Dapagliflozin Versus Placebo on Left Ventricular Remodeling in Patients With Diabetes and Heart Failure: The REFORM Trial

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OBJECTIVE

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

RESEARCH DESIGN AND METHODS

We randomized 56 patients with T2DM and HF with LV systolic dysfunction to dapagliflozin 10 mg daily or placebo for 1 year, on top of usual therapy. The primary end point was difference in LV end-systolic volume (LVESV) using cardiac MRI. Key secondary end points included other measures of LV remodeling and clinical and biochemical parameters.

RESULTS

In our cohort, dapagliflozin had no effect on LVESV or any other parameter of LV remodeling. However, it reduced diastolic blood pressure and loop diuretic requirements while increasing hemoglobin, hematocrit, and ketone bodies. There was a trend toward lower weight.

CONCLUSIONS

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

Type 2 diabetes mellitus (T2DM) and heart failure (HF) commonly coexist 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 patients with T2DM with varying CV risk (n = 34,322) showed an overall 14% reduction in major adverse CV events and 24% reduction in composite of CV mortality and HF hospitalization (2). In the Dapagliflozin in Patients With Heart Failure trial (DAPA-HF), dapagliflozin was compared against standard of care in 4,744 patients with established HF and a striking 30% reduction in HF hospitalization, 18% reduction in CV death, and significant improvements in HF symptom burden were found (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 to explain the substantial improvements in HF outcomes seen in large clinical trials.

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RESEARCH DESIGN AND METHODS

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) remodeling (i.e., LV volumes, mass, and ejection fraction [EF]) using cardiac MRI (CMR). Fifty-six patients were randomized 1:1 to either dapagliflozin 10 mg/day or placebo for 1 year. Participants had a diagnosis of T2DM and history of symptomatic HF with a previously documented reduction in EF using echocardiography. They were on stable therapy for at least 3 months before recruitment, with a maximum loop diuretic dose of 80 mg/day and baseline estimated glomerular filtration rate (eGFR) of $\geq$45 mL/min/1.73 m^2.

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

Statistical Analysis

Data were 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 χ^2 test. A two-sided $P < 0.05$ was taken as significant. Analysis was performed using R version 3.4.3 for Windows.

RESULTS

Mean age was 67.1 years, and the majority were male (66.1%) with an average BMI of 32.5 kg/m^2. The majority (87.5%) were in New York Heart Association functional class I or II, indicating mild HF, with the most common etiology being ischemic heart disease. Mean baseline HbA_{1c} was 60.9 mmol/mol (7.7%), and the mean eGFR was 72.0 mL/min/1.73 m^2. Other baseline values are listed in Supplementary Table 1.

After 1 year, there was no significant change in LVESV (4.82 mL [95% CI −13.28 to 22.93]; $P = 0.594$). There was no effect on LVEDV (7.83 mL [−15.05 to 30.70]; $P = 0.495$), LVMI (2.5 g/m^2 [−3.95 to 8.95]; $P = 0.440$), or LVEF (0.96% [−3.32 to 4.69]; $P = 0.732$) (Table 1).

Dapagliflozin significantly reduced diastolic blood pressure (BP) (−8.15 mmHg [95% CI −13.02 to 3.28]; $P = 0.001$), but there was no difference in systolic BP or heart rate. Dapagliflozin increased hemoglobin (0.86 g/dL [0.27–1.46]; $P = 0.005$), hematocrit (2.89% [1.14–4.64]; $P = 0.002$), and fasting β-hydroxybutyrate (ketone body) (0.04 mmol/L [0.01–0.07]; $P = 0.022$). There was a trend toward lower weight (−2.26 kg [−4.83 to 0.31]; $P = 0.083$).

Patients on dapagliflozin required less loop diuretic therapy (−29.06 mg [95% CI −42.17 to −15.95]; $P < 0.001$) and were more likely to stop or reduce their loop diuretic dose (53.6% vs. 10.7%; $P = 0.001$). There was no significant difference in HbA_{1c} or eGFR at the end of 1 year.

Adverse Events

There were five deaths in total: one cancer death in the dapagliflozin arm and one cancer and three CV deaths in the placebo arm. Three acute coronary syndromes occurred in the placebo arm but none in the dapagliflozin arm. There was one HF hospitalization in each arm and no difference in the incidence of serious adverse events between the two arms.

Significantly more instances of major decline in renal function (sustained >20% increase in creatinine or eGFR <45 mL/min/1.73 m^2) were found in the dapagliflozin arm compared with placebo (28.6% vs. 0%; $P = 0.008$). This decline 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, there was a significant difference in diastolic BP, loop diuretic requirements, hemoglobin, hematocrit, and fasting ketone levels between groups. There was also a trend toward lower weight.

Reversing LV remodeling is an important factor in reducing mortality and morbidity in patients with HF (7,8). Therefore, the apparent absence of an effect on LV remodeling 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 as a result of 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 remodeling, to explain these effects of SGLT2i. Some secondary outcomes of this study may help to 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. 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 requirements. This led to a cautious selection of participants with milder HF on modest doses of diuretics. Ongoing work in a similar trial investigating SGLT2i on LV remodeling with a different agent of this class (NCT03485092, ClinicalTrials.gov) will help to validate our findings.

Table 1—Primary and key secondary outcomes

Outcome	Dapagliflozin (n = 28), mean (SD)	Placebo (n = 28), mean (SD)	Adjusted treatment effect (95% CI)	P value
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
LVMI (g/m^2)	4.0 (11.1)	0.6 (11.7)	2.5 (−3.95 to 8.95)	0.44
LV stroke volume (mL)	0.0 (6.5)	−2.9 (6.2)	1.86 (−1.52 to 5.24)	0.273
Indexed LA volume (mL/m^2)	−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)	0.73 (5.3)	−2.26 (−4.83 to 0.31)	0.083
Systolic BP (mmHg)	−2.6 (18.9)	3.6 (18.7)	−4.7 (−14.51 to 5.11)	0.34
Diastolic BP (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
HbA_{1c} (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

BHB, β-hydroxy butyrate; LA, left atrial. †Analysis excludes large outliers; one patient from each arm because of excessive weight gain and loss (dapagliflozin n = 27, placebo n = 27). ‡Bumetanide dose converted to equivalent frusemide dose (1 mg bumetanide = 40 mg frusemide).

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 remodeling. This warrants further investigation to understand potentially novel mechanisms that may be responsible for dapagliflozin's effect in improving HF outcomes.

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Author Contributions. J.S.S.S. codeveloped the hypothesis; collected, compiled, and analyzed the data; and authored the manuscript. I.R.M. analyzed the CMR images and critically appraised the manuscript. K.V., A.F., M.M., and S.G. helped with data collection. P.T.D., E.R.P., A.D.S., and C.C.L. codeveloped the hypothesis and critically appraised the manuscript. A.M.J.C., J.G., F.K., and J.G.H. appraised the manuscript. C.C.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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