The effect of empagliflozin on contractile reserve in heart failure: Prespecified sub-study of a randomized, double-blind, and placebo-controlled trial

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Background Sodium-glucose co-transporter-2 inhibitors improve cardiac structure but most studies suggest no change in left ventricular (LV) systolic function at rest. Whether sodium-glucose co-transporter-2 inhibitors improve LV contractile reserve is unknown. We investigated the effect of empagliflozin on LV contractile reserve in patients with heart failure (HF) and reduced ejection fraction.

Methods Prespecified sub-study of the Empire HF trial, a double-blind, placebo-controlled, and randomized trial. Patients with LV ejection fraction (LVEF) ≤ 40% on guideline-directed HF therapy were randomized (1:1) to empagliflozin 10 mg or placebo for 12 weeks. The treatment effect on contractile reserve was assessed by low dose dobutamine stress echocardiography.

Results In total, 120 patients were included. The mean age was 68 (SD 10) years, 83% were male, and the mean LVEF was 38 (SD 10) %. Respectively 60 (100%) and 59 (98%) patients in the empagliflozin and placebo groups completed stress echocardiography. No statistically significant effect of empagliflozin was observed for the contractile reserve assessed by LV-GLS (adjusted mean absolute change, empagliflozin vs placebo, 0.7% [95% confidence interval {CI} –0.5 to 2.0, $P = .25$]) or LVEF (adjusted mean absolute change, empagliflozin vs placebo, 2.2% [95% CI –1.4 to 5.8, $P = .22$]) from baseline to 12 weeks. LV-GLS contractile reserve was associated with accelerometer-measured daily activity level (coefficient –24 accelerometer counts [95% CI –46 to –1.8, $P = .03$]).

Conclusions Empagliflozin for 12 weeks added to guideline-directed HF therapy did not improve LV contractile reserve in patients with HF and reduced ejection fraction. (Am Heart J 2022;250:57–65.)

Treatment with sodium-glucose co-transporter-2 (SGLT2) inhibitors has demonstrated reductions in mortality and heart failure (HF) hospitalizations in patients with HF and reduced ejection fraction (HFrEF).[1,2] A number of hypotheses have been put forward on the possible underlying mechanisms, including effects on cardiac structure and function.[3] While only left ventricular (LV) mass is reduced in type 2 diabetes without HF,[4,5] LV dilatation is consistently improved in HFrEF patients,[6-8] and with a further left atrial volume reduction reported by some.[8] These changes suggest improvements in cardiac loading conditions and reverse cardiac remodeling. Despite the lack of SGLT2 inhibitor receptors in the heart, other proposed effects to support

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improvements in cardiac remodeling and contractility include sodium-hydrogen exchanger inhibition with improved calcium handling in the myocardium,[9,10] and increased availability of ketone bodies as an energy-efficient fuel.[11] However, in HFrEF patients, conflicting results have been reported on the effect of SGLT2 inhibitors on LV systolic function at rest and supplemental investigations during stress are lacking, as assessment of contractile reserve may be more sensitive to detect potential improvements in the systolic function.[6-8] The observed cardiac effects with SGLT2 inhibitors at rest, together with the proposed beneficial alterations in cardiac calcium handling and energy metabolism,[10,15] suggest that improvements in LV contractile reserve may be anticipated with this class of drugs. In fact, contractile reserve has been demonstrated to be improved with empagliflozin in a porcine model of HFrEF using cardiac magnetic resonance during dobutamine infusion at low dose.[16] Also, SGLT2 inhibitors reduce aortic stiffness and afterload,[17] so an improvement in systolic function could be expected. LV contractile reserve is an independent predictor of cardiovascular mortality and predicts the response to cardiac resynchronization therapy.[12-14] Thus, improved LV contractile reserve could potentially link the proposed cellular mechanisms in the heart with the reductions in adverse clinical outcomes observed with SGLT2 inhibitors. Therefore, we investigated the effect of the SGLT2 inhibitor empagliflozin on LV contractile reserve in patients with HFrEF.

Methods

Study overview

The present study was conducted as part of the Empire HF trial which has been previously reported.[18,19] In brief, this was an investigator-initiated, double-blind, and placebo-controlled trial, investigating the short-term effects of empagliflozin in patients with stable, chronic HFrEF. No significant change in N-terminal pro-brain natriuretic peptide, the primary endpoint of the study, was observed.[19] The research protocol complies with the Declaration of Helsinki and the study was approved by an institutional review board (Danish National Committee on Health Research Ethics, number H-17010756). Written informed consent was obtained from all patients. The study was prospectively registered with ClinicalTrials.gov (NCT03198585). This research was supported by The Danish Heart Foundation, The Research Council and The Research and Innovation Foundation of the Department of Cardiology at Herlev and Gentofte University Hospital, The A.P. Møller Foundation for the Advancement of Medical Science, and The Capital Region of Denmark. The manufacturer of empagliflozin had no role in any aspect of the study. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Patients

Included patients constituted a subgroup of the total Empire HF study population and were recruited from 4 specialized HF outpatient clinics in Denmark.[18] Patients on stable doses of guideline-directed HF therapy, in New York Heart Association functional class I to III, and with a LV ejection fraction (LVEF) $\leq$ 40% were eligible. Patients with type 2 diabetes were required to be on stable doses of anti-diabetic drugs prior to study inclusion. Patients treated with an SGLT2 inhibitor at the screening visit were not eligible. The full list of inclusion and exclusion criteria has previously been reported.[18]

Randomization

At the baseline visit, eligible patients were randomly assigned (1:1) to receive oral empagliflozin 10 mg or matching placebo once daily for 12 weeks. An independent institution, The Glostrup Hospital Pharmacy (Glostrup, Denmark), computer-generated the allocation sequence with random numbers in permuted blocks of 10. No stratification was performed. Study investigators and patients were blinded to treatment allocations for the duration of the study.

Echocardiography

Transthoracic echocardiography was performed at the baseline visit and repeated after 12 weeks (90 $\pm$ 15 days) at The Herlev and Gentofte University Hospital (Herlev, Denmark). Patients performed an overnight fast and paused beta-blocker therapy and nitrates for 24 hours prior to the examination. A Vivid E9 ultrasound system with a M5S probe was used for all examinations (General Electric Healthcare, Chicago, IL) and were performed by a single investigator. The full standardized resting echocardiography has previously been described in detail.[8] Following the resting echocardiography, 2-dimensional images were obtained during infusion of dobutamine at a dose of respectively 5, 10, and 20 μg/kg/min with dose increments every 3 minutes as part of the standardized dobutamine stress echocardiography, in order to obtain LV global longitudinal strain (LV-GLS) and LVEF contractile reserve during stress. Blood pressure was not measured during the dobutamine stress procedure as this is not part of the standard procedure at our institution. Analyses of the echocardiograms were performed collectively after completion of the study in random order by investigators blinded to treatment allocation, using the EchoPAC software (version 203, GE, Chicago, IL). LV-GLS was obtained by automatic myocardial speckle tracking of the LV in the 3 standard apical views (4-chamber, 2-chamber, and long-axis). A frame rate greater than 50 frames per second was used. The reported LV-GLS was the mean systolic midwall strain cal-

culated from a 17-segment LV model with at least 15 segments available for analysis. For patients in atrial fibrillation, at least 5 beats were recorded and the LV-GLS analysis was performed on a representative beat. For LVEF, the endocardial boarder of the LV was manually traced during end-systole and end-diastole in the apical 4-chamber and 2-chamber views to obtain the LV volumes. From these, LVEF was calculated using the biplane method of disks (Modified Simpson's Rule). In order to minimize the measurement variability, the manual tracings were repeated 3 times each on representative beats and the mean was used for the LVEF calculation. Patients with frequent premature ventricular contractions or poor-quality images were not analyzed. The variability for the LVEF measurements at rest has previously been reported, with an intraclass correlation coefficient of 0.62 and mean percentage error of 9.4% for the intraobserver variability, and an intraclass correlation coefficient (of 0.68 and mean percentage error of 11.8% for the interobserver variability.[8] No reproducibility analyses were performed for LV-GLS at rest or for the echocardiographic measures at stress. The reproducibility for resting LV-GLS is generally better than for LVEF and remains highly reproducible during stress.[20,21]

Other investigations

An accelerometer (Actigraph wGT3x-BT, Actigraph, Pensacola, FL) was worn by each patient for 7 days in conjunction with the baseline and 12-week visits. Using a standardized procedure, the average daily amount of moderate to vigorous physical activity was obtained.[19] Physical activity was expressed as arbitrary accelerometer counts, with higher values representing more time spend in moderate to vigorous physical activity. Accelerometer-measured physical activity provides information about the daily physical activity in free-living conditions and decreased physical activity assessed by accelerometry carries relevant prognostic information in patients with HF.[22]

Study endpoints

Prespecified endpoints were the between-group difference in the change of LV contractile reserve from baseline to 12 weeks.[18] LV contractile reserve was defined as the absolute change in LV-GLS or LVEF from rest to 20 μg/kg/min dobutamine stress. The presence of a clinically significant LV contractile reserve was defined as an absolute decrease in LV-GLS of ≥ 2% or an absolute increase in LVEF of ≥ 5%.[23] The response with inotropy was defined as the LV-GLS or LVEF at 20 μg/kg/min dobutamine stress. LV-GLS and LVEF values are shown as absolute values in accordance with current recommendations.[24]

Statistical analyses

A total of 72 patients were required to detect a relative improvement of 20% (SD 30%) with empagliflozin vs placebo in LV-GLS contractile reserve from baseline to 12 weeks, with a power of 0.80 and a significance level of 0.05. To allow for dropouts, all 120 patients enrolled at The Herlev and Gentofte University Hospital (Herlev, Denmark) as part of the main Empire HF trial, were enrolled in the present sub-study.[18]

All patients with complete data were included in the statistical analyses. Skewed variables compromising model assumptions were log-transformed prior to analysis. Within-group changes in LV-GLS, LVEF, and heart rate as response to 20 μg/kg/min dobutamine stress were analyzed using paired *t* tests. The primary analysis, the treatment effect on LV-GLS contractile reserve, was analyzed in an analysis of covariance (ANCOVA) model with the absolute change from baseline to 12 weeks in LV-GLS contractile reserve as the endpoint, and with adjustment for the baseline LV-GLS contractile reserve, the baseline heart rate response to dobutamine stress, age as a continuous variable, sex, and the treatment group. Subgroup analyses were performed post hoc by including the subgroup and its interaction with the covariates and the allocated groups in the ANCOVA model. The treatment effect on LVEF was analyzed in a similar manner.

Sensitivity analyses included investigation of the treatment effect on LV-GLS or LVEF at 20 μg/kg/min dobutamine stress analyzed in similar ANCOVA models as described above.

Moreover, comparisons of the number of patients with a clinically relevant LV contractile reserve were performed using Fisher's exact test.

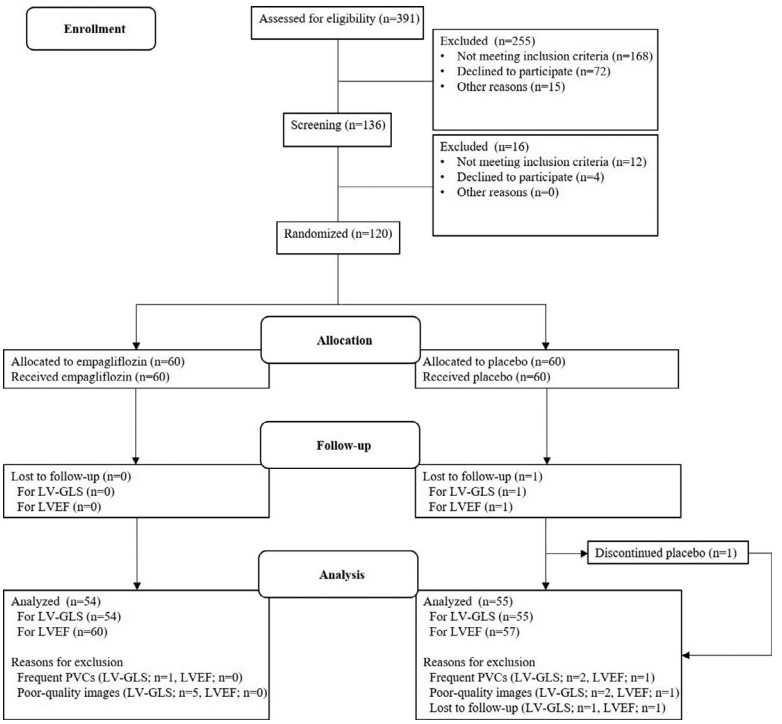
In supplemental analyses, simple linear regressions were performed to assess the association between the LV-GLS or LVEF contractile reserve and the accelerometer-measured daily activity level at baseline.

The statistical analyses were performed using the statistical software R for Windows (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria). Normally distributed data are presented as mean (SD) and skewed data as median (interquartile range [IQR]). Results are reported with 95% confidence intervals (CI) and a 2-sided *P*-value $<.05$ is applied to conclude statistical significance. Authors J.J. and M.S. had full access to all the data in the study and take responsibility for its integrity and the data analysis.

Results

Patients were screened for eligibility from June 29, 2017 to July 15, 2019. In total, 391 patients were screened and 120 (31%) were randomized (Figure 1). Baseline characteristics were well-balanced between the allocated groups (Table 1). Included patients represented mildly symptomatic patients with HFrEF. The median N-

Figure 1



Trial profile. LV-GLS, left ventricular global longitudinal strain; LVEF, left ventricular ejection fraction. PVCs, premature ventricular contractions.

terminal pro-brain natriuretic peptide was moderately elevated at 600 (IQR 355-1090) pg/mL and the mean LVEF was moderately reduced at 38 (SD 10) % as was the mean LV-GLS at -12 (SD 3.6) %. Most patients (59%) had ischemia as the primary cause of HF. Two patients (3.3%) in the placebo group were potentially paced from the right ventricle during the dobutamine stress protocol. Generally, high proportions of guideline-directed HF therapy were recorded in the study population, including beta-blocker in 97% of enrolled patients. The adherence to and safety of empagliflozin in this subgroup of the Empire HF trial have previously been reported.[25] The median adherence to the allocated treatment was 100% (IQR 99-100), and the safety profile was in accordance with the known profile of SGLT2 inhibitors as reported in larger studies.[1,2]

For the analyses of LV-GLS, 54 patients (90%) of 60 patients in the empagliflozin group and 55 patients (92%) of 60 patients in the placebo group were included. For LVEF, 60 patients (100%) in the empagliflozin group and 57 patients (95%) in the placebo group were analyzed. One patient (0.8%) of the 120 randomized patients dropped out at own request and was lost to follow-up. Other reasons for excluding patients from the analyses are reported in Figure 1.

In both the empagliflozin group and the placebo group, dobutamine was associated with significant increase in LVEF, decrease in LV-GLS, and increase in heart rate both at baseline and after 12 weeks (Table 2).

For the contractile reserve assessed by either LV-GLS or LVEF, no statistically significant effects were observed with empagliflozin (adjusted mean absolute changes from baseline to 12 weeks, empagliflozin vs placebo, 0.7% [95% CI −0.5 to 2.0; $P = .25$] for LV-GLS contractile reserve and 2.2% [95% CI −1.4 to 5.8; $P = .22$] for LVEF contractile reserve; Figure 2). These findings were generally consistent across subgroups specified by age, sex, body mass index, HF-related symptoms, daily activity level, glomerular filtration rate, baseline LV-GLS, baseline LVEF, baseline N-terminal pro-brain natriuretic peptide, the presence of ischemic heart disease, or treatment with sacubitril-valsartan, mineralocorticoid receptor antagonist, or loop diuretic (Supplemental Figures 1 and 2). In sensitivity analyses, the observed responses with inotropy were not statistically significant with empagliflozin compared to placebo (adjusted mean absolute changes from baseline to 12 weeks, empagliflozin vs placebo, 0.9% [95% CI −0.4 to 2.2; $P = .16$] for the LV-GLS response and 1.4% [95% CI −1.4 to 4.3; $P = .33$] for the LVEF response with inotropy). Ten (19%) of 54

Table 1. Baseline characteristics

	Empagliflozin (n = 60)	*Placebo (n = 60)*
Age (y), mean (SD)	68 (10)	67 (10)
Male sex	47 (78)	52 (87)
BMI (kg/m^2), mean (SD)	29 (4.4)	30 (5.0)
White race	57 (95)	59 (98)
NYHA functional class		
I	5 (8.3)	7 (12)
II	47 (78)	50 (83)
III	8 (13)	3 (5.0)
Systolic blood pressure (mmHg), mean (SD)	121 (17)	123 (16)
Heart rate (beats per min), mean (SD)	69 (12)	72 (13)
NT-proBNP (pg/mL), median (IQR)	586 (349-1068)	623 (375-1098)
Ischemia as primary cause of heart failure	35 (58)	36 (60)
Heart failure duration (mo), median (IQR)	31 (13-58)	26 (15-59)
One or more previous heart failure hospitalizations	36 (60)	36 (60)
History of type 2 diabetes	6 (10)	6 (10)
History of ischemic heart disease	36 (60)	39 (65)
History of atrial fibrillation or flutter	24 (40)	25 (42)
History of chronic kidney disease, stage 3	10 (17)	9 (15)
ACE inhibitor, ARB or sacubitril-valsartan	55 (92)	59 (98)
Sacubitril-valsartan	22 (37)	23 (38)
Beta-blocker	58 (97)	58 (97)
Mineralocorticoid receptor antagonist	40 (67)	43 (72)
CRT[*]	8 (13)	8 (13)
ICD[†]	23 (38)	22 (37)
Loop diuretic	39 (65)	35 (58)
Long-acting nitrates	4 (6.7)	5 (8.3)
Resting echocardiographic parameters, mean (SD)		
LVEDV (mL)	147 (64)	148 (61)
LVEDVI (mL/m^2)	72 (31)	71 (29)
LVESV (mL)	95 (49)	95 (48)
LVESVI (mL/m^2)	47 (24)	45 (23)
LAVI (mL/m^2)	36 (13)	37 (13)
LVMI (g/m^2)	110 (35)	105 (30)
RWT (%)	0.3 (0.1)	0.3 (0.1)
LV-GLS (%)	–12 (3.8)	–12 (3.3)
LVEF (%)	37 (9.3)	38 (10)

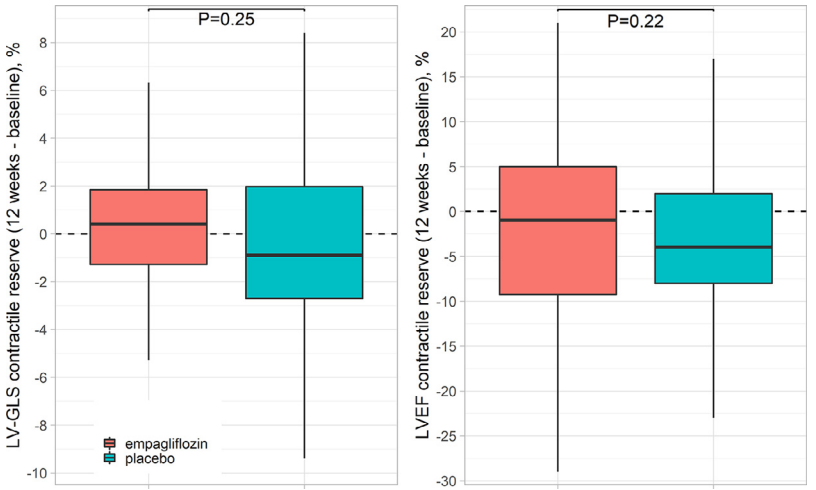
Numbers are counts (%) unless stated otherwise.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LAVI, left atrial volume index; LVEDV, left ventricular end-diastolic volume; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVESVI, left ventricular end-systolic volume index; LV-GLS, left ventricular global longitudinal strain; LVMI, left ventricular mass index; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-b-type natriuretic peptide; NYHA, New York Heart Association; ; RWT, relative wall thickness; SD, standard deviation.
[*] CRT with or without ICD.
[†] ICD or CRT with ICD.

Table 2. LV-GLS, LVEF, and heart rate response to dobutamine

Variable	*Group*	*Baseline visit*	*12-wk visit*
		Absolute response (stress – rest), Mean (95% CI)	Absolute response (stress – rest), Mean (95% CI)
LV-GLS, %	Placebo	–2.7 (–1.7 to –3.8); P <.0001	–3.3 (–2.3 to –4.3); P < .0001
	Empagliflozin	–3.0 (–2.2 to –3.8); P <.0001	–2.9 (–2.1 to –3.6); P < .0001
LVEF, %	Placebo	12 (9.7 to 15); P < .0001	8.8 (5.8 to 12); P < .0001
	Empagliflozin	13 (10 to 16); P < .0001	11 (8.8 to 13); P < .0001
Heart rate, bpm	Placebo	14 (9.3 to 18); P < .0001	14 (9.5 to 19); P < .0001
	Empagliflozin	13 (7.8 to 18); P < .0001	16 (9.5 to 23); P < .0001

Absolute LV-GLS, LVEF, and heart rate response during dobutamine stress echocardiography at baseline and 12 wk in the empagliflozin group and the placebo group. A more negative LV-GLS or positive LVEF response represent an increase in contractility. Stress denotes 20 μg/kg/min of dobutamine.
Abbreviations: bpm, beats per minute; CI, confidence interval; LV-GLS, left ventricular global longitudinal strain; LVEF, left ventricular global longitudinal strain.

Figure 2



Treatment effect on LV-GLS and LVEF contractile reserve. Raw data on the absolute change in left ventricular contractile reserve assessed by LV-GLS (left panel) and LVEF (right panel) from baseline to 12 weeks in the empagliflozin (red) and placebo group (green). A more negative LV-GLS or positive LVEF change represent an improvement in contractile reserve. The dashed line represents no change. The box represents the median and interquartile range. Whiskers represent 1.5 times the interquartile range. *P*-values are from the adjusted ANCOVA models. LV-GLS, left ventricular global longitudinal strain. LVEF, left ventricular ejection fraction. (Color version of figure is available online.)

patients in the empagliflozin group and 15 (27%) of 55 patients in the placebo group had a clinically relevant decrease in LV-GLS contractile reserve from baseline to 12 weeks (odds ratio, empagliflozin vs placebo, 0.61 [95% CI 0.24-1.50; $P = .36$]). Further, 17 (28%) of 60 patients in the empagliflozin group compared to 13 (23%) of 57 patients in the placebo group had a clinically relevant increase in LVEF (odds ratio, empagliflozin vs placebo, 1.34 [95% CI 0.58-3.09; $P = .53$]).

In supplemental analyses, an increase in baseline daily activity level was significantly associated with a decrease in LV-GLS contractile reserve, but not with contractile reserve assessed by LVEF (Supplemental Figure3).

Discussion

The main findings of the present study were that 12 weeks treatment with empagliflozin in patients with HFrEF did not increase the cardiac contractile reserve as assessed by low dose dobutamine stress echocardiography.

To our knowledge, this is the first study to investigate the effect of an SGLT2 inhibitor on cardiac contractile reserve. We have previously observed reductions in fluid volumes, cardiac preload, and cardiac chamber sizes, but without an effect on LV systolic function at rest.[8,25,26] These changes indicate that improvement in cardiac contractile reserve may be plausible with SGLT2 inhibitor therapy. The reasons for the lack of effect on cardiac contractile reserve may in theory be explained by the characteristics of the included patients. A large proportion had an ischemic etiology of their HF, with less likelihood of viable myocardium and improvement in contractile reserve. However, this remains speculative as our data actually indicate the presence of myocardial viability in the subgroup with an ischemic etiology of HF and this was also observed in the STICH trial.[27] Yet, while no differences in the treatment effects were observed between patients with ischemic vs nonischemic HF in the present study, such differences cannot be excluded based on the small sample size in these subgroup analyses.

Moreover, patients had an adequately high baseline contractile reserve to potentially respond to the therapy, as compared to the baseline contractile reserve in responders to cardiac resynchronization therapy.[13,14] Poor adherence or inadequate dosing (10 mg instead of 25 mg) of empagliflozin may be other plausible explanations for the lack of effect, yet we observed a high adherence, underpinned by a ~4% increase in hematocrit with empagliflozin,[25] and other relevant cardiac changes to therapy as stated above. Empagliflozin improved baseline LVEF in porcine and rat HFrEF models,[16,28] and the EMPA-TROPISM trial reported an improvement on resting LVEF after 6 months in HFrEF patients.[6] This may indicate that a longer treatment period is required to induce an effect on LV systolic function at rest. Whether this also applies to effects on LV contractile reserve remain unknown. Also, uncertainty remains regarding the effect of SGLT2 inhibitors on resting LV systolic function, even during longer treatment periods, as the SUGAR-

DM-HF and REFORM trials reported no effects after 9 and 12 months, respectively.[7,29] After 12 weeks, we observed modest reductions in LV and left atrial volumes with empagliflozin without effects on resting LVEF or LV-GLS.[8] Clinically significant reverse cardiac remodeling is generally expected beyond 12 weeks of treatment with other treatments for heart failure, thus supporting that the treatment period of the present study may have been too short to find changes in contractile reserve with empagliflozin.[30]

While changes in fluid reduction and cardiac loading conditions seem evident with SGLT2 inhibitor therapy,[25,26] further research is needed to consolidate the possible effect on cardiac remodeling and will shed light on the lack of effect in the present study. Despite the proposed thrifty substrate theory,[11] with an increased supply of energy efficient ketone bodies to the myocardium as a response to SGLT2 inhibitor therapy, and the finding that ketone infusion increase LV systolic function,[31] it still remains to be investigated whether SGLT2 inhibitor therapy induces relevant increases in ketone bodies to increase contractile reserve and this needs further investigation in future studies. We have previously demonstrated that the loss in fat mass is insignificant during short-term treatment with empagliflozin in patients with HFrEF, and does not increase cardiac output with exercise, which indirectly argues against the thrifty substrate theory.[26,32] Moreover, the absolute increase in ketone bodies seems small with empagliflozin treatment compared to the levels obtained by ketone infusion.[31,33] Also, the sodium-hydrogen exchanger inhibitor theory documented in animal models as a potential pathway for reverse cardiac remodeling and improved contractility with SGLT2 inhibitors awaits further confirmation in patients with HFrEF.[9,10]

In addition to the traditional measure of LV systolic function we investigated the effect on contractile reserve as assessed by LV-GLS, which to our knowledge has only been investigated at rest in 2 other trials in patients with HFrEF.[7,34] Further research is needed to establish it as an endpoint widely used in clinical trials. However, LV-GLS has shown to be more sensitive to detect LV dysfunction than LVEF,[35] and substantiates the lack of effect regarding LV contractile reserve in the present study.

A weak association between daily activity level and contractile reserve assessed by LV-GLS, not LVEF, was present. Our analyses generate important data to understand accelerometer-measured daily activity level as a new endpoint in HF trials. Future studies should explore which physiological and clinical variables that limit the patients in their daily physiological performance.

Methodological considerations

The present study has some limitations. First, a stress stimulus of 20 μg/kg/min dobutamine (instead of 10 μg/kg/min) was chosen as a high proportion of patients on beta-blocker therapy—with known counteracting effects to dobutamine—were included. Second, the endpoints of interest, cardiac contractile reserve, include 2 measurements (rest and 20 μg/kg/min) at each of the 2 visits (baseline and 12 weeks). As some degree of variation is inevitably introduced at each measurement, this dual measurement approach may reduce the ability to detect a true treatment effect. The observed variability for both the LV-GLS and LVEF contractile reserve may indicate that a larger sample is necessary in future trials when using these endpoints to assess treatment effects. Third, an effect of empagliflozin on resting LV systolic function could potentially mask a true treatment effect on the LV contractile reserve. However, no effect of empagliflozin was observed on resting LV-GLS or LVEF.[8] Additionally, similar results were observed in sensitivity analyses looking only at the LV function at stress, without inclusion of the baseline measurements. Fourth, when aortic stenosis severity is evaluated, a change in stroke volume of 20% or more is used as a measure of contractile reserve during low-dose dobutamine stress.[36] Whether this estimate should be used in future HF studies warrants further investigations. Fifth, the included patients were treated with high proportions of guideline-directed therapies for HFrEF and had only moderately decreased LV systolic function at baseline, which might limit the room for further improvements. Sixth, more methodological studies on LV-GLS as a measure during dobutamine stress in HF is needed, for example regarding whether infarcted and nonviable myocardial areas bias the estimate. However, it should be noted that we did not observe any difference in the effect of empagliflozin on neither LVEF nor LV-GLS contractile reserve when comparing patients with and without ischemic heart disease. Seventh, as some patients were excluded from the analyses, the possibility of attrition bias is introduced. However, the risk of attrition bias is limited as the number of excluded patients was low and similarly distributed in the allocated groups.

Clinical perspectives

SGLT2 inhibitors have proven to reduce mortality and HF hospitalizations in patients with HFrEF. Moreover, beneficial effects on cardiac structure at rest have been demonstrated. Yet, current data imply that improvement in cardiac systolic function at rest should not be anticipated in patients treated with this class of drugs. Similarly, the present study indicates that no substantial improvement in cardiac systolic function during stress should be anticipated.

Conclusion

Empagliflozin 10 mg once daily for 12 weeks in addition to guideline-directed HF therapy did not substantially improve left ventricular contractile reserve in patients with stable, chronic HFrEF as compared to

placebo. Future studies should focus on small changes in the metabolism and contractility of the myocardium with other imaging modalities during treatment with SGLT2 inhibitors.

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Conflict of interest

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Supplementary data

Supplemental Figures 1-3.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2022.04.008.

References

1. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995–2008.
2. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383:1413–24.
3. Cowie MR, Fisher M. Sglt2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. Nat Rev Cardiol 2020;17:761–72.
4. Verma S, Mazer CD, Yan AT, et al. Effect of empagliflozin on left ventricular mass in patients with type 2 diabetes mellitus and coronary artery disease: the empa-heart cardiolink-6 randomized clinical trial. Circulation 2019;140:1693–702.
5. Ersboll M, Jurgens M, Hasbak, et al. Effect of empagliflozin on myocardial structure and function in patients with type 2 diabetes at high cardiovascular risk: Tthe simple randomized clinical trial. Int J Cardiovasc Imaging 2021;38:579–87.
6. Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA, et al. Randomized trial of empagliflozin in nondiabetic patients with heart failure and reduced ejection fraction. J Am Coll Cardiol 2021;77:243–55.
7. Lee MMY, Brooksbank KJM, Wetherall K, et al. Effect of empagliflozin on left ventricular volumes in patients with type 2 diabetes, or prediabetes, and heart failure with reduced ejection fraction (sugar-dm-hf). Circulation 2021;143:516–25.
8. Omar M, Jensen J, Ali M, et al. Associations of empagliflozin with left ventricular volumes, mass, and function in patients with heart failure and reduced ejection fraction: a substudy of the empire hf randomized clinical trial. JAMA Cardiol 2021;6:836–40.
9. Baartscheer A, Schumacher CA, Wust RC, et al. Empagliflozin decreases myocardial cytoplasmic na(+) through inhibition of the cardiac na(+)/h(+) exchanger in rats and rabbits. Diabetologia 2017;60:568–73.
10. Packer M, Anker SD, Butler J, et al. Effects of sodium-glucose cotransporter 2 inhibitors for the treatment of patients with heart

failure: proposal of a novel mechanism of action. JAMA Cardiol 2017;2:1025–9.
11. Ferrannini E, Mark M, Mayoux E. Cv protection in the empa-reg outcome trial: A "thrifty substrate" hypothesis. Diabetes Care 2016;39:1108–14.
12. Paraskevaidis IA, Ikonomidis I, Simitsis P, et al. Multidimensional contractile reserve predicts adverse outcome in patients with severe systolic heart failure: a 4-year follow-up study. Eur J Heart Fail 2017;19:846–61.
13. Lancellotti P, Senechal M, Moonen M, et al. Myocardial contractile reserve during exercise predicts left ventricular reverse remodelling after cardiac resynchronization therapy. Eur J Echocardiogr 2009;10:663–8.
14. Kloosterman M, Damman K, Van Veldhuisen DJ, et al. The importance of myocardial contractile reserve in predicting response to cardiac resynchronization therapy. Eur J Heart Fail 2017;19:862–9.
15. Selvaraj S, Kelly DP, Margulies KB. Implications of altered ketone metabolism and therapeutic ketosis in heart failure. Circulation 2020;141:1800–12.
16. Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, et al. Empagliflozin ameliorates adverse left ventricular remodeling in nondiabetic heart failure by enhancing myocardial energetics. J Am Coll Cardiol 2019;73:1931–44.
17. Requena-Ibanez JA, Santos-Gallego CG, Rodriguez-Cordero A, et al. Mechanistic insights of empagliflozin in nondiabetic patients with hfref: from the empa-tropism study. JACC Heart Fail 2021;9:578–89.
18. Jensen J, Omar M, Kistorp C, et al. Empagliflozin in heart failure patients with reduced ejection fraction: a randomized clinical trial (empire hf). Trials 2019;20:374.
19. Jensen J, Omar M, Kistorp C, et al. Twelve weeks of treatment with empagliflozin in patients with heart failure and reduced ejection fraction: a double-blinded, randomized, and placebo-controlled trial. Am Heart J 2020;228:47–56.
20. Farsalinos KE, Daraban AM, Unlu S, et al. Head-to-head comparison of global longitudinal strain measurements among nine different vendors: The eacvi/ase inter-vendor comparison study. J Am Soc Echocardiogr 2015;28:1171–81.
21. Yamada A, Luis SA, Sathianathan D, et al. Reproducibility of regional and global longitudinal strains derived from two-dimensional speckle-tracking and doppler tissue imaging between expert and novice readers during quantitative dobutamine stress echocardiography. J Am Soc Echocardiogr 2014;27:880–7.
22. Tan MKH, Wong JKL, Bakrania K, et al. Can activity monitors predict outcomes in patients with heart failure? A systematic review. Eur Heart J Qual Care Clin Outcomes 2019;5:11–21.
23. De Luca A, Stolfo D, Caiffa T, et al. Prognostic value of global longitudinal strain-based left ventricular contractile reserve in candidates for percutaneous correction of functional mitral regurgitation: implications for patient selection. J Am Soc Echocardiogr 2019;32:1436–43.
24. Voigt JU, Pedrizzetti G, Lysyansky P, et al. Definitions for a common standard for 2d speckle tracking echocardiography: consensus document of the eacvi/ase/industry task force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging 2015;16:1–11.
25. Jensen J, Omar M, Kistorp C, et al. Effects of empagliflozin on estimated extracellular volume, estimated plasma volume, and measured glomerular filtration rate in patients with heart failure (empire hf renal): a prespecified substudy of a double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 2021;9:106–16.
26. Omar M, Jensen J, Frederiksen PH, et al. Effect of empagliflozin on hemodynamics in patients with heart failure and reduced ejection fraction. J Am Coll Cardiol 2020;76:2740–51.
27. Panza JA, Ellis AM, HR Al-Khalidi, et al. Myocardial viability and long-term outcomes in ischemic cardiomyopathy. N Engl J Med 2019;381:739–48.
28. Yurista SR, Sillje HHW, Oberdorf-Maass SU, et al. Sodium-glucose co-transporter 2 inhibition with empagliflozin improves cardiac function in non-diabetic rats with left ventricular dysfunction after myocardial infarction. Eur J Heart Fail 2019;21:862–73.
29. Singh JSS, Mordi IR, Vickneson K, et al. Dapagliflozin versus placebo on left ventricular remodeling in patients with diabetes and heart failure: the reform trial. Diabetes Care 2020;43:1356–9.
30. Aimo A, Gaggin HK, Barison A, et al. Imaging, biomarker, and clinical predictors of cardiac remodeling in heart failure with reduced ejection fraction. JACC Heart Fail 2019;7:782–94.
31. Nielsen R, Moller N, Gormsen LC, et al. Cardiovascular effects of treatment with the ketone body 3-hydroxybutyrate in chronic heart failure patients. Circulation 2019;139:2129–41.
32. Jensen J, Omar M, Kistorp C, et al. Metabolic effects of empagliflozin in heart failure: a randomized, double-blind, and placebo-controlled trial (empire hf metabolic). Circulation 2021;143:2208–10.
33. Lauritsen KM, Nielsen BRR, Tolbod LP, et al. Sglt2 inhibition does not affect myocardial fatty acid oxidation or uptake, but reduces myocardial glucose uptake and blood flow in individuals with type 2 diabetes: a randomized double-blind, placebo-controlled crossover trial. Diabetes 2021;70:800–8.
34. Desai AS, Solomon SD, Shah AM, et al. Effect of sacubitril-valsartan vs enalapril on aortic stiffness in patients with heart failure and reduced ejection fraction: a randomized clinical trial. JAMA 2019;322:1077–84.
35. Potter E, Marwick TH. Assessment of left ventricular function by echocardiography: the case for routinely adding global longitudinal strain to ejection fraction. JACC Cardiovasc Imaging 2018;11:260–74.
36. Vahanian A, Beyersdorf F, Praz F, et al. 2021 esc/eacts guidelines for the management of valvular heart disease. Eur Heart J 2022;43:561–632.