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Twelve weeks of treatment with empagliflozin in patients with heart failure and reduced ejection fraction: A double-blinded, randomized, and placebo-controlled trial

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Aims To investigate the effect of the sodium-glucose co-transporter-2 inhibitor empagliflozin on N-terminal pro-b-type natriuretic peptide (NT-proBNP) in patients with heart failure (HF) and reduced ejection fraction (HFrEF).

Methods and Results Empire HF was an investigator-initiated, multi-center, double-blinded, placebo-controlled, randomized trial. Patients with mildly symptomatic HFrEF, mean (standard deviation (SD)) age 64 (11) years, 85% male, and mean left ventricular ejection fraction 29% (8), on recommended HF therapy were assigned to receive either empagliflozin 10 mg once daily or placebo for 12 weeks. The primary endpoint was the between-group difference in the change of NT-proBNP from baseline to 12 weeks. In total, 95 patients were assigned to empagliflozin and 95 to placebo. No significant difference in the change of NT-proBNP with empagliflozin versus placebo was observed [Empagliflozin: baseline, median (interquartile range (IQR)) 582 (304-1020) pg/mL, 12 weeks, 478 (281-961) pg/mL; Placebo: baseline, 605 (322-1070) pg/mL, 12 weeks, 520 (267-1075) pg/mL, adjusted ratio of change empagliflozin/placebo 0.98; 95% confidence interval (CI) 0.82-1.11, $P = 0.7$]. Further, no significant difference was observed in accelerometer-measured daily activity level [adjusted mean difference of change, empagliflozin versus placebo, -26.0 accelerometer counts; 95% CI -88.0 to 36.0, $P = 0.4$] or Kansas City Cardiomyopathy Questionnaire Overall Summary Score [adjusted mean difference of change, empagliflozin versus placebo 0.8; 95% CI -2.3 to 3.9, $P = 0.6$].

Conclusion In low-risk patients with HFrEF with mild symptoms and on recommended HF therapy, empagliflozin did not change NT-proBNP after 12 weeks. Further, no change in daily activity level or health status was observed. (Am Heart J 2020;228:47-56.)

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Introduction

In type 2 diabetes (T2D), sodium-glucose co-transporter-2 (SGLT2) inhibitors reduce the risk of cardiovascular death or hospitalization for heart failure (HF) with similar benefit in patients with and without a history of HF.[1-4] In the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, dapagliflozin reduced the risk of cardiovascular death and worsening HF in patients with established HF with reduced ejection fraction (HFrEF), regardless of the presence of T2D.[5,6] Furthermore, treatment with dapagliflozin was associated with a reduction in plasma concentrations of N-terminal pro-b-type natriuretic peptide (NT-proBNP) after 8 months of treatment.[5,6] However, in the Dapagliflozin Effects on Biomarkers, Symptoms and Functional Status in Patients with HF with Reduced Ejection Fraction (DEFINE-HF) trial, dapagliflozin did not lower NT-proBNP in patients with HFrEF after 12 weeks of treatment.[7] At present, it is unknown whether

another frequently used SGLT2 inhibitor, empagliflozin, can reduce NT-proBNP and improve clinical HF outcomes in patients with HFrEF without T2D.[8,9] In this randomized placebo-controlled trial, we examined the effect of empagliflozin on NT-proBNP in patients with HFrEF.

Methods

Setting

The full study protocol has previously been published.[10] In brief, the Empire HF trial was an investigator-initiated, multicenter, double-blinded, placebo-controlled, randomized trial assigning patients (1:1) to empagliflozin or placebo. Recruitment took place between June 29, 2017, and September 10, 2019, and the study ended on January 17, 2020, when 190 randomized patients had completed the study as planned. The study was independently monitored in accordance with the Good Clinical Practice standards and complies with the Declaration of Helsinki, the locally appointed ethics committee approved the research protocol and informed consent was obtained from the patients. The manufacturer of empagliflozin had no part in the study.

Patients

The full list of inclusion and exclusion criteria is presented in the **Supplementary material, Section B**. Patients with New York Heart Association (NYHA) functional class I-III symptoms and a left ventricular ejection fraction (LVEF) of 40% or lower were recruited from the participating HF outpatient clinics, with no requirement to plasma concentrations of NT-proBNP at screening or randomization. Treatment with stable recommended HF therapy, and stable recommended antidiabetic therapy in patients with T2D, was required at least 30 days before randomization.

Randomization and blinding

Eligible patients were assessed at a screening visit and entered a screening period where the baseline daily activity level was assessed. All other procedures were performed at the following baseline visit where eligible patients were randomly assigned to treatment with empagliflozin or matching placebo. The allocation sequence was generated by the independent Glostrup Hospital Pharmacy using computer-generated random numbers in blocks of 10 without stratification. Study investigators and patients were blinded to treatment allocation for the duration of the study. Data analyses were performed blinded to treatment allocation.

Procedures

After randomization, patients entered a 12-week treatment period with empagliflozin 10 mg once daily or placebo. Changes in background therapy were only encouraged if side effects were suspected. The 12-week procedures were performed at the end-of-study visit, performed on day 90±15 days from the baseline visit.

Plasma concentrations of NT-proBNP were analyzed on fasting blood samples, which were immediately centrifuged upon collection and stored at -80^{0}C. A batch analysis was performed in March 2020 at a central laboratory blinded to treatment allocation (Atellica IM NT-proBNP assay on Atellica IM analyzer platform, Siemens Healthineers, Erlangen, Germany).[11]

Daily activity level was assessed using the Actigraph wGT3X-BT accelerometer (Actigraph, Pensacola, FL).[12] Patients were instructed to wear the accelerometer around the waist continuously for 7 days, including during sleep, and to remove the device only to avoid contact with water. Daily activity level is reported in accelerometer counts, with higher counts reflecting higher daily activity level. Moreover, a subgroup of the study population performed the 6-minute walk test (**Supplementary material, Section C**).

Health status was quantified using the Kansas City Cardiomyopathy Questionnaire (KCCQ).[13] The KCCQ is self-administered and consists of 23 items, summarized in the Overall Summary Score (KCCQ-OSS), the Clinical Summary Score (KCCQ-CSS), and the Total Symptom Score (KCCQ-TSS). Scores range from 0 to 100, with higher scores reflecting better health status. Patients completed the questionnaire on their own before any other procedures were performed. All adverse events were reported by study investigators.

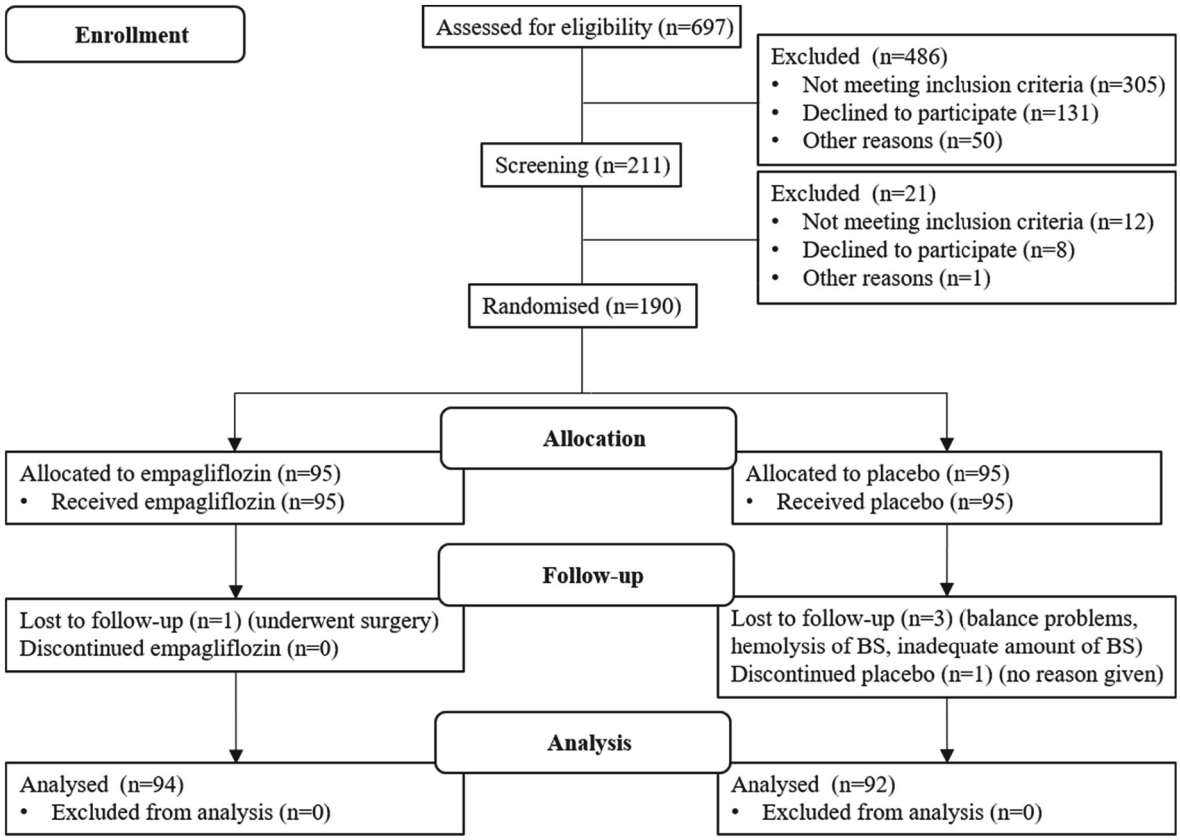
Endpoints

The primary endpoint was the between-group difference in the change of NT-proBNP from baseline to 12 weeks. Secondary endpoints included the between-group difference in the change of daily activity level and health status from baseline to 12 weeks. Exploratory endpoints included the between-group difference in the change of hematocrit, systolic blood pressure, body weight and estimated glomerular filtration rate (eGFR) from baseline to 12 weeks. Prespecified safety endpoints included events of urinary tract infection, genital infection, hypoglycemia, bone fracture, ketoacidosis, amputation, Fournier's gangrene, thromboembolic events, hospitalizations with volume depletion, and hospitalizations with acute renal failure.

Statistical analysis

To test the primary hypothesis of a 30% (standard deviation (SD) 70%) reduction in plasma concentrations of NT-proBNP between the empagliflozin group and the placebo group at 12 weeks, with a power of 0.80 and a significance level of .05, a total sample size of 172 patients randomly assigned to two groups was required. The primary endpoint was log-transformed and analyzed using a prespecified analysis of covariance (ANCOVA) with the log-transformed plasma concentrations of NT-proBNP, age, gender, history of T2D, and site of randomization as baseline covariates. The primary

Figure 1



Flow diagram of the empire HF trial.

analysis was performed in the intention-to-treat (ITT) population without imputation of missing values. Prespecified sensitivity analyses included analysis in the per-protocol population and analysis in the ITT population with missing NT-proBNP values imputed using multiple imputations.[14] Prespecified subgroup analyses were performed for the primary endpoint, with *P*-values adjusted using the method of Benjamini and Hochberg which controls the false discovery rate (FDR). An exploratory analysis comparing the proportion of patients with a reduction in NT-proBNP ≥30% was performed using Fischer's exact test.[15]

Secondary and exploratory continuous endpoints were analyzed in prespecified ANCOVA models. Substantially skewed endpoints were log-transformed prior to analysis. Analysis of daily activity level was performed in a modified ITT population, all other secondary and exploratory analyses were performed in the ITT population (**Supplementary material, Sections C-E**). An exploratory analysis comparing the proportion of patients with ≥5-point improvement or deterioration in the KCCQ-OSS was performed using Fischer's exact test.[16] An exploratory analysis compared the 6-minute walking distance (6MWD) with the accelerometer-measured daily activity level in simple linear regressions. Secondary and exploratory analyses were not adjusted for multiplicity.

Statistical testing was performed at a two-sided significance level of 0.05 and estimates with their 95% confidence intervals (CIs) were calculated. All analyses were performed using R for Windows (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria). Unless stated otherwise, normally distributed continuous data are presented as mean (SD), non-normally distributed as median (interquartile range (IQR)), and categorical data as absolute numbers (%).

Results

We assessed 697 patients for eligibility of whom 190 were eligible for randomization (Figure 1). Baseline characteristics were similar in patients allocated to empagliflozin and placebo (Table I). The randomized patients were primarily males (85%), in NYHA functional class II (78%) and 52% had one or more previous hospitalizations for HF. Mean LVEF was 29%[8] and plasma concentration of NT-proBNP moderately elevated with a

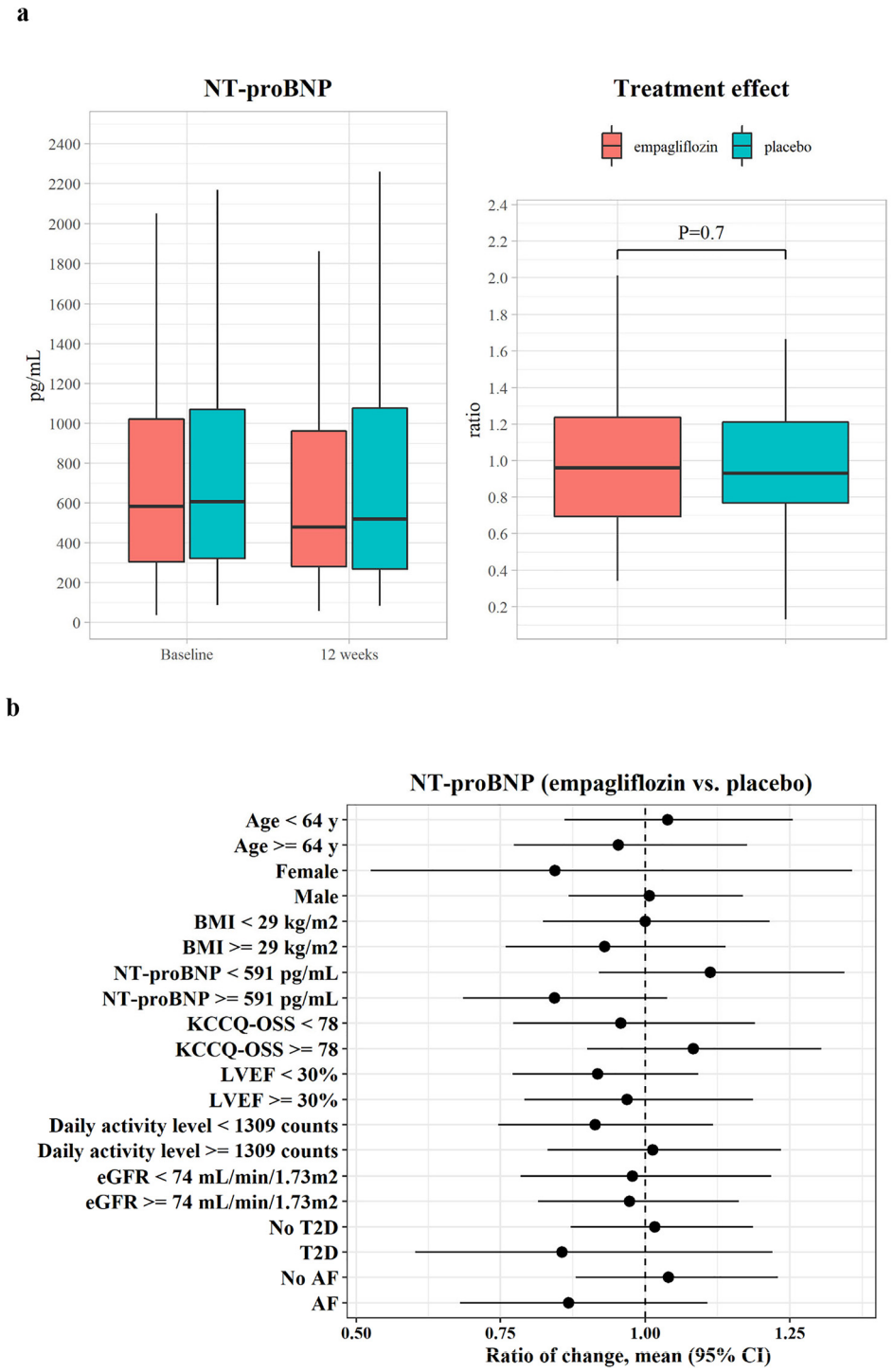
Table I. Baseline characteristics of randomized patients

	Empagliflozin (n = 95)	Placebo (n = 95)
Age (years), median (IQR)	64 [57-73]	63 [55-72]
Male sex	79 (83)	83 (87)
BMI (kg/m^2), median (IQR)	29 [27-33]	29 [26-33]
Caucasian	92 (97)	94 (99)
NYHA functional class		
I	5 (5.3)	7 (7.4)
II	72 (76)	77 (81)
III	18 (19)	11 (12)
Heart rate/min, median (IQR)	68 [63-77]	70 [63-80]
Systolic blood pressure (mmHg), median (IQR)	117 [107-130]	122 [109-132]
Peripheral edema	9 (9.5)	13 (14)
Jugular vein distension	0 (0.0)	1 (1.1)
LVEF (%), median (IQR)	30 [25-35]	30 [25-35]
NT-proBNP (pg/mL), median (IQR)		
All (n = 190)	582 (304-1020)	605 (322-1070)
Sinus rhythm (n = 120)	419 (277-672)	452 (244-780)
Atrial fibrillation or flutter (n = 70)	1050 (456-1845)	993 (584-1480)
Primary cause of HF		
Ischemic	48 (51)	49 (52)
Non-Ischemic	47 (49)	46 (48)
HF duration (months), median (IQR)	35 (12-67)	27 (13-62)
Number of HF hospitalizations		
0	46 (48)	45 (47)
1	39 (41)	37 (39)
2≤	10 (11)	13 (14)
T2D, history of or newly diagnosed	19 (20)	14 (15)
Newly diagnosed T2D[a]	8 (8.4)	1 (1.1)
HbA1c (mmol/mol), median (IQR)	40 (36-43)	39 (36-42)
Ischemic heart disease	50 (53)	53 (56)
Atrial fibrillation or flutter	36 (38)	34 (36)
Chronic kidney disease, stage 3	11 (12)	12 (13)
eGFR (mL/min/1.73m^2), median (IQR)	73 [57-89]	74 [60-89]
CRT[b]	18 (19)	18 (19)
ICD[c]	45 (47)	46 (48)
ACE inhibitor, ARB or sacubitril-valsartan	90 (95)	92 (97)
Sacubitril-valsartan	31 (33)	27 (28)
Beta-blocker	91 (96)	89 (94)
MRA	62 (65)	63 (66)
Digitalis	2 (2.1)	2 (2.1)
Loop diuretic	62 (65)	59 (62)
Long-acting nitrates	4 (4.2)	5 (5.3)
Lipid lowering medication[d]	60 (63)	65 (68)
Antithrombotic or anticoagulant medication[e]	73 (77)	70 (74)
Antidiabetic medication in patients with a history of T2D	**n = 11**	**n = 13**
Metformin	10 (91)	7 (54)
Sulfonylurea	2 (18)	1 (7.7)
DPP-4 inhibitor	0 (0.0)	5 (39)
GLP-1 receptor agonist	1 (9.1)	4 (31)
Insulin	5 (46)	3 (23)

Numbers are counts (%) unless stated otherwise. Both normally and non-normally distributed continuous variables are presented as median (IQR). IQR, interquartile range; BMI, body mass index; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-b-type natriuretic peptide; HF, heart failure; T2D, type 2 diabetes; Hba1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; DPP-4, Dipeptidyl peptidase 4; GLP-1, Glucagon-like peptide 1. [a]Defined as an HbA1c equal to or above 48 mmol/mol at both screening and randomization in patients without a history of type 2 diabetes. [b]Including CRT with or without ICD. [c]Including ICD or CRT with ICD. [d]Including statins, ezetemibe, fibrates, anion exchange resins and/or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor. [e]Including acetylsalicylic acid (ASA), Adenosine diphosphate (ADP) receptor blockers, vitamin K antagonist, Non-Vitamin K antagonist oral anticoagulants (NOACs), dipyridamole and others.

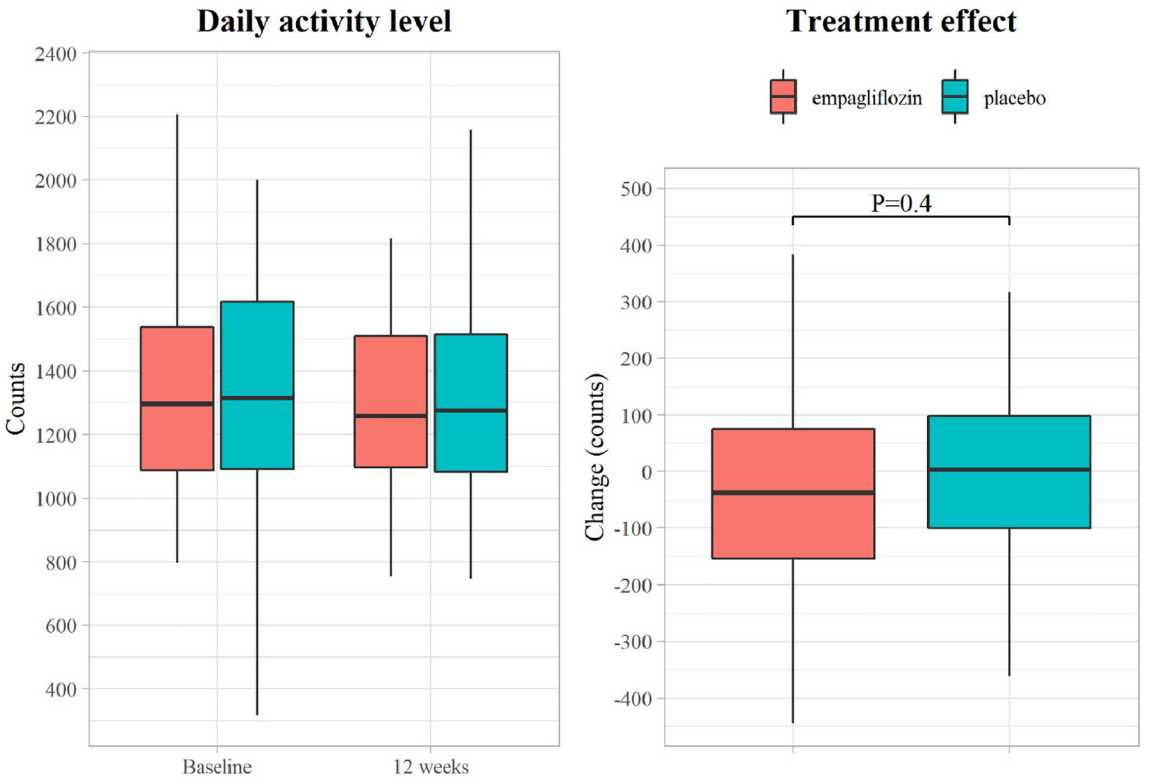
median of 591 (304-1048) pg/mL. T2D was present in 18%, and atrial fibrillation or flutter in 37%. A high proportion was on recommended HF therapy; 96% of patients were receiving an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or sacubitril-valsartan (31% sacubitril-valsartan); 96% were

Figure 2



A, NT-proBNP at baseline and 12 weeks, and the unadjusted relative treatment effect in the empagliflozin and placebo group with P-value from the adjusted analysis. The whiskers represent 1.5 × IQR. **B,** Change in NT-proBNP in subgroups.All subgroups were prespecified, except patients with AF or not. Median reported for all continuous variables. BMI, body mass index; NT-proBNP, N-terminal pro-b-type natriuretic peptide; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; T2D, history of or newly diagnosed type 2 diabetes; AF, atrial fibrillation or flutter; CI, confidence interval. Unadjusted P-value for interaction = 0.05 for NT-proBNP subgroups, all other unadjusted and FDR-adjusted P-values for interaction > 0.05.

Figure 3



Daily activity level at baseline and 12 weeks, and the unadjusted absolute treatment effect in the empagliflozin and placebo group with *P* value from the adjusted analysis. The whiskers represent 1.5 × IQR.

treated with a beta-blocker and 66% with a mineralocorticoid receptor antagonist; 19% had a cardiac resynchronization therapy (CRT) device and 48% had an implantable cardioverter-defibrillator (ICD). The median adherence rate to the allocated treatment was 100% (98.9-100) **(Supplementary material, Section F).** A total of 44 (23%) of the included patients with sinus rhythm and 40 (21%) with atrial fibrillation or flutter had fulfilled the criteria for inclusion in the DAPA-HF trial.

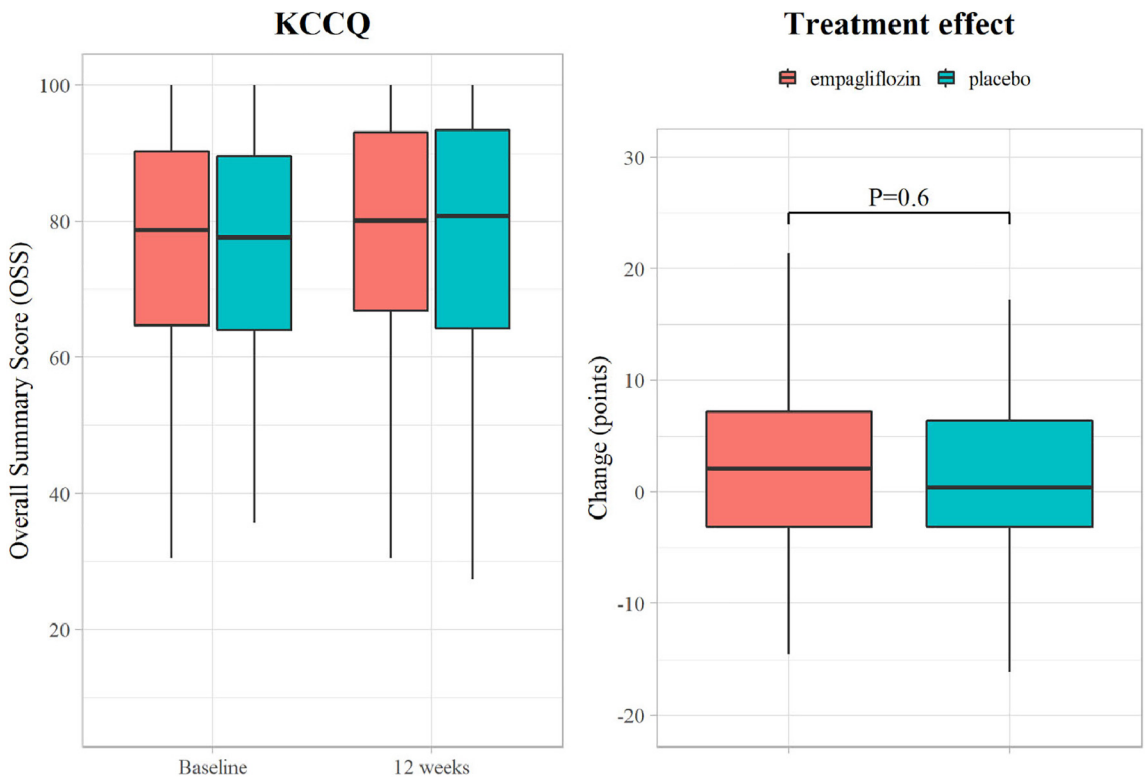
NT-proBNP

The 12-week visit was missed in 2 patients due to causes unrelated to the study, and 2 patients had blood samples which could not be analyzed (Figure 1). In total, 94 in the empagliflozin group and 92 in the placebo group were included in the analysis. The primary endpoint, the between-group difference in the change of NT-proBNP from baseline to 12 weeks was not significant [Empagliflozin: baseline, median (IQR) 582 (304-1020) pg/mL, 12 weeks, 478 (281-961) pg/mL; Placebo: baseline, 605 (322-1070) pg/mL, 12 weeks, 520 (267-1075) pg/mL with adjusted ratio of change empagliflozin/placebo 0.98; 95% confidence interval (CI) 0.82-1.11, $P = .7$] (Figure 2a). NT-proBNP did not change significantly over time in neither the empagliflozin ($P = .1$) nor in the placebo group ($P = .2$). Analysis of the primary endpoint in the ITT population with imputation and analysis in the per-protocol population yielded similar results [all $P = .7$]. The results were consistent within the prespecified subgroups, except of a trend towards an effect in patients with NT-proBNP ≥591 pg/L [adjusted ratio of change empagliflozin/placebo 0.81; 95% CI 0.54-1.04, unadjusted *P*-value for interaction = .05 (FDR-adjusted $P = .5$)] (Figure 2b). In the exploratory analysis, a reduction in NT-proBNP ≥30% was observed in 27 of 94 patients (29%) in the empagliflozin group and 18 of 92 patients (20%) in the placebo group, with no significant between-group difference [empagliflozin versus placebo odds ratio (OR) 1.66; 95% CI 0.84-3.28, $P = .2$].

Daily activity level

The baseline or the 12-week activity measurement was missed in 17 patients due to logistic problems or technical issues with the accelerometer, and 7 patients had inadequate accelerometer data with less than 4 valid days. In total, 82 in the empagliflozin group and 84 in the

Figure 4



KCCQ-OSS score at baseline and 12 weeks, and the unadjusted absolute treatment effect in the empagliflozin and placebo group with P-value from the adjusted analysis. The whiskers represent 1.5 × IQR.

placebo group were included in the analysis. The secondary endpoint, the between-group difference in the change of daily activity level in the empagliflozin group compared with the placebo was not significant [Empagliflozin: baseline, mean (SD) 1365 (391) accelerometer counts, 12 weeks, 1310 (324) accelerometer counts; Placebo: baseline, 1335 (370) accelerometer counts, 12 weeks, 1330 (358) accelerometer counts with adjusted mean difference of change empagliflozin versus placebo -26.0 accelerometer counts; 95% CI -88.0 to 36.0, P = .4] (Figure 3). In an exploratory analysis, a significant association between the 6MWD and the accelerometer-measured daily activity level was observed in a representative subgroup of the study population (**Supplementary material, Section C**).

Health status

In total, 94 in the empagliflozin group and 92 in the placebo group completed KCCQ at both visits. The between-group difference in KCCQ-OSS was not significant [Empagliflozin: baseline, mean (SD) 75.6 (18.3), 12 weeks, 77.6 (17.6). Placebo: baseline, 74.9 (17.8), 12 weeks, 76.8 (19.8) with adjusted mean difference of change empagliflozin versus placebo 0.8; 95% CI -2.3 to 3.9, P = .6] (Figure 4). Similar results were observed for KCCQ-CSS and KCCQ-TSS (**Supplementary material, Section D**). In the exploratory analysis, improvement in KCCQ-OSS ≥5 was observed in 40 of 94 patients (43%) in the empagliflozin group and 39 of 92 patients (42%) in the placebo group, with no significant between-group difference [Empagliflozin versus placebo odds ratio (OR) 1.01; 95% CI 0.56-1.80, P = 1.0]. A deterioration in KCCQ-OSS ≥5 was observed in 20 of 94 patients (21%) in the empagliflozin group and 16 of 92 patients (17%) in the placebo group, with no significant between-group difference [empagliflozin versus placebo OR 1.28; 95% CI 0.62-2.67, P = .6].

Supplementary analyses

In prespecified exploratory analyses, significant differences in the change of hematocrit, systolic blood pressure and body weight with empagliflozin versus placebo were observed, with an increase in hematocrit, and decreases in systolic blood pressure and body weight. No significant difference in the change of eGFR was observed (**Supplementary material, Section E**).

Safety

A summary of prespecified safety endpoints, hospitalizations for HF and deaths during the on-treatment period is presented in the **Supplementary material, Section G.** In total, 11 patients were hospitalized, and no patients died during the study. Observed frequencies were too low to allow for statistical analysis of differences between allocated groups. No adverse events led to treatment discontinuation.

Discussion

Main findings

In low-risk patients with HFrEF with mild symptoms on recommended HF therapy, empagliflozin did not change NT-proBNP after 12 weeks. Further, no change in daily activity level or health status was observed with empagliflozin.

The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial in patients with T2D and established cardiovascular disease demonstrated a significant reduction in cardiovascular death or hospitalization for HF in patients with or without investigator-reported HF, a benefit observed within few months of initiating treatment with empagliflozin.[2,17] This prompt treatment effect, could suggest an underlying hemodynamic mechanism, including a lowering of intracardiac pressures.[18,19] A reduction of filling pressures would be anticipated to be associated with an early decrease in plasma concentrations of NT-proBNP. Based on this, we hypothesized in the Empire HF trial that 12 weeks of treatment with empagliflozin would reduce NT-proBNP in patients with established HFrEF on recommended HF therapy. However, in accordance with the results from the DEFINE-HF and the Effects of Empagliflozin on Cardiac Structure in Patients with Type 2 Diabetes (EMPA-HEART Cardiolink-6) trials,[7,8] we did not observe this early effect on plasma concentrations of NT-proBNP after initiation of treatment with an SGLT2 inhibitor.

Compared with the DAPA-HF and DEFINE-HF trials,[5,7] the Empire HF trial included a larger proportion of Caucasian males, and patients with better functional capacity as well as lower plasma concentrations of NT-proBNP. Further, a lower proportion of the patients had T2D and a lower proportion was treated with a loop diuretic or digitalis. Both the Empire HF and DEFINE-HF trials had a higher proportion of patients treated with sacubitril-valsartan, a CRT and/or an ICD device than the DAPA-HF trial. These differences suggest that patients included in the Empire HF trial were well-treated with recommended HF therapy, had mild symptoms, and a relatively low-risk for cardiovascular events estimated by the plasma concentrations of NT-proBNP.[20] Thus, it could be speculated that the current study included patients where additional treatment effects were difficult to obtain. However, subgroup analyses showed an apparently larger effect in patients with NT-proBNP ≥591 pg/mL (median ≈ DAPA-HF inclusion criteria) than in patients with NT-proBNP below the median (Figure 2b). Whether this observation reflects a true effect of empagliflozin on NT-proBNP already after 12 weeks in patients with NT-proBNP ≥591 pg/mL remains to be determined. We believe the present study population is representative of an important proportion of patients with HFrEF in everyday clinical practice. Increased plasma concentrations of NT-proBNP were not an inclusion criterion in the present trial. It may explain why plasma concentrations of NT-proBNP are lower than the ones observed in e.g. the DAPA-HF trial and the patients included in the present trial may primarily represent the best 1/3 of contemporarily treated patients with HFrEF.[21]

Due to the lack of effect of empagliflozin 10 mg on plasma concentrations of NT-proBNP, it may be speculated that either the patient adherence was poor or that the dose of empagliflozin was too low for patients without T2D. However, during monitoring of the study, no poor adherence was observed, and in prespecified exploratory analyses, a significant treatment effect on hematocrit, systolic blood pressure, and body weight was observed (**Supplementary material, Section E**).[6,17] Therefore, poor patient adherence to treatment or inadequate dosing of empagliflozin are probably not reasons for the lack of effect on NT-proBNP.

In contrast with the present study, the DAPA-HF trial, a 20% reduction in NT-proBNP after 8 months was observed.[5] Therefore, it may be proposed that the chosen treatment period was to short or that only dapagliflozin, and not empagliflozin, reduces NT-proBNP. However, in the DEFINE-HF trial,[7] no effect of dapagliflozin on NT-proBNP was observed after 12 weeks in HFrEF patients with a median NT-proBNP of 1136 pg/mL, which supports that no difference exists between dapagliflozin and empagliflozin for the effect on natriuretic peptides. The effect on NT-proBNP after a longer treatment period in the DAPA-HF trial is in contrast with the prompt effect of SGLT2 inhibitors on clinical HF outcomes.[1,5] This may be explained by counteracting stimuli on NT-proBNP during treatment with SGLT2 inhibitors. An increase in hematocrit may reflect a diuretic effect and a decrease in systolic blood pressure a reduction in afterload which together induce a decrease in NT-proBNP release,[22] versus a small decline in eGFR and body weight which may oppose this effect, probably by a decrease in clearance of NT-proBNP.[6,23,24]

Considering the results of the DAPA-HF trial,[5,25] which demonstrated an effect of an SGLT2 inhibitor on mortality, morbidity and health status (true clinical endpoints) in patients with HFrEF,[5,25] it may be proposed that we chose the wrong endpoint (surrogate) in the Empire HF trial. Our results, therefore, re-emphasize the complexity of selecting the right surrogate endpoint in HF trials.[26] The observed effects in the

Empire HF trial on hematocrit, systolic blood pressure, and body weight suggest that 10 mg of empagliflozin has metabolic and hemodynamic effects even in mildly symptomatic HFrEF patients with a lower risk of clinical HF outcomes than the patients included in the DAPA-HF trial.[5]

No change in daily activity level assessed by accelerometry or health status assessed by KCCQ was observed in the Empire HF trial. In that framework, it should be noted that the health status at baseline was better compared with both the DEFINE-HF and DAPA-HF trials across the KCCQ scores,[7,25] emphasizing that further improvements were less likely to occur. Activity level assessed by accelerometry is a relatively new endpoint in clinical HF trials,[27] for which reason we evaluated it against the 6-minute walk test.[28] There was a clear association between the 6MWD and the accelerometer-measured daily activity level, suggesting that the accelerometer detect a meaningful physiological measure for HF research (**Supplementary material, Section C**).

Methodological considerations

The generalizability of our findings needs to be discussed. The results should not be extrapolated to patients with HFrEF and higher plasma concentrations of NT-proBNP and/or who are more symptomatic. Based on the presented data, and the results from other studies including patients with T2D and cardiovascular disease, or HFrEF patients with more symptoms and a worse health status,[7,8] the effect of 12 weeks treatment with empagliflozin on plasma concentrations of NT-proBNP is probably less than 30% and a longer treatment period is likely needed to observe an eventually smaller effect on NT-proBNP.

Clinical perspectives

The results of the Empire HF trial (and DEFINE-HF) indicate that plasma concentrations of NT-proBNP do not necessarily decrease despite initiation of a treatment that reduces morbidity and mortality. Clinicians should be aware of this to guide their patients sufficiently. Moreover, considering the results of the DEFINE-HF trial and the present study, it is likely that the observed clinical benefits of SGLT2 inhibitors are not mediated by an initial decrease in NT-proBNP in HFrEF patients with and without T2D. Finally, in patients not fulfilling the inclusion criteria of the DAPA-HF trial according to functional class and NT-proBNP, it may be speculated that an SGLT2 inhibitor does not rapidly improve symptoms and quality of life.

In conclusion, empagliflozin 10 mg once daily did not change NT-proBNP after 12 weeks in low-risk patients with HFrEF with mild symptoms receiving recommended HF therapy. Further, no change in daily activity level or health status was observed.

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Declaration of competing interest

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Appendix A. Supplementary data

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