placebo (Fig. 1d and Table 2). In addition, as previously described, empagliflozin treatment led to a significant increase in hematocrit and hemoglobin levels after 3 months, an effect not yet present after 1 or 3 days of treatment (Table 2). 24 hrs urinary sodium excretion increased in empagliflozin-treated patients without reaching statistical significance (Table 2). In addition, empagliflozin increased electrolyte-free water clearance from 166 ± 830 mL/24 hrs at baseline to 417 ± 802 mL/24 hrs after 1 day (p = 0.011), an effect that was sustained over the 3 month study period (Table 2).

Effect Of Empagliflozin On Hemodynamic Parameters

Empaglifozin did not affect left ventricular systolic function as indicated by unchanged left ventricular EF and GLS values (Table 2). However, empagliflozin significantly improved left ventricular filling pressure as assessed by early mitral inflow velocity relative to early diastolic left ventricular relaxation (E/e') as the main measure of diastolic function, which became significant at day 1 of treatment (baseline: 9.2 ± 2.6; day 1: 8.5 ± 2.2; p = 0.005) and remained apparent throughout the study (Fig. 2a and Table 2). Moreover, empagliflozin treatment significantly reduced early mitral inflow velocity (E) (baseline: 0.80 ± 0.20 m/sec; day 1: 0.73 ± 0.20 m/sec; p = 0.003) (Fig. 2b), but no differences were observed for early diastolic left ventricular relaxation (e') (Table 2). No difference in heart rate was observed in-between study groups while empagliflozin reduced blood pressure over time, although not reaching statistical significance (Table 2).

Further analyses did not detect treatment dependent effects on left ventricular mass index, atrial volume index, NT-proBNP or aldosterone levels between groups during the 3 months treatment period (Table 2).

Changes in E/e' did not correlate with changes in urinary volume, urinary glucose or sodium excretion, left ventricular mass index, electrolyte-free water clearance or changes in hematocrit (Supplementary table). In addition, analyses of changes of E/e' (Fig. 3a) or E (Fig. 3b) versus baseline confirmed the significant reduction in empagliflozin treated patients. Empagliflozin was not found to significantly affect systemic vascular resistance index (SVRI) and cardiac index (CI) as assessed by non-invasive pulse wave contour analysis (ClearSight System®) (Supplementary figure and Table 2).

Discussion

In this randomized, placebo-controlled, double-blind study in patients with T2D and prevalent ASCVD or high CV risk, resembling the populations studied in CVOTs with SGLT2 inhibitors, empagliflozin a rapidly improved left ventricular filling pressure as shown by a reduction of early mitral inflow velocity relative to early diastolic left ventricular relaxation (E/e') as a main measure of diastolic function, an effect already significant after one day of treatment and sustained until the end of the study. This was attributable to reduced early diastolic transmitral inflow (E), most likely a consequence of persistently increased diuresis induced by empagliflozin being apparent throughout the whole study period. Diuretic effects of SGLT2 inhibition differs in comparison to classical diuretic drugs like loop diuretics. Acutely, loop diuretics increase urine excretion by reducing intravasal volume with apparent hemoconcentration and the diuretic-induced preload reduction impairs cardiac output with a compensatory increase in heart rate and systemic vascular resistance[10]. In contrast, SGLT2 inhibition in our study rapidly expanded urinary volume excretion already after one day - along with an increase in electrolyte-free water clearance - without early hemoconcentration (shown by a lack of effect on hemoglobin and hematocrit on day 1 and 3) or effects on cardiac index, systemic vascular resistance, or heart rate. It has been suggested that SGLT2 inhibition more efficiently reduces interstitial relative to intravasal volume while the opposite occurs with loop diuretics[11]. Consistently, the finding of a limited reflex neurohumoral stimulation seen upon empagliflozin treatment in our study may point to the interstitial compartment as the primary source of rapid volume unloading by empagliflozin.

The main - albeit exploratory - finding of our study, the early and sustained improvement of left ventricular filling pressure as indicated by E/e' in empagliflozin treated patients might provide important information to better understand the early beneficial effects on HF hospitalization seen in SGLT2 inhibitor outcome trials. Baseline E/e' values in our study indicated early diastolic dysfunction in our patient population with an E/e' cut-off value above nine. Given that impaired diastolic function is a crucial pathophysiological feature of HF, mainly HFpEF, - often present long before HF becomes clinical apparent - our data bolster the hypothesis that SGLT2 inhibitors could prevent the development of HF by improving left ventricular filling pressure in patients with T2D. A observatory study of 37 patients with T2D demonstrated a reduction in E/e' as well as a decrease in systolic blood pressure and LVMI after 3 months of treatment with canagliflozin and in this study the increase in hemoglobin levels was an independent predictor for changes in E/e' [12]. In contrast, Soga et al. observed a decrease in E/e' unrelated to changes of hemoglobin or blood pressure in 58 T2D patients with HF treated for 6 months with dapagliflozin under non-randomised conditions with the improvement in diastolic function being paralleled by a reduction in LVMI [13]. Our randomized, placebo-controlled study extends the understanding of SGLT2 inhibitors' effect on diastolic function by demonstrating time dependent effects of empagliflozin on left ventricular filling pressure being apparent already after 1 day of treatment.

This study has certain limitations. The immediate reduction of E/e' upon empagliflozin treatment, is an exploratory finding in a limited number of patients, and warrants confirmation in a larger study with changes in diastolic function defined as primary outcomes.

Conclusion

Taken together, our data suggest that empagliflozin treatment of patients with T2D and ASCVD/high CV risk leads to an immediate volume unloading and a rapid and sustained improvement of left ventricular filling pressure. These mechanisms could contribute to the early beneficial effects of SGLT2 inhibitors on HF hospitalisation seen in various SGLT2 inhibitor CVOTs.

Declarations

Ethics approval and consent to participate

This study was approved by ethics committee of University Hospital Aachen (reference number: EK 250/16). All subjects gave written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

MR, KT, NUKH, AS and JM report no potential conflict of interest, EA did receive personal fees from AstraZeneca und Novartis and receive research grants from Bayer und Novartis, MB served as a consultant and gave talks for Abbott, Amgen, Astra-Zeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers-Sqibb, Cytokinetics, Medtronic, Novartis, Servier; NM has received support for clinical trial leadership from Boehringer Ingelheim, Novo Nordisk, served as a consultant to Boehringer Ingelheim, Merck, Novo Nordisk, AstraZeneca, BMS, received grant support from Boehringer Ingelheim, Merck, Novo Nordisk, and served as a speaker for Boehringer Ingelheim, Merck, Novo Nordisk, Lilly, BMS, and Astra Zeneca. NM declines all personal compensation from pharma or device companies. ML received grants and personal fees from Boehringer Ingelheim, MSD and Novo Nordisk, personal fees from Amgen, Sanofi, Astra Zeneca, Bayer and Lilly.

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Authors' contributions

MR and KT researched data and wrote the manuscript. NUKH researched data. JM performed laboratory analyses. AK analyzed the data. AS, EA and MB contributed to the discussion. NM and ML reviewed and edited the manuscript. All authors have read and approved the manuscript as submitted.

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References

1. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Biomath D, Devins T, Johansen O, Woerle HJ, Broedl UC, Inzucchi SE, Empagliflozin. Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *The New England Journal of Medicine*. 2015;373.
2. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med*. 2017.
3. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM. Mahaffey KW and Investigators CT. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019;380:2295–306.
4. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2018.
5. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Sabatine MS. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. 2018.
6. Marx N, McGuire DK. Sodium-glucose cotransporter-2 inhibition for the reduction of cardiovascular events in high-risk patients with diabetes mellitus. *Eur Heart J*. 2016.
7. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia. 2018;61:2108–17.
8. Wanner C, Marx N. SGLT2 inhibitors: the future for treatment of type 2 diabetes mellitus and other chronic diseases. Diabetologia. 2018;61:2134–9.
9. Broch O, Renner J, Gruenewald M, Meybohm P, Schottler J, Caliebe A, Steinfath M, Malbrain M, Bein B. A comparison of the Nexfin(R) and transcardiopulmonary thermodilution to estimate cardiac output during coronary artery surgery. Anaesthesia. 2012;67:377–83.
10. Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. Ann Intern Med. 1985;103:1–6.
11. Hallow KM, Helmlinger G, Greasley PJ, McMurray JJV, Boulton DW. Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. Diabetes Obes Metab. 2018;20:479–87.
12. Matsutani D, Sakamoto M, Kayama Y, Takeda N, Horiuchi R, Utsunomiya K. Effect of canagliflozin on left ventricular diastolic function in patients with type 2 diabetes. Cardiovasc Diabetol. 2018;17:73.
13. Soga F, Tanaka H, Tatsumi K, Mochizuki Y, Sano H, Toki H, Matsumoto K, Shite J, Takaoka H, Doi T, Hirata KI. Impact of dapagliflozin on left ventricular diastolic function of patients with type 2 diabetic mellitus with chronic heart failure. Cardiovasc Diabetol. 2018;17:132.

Figures

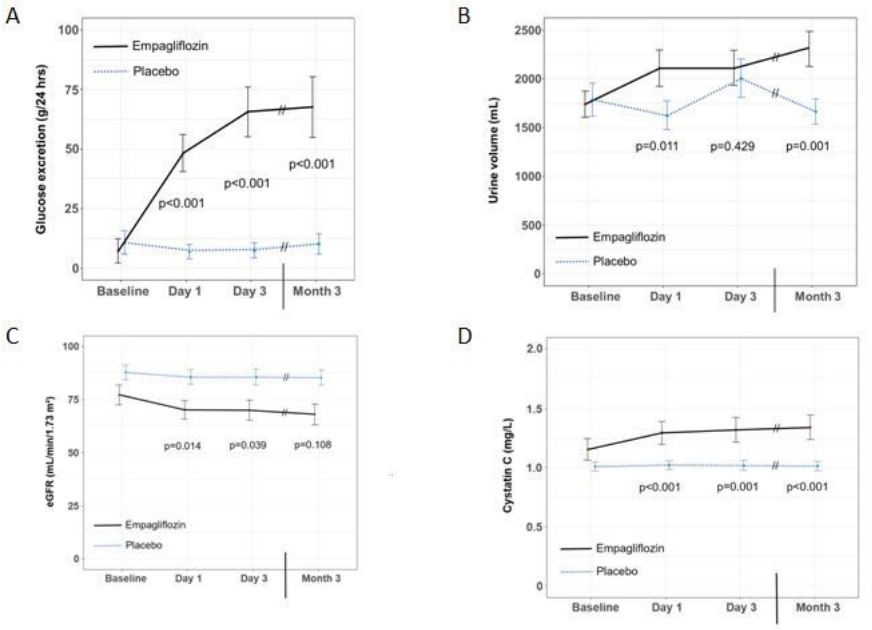

Figure 1

Metabolic parameters and renal function. Urinary glucose excretion (A), 24 hrs urinary volume (B), eGFR (C), and plasma cystatin C levels (D) in patients with type 2 diabetes treated with empagliflozin (n=20; black line) or placebo (n=22; blue dotted line). Data are shown as mean ± standard error at baseline, after 1 day, 3 days, and 3 months. p-values are calculated from Wald tests for the intervention effect at each visit.

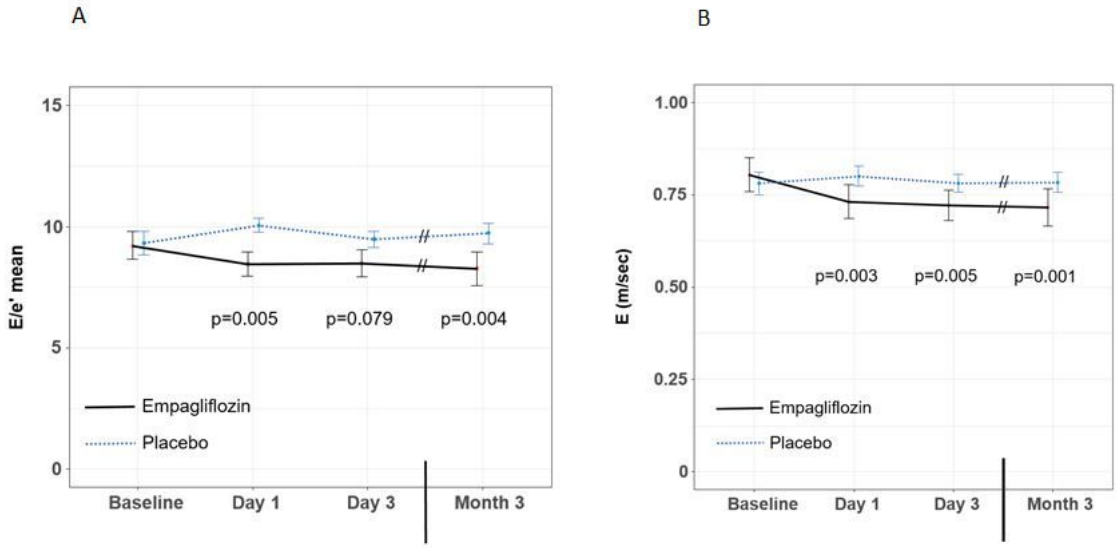

Figure 2

Left ventricular diastolic function. Early mitral inflow velocity relative to early diastolic left ventricular relaxation (E/e') in patients with type 2 diabetes treated with empagliflozin (n=20; black line) or placebo (n=22; blue dotted line). Data are shown as mean ± standard error at baseline, after 1 day, 3 days, and 3 months. p-values are calculated from Wald tests for the intervention effect at each visit.

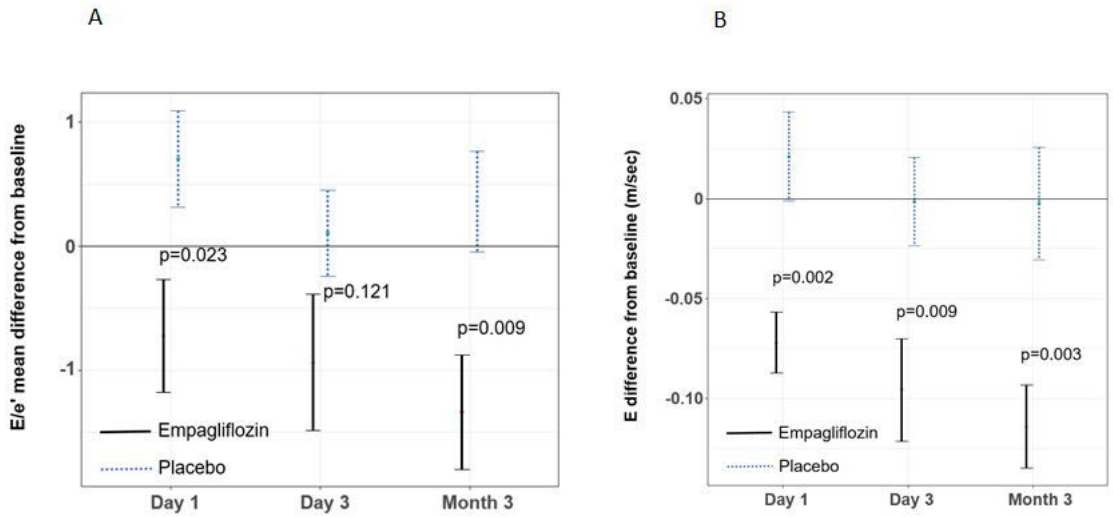

Figure 3

Left ventricular diastolic function. Differences from baseline. Early mitral inflow velocity relative to early diastolic left ventricular relaxation (E/e') (A) and early mitral inflow velocity (E) (B) in patients with type 2 diabetes treated with empagliflozin (n=20; black line) or placebo (n=22; blue dotted line). Data are shown as mean ± standard error at baseline, after 1 day, 3 days, and 3 months. p-values are from t-tests for independent samples performed on differences from baseline at respective time points in the treatment and placebo group.

Supplementary Files

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- SupplementaryfigureEMPAHemodynamics20200719MR.pptx
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