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**CLINICAL RESEARCH**
*Heart failure and cardiomyopathies*

# Empagliflozin, irrespective of blood pressure, improves outcomes in heart failure with preserved ejection fraction: the EMPEROR-Preserved trial

**Michael Böhm [1]*, Stefan Anker [2,3], Felix Mahfoud [1], Lucas Lauder [1], Gerasimos Filippatos [4], João Pedro Ferreira [5,6], Stuart J. Pocock [7], Martina Brueckmann [8,9], Ilias Saloustros[10], Elke Schüler[11], Christoph Wanner [12], Faiez Zannad [5,6], Milton Packer [13,14], and Javed Butler[13,15], on behalf of the EMPEROR-Preserved Trial Committees and Investigators**

[1]Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Saarland University, Kirrberger Str. 1, 66421 Homburg, Saarland, Germany; [2]Department of Cardiology (CVK), and Berlin Institute of Health Center for Regenerative Therapies (BCRT), Augustenburger Platz 1, 13353 Berlin, Germany; [3]Centre for Cardiovascular Research (DZHK) partner site Berlin, Charité Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany; [4]National and Kapodistrian University of Athens School of Medicine, Athens University Hospital Attikon, 1Rimini St, 12462 Athens, Greece; [5]Université de Lorraine, Centre d'Investigation Clinique- Plurithématique Inserm CIC-P 1433, 54500 Vandoeuvre-Les-Nancy, France; [6]Inserm U1116, CHRU Nancy Brabois, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), 54500 Vandoeuvre-Les-Nancy, France; [7]Department of Medical Statistics, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, UK; [8]Boehringer Ingelheim International, Binger Str. 173, 55218 Ingelheim, Rheinland-Pfalz, Germany; [9]First Department of Medicine, Faculty of Medicine Mannheim, University of Heidelberg, Grabengasse 1, 69117 Heidelberg, Baden-Württemberg, Germany; [10]Medical Department, Boehringer Ingelheim TA Cardiometabolism Respiratory Medicine, Ringstr. 173, 55218 Ingelheim, Germany; [11]Mainanalytics GmbH, Sulzbach, Otto-Volger-Str. 3c, 65843 Sulzbach/Taunus, Hessen, Germany; [12]Medizinische Klinik und Poliklinik 1, Schwerpunkt Nephrologie, Universitätsklinikum Würzburg. Oberdürrbacher Str. 6, 97080 Würzburg, Bayern, Germany; [13]Baylor Heart and Vascular Institute, Baylor University Medical Center, 3500 Gaston Ave, Dallas, TX 75246, USA; [14]Imperial College, Exhibition Road, SW7 2AZ London, UK; and [15]Department of Medicine, Department of Medicine (L650), University of Mississippi School of Medicine, 2500 N. State St, Jackson, MS 39216, USA

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## Abstract

**Aims** Empagliflozin reduces the risk of cardiovascular death or heart failure (HF) hospitalization in patients with HF and preserved ejection fraction. This study aims to evaluate if systolic blood pressure (SBP) moderates these effects.

**Methods and results** The association of SBP and the treatment effects of empagliflozin in EMPEROR-Preserved (empagliflozin outcome trial in patients with chronic heart failure with preserved ejection fraction) was evaluated. Randomized patients ($n = 5988$) were grouped according to SBP at baseline (<110 mmHg, $n = 455$; 110–130 mmHg, $n = 2415$; > 130 mmHg, $n = 3118$). The effect of empagliflozin on blood pressure, cardiovascular death or HF hospitalization (primary outcome), total HF hospitalizations, and rate of decline in estimated glomerular filtration rate was studied. Over a median of 26.2 months, the placebo-corrected decline was small and not significantly different across baseline SBP. On placebo, the risk of cardiovascular death or hospitalization for HF was 8.58 at >130 mmHg, 8.26 at 110–130 mmHg, and 11.59 events per 100 patient-years at <110 mmHg ($P = 0.12$ vs. > 130 mmHg, $P = 0.08$ vs. 110–130 mmHg). There was no evidence for baseline SBP moderating the effect of empagliflozin on risk of HF events (primary endpoint interaction $P = 0.69$, recurrent HF hospitalizations interaction $P = 0.55$). When comparing empagliflozin with placebo, SBP did not meaningfully associate with adverse events such as hypotension, volume depletion, and acute renal failure.

**Conclusion** In EMPEROR-Preserved, empagliflozin was effective and safe without SBP meaningfully moderating empagliflozin's treatment effects. This analysis of EMPEROR-Preserved shows that empagliflozin can be used safely and effectively without blood pressure being a meaningful moderator of the drug benefit.

**Clinical Trial Registration** URL: https://www.clinicaltrials.gov Unique identifier: NCT03057951

* Corresponding author. Tel: (+49) 6841 16 15031, Fax: (+49) 6841 16 15032, Email: michael.boehm@uks.eu

## Structured Graphical Abstract

### Key Question

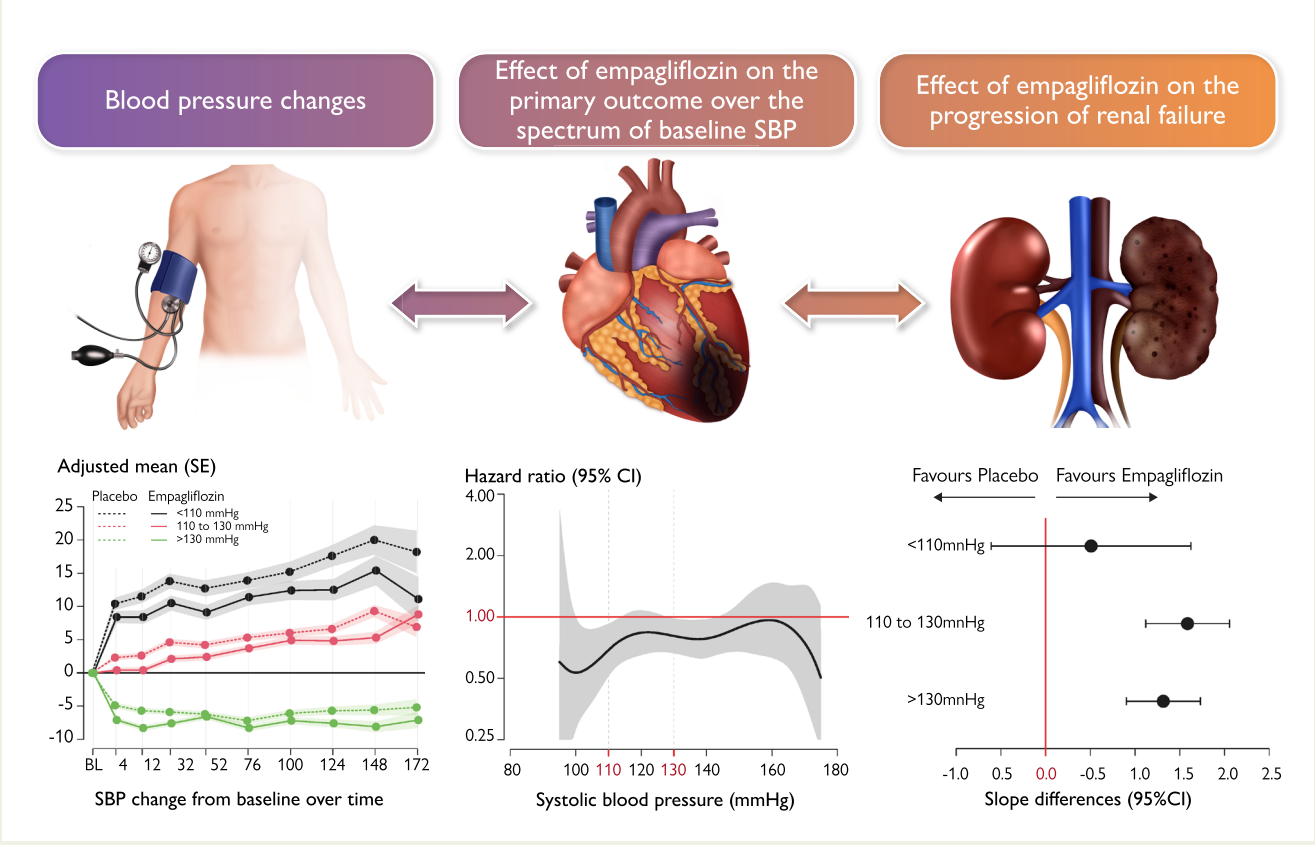
Empagliflozin reduces the risk of cardiovascular death or heart failure (HF) hospitalization in patients with HF and preserved ejection fraction. The interaction of this beneficial effect with baseline blood pressure remains unknown.

### Key Finding

In the EMPEROR-preserved trial the placebo corrected changes of systolic blood pressure were small and not significantly different across baseline systolic blood pressure groups. On placebo, the risk of hospitalization for HF increased with lower blood pressure. The beneficial effects of empagliflozin on the primary endpoint and on progression of renal failure were similar irrespective of blood pressure.

### Take Home Message

Systolic blood pressure does not modify the effect of empagliflozin on risk. Low blood pressure should not be a barrier to start empagliflozin.




Effect of empagliflozin on blood pressure and outcomes. Effect of empagliflozin on systolic blood pressure (SBP) according to baseline SBP (top), effect of Empa on the primary outcome over the spectrum of baseline SBP (middle), and effect of Empa on the slope of change in estimated glomerular filtration rate (adjusted mean difference, mL/min/1.73 $m^2$/year) (bottom).

**Keywords** Empagliflozin • Systolic blood pressure • Heart failure • Preserved ejection fraction • Cardiovascular outcomes • Kidney outcomes

# Introduction

Empagliflozin reduced cardiovascular death and heart failure hospitalization in patients with preserved ejection fraction.[1] Hypertension is the most common comorbidity and etiological trigger of heart failure with preserved ejection fraction (HFpEF) as pressure overload produces left ventricular hypertrophy, diastolic dysfunction, abnormal arterial-ventricular coupling, and other complications such as kidney failure.[2–4] Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce systolic blood pressure (SBP) in patients with diabetes and hypertension,[5,6] while in heart failure with reduced ejection fraction (HFrEF), only patients with a high baseline SBP had a significant and meaningful

reduction.[7,8] Registry data show an increase of heart failure outcomes and death for patients with SBP <110 mmHg, which was more pronounced than the risk observed for patients with SBP >140–150 mmHg without differences between HFrEF and HFpEF.[9] This U-shaped blood pressure (BP)-risk association might not be related to a causality rather than reflecting reverse causation as low BP selects patients with more advanced heart failure and frailty.[7,10] In EMPEROR-Preserved (empagliflozin outcome trial in patients with chronic heart failure with preserved ejection fraction), we studied the effect of empagliflozin on SBP and its effects on heart failure outcomes and estimated glomerular filtration rate (eGFR) decline across baseline SBP levels in heart failure with ejection fraction >40%.

# Methods

## Study design

The design and results of the EMPEROR-Preserved trial have been published previously.[1,11] The ethics committees of each of the participating institutions approved the protocol, and all patients gave written informed consent. The registration identifier at ClinicalTrials.gov is NCT03057951.

## Studied patients and procedures

Patients with heart failure and ejection fraction >40% were screened, and those fulfilling eligibility criteria were randomized double-blind in a 1:1 fashion to receive placebo or empagliflozin 10 mg daily in addition to their usual therapy for heart failure. Patients with or without diabetes were enrolled. During follow-up, all accompanying treatments could be altered or initiated according to the changes in the clinical status of the patients at the clinical discretion of the investigator. At the screening visit, after the patient had rested quietly in the seated position for 5 min, three attended BP measurements were recorded, and the mean of these three BP values was used to determine eligibility. BP was taken at every subsequent visit using a standard manometer with an appropriate size cuff at the same arm in a sitting position after 5 min of rest.

Patients were assessed at study visits for major outcomes, vital signs, eGFR by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), adverse events and changes in medications or clinical status that reflected changes in the course of heart failure. All randomized individuals were followed for the occurrence of pre-specified outcomes for the entire duration of the trial regardless of whether the study participants had taken the study medication or were adherent with the study procedures according to the intention to treat principle. At the end of double-blind therapy, treatment with study medication was stopped, and patients underwent a follow-up visit including assessment of eGFR 23–45 days later unconfounded by the presence of the study medication.

## Outcome measures

The primary endpoint of the composite of adjudicated cardiovascular death or hospitalization for heart failure was analysed as time-to-first event. The first secondary endpoint was the occurrence of all adjudicated hospitalizations for heart failure including first and recurrent events. The second secondary endpoint was the analysis of the slope of the change in eGFR during double-blind treatment.

## SBP analyses

Patients were grouped according to their baseline SBP: < 110 mmHg, 110–130 mmHg, and >130 mmHg. Patients were grouped below and above the optimal guideline-recommended SBP targets in cardiovascular high-risk patients (120–130 mmHg). In total, 110–120 mmHg is a grey zone, but outcomes increase below 110 mmHg in observational studies. Systolic blood pressure <110 mmHg was chosen as physicians might be reluctant to use medication at this level. These cut-offs were pre-specified for EMPEROR-Preserved. The same cut-offs were used previously in EMPEROR-Reduced.[8] We evaluated the risk of heart failure hospitalization, cardiovascular death (descriptively by event per 100 patient-years), and eGFR decline in these groups in patients treated with placebo, and we compared the effects of empagliflozin vs. placebo on efficacy variables in these SBP categories. Furthermore, in order to understand the influence of post-randomization changes in SBP in mediating the effects of empagliflozin, we studied the treatment effects of empagliflozin using SBP at baseline, Week 4 and time-updated SBP (using the same SBP groups) as a covariate (landmark analyses). We examined the influence of baseline SBP on the occurrence of hypotension, symptomatic hypotension, acute renal failure, and volume depletion in the placebo and empagliflozin groups. Acute renal failure is defined by the standard MedDRA (Medical Dictionary for Regulatory Activities) query 'Acute renal failure' (narrow scope). Hypotension and volume depletion are based on customized MedDRA queries, while symptomatic hypotension was based on investigator information (case report form tick box).

## Statistical analyses

The effect of empagliflozin compared with placebo on the time-to-first event analyses was examined using Cox proportional hazard regression models with pre-specified covariates of age, sex, geographical region, diabetes status at baseline, left ventricular ejection fraction, and eGFR at baseline. The interaction between (continuous using cubic splines) SBP and treatment group on the occurrence of the pre-specified outcomes was tested using a treatment-by-SBP interaction term. The first secondary outcome of total (first and recurrent) heart failure hospitalizations was evaluated with the use of the joint frailty model that accounted for informative censoring because of cardiovascular death. Changes in SBP and diastolic BP (DBP) were analysed in a mixed model with repeated measures (MMRM). Between-group differences in the slope of change in eGFR were analysed using a random intercept random slope model using on-treatment data. The slope, the joint frailty, and the MMRM models included the same covariates as the Cox model.

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). All *P*-values reported are two-sided, and $P < 0.05$ was considered as statistically significant in all cases. No adjustments for multiple testing were made from the exploratory nature of the study.

# Results

## Patient characteristics

A total of 5988 patients were randomly assigned to receive either empagliflozin (2997 patients, 10 mg once daily) or placebo (2991 patients, Supplementary material online, *Figure S1*). *Table 1* presents the baseline characteristics of patients across SBP categories. Modest interactions of SBP with race and region were observed. Those with lower SBP had a greater severity of heart failure, as evidenced by higher N-terminal pro-B-type natriuretic peptide plasma concentrations, higher heart rate, a higher likelihood of having experienced a heart failure hospitalization in the last 12 months, a higher prevalence of diabetes, lower eGFR and a higher prevalence of albuminuria.

## Association of blood pressure with outcomes

The relationship of baseline SBP to the severity of heart failure was further investigated by calculating incidence rates for major endpoints in patients treated with placebo. The incidence rate per 100 patient-years of follow-up for the primary endpoint increased from 8.58 in patients with an SBP >130 mmHg and 8.26 in patients with an SBP of 110–130 mmHg to 11.59 in patients with an SBP <110 mmHg. ($P = 0.12 >$

**Table 1 Baseline characteristics by systolic blood pressure groups**

| | Systolic blood pressure group | | | | | | |
|---|---|---|---|---|---|---|---|
| | <110 mmHg | | 110–130 mmHg | | >130 mmHg | | *P*-value[c] |
| Number of patients | 455 | | 2415 | | 3118 | | |
| **Sex [*n* (%)]** | | | | | | | 0.2370 |
| Male | 244 | (53.6%) | 1367 | (56.6%) | 1701 | (54.6%) | |
| Female | 211 | (46.4%) | 1048 | (43.4%) | 1417 | (45.4%) | |
| **Race [*n* (%)]** | | | | | | | 0.0002 |
| White | 309 | (67.9%) | 1846 | (76.4%) | 2387 | (76.6%) | |
| Black/African–American | 21 | (4.6%) | 93 | (3.9%) | 144 | (4.6%) | |
| Asian | 96 | (21.1%) | 332 | (13.7%) | 396 | (12.7%) | |
| Other including mixed race | 29 | (6.4%) | 143 | (5.9%) | 190 | (6.1%) | |
| Missing | 0 | | 1 | (<0.1%) | 1 | (<0.1%) | |
| **Region [*n* (%)]** | | | | | | | <0.0001 |
| North America | 82 | (18.0%) | 291 | (12.0%) | 346 | (11.1%) | |
| Latin America | 128 | (28.1%) | 659 | (27.3%) | 728 | (23.3%) | |
| Europe | 126 | (27.7%) | 1039 | (43.0%) | 1524 | (48.9%) | |
| Asia | 88 | (19.3%) | 268 | (11.1%) | 330 | (10.6%) | |
| Other | 31 | (6.8%) | 158 | (6.5%) | 190 | (6.1%) | |
| LVEF [% (SD)] | 54.1% | (9.0) | 53.8 | (8.8) | 54.8 | (8.7) | 0.0001 |
| Baseline NT-proBNP (median pg/mL) [(Q1;Q3)] | 1104 | (557;2092) | 1018 | (511;1827) | 913 | (482;1630) | <0.0001[d] |
| **Baseline BP [mmHg, *n* (%)]** | | | | | | | NA |
| SBP < 140 and DBP < 90 | 455 | (100.0%) | 2346 | (97.1%) | 1025 | (32.9%) | |
| SBP ≥ 140 or DBP ≥ 90 | 0 | | 69 | (2.9%) | 2093 | (67.1%) | |
| Baseline heart rate (bpm, SD) | 71.7 | (12.6) | 70.7 | (12.2) | 69.9 | (11.5) | 0.0021 |
| Baseline weight (kg, SD) | 77.79 | (18.79) | 80.94 | (19.05) | 83.09 | (19.67) | <0.0001 |
| Baseline BMI (kg/m$^2$, SD) | 28.78 | (5.82) | 29.39 | (5.64) | 30.34 | (6.00) | <0.0001 |
| Baseline eGFR according to CKD–EPI (mL/min/1.73 m$^2$, SD) | 60.0 | (21.6) | 60.3 | (19.8) | 61.0 | (19.6) | 0.1689 |
| **Baseline eGFR according to CKD–EPI [mL/min/1.73 m$^2$, *n* (%)]** | | | | | | | 0.1264 |
| ≥ 60 | 225 | (49.5%) | 1180 | (48.9%) | 1593 | (51.1%) | |
| < 60 | 230 | (50.5%) | 1233 | (51.1%) | 1525 | (48.9%) | |
| Missing | 0 | | 2 | (0.1%) | 0 | | |
| **Baseline urine albumin–to–creatinine ratio [mg/g, *n* (%)]** | | | | | | | <0.0001 |
| Normal (<30) | 300 | (65.9%) | 1529 | (63.3%) | 1645 | (52.8%) | |
| Microalbuminuria (30 to ≤300) | 136 | (29.9%) | 713 | (29.5%) | 1011 | (32.4%) | |
| Macroalbuminuria (>300) | 18 | (4.0%) | 160 | (6.6%) | 451 | (14.5%) | |
| Missing | 1 | (0.2%) | 13 | (0.5%) | 11 | (0.4%) | |
| Baseline haemoglobin (g/dL, SD) | 13.24 | (1.61) | 13.25 | (1.55) | 13.31 | (1.58) | 0.3921 |
| **History of atrial fibrillation or atrial flutter[a] [*n* (%)]** | | | | | | | <0.0001 |
| No | 185 | (40.7%) | 1096 | (45.4%) | 1563 | (50.1%) | |
| Yes | 270 | (59.3%) | 1314 | (54.4%) | 1551 | (49.7%) | |

*Continued*

**Table 1** *Continued*

| | Systolic blood pressure group | | | | | | |
|---|---|---|---|---|---|---|---|
| | <110 mmHg | | 110–130 mmHg | | >130 mmHg | | *P*-value[c] |
| Missing | 0 | | 5 | (0.2%) | 4 | (0.1%) | |
| Baseline HS Troponin T (ng/L, SD) | 25.24 | (34.87) | 23.46 | (23.90) | 23.70 | (33.28) | 0.8831[d] |
| History of HHF (in the last 12 months)[b] [*n* (%)] | 124 | (27.3%) | 569 | (23.6%) | 676 | (21.7%) | 0.0173 |
| **Cause of HF [*n* (%)]** | | | | | | | 0.8633 |
| Ischaemic | 142 | (31.2%) | 852 | (35.3%) | 1123 | (36.0%) | |
| Non–ischaemic | 313 | (68.8%) | 1562 | (64.7%) | 1995 | (64.0%) | |
| Missing | 0 | | 1 | (<0.1%) | 0 | | |
| **Diabetes at baseline [*n* (%)]** | | | | | | | <0.0001 |
| Diabetic | 194 | (42.6%) | 1116 | (46.2%) | 1628 | (52.2%) | |
| Non–diabetic | 261 | (57.4%) | 1299 | (53.8%) | 1490 | (47.8%) | |
| **ACE inhibitors/ARBs/ARNi** | 347 | (76.3%) | 1908 | (79.0%) | 2577 | (82.6%) | 0.0001 |
| ACE inhibitors/ARBs[e] | 320 | (70.3%) | 1852 | (76.7%) | 2533 | (81.2%) | <0.0001 |
| ARNi | 29 | (6.4%) | 59 | (2.4%) | 46 | (1.5%) | <0.0001 |
| Beta-Blockers | 402 | (88.4%) | 2103 | (87.1%) | 2662 | (85.4%) | 0.0774 |
| Diuretics | 412 | (90.5%) | 2112 | (87.5%) | 2639 | (84.6%) | 0.0002 |
| Mineralocorticoid receptor antagonists | 234 | (51.4%) | 1028 | (42.6%) | 982 | (31.5%) | <0.0001 |
| Cardiac glycosides | 45 | (9.9%) | 249 | (10.3%) | 262 | (8.4%) | 0.0475 |
| Nitrates | 49 | (10.8%) | 295 | (12.2%) | 402 | (12.9%) | 0.3944 |
| Calcium channel blockers | 85 | (18.7%) | 621 | (25.7%) | 1119 | (35.9%) | <0.0001 |
| Lipid lowering drugs | 293 | (64.4%) | 1723 | (71.3%) | 2226 | (71.4%) | 0.0071 |
| Platelet aggregation inhibitors (excl. heparin) | 190 | (41.8%) | 1106 | (45.8%) | 1539 | (49.4%) | 0.0014 |
| Anticoagulants | 249 | (54.7%) | 1241 | (51.4%) | 1422 | (45.6%) | <0.0001 |
| **NYHA class at baseline [*n* (%)]** | | | | | | | 0.0089 |
| I/II | 346 | (76.0%) | 2002 | (82.9%) | 2539 | (81.4%) | |
| III | 107 | (23.5%) | 404 | (16.7%) | 572 | (18.3%) | |
| IV | 2 | (0.4%) | 9 | (0.4%) | 7 | (0.2%) | |

[a]Defined as atrial fibrillation or atrial flutter reported in any ECG before treatment intake or history of atrial fibrillation or atrial flutter reported as medical history.
[b]Reported either on heart failure history and diagnosis or Health Care Resource Utilization form.
[c]ANOVA for continuous variables and $\chi^2$ test for categorical variables.
[d]based on log–transformed results.
[e]Excluding valsartan when taken with sacubitril, because sacubitril/valsartan is shown as ARNi.
LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; BMI, body mass index; eGFR, estimated glomerular filtration rate; HS, high sensitive; HF, heart failure; HHF, hospitalization for heart failure; NYHA, New York Heart Association; SD, standard deviation.

130 vs. < 110 mmHg, $P = 0.08$ 110–130 vs. < 110 mmHg for comparison of absolute differences in incidence rates).

The incidence rate for cardiovascular death was higher with SBP <110 mmHg [6.61 (4.49–9.13)] compared with 3.04 (2.40–3.75, $P < 0.0001$ vs. < 110 mmHg) at 110–130 mmHg and 4.01 (3.36–4.71, $P = 0.008$ vs. < 110 mmHg) at >130 mmHg events per 100 patient-years. For all-cause death, incidence rates per 100 patient-years were 8.53 (6.09–11.37) for <110 mmHg compared with 5.81 (4.91–6.78) for 110–130 mmHg ($P = 0.013$ vs. 110 mmHg), and 7.07 (6.20–8.00) for >130 mmHg ($P = 0.17$ vs. < 110 mmHg).

## Effect of empagliflozin on blood pressure

The placebo corrected decreases of SBP and DBP were modest (2–4 mmHg drop) and not statistically different across the baseline SBP groups (*Figure 1*). The time course of SBP and DBP in the two treatment groups by baseline SBP categories is shown in Supplementary material online, *Figures S2A* (SBP) and *S2B* (DBP). In patients with <110 mmHg SBP, there was an increase of SBP (see Supplementary material online, *Figure S2A*) and of DBP (see Supplementary material online, *Figure S2B*) from 4 to 172 weeks on placebo and on empagliflozin. A slight increase was observed at 110–130 mmHg, while there was

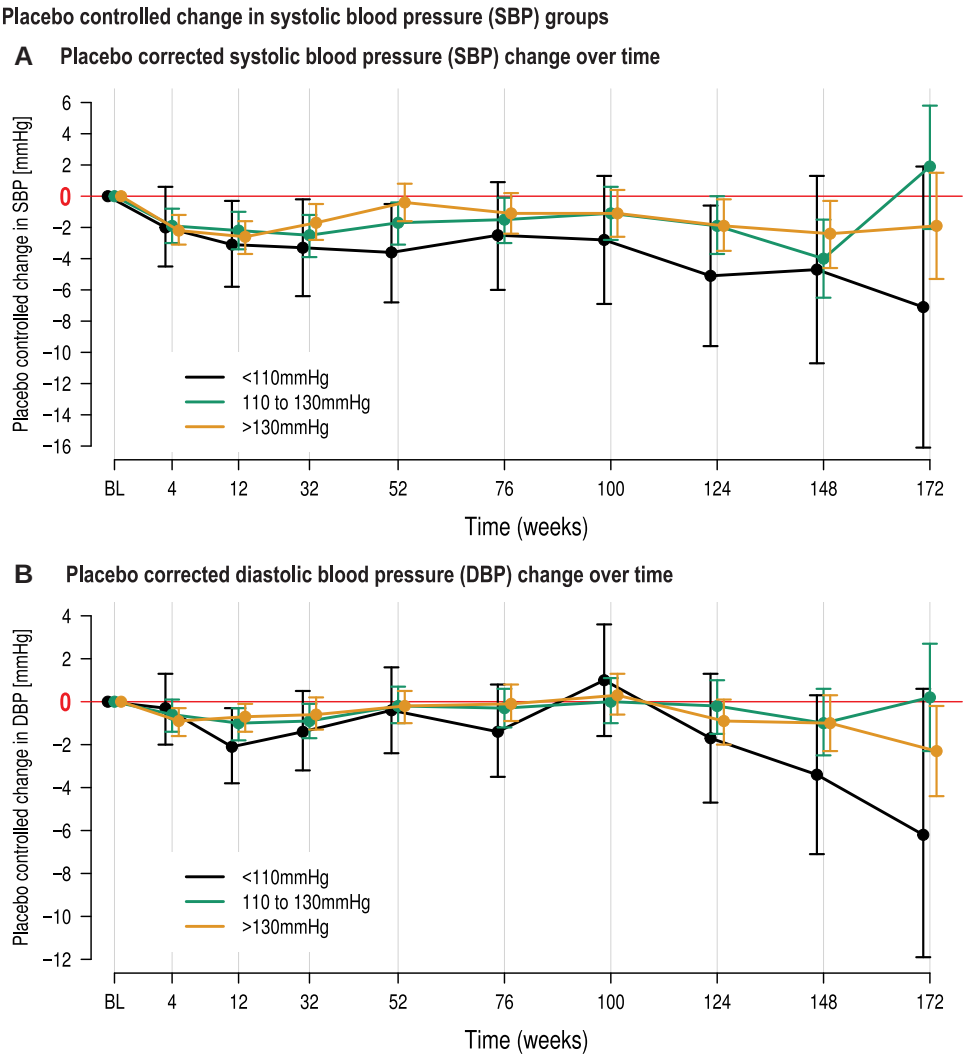



**Figure 1** Placebo corrected change of systolic and diastolic blood pressure. Placebo corrected change in systolic blood pressure (SBP) (*A*) and placebo corrected diastolic blood pressure (DBP) (*B*) over time. The mixed model with repeated measures included age, baseline eGFR, ejection fraction, region, baseline diabetes status, and sex and revealed *P* interaction values >0.1 for SBP and for DBP (except at week 172) ($P = 0.08$, for DBP).

a decrease at >130 mmHg with placebo and empagliflozin on SBP (A) and DBP (B). We further studied SBP and DBP according to the presence of diabetes (see Supplementary material online, *Table S1*). There were no clinically relevant differences between patients with and without diabetes. Furthermore, the effects of empagliflozin compared with placebo were similar between patients with ejection fraction 40–49% (heart failure with mildly reduced ejection fraction, HFmrEF) and ≥50% (true HFpEF) (see Supplementary material online, *Table S2*).

## Adverse events

The incidence of any adverse events and events leading to discontinuation of the study drug was lower on empagliflozin compared with placebo across all baseline SBP groups. The incidence rates of acute renal failure were overall low and again lower on empagliflozin than on placebo. The incidence rates of volume depletion, hypotension, and symptomatic hypotension were higher at lower SBP and numerically higher on empagliflozin than on placebo. Nevertheless, these events had a low incidence rate (for volume depletion 8.77/100 patient-years placebo vs. 11.77/100 patient-years on empagliflozin, hypotension 7.97/100 patient-years placebo vs. 9.96/100 patient-years, empagliflozin). The rates were lower at higher BP (volume depletion: 4.5/100 patient-years placebo vs. 5.7/100 patient-years on empagliflozin, hypotension 4.04/100 patient-years placebo vs. 4.92/100 patient-years on empagliflozin) (*Table 2*).

## Effect of empagliflozin on renal function

*Figure 2* demonstrates the change in eGFR on empagliflozin or placebo at baseline SBP <110 mmHg, 110–130 mmHg, > 130 mmHg and the slope of eGFR from 4 weeks onwards in the three baseline SBP groups. Empagliflozin reduced the slope of eGFR compared with placebo with significant interaction between the three baseline SBP groups (*P* for interaction <0.0001).

**Table 2** Adverse events

| Number of patients | < 110 mmHg | | | | | 110–130 mmHg | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Empagliflozin | | Placebo | | | Empagliflozin | | Placebo | | |
| | 228 | | 227 | | | 1213 | | 1202 | | |
| | *n* (%) | IR/100 pt-yrs | *n* (%) | IR/100 pt-yrs | *P*-value[a] for treatment comparison | *n* (%) | IR/100 pt-yrs | *n* (%) | IR/100 pt-yrs | *P*-value[a] for treatment comparison |
| Patients with any adverse events | 211 (92.5) | 239.82 | 201 (88.5) | 194.75 | 0.16 | 1047 (86.3) | 133.24 | 1031 (85.8) | 142.47 | 0.68 |
| Patients with adverse events leading to drug discontinuation | 39 (17.1) | 9.49 | 51 (22.5) | 12.31 | 0.23 | 233 (19.2) | 10.29 | 187 (15.6) | 8.20 | 0.02 |
| **Adverse events of special interest** | | | | | | | | | | |
| Acute renal failure | 27 (11.8) | 7.11 | 31 (13.7) | 7.93 | 0.74 | 146 (12.0) | 6.84 | 155 (12.9) | 7.21 | 0.50 |
| Volume depletion | 43 (18.9) | 11.77 | 34 (15.0) | 8.77 | 0.25 | 154 (12.7) | 7.35 | 127 (10.6) | 5.91 | 0.10 |
| Hypotension | 37 (16.2) | 9.96 | 31 (13.7) | 7.97 | 0.37 | 136 (11.2) | 6.43 | 113 (9.4) | 5.22 | 0.15 |
| Symptomatic hypotension | 26 (11.4) | 6.81 | 19 (8.4) | 4.78 | 0.20 | 85 (7.0) | 3.89 | 67 (5.6) | 3.03 | 0.15 |

| Number of patients | > 130 mmHg | | | | | |
|---|---|---|---|---|---|---|
| | Empagliflozin | | Placebo | | | |
| | 1555 | | 1560 | | | |
| | *n* (%) | IR/100 pt-yrs | *n* (%) | IR/100 pt-yrs | *P*-value for treatment comparison | *P*-value[a] for trend test |
| Patients with any adverse events | 1316 (84.6) | 128.21 | 1353 (86.7) | 147.92 | 0.10 | 0.11 |
| Patients with adverse events leading to drug discontinuation | 299 (19.2) | 10.20 | 313 (20.1) | 10.83 | 0.57 | 0.03 |
| **Adverse events of special interest** | | | | | | |
| Acute renal failure | 190 (12.2) | 6.86 | 198 (12.7) | 7.21 | 0.60 | 0.99 |
| Volume depletion | 159 (10.2) | 5.70 | 125 (8.0) | 4.50 | 0.03 | 0.93 |
| Hypotension | 138 (8.9) | 4.92 | 113 (7.2) | 4.04 | 0.09 | 0.98 |
| Symptomatic hypotension | 86 (5.5) | 3.01 | 70 (4.5) | 2.46 | 0.18 | 0.87 |

[a]Logistic regression comparing frequencies.

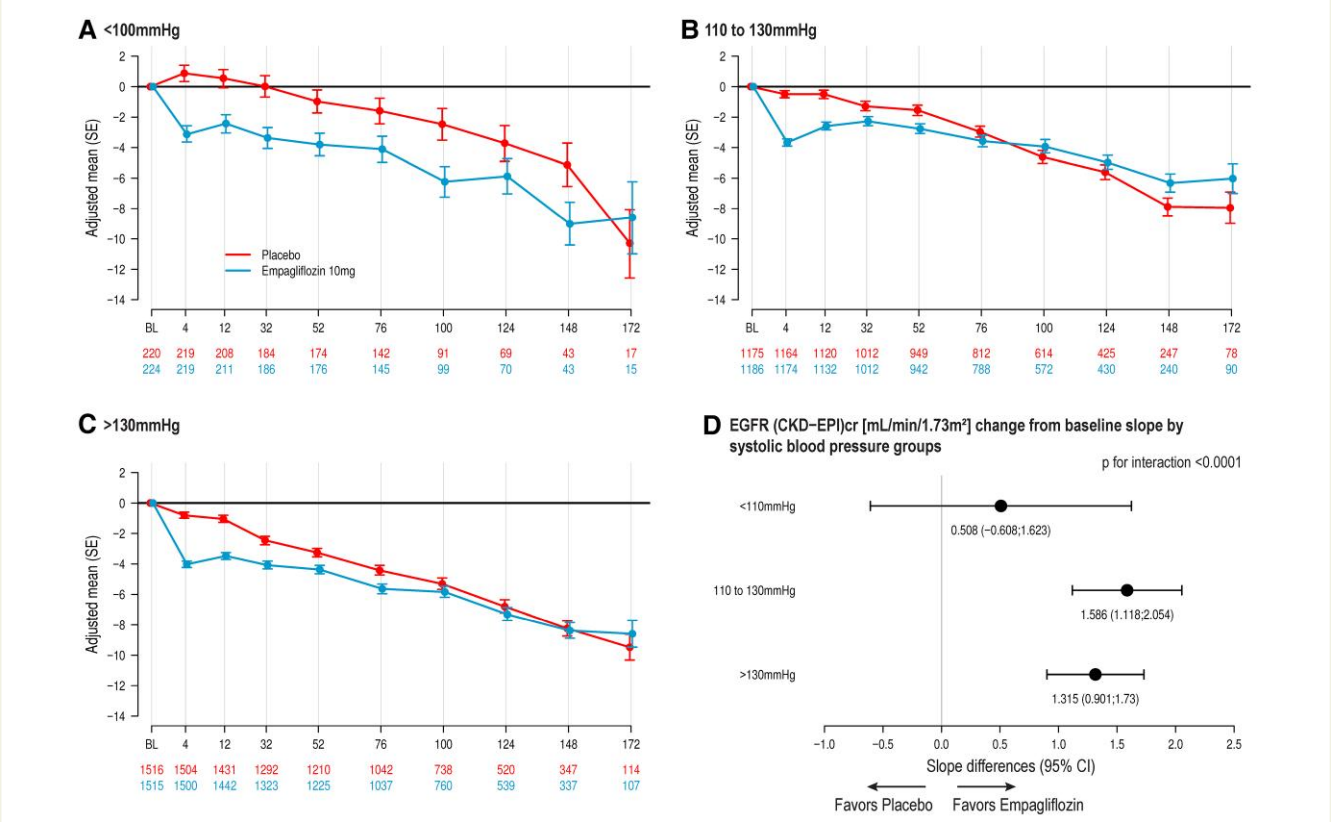



**Figure 2** Change of eGFR over time according to baseline systolic blood pressure. Change in estimated glomerular filtration rate (eGFR) over time in patients on empagliflozin or placebo in patients with a baseline <110 mmHg (*A*), 110–130 mmHg (*B*), > 130 mmHg (*C*), and efficacy by baseline systolic blood pressure (SBP) groups for the slope of eGFR (*D*). eGFR was determined by using the Chronic Kidney Disease Epidemiology Collaboration equation.

## Effect of empagliflozin on outcomes

The cumulative incidence function for the primary outcome (cardiovascular death or heart failure hospitalization) according to SBP is shown in *Figure 3A*. There was a reduction of the primary outcome in all BP groups without a significant difference (*P* for interaction = 0.69) across groups (*Figure 3A*). Similar results were observed with time to first adjudicated heart failure hospitalization (*Figure 3B*, *P* for interaction = 0.46) and recurrent heart failure hospitalizations (*Figure 3C*, *P* for interaction = 0.55). The hazard ratios (left), the event rates (middle), and the treatment effects as a continuous variable across the spectrum of baseline SBP using cubic splines are depicted in *Figure 4* on the primary outcome (*Figure 4A*) and the time to first adjudicated hospitalization for heart failure (*Figure 4B*). There was a homogeneous treatment effect without interaction with baseline SBP for the primary endpoint (*P* = 0.58) and time to first adjudicated hospitalization for heart failure (*P* for interaction = 0.66). The event rates for the primary outcome and heart failure hospitalization were higher at baseline SBP <110 mmHg on empagliflozin and placebo, while the treatment effect was similar across the entire spectrum of baseline SBP (*Figure 4*, right). Empagliflozin's treatment effects were not different on cardiovascular death (*P* for interaction 0.29) and all-cause death (*P* for interaction 0.84) across all SBP groups. Next, we evaluated in a landmark analysis the treatment effect of empagliflozin in a standard model and by including baseline SBP, and additionally SBP at 4 weeks and time-updated mean SBP. With all models, the hazard ratio was 0.80 (*P* = 0.0014–0.0016) for the primary endpoint and 0.72–0.73 (*P* = 0.0001–0.0002) for the first adjudicated hospitalization for heart failure (*Table 3*).

# Discussion

In EMPEROR-Preserved, there was a small placebo-corrected SBP decline by empagliflozin compared with placebo with an overall increase of SBP at low baseline SBP and a small drop of SBP at high baseline SBP on placebo and on empagliflozin possibly reflecting regression to the mean. In HFpEF, the outcome rates of the primary outcome were higher at low SBP (<110 mmHg) but the treatment effect of empagliflozin on heart failure outcomes was not significantly related to baseline SBP with a similar risk reduction of heart failure hospitalization and cardiovascular death. Empagliflozin had minor effects on hypotension and volume depletion, while some fewer events were observed for acute renal failure (*Structured Graphical Abstract*).

HFpEF is a heterogeneous condition with hypertension being one of the most prevalent and possible etiological factors promoting the progression of hypertrophy to failure[12,13] with more patients presenting with a history of hypertension in HFpEF than in HFrEF.[14] A higher prevalence of high BP in HFpEF compared with HFrEF is shown by the finding that 52.0% of the patients had an SBP of >130 mmHg and 7.6% of <110 mmHg in EMPEROR-Preserved (herein), while in

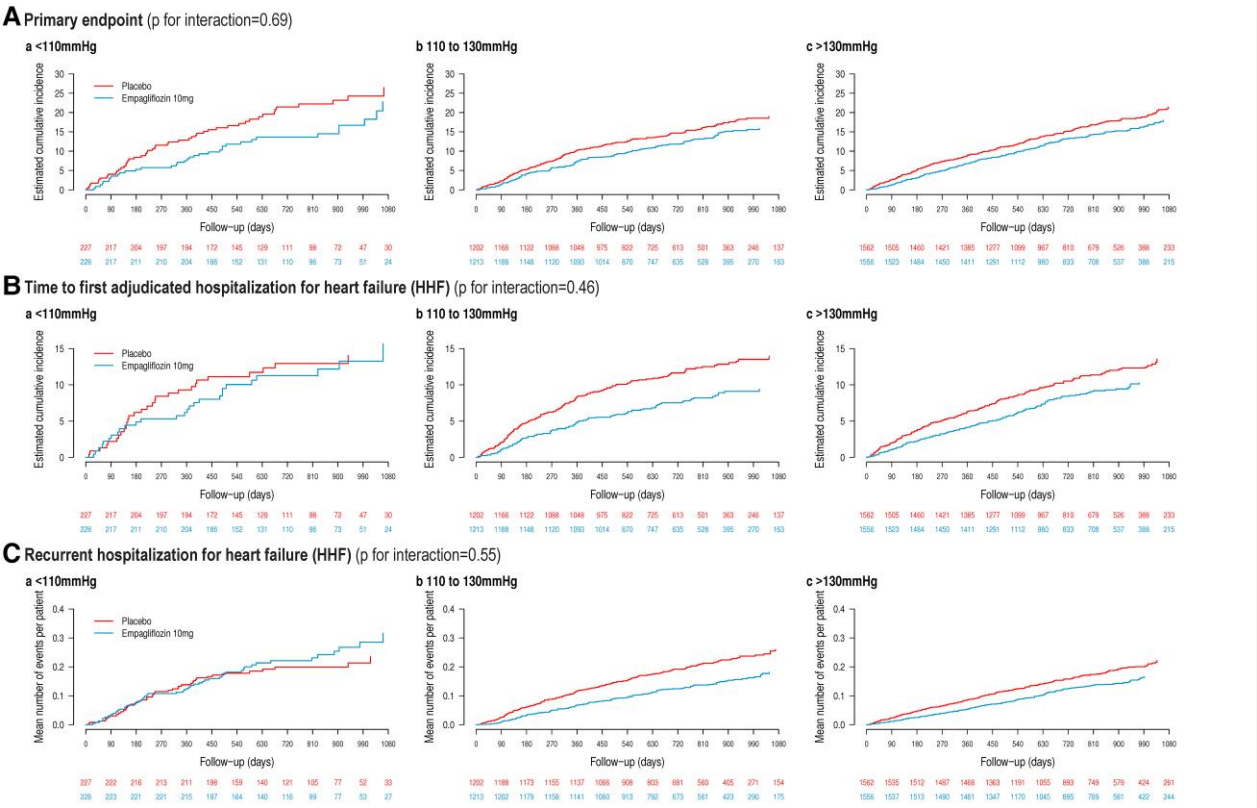



**Figure 3** Outcomes across systolic blood pressure. Cumulative incidence function of the effect of empagliflozin and placebo on the primary outcome (*A*, composite of heart failure hospitalization or cardiovascular death), time to first adjudicated hospitalization for heart failure (*B*), and recurrent hospitalization for heart failure (*C*) by baseline systolic blood pressure groups of <110 mmHg (left, a), 110–130 mmHg (middle, b), and >130 mmHg (right, c). *P*-values for interaction are derived from Cox regression model.

EMPEROR-Reduced 28.2% were at >130 mmHg and 24.2% had an SBP of <110 mmHg.[8]

Patients with heart failure are often undertreated when SBP is low, although they have a worse prognosis than those with a higher SBP.[9,15–17] Interestingly, the U- and J-shaped association of SBP and DBP on mortality appears to be similar in HFrEF and HFpEF.[9] Herein, we show that the primary outcome and cardiovascular death was increased in patients at SBP <110 mmHg compared with >110 mmHg. This finding is similar to previous HFrEF trials[7,8,18] with treatment effects of SGLT2 inhibitors[7,8] and sacubitril/valsartan[18] being similar across SBP groups. We extended those findings to HFpEF patients by showing that the effect of empagliflozin is similar across baseline SBP groups in EMPEROR-Preserved.

In EMPEROR-Preserved, 90.6% of patients had a history of hypertension. Although high SBP is a major driver for the development of HFpEF, we still found a significant number with normal or low SBP. Nevertheless, the proportion of patients with low SBP <110 mmHg is lower than in HFrEF.[8] A reduced myocardial systolic or diastolic function has been speculated to be involved in drops of SBP over time, previously termed 'decapitated hypertension',[19] also observed in PARAGON-HF in HFpEF patients,[18] and associated with increased HF events in HFrEF and HFpEF.[9,10,18] Similar findings of an increased risk for cardiovascular outcomes at low SBP have also been shown in patients after myocardial infarction or stroke or known coronary artery disease.[20,21] Nevertheless, in HFpEF as in HFrEF,[7,8] SBP appears not to be an effect modifier of the cardio-renal effects of empagliflozin and, thus, might not contribute mechanistically to the treatment effect of empagliflozin.

As the effect of empagliflozin is maintained at SBP <110 mmHg, it is important that the protective effect does not come at a meaningfully increased cost of safety outcomes. There was only a slight increase of incident hypotension or volume depletion, while the incidence of acute renal failure was reduced. These observations are of clinical relevance as physicians are often reluctant to initiate treatment due to the fear of these adverse events at low SBP.[22]

## Limitations

This study is a *post-hoc* secondary analysis of a randomized trial, and randomization was not stratified by SBP. Unmeasured confounding could have affected the results. The distribution of SBP in HFpEF and EMPEROR-Preserved is different to HFrEF and EMPEROR-Reduced with a rather low number of patients at low baseline SBP. Nevertheless, this is the largest study on HFpEF showing significant treatment effects of the SGLT2 inhibitor empagliflozin with a clear homogeneity of risk reduction across baseline SBP groups.

# Conclusion

Empagliflozin reduces the risk of heart failure hospitalization, cardiovascular death, and eGFR decline independently of baseline SBP. The

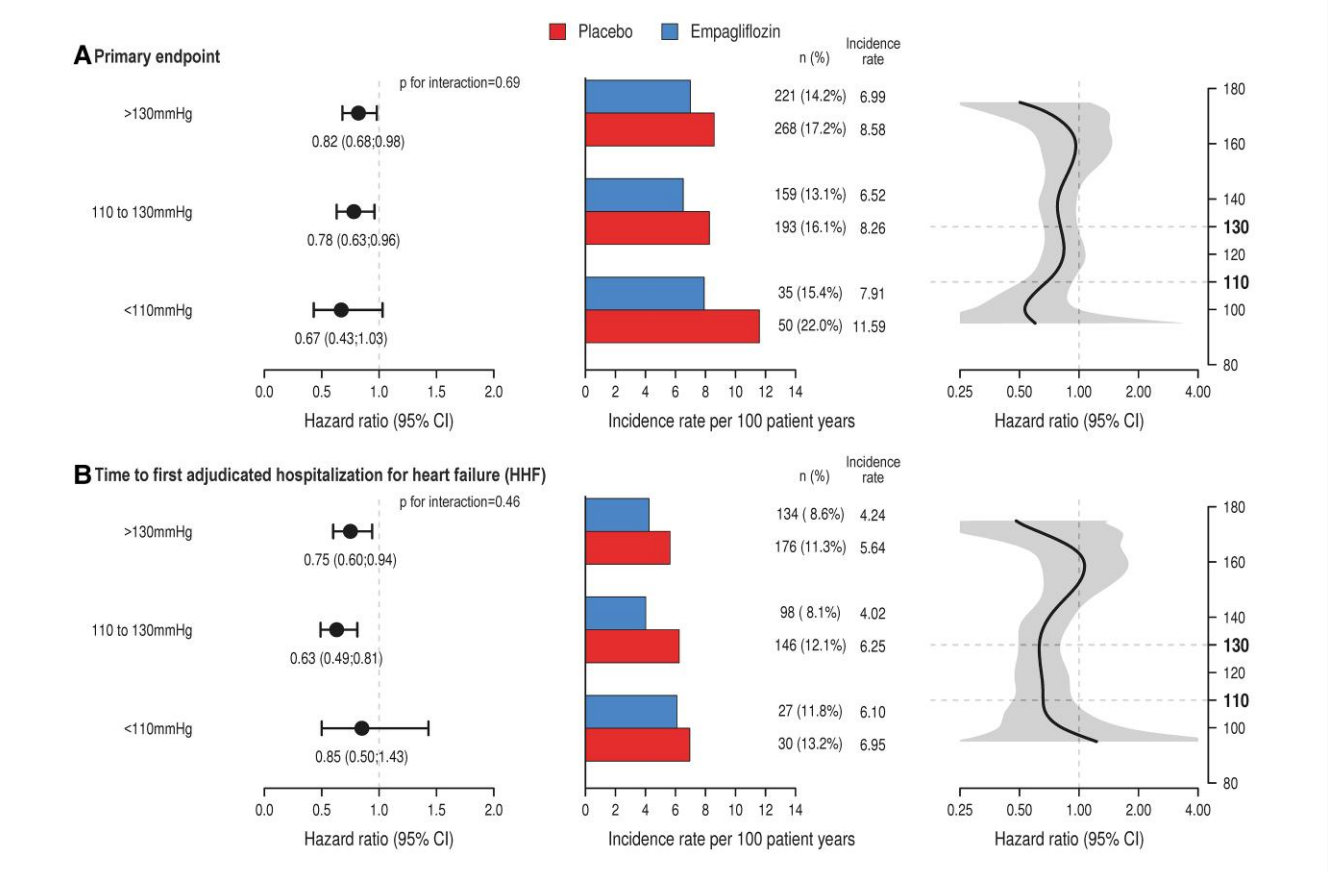



**Figure 4** Treatment effect according to baseline systolic blood pressure. Hazard ratio (left), incident rate per 100 patient-years (middle), and hazard ratio modelled as a continuous variable using cubic splines (right) for empagliflozin compared with placebo according to baseline systolic blood pressure (SBP) for the primary outcome (composite of first heart failure hospitalization or cardiovascular death) (*A*) and time to first adjudicated hospitalization for heart failure (B). CI: confidence interval.

**Table 3 Landmark analysis**

| | Primary endpoint | | First adjudicated HHF | |
|---|---|---|---|---|
| | **Empagliflozin** | **Placebo** | **Empagliflozin** | **Placebo** |
| Number of events/number of patients at risk (%) | 390/2912 (13.4) | 468/2881 (16.2) | 242/2912 (8.3) | 321/2881 (11.1) |
| **Standard model** | | | | |
| HR (95% CI) | 0.80 (0.70, 0.92) | | 0.72 (0.61, 0.85) | |
| *P*-value | 0.0014 | | 0.0001 | |
| **Standard model plus baseline SBP (3 cat.)** | | | | |
| HR (95% CI) | 0.80 (0.70, 0.92) | | 0.72 (0.61, 0.85) | |
| *P*-value | 0.0015 | | 0.0001 | |
| **Standard model plus baseline SBP (3 cat.) and SBP at week 4 (3 cat.)** | | | | |
| HR (95% CI) | 0.80 (0.70, 0.92) | | 0.72 (0.61, 0.86) | |
| *P*-value | 0.0016 | | 0.0002 | |
| **Standard model plus baseline SBP (3 cat.) and SBP at week 4 (3 cat.) + time-updated mean** | | | | |
| HR (95% CI) | 0.80 (0.70, 0.92) | | 0.73 (0.61, 0.86) | |
| *P*-value | 0.0016 | | 0.0002 | |

Standard model based on a Cox regression model with terms for age, baseline eGFR (CKD–EPI) baseline LVEF, region, diabetes status, sex, and treatment.
Only patients with an on-treatment SBP measurement at the Week 4 visit without an event or censoring before the day of the visit 4 SBP measurement are included in the landmark analysis.

marginal changes of placebo-corrected SBP on treatment are not responsible for risk reduction with empagliflozin supported by the landmark analysis exploring time-updated SBP on empagliflozin effects. Treatment with empagliflozin is not accompanied by meaningful concerns of symptomatic hypotension or volume depletion but even reduces incident renal failure. A low SBP should not be a barrier for treatment initiation with empagliflozin in heart failure patients with LVEF >40%.

# Author contribution

All authors participated in the design of the study, the interpretations of the data, and the writing of the article. The statistical analysis was done by E.S. M.B. drafted the manuscript. All authors were committee members or investigators of the EMPEROR-Preserved trial, or representatives of the Sponsor.

# Supplementary data

Supplementary data are available at *European Heart Journal* online.

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# Data availability

All authors were involved in the EMPEROR trial, which was funded by Boehringer Ingelheim and Eli Lilly. To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to relevant material. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete and other criteria are met. Researchers should use the https://vivli.org/link to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.

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