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Published in:
Diabetes Care

DOI:
10.2337/dc19-2187

Publication date:
2020

Document Version
Peer reviewed version

Dapagliflozin vs. placebo on left ventricular remodeling in patients with diabetes mellitus and heart failure: The REFORM Trial.

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Total number of words= 1198 *(main body)*, References=12; Table=1, Supplementary Table=1

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Abstract:

Objective:

Determine the effects of dapagliflozin in patients with heart failure(HF) and type 2 diabetes(T2DM) on left ventricular(LV) remodelling using cardiac MRI.

Research Design and Methods:

We randomized 56 patients with T2DM and HF with LV systolic dysfunction to dapagliflozin 10mg daily or placebo for one year, on top of usual therapy. Primary endpoint was difference in LV end-systolic volume(LVESV) using cardiac MRI. Key secondary endpoints included other measures of LV remodelling, clinical and biochemical parameters.

Results:

In our cohort, Dapagliflozin had no effect on LVESV or any other parameter of LV remodelling. It however, reduced diastolic BP and loop diuretic requirements, while increasing hemoglobin, hematocrit and ketone bodies. There was a trend towards lower weight.

Conclusions:

We were unable to determine with certainty if dapagliflozin in patients with T2DM and HF had any effect on LV remodelling. Whether the benefits of dapagliflozin in HF are due to remodelling or other mechanisms remains unknown.

Introduction:

Type 2 diabetes mellitus(T2DM) and heart failure(HF) commonly co-exist and can be lethal.(1) The sodium-glucose linked transporter 2 inhibitor (SGLT2i) is a new class of diabetes therapy that reduces HF hospitalization and cardiovascular(CV) death.

A meta-analysis of CV outcome trials of T2DM patients with varying CV risk (n=34,322) showed an overall 14% reduction in major adverse cardiovascular events and 24% reduction in composite of CV mortality and HF hospitalization.(2) In the DAPA-HF trial, dapagliflozin was compared against standard of care in 4744 patients with established HF and found a striking 30% reduction in HF hospitalization, 18% reduction in CV death and significant improvements in HF symptom burden.(3)

SGLT2i clearly results in a significant reduction in HF risk, however the mechanism of these effects is unclear. The main objective of this work was to determine the cardiac effects of dapagliflozin in patients with HF and T2DM, to help explain the substantial improvements in HF outcomes seen in large clinical trials.

Methods and design:

The trial design and methods have been described previously.(4)

Briefly, this single center, placebo-controlled clinical trial was designed to look for changes in three parameters of left ventricular (LV) remodelling (i.e. LV volumes, mass and ejection fraction) using cardiac magnetic resonance (CMR) imaging. 56 patients were randomized 1:1 to either dapagliflozin 10mg/day or placebo for 1 year. Participants had a diagnosis of T2DM and history of symptomatic HF with a previously documented reduction in ejection fraction (EF) using echocardiography. They were on stable therapy for at least 3 months prior to recruitment, with a maximum loop diuretic dose of 80 mg/day and baseline eGFR of ≥ 45 mls/min/1.73m^2.

The primary outcome was change in LV end-systolic volume (LVESV). Key secondary outcomes included LV end-diastolic volume (LVEDV), indexed-LV mass (LVMI) and LVEF as well as a range of clinical and biochemical markers of HF. The CMR imaging protocol and reproducibility of analysis have been published previously.(5; 6)

Statistical analysis:

Data was analyzed by intention to treat with single mean imputation of missing values. All continuous outcomes were analyzed using multiple linear regression, controlling for baseline values, age, sex and renal function. Categorical outcomes were analyzed using Pearson's chi-square. A two-sided p value of <0.05 was taken as significant. Analysis was performed using R version 3.4.3 for windows.

Results:

Mean age was 67.1 years, majority male (66.1%) with an average BMI of 32.5 mg/m^2. Majority (87.5%) were in NYHA functional class I or II, indicating mild HF, with the commonest etiology being ischemic heart disease. Mean baseline HbA1c was 60.9 mmol/mol (7.7%), and the mean estimated glomerular filtration rate (eGFR) was 72.0 ml/min/1.73 m^2. Other baseline values are listed on Supplementary Table 1.

After 1 year, there was no significant change in LVESV; +4.82 ml;(95%CI-13.28-22.93) p=0.594. There was no effect on LVEDV; +7.83 ml;(95%CI-15.05-30.70) p=0.495, LVMI; +2.5 g/m2;(95%CI-3.95-8.95) p=0.440 or LVEF +0.96%;(95%CI-3.32-4.69) p=0.732. (Table 1)

Dapagliflozin significantly reduced diastolic blood pressure (BP); -8.15mmHg ;(95%CI-13.02- -3.28) p=0.001, but there was no difference in systolic BP or heart rate.

Dapagliflozin increased hemoglobin; +0.86 g/dl;(95%CI 0.27-1.46) p=0.005, hematocrit +2.89%; (95%CI 1.14 - 4.64) p=0.002 and fasting beta-hydroxybutyrate (ketone body); +0.04 mmol/L;(95%CI 0.01-0.07) p=0.022. There was a trend towards lower weight; -2.26kg;(95%CI -4.83-0.31) p=0.083.

Patients on dapagliflozin required less loop diuretic therapy; -29.06mg; (95%CI-42.17- -15.95) p<0.001 and were more likely to stop or reduce their loop diuretic dose; 53.6%vs10.7%; p=0.001.

There was no significant difference in HbA1c or eGFR at the end of 1 year.

Adverse events:

There were 5 deaths in total; 1 cancer death in the dapagliflozin arm, 1 cancer and 3 cardiovascular deaths in the placebo arm.

There were 3 acute coronary syndromes in the placebo arm but none in dapagliflozin arm. There was 1 HF hospitalization in each arm. There was no difference in the incidence of serious adverse events between the two arms.

There were significantly more instances of major decline in renal function (sustained >20% increase in creatinine or eGFR <45 ml/min/1.73 m2) in the dapagliflozin arm compared to placebo; 28.6% vs 0% p=0.008. This was transient and resolved after reduction of loop diuretic dose without any change in dapagliflozin dose.

Conclusions:

In this mechanistic study of SGLT2i in patients with HF and T2DM, we observed that 1 year of dapagliflozin therapy did not reverse LV remodeling. However, we observed a significant difference in diastolic BP, loop diuretic requirements, hemoglobin, hematocrit and fasting ketone levels between groups. There was also a trend towards lower weight.

Reversing LV remodelling is an important factor in reducing mortality and morbidity in patients with HF.(7; 8) Therefore, the apparent absence of an effect on LV remodelling in this study, if true, is intriguing given the striking improvements in HF outcomes demonstrated in large clinical trials of SGLT2i.

The DAPA-HF trial showed a reduction in HF hospitalization (seen almost immediately) and mortality (seen later). The rapid onset of the hospitalization benefit is unlikely to be the result of LV remodeling, and it is postulated to be due to the diuretic effect of SGLT2i. We observed significantly reduced loop diuretic requirements in participants taking dapagliflozin, supporting this hypothesis. Reduced congestion due to osmotic diuresis is a plausible explanation for reduction in HF hospitalizations. This diuretic effect may also be responsible for the difference in the diastolic BP observed between groups. However, these effects cannot explain the substantial mortality benefits. Our findings suggest that other mechanisms should be considered, beyond the established paradigm of LV remodelling, to explain these effects

of SGLT2i. Some secondary outcomes of this study may help guide future investigation into potential mechanisms.

We observed significantly higher hemoglobin, hematocrit and fasting ketones in the dapagliflozin group. Although this has been seen in other preclinical and clinical trials of SGLT2i, we are the first to report this in the HF population. Preliminary research suggests that utilization of ketone bodies as an alternative fuel by cardiomyocytes may improve cardiac efficiency.(9) SGLT2i also increases erythropoietin production by renal cortical fibroblasts, contributing to increased hemoglobin and hematocrit, thereby potentially improving myocardial oxygenation.(10; 11) We did not, however, explore the effects of dapagliflozin on myocardial energetics or other direct cardiac effects that have been proposed by others.(12) Clearly, more work is needed.

Our study is limited by the mild severity of HF and small sample size. This limits the certainty of our findings and makes the case for a larger, more adequately powered trial. Additionally, the adjustment of loop diuretic dose may have affected ventricular volume / loading as well. At the time of conceptualization of this study in 2014, there was little experience with the use of this drug class in patients with HF and concomitant loop diuretic. This led to a cautious selection of participants with milder HF, on modest doses of diuretics. Ongoing work in a similar trial investigating SGLT2 inhibition on LV remodeling with a different agent of this class (NCT03485092) will help validate our findings.

In summary, we showed that 1 year of dapagliflozin therapy in patients with mild HF and T2DM reduced loop diuretic requirements but we did not detect any change in CMR measures of LV remodelling. This warrants further investigation to understand potentially novel mechanisms that may be responsible for its effect in improving HF outcomes.

Acknowledgements:

The authors would like to thank The Scottish Health Research Register (SHARE), Scottish Primary Care Research Network (SPCRN) and Health Informatics Centre (HIC) for their help in recruiting participants for this study, the Immunoassay Biomarker Core Laboratory University of Dundee for performing the blood biomarker analysis; Petra Rauchhaus for her advice on statistical analysis. Tayside Clinical Trials Unit (TASC), University of Dundee, for their support on the management and governance of this study. We are also very grateful for the assistance of Fatima Baig and Isobel Ovens throughout the trial. This study was funded by a grant from the European Foundation for the Study of Diabetes, Clinical Diabetes Research Programme in Macrovascular Complications of Diabetes. IRM is supported by an NHS Education for Scotland/Chief Scientist Office Post-Doctoral Clinical Lectureship (PCL 17/07). MM is supported by the British Heart Foundation (grant number PG/14/4/30539).

Author contributions:
JSS co-developed the hypothesis, collected, compiled and analyzed the data and authored the manuscript. IRM analyzed the cardiac MRI images and critically appraised the manuscript. AF, KV, MM, SG helped with data-collection. AMJC, JG, FK, JGH appraised the manuscript. PTD, ERP, ADS and CCL co-developed the hypothesis and critically appraised the manuscript. CCL is also the guarantor of this work.

Conflict of interest statement:
JSS declares receiving speaker fees from Boehringer Ingelheim.
PTD has received grants from Shire Pharmaceuticals and Gilead Sciences. PTD is a member of the New Drugs Committee of the Scottish Medicines Consortium.
ERP declares receiving personal, non-specific speaker fees from Lilly Pharmaceuticals.
ADS declares receiving funding from Astra Zeneca for research on the effects of dapagliflozin on the heart.
CCL declares receiving consultancy fees and/or research grants from Amgen, AstraZeneca, MSD, Novartis, and Servier.
IRM, AF, KV, MM, AMJC, SG, JG, FK, JGH declare no conflict of interest

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Table 1. Primary and key secondary outcomes.

Outcome	**Dapagliflozin (n=28)**	**Placebo (n=28)**	**Adjusted treatment effect**	**p value**
	Mean (SD)	**Mean (SD)**	**(95% CI)**	
LVESV (ml)	-8.9 (32.7)	-18.8 (51.0)	4.82 (-13.28 to 22.93)	0.594
Indexed LVESV (ml/m^2)	-4.5 (16.7)	-10.5 (26.2)	2.49 (-6.30 to 11.28)	0.571
LVEDV (ml)	-7.7 (40.5)	-24 (55.9)	7.83 (-15.05 to 30.70)	0.495
Indexed LVEDV* (ml/m^2)	-4.3 (19.8)	-13.4 (29.0)	3.9 (-7.05 to 14.85)	0.478
LVEF (%)	2.6 (6.7)	1.4 (9.6)	0.69 (-3.32 to 4.69)	0.732
LV Mass Index (g/m^2)	4.0 (11.1)	0.6 (11.7)	2.5 (-3.95 to 8.95)	0.44
LV Stroke Vol (ml)	0.0 (6.5)	-2.9 (6.2)	1.86 (-1.52 to 5.24)	0.273
Indexed LA Volume (ml/m2)	-1.7 (13.5)	-1.5 (15.0)	-2.6 (-9.67 to 4.48)	0.464
Weight (kg)	-1.4 (4.4)	0.15 (6.0)	-1.36 (-4.14 to 1.42)	0.329
Weight† (kg)	-1.9 (4)	0.73 (5.3)	-2.26 (-4.83 to 0.31)	0.083
SBP (mmHg)	-2.6 (18.9)	3.6 (18.7)	-4.7 (-14.51 to 5.11)	0.34

DBP (mmHg)	-0.4 (7.4)	8.8 (11.9)	-8.15 (-13.02 to -3.28)	0.001
Heart rate (beats/min)	-4.6 (10.8)	-1.3 (11.1)	-2.26 (-7.88 to 3.36)	0.424
Hemoglobin (g/dL)	1.1 (1.1)	0.0 (1.4)	0.86 (0.27 to 1.46)	0.005
Hematocrit (%)	4.0 (3.0)	0.0 (4.0)	2.89 (1.14 to 4.64)	0.002
HbA1c (mmol/mol)	-4.0 (10.4)	-1.2 (11.6)	-1.49 (-6.95 to 3.97)	0.586
BHB (mmol/L)	0.03 (0.06)	0 (0.06)	0.04 (0.01 to 0.07)	0.022
Serum creatinine (µmol/L)	5.3 (12.8)	4.6 (12.1)	1.46 (-5.56 to 8.47)	0.679
eGFR	-1.2 (12.0)	-5.3 (13.1)	1.96 (-4.78 to 8.70)	0.563
Loop diuretic dose‡ (mg)	-16.0 (18.1)	12.3 (28.3)	-29.06 (-42.17 to -15.95)	<0.001

Abbreviations: SD=Standard deviation; CI=Confidence interval; LVEDV=Left ventricular end diastolic volume; LVESV=Left ventricular end systolic volume; LVEF=Left ventricular ejection fraction; LV=Left ventricular; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; BHB=Beta-hydroxy butyrate;

†=analysis excludes large outliers; 1 patient from each arm due to excessive weight gain and loss (see methods) –dapagliflozin (n=27), placebo (n=27);

‡=Bumetanide dose converted to equivalent frusemide dose (1mg bumetanide=40mg frusemide)