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ORIGINAL RESEARCH ARTICLE

Blinded Withdrawal of Long-Term Randomized Treatment With Empagliflozin or Placebo in Patients With Heart Failure

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BACKGROUND: It is not known whether the benefits of sodium-glucose cotransporter 2 inhibitors in heart failure persist after years of therapy.

METHODS: In the EMPEROR-Reduced (Empagliflozin Outcome Trials in Chronic Heart Failure With Reduced Ejection Fraction) and EMPEROR-Preserved (Empagliflozin Outcome Trials in Chronic Heart Failure With Preserved Ejection Fraction) trials, patients with heart failure were randomly assigned (double-blind) to placebo or empagliflozin 10 mg/day for a median of 16 and 26 months, respectively. At the end of the trials, 6799 patients (placebo 3381, empagliflozin 3418) were prospectively withdrawn from treatment in a blinded manner, and, of these, 3981 patients (placebo 2020, empagliflozin 1961) underwent prespecified in-person assessments after ≈30 days off treatment.

RESULTS: From 90 days from the start of closeout to the end of double-blind treatment, the annualized risk of cardiovascular death or hospitalization for heart failure was lower in empagliflozin-treated patients than in placebo-treated patients (10.7 [95% CI, 9.0–12.6] versus 13.5 [95% CI, 11.5–15.6] events per 100 patient-years, respectively; hazard ratio 0.76 [95% CI, 0.60–0.96]). When the study drugs were withdrawn for ≈30 days, the annualized risk of cardiovascular death or hospitalization for heart failure increased in patients withdrawn from empagliflozin but not in those withdrawn from placebo (17.0 [95% CI, 12.6–22.1] versus 14.1 [95% CI, 10.1–18.8] events per 100 patient-years for empagliflozin and placebo, respectively). The hazard ratio for the change in risk in the patients withdrawn from empagliflozin was 1.75 (95% CI, 1.20–2.54), P=0.0034, whereas the change in the risk in patients withdrawn from placebo was not significant (hazard ratio 1.12 [95% CI, 0.76–1.66]); time period-by-treatment interaction, P=0.068. After withdrawal, the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score declined by 1.6±0.4 in patients withdrawn from empagliflozin versus placebo (P<0.0001). Furthermore, withdrawal of empagliflozin was accompanied by increases in fasting glucose, body weight, systolic blood pressure, estimated glomerular filtration rate, N-terminal pro-hormone B-type natriuretic peptide, uric acid, and serum bicarbonate and decreases in hemoglobin and hematocrit (all P<0.01). These physiological and laboratory changes were the inverse of the effects of the drug seen at the start of the trials during the initiation of treatment (≈1–3 years earlier) in the same cohort of patients.

CONCLUSIONS: These observations demonstrate a persistent effect of empagliflozin in patients with heart failure even after years of treatment, which dissipated rapidly after withdrawal of the drug.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifiers: NCT03057977 and NCT03057951.

Key Words: empagliflozin ■ heart failure ■ sodium-glucose transporter 2 inhibitors ■ substance withdrawal syndrome

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Clinical Perspective

What Is New?

- At the end of the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction) and EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction) trials, 6799 patients with heart failure who had been randomly assigned (double-blind) to placebo or empagliflozin 10 mg/day for 1 to 3 years were prospectively withdrawn (by protocol) from treatment for ≈30 days, with blinded prespecified clinical, physiological, and laboratory assessments immediately before and after treatment withdrawal.
- When compared with patients withdrawn from placebo, patients withdrawn from treatment with empagliflozin showed increased risk of major heart failure events and worsening health status, along with physiological and laboratory changes that were the inverse of those seen during the initiation of treatment 1 to 3 years earlier.

What Are the Clinical Implications?

- It is not known whether the benefits of foundational drugs persist after years of treatment, because formal withdrawal trials have not been performed.
- We demonstrated a persistent effect of empagliflozin in patients with heart failure even after years of treatment, which dissipated rapidly after withdrawal of the drug. These findings indicate that tolerance does not develop during long treatment and that abrupt cessation of empagliflozin even for short periods of time may have serious consequences.
- The proximal tubular effect of SGLT2 inhibitors elicits counterregulatory downstream antinatriuretic and antiaquaretic mechanisms, and abrupt withdrawal may allow these mechanisms to produce rebound phenomena.

Nonstandard Abbreviations and Acronyms

eGFR	estimated glomerular filtration rate
EMPEROR	Empagliflozin Outcome Trials in Chronic Heart Failure
EMPEROR-Preserved	Empagliflozin Outcome Trials in Chronic Heart Failure With Preserved Ejection Fraction
EMPEROR-Reduced	Empagliflozin Outcome Trials in Chronic Heart Failure With Reduced Ejection Fraction
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire Clinical Summary Score
NT-proBNP	N-terminal pro-hormone B-type natriuretic peptide
SGLT2	sodium-glucose cotransporter 2
TRED-HF	A Pilot Feasibility Study in Recovered Heart Failure

Clinical trials have established the efficacy of inhibitors of the renin-angiotensin system, β-blockers, mineralocorticoid receptor antagonists, neprilysin inhibitors, and sodium-glucose cotransporter 2 (SGLT2) inhibitors in patients with heart failure.[1,2] Recommended practice is to maintain these drugs indefinitely in patients who can tolerate therapy, on the basis of the assumption that pharmacological tolerance does not develop during prolonged administration; yet, tolerance is common with many drugs for heart failure.[3–6] Absence of a change in clinical and physiological variables after the withdrawal of a drug would support the development of tolerance.

Some observational studies have compared the clinical course of patients in whom treatment was stopped for a specific clinical reason with the course of patients who were maintained on therapy, typically showing that patients who discontinued treatment fared worse than those who continued on treatment.[7–11] However, these studies are substantially confounded, because the reasons for stopping treatment (rather than its discontinuation) drives the unfavorable prognosis of these patients. The durability of a drug effect can only be assessed in a protocol-specified manner, either in (1) a randomized blinded trial of placebo versus active treatment in a cohort of patients who received long-term therapy or (2) a blinded withdrawal trial of patients who have received long-term randomized treatment with placebo or active therapy. Although both approaches have been used in the past,[12,13] large-scale withdrawal trials have not been performed after long-term treatment with any of the currently recommended foundational drugs for heart failure. The TRED-HF trial (Pilot Feasibility Study in Recovered Heart Failure)[14] performed an open-label withdrawal of several drugs, but it studied only 51 asymptomatic patients with a nonischemic cardiomyopathy with a recovered ejection fraction, and it primarily assessed biomarkers of ventricular function.

In contrast with other landmark trials in heart failure, the EMPEROR (Empagliflozin Outcome Trials in Chronic Heart Failure) program with empagliflozin was designed so that all patients completing double-blind therapy underwent a protocol-specified withdrawal of their study medication for ≈30 days after receiving ≈1 to 3 years of treatment, thus allowing patients withdrawn from the SGLT2 inhibitor to be compared with patients withdrawn from placebo. Withdrawal measurements were made

without knowledge of the patient's treatment assignment. A formal evaluation of long-term persistence of a drug effect is relevant, because the natriuretic effect of SGLT2 inhibitors becomes attenuated within a short time after the initiation of therapy.[15–20]

METHODS

The EMPEROR Program consisted of 2 simultaneously conducted, multicenter double-blind randomized parallel-group placebo-controlled trials, which evaluated patients with chronic heart failure with an ejection fraction ≤40% (enrolled in EMPEROR-Reduced [Empagliflozin Outcome Trials in Chronic Heart Failure With Reduced Ejection Fraction]) or >40% (enrolled in EMPEROR-Preserved [Empagliflozin Outcome Trials in Chronic Heart Failure With Preserved Ejection Fraction]).[21,22] The 2 trials were performed by the same Executive Committee, and major clinical events were adjudicated by the same end point adjudication committee. It was prespecified that patient-level data would be combined for relevant analyses.[23]

Data Sharing

To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the International Committee of Medical Journal Editors criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data. 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 article and secondary analyses in peer-reviewed journals and regulatory and reimbursement activities are completed, normally within 1 year after the marketing application has been granted by major Regulatory Authorities. 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.

Patient Population

The design and primary results of both trials have been previously published.[21,22] Participants were men or women, ≥18 years of age with New York Heart Association functional class II to IV heart failure for ≥3 months. Patients were required to have an elevated N-terminal pro-hormone B-type natriuretic peptide (NT-proBNP) levels (ie, >300 pg/mL if the ejection fraction was >40%; ≥2500 pg/mL if the ejection fraction was 36%–40%; ≥1000 pg/mL if the ejection fraction was 31%–35%; and ≥600 pg/mL if the ejection fraction was ≤30% or if patients had been hospitalized for heart failure within 12 months). If patients had atrial fibrillation, these thresholds were doubled in EMPEROR-Reduced and tripled in EMPEROR-Preserved. In both trials, patients were randomly assigned to receive either placebo or empagliflozin (10 mg once daily), in addition to recommended therapy. Eligible patients were randomly assigned to placebo or empagliflozin 10 mg daily, which were added to all recommended therapy for heart failure, for the duration of double-blind follow-up (median 16 months in EMPEROR-Reduced and 26 months in EMPEROR-Preserved). Randomization was stratified by geographical region, diabetes status, and estimated glomerular filtration rate (eGFR, <60 or ≥60 mL·min^{-1}·1.73 m^{-2}) in EMPEROR-Reduced and by the same variables and also by left ventricular ejection fraction (<50% or ≥50%) in EMPEROR-Preserved. The protocol was approved by the local ethical committee at each of the participating sites, and all patients gave written informed consent.

Withdrawal of Randomized Double-Blind Treatment

As specified in the original protocol for both trials, all surviving patients who completed the double-blind active treatment phase as planned were to stop taking their study drugs and return ≈30 days later for a repeat clinical and laboratory assessment. Data on the occurrence of heart failure events before and after the cessation of treatment were collected either in person or by telephone in 6799 patients, which represented >93% of patients who were still taking their study medications 90 days before the start of the closeout period. Furthermore, more than half of the patients who stopped double-blind treatment as planned returned for a formal 30-day posttreatment study visit for the assessment of health status (by the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score [KCCQ-CSS]), physical examination and laboratory testing. This in-person 30-day posttreatment visit occurred less frequently in the EMPEROR-Reduced trial (compared with the EMPEROR-Preserved trial) due to the restriction on patient-investigator interactions during the height of the COVID-19 pandemic.

Clinical and Laboratory Assessments

The principal clinical assessments were (1) the risk of cardiovascular death and heart failure hospitalization during the 30-day off-treatment period, compared with the period starting 90 days before the start of the closeout of each trial to the planned end of double-blind therapy; and (2) the KCCQ-CSS, assessed during the last double-blind visit and during the 30-day posttreatment visit. In addition, the following physical examination and laboratory evaluations were performed at the last double-blind on-treatment visit and at the time of the 30-day off-treatment follow-up visit: (1) systolic blood pressure; (2) body weight; (3) hemoglobin and hematocrit; (4) eGFR; (5) NT-proBNP; (6) uric acid; (7) fasting glucose; (8) serum albumin; and (9) serum sodium, potassium, and bicarbonate. To provide context for these observations, changes in KCCQ-CSS and laboratory tests (except for fasting glucose) were examined after 4 and 12 weeks (for laboratory tests) and after 12 weeks (for KCCQ-CSS) after the initiation of double-blind randomized therapy in the same patients who had valid measurements during the withdrawal period.

Statistical Analysis

The clinical features of the patients who participated and did not participate in the withdrawal study were compared using the *t*-test for continuous variables and χ^2 tests for categorical variables. Changes in laboratory assessments and KCCQ at on-treatment visits at weeks 4, 12, and last-value-on-treatment and measurements 30 days after planned treatment discontinuation were evaluated by a mixed model for repeated measures.

The mixed model for repeated measures compared the treatment effects at the withdrawal versus effects at last-value-on-treatment, and, to evaluate the possibility of a mirroring effect during withdrawal compared with the initiation of treatment, all mixed model for repeated measures models were based on the cohort of ≈4000 patients who contributed a valid withdrawal measurement after planned withdrawal (ie, measurements during initiation were performed in the same cohort who had measurements during withdrawal). We focused on between-group differences in the change from baseline at week 4 (or week 12 for KCCQ-CSS), and between-group differences at the end of withdrawal compared with the last-value-on-treatment, as well. Measurements after drug withdrawal were considered valid if made 23 to 45 days after the planned cessation of treatment, but patients who started open-label therapy with a SGLT2 inhibitor during the withdrawal period were not included in the analysis. The mixed model for repeated measures models were adjusted for baseline covariates of sex, age, study, diabetes status, eGFR, left ventricular ejection fraction and region, and the-baseline-for-the-evaluated-parameter-by-visit interaction, and they included a covariate for the time of recruitment, thus reflecting the different possible follow-up visits in this event-driven trial.

Between-group differences in the risk of the composite of cardiovascular death or heart failure hospitalization were assessed during 2 periods: (1) from 90 days before the start of the closeout period up to the planned end of double-blind treatment and (2) from the end of double-blind treatment to the end of the withdrawal phase (which was planned for 30±7 days but included data up to 45 days after treatment discontinuation, so as to be consistent with the prespecified cutoff for valid postwithdrawal assessments). The periods were compared on the basis of the patients at risk during each time frame. The hazard ratios and 95% CIs were calculated using a Cox regression model, which was adjusted for the prespecified baseline covariates of age, sex, geographical region, diabetes, left ventricular ejection fraction, eGFR, and trial (EMPEROR-Reduced or EMPEROR-Preserved). In addition, we adjusted for baseline high-sensitivity cardiac troponin T and N-terminal pro-B type natriuretic peptide (NT-proBNP), the most important predictors of the primary outcome in the EMPEROR trial program,[24,25] and for the use of foundational drugs for heart failure, as well (ie, mineralocorticoid receptor antagonist and sacubitril/valsartan) at time of the start of the 2 study periods. The assumption of proportional hazards was tested, and no violations were observed. Differences in hazard ratios between the treatment groups and across the 2 time periods were evaluated by a period-by-treatment interaction term in the model. Spearman correlation coefficient ρ was used to evaluate correlation of changes among hematocrit and NT-proBNP, body weight, and albumin within each treatment group in each of the 2 time periods.

All analyses were performed using SAS, version 9.4 (SAS Institute). All reported *P* values are 2 sided, with $P<0.05$ considered to be statistically significant.

RESULTS

Of the 3730 patients randomly assigned into the EMPEROR-Reduced trial, 2925 patients (1446 placebo and 1479 empagliflozin) survived and were still taking their study medications until 90 days before the start of the closeout period. Because of variations in the start of closeout between sites and patients, the median duration of the end of double-blind phase was 110 days (interquartile range, 99–135 days). Because of COVID-19 restrictions, only 934 patients (25.0% of the total number of randomly assigned patients and 34.2% of the total number of eligible patients who completed double-blind treatment) attended a formal 30-day off-treatment in-person study visit and provided valid postwithdrawal evaluation of KCCQ-CSS and laboratory tests. The median time from the last double-blind assessment to the off-treatment assessment was 29 days (interquartile range, 28–35 days). Of the 5988 patients randomly assigned into the EMPEROR-Preserved trial, 4368 patients (2177 placebo and 2191 empagliflozin) survived and were still taking their study medications until 90 days before the start of the closeout period. Because of variations in the start of closeout between sites, the median duration of the end of double-blind phase was 129 days (interquartile range, 120–142 days). Of these, 3047 patients (50.9% of the total number of randomly assigned patients and 74.4% of the total number of eligible patients who completed double-blind treatment) underwent a formal 30-day off-treatment in-person study visit and provided valid postwithdrawal evaluation of KCCQ and laboratory tests. The median time from the last double-blind assessment to the off-treatment assessment was 28 days (interquartile range, 28–33 days).

When the 2 trials were combined (Figure S1), of 9718 patients who were randomly assigned to double-blind therapy, 7293 were receiving double-blind treatment 90 days before the start of the closeout period (placebo 3623, empagliflozin 3670). Of these, 6799 patients (placebo 3381, empagliflozin 3418) completed double-blind treatment and provided data after withdrawal, and, of these, 3981 patients (placebo 2020, empagliflozin 1961) completed the ≈30-day withdrawal period and underwent valid in-person off-treatment clinical and laboratory assessments. A total of 92 patients who started open-label therapy with a SGLT2 inhibitor during the withdrawal period were not included in the analysis.

Table S1 and Table S2 show the baseline prerandomization characteristics in the patients who contributed or did not contribute data to the evaluation of end-of-trial heart failure events during the withdrawal period or contributed or did not contribute data to the evaluation of paired assessments of KCCQ-CSS and laboratory tests at the end of double-blind treatment and ≈30 days after withdrawal. In both instances, the patients who survived to participate in the withdrawal phase of the trials had less severe heart failure (as reflected by New York Heart Association functional class, ejection fraction, NT-proBNP and troponin levels, and recency of a heart failure hospitalization) and had fewer or less severe

comorbidities (as reflected by diabetes and eGFR), compared with the full cohort of originally randomly assigned patients. In both Table S1 and Table S2, the placebo and empagliflozin groups were balanced for all reported characteristics.

At the end of double-blind treatment immediately before the 30-day withdrawal period, compared with the placebo group, the patients in the empagliflozin group had higher KCCQ-CSS scores, hemoglobin, and hematocrit, and lower systolic blood pressure, NT-proBNP, serum uric acid, and serum bicarbonate levels (all $P<0.05$; Table 1).

Clinical Assessments

During the 90 days before the start of closeout until the end of double-blind treatment, the annualized risk of cardiovascular death or hospitalization for heart failure was lower in the empagliflozin group than in the placebo group (10.7 [95% CI, 9.0–12.6] versus 13.5 [95% CI, 11.5–15.6] events per 100 patient-years, respectively; hazard ratio 0.76 [95% CI, 0.60–0.96]). However, when the study drugs were withdrawn for ≈30 days, the annualized risk of major heart failure events increased in patients withdrawn from empagliflozin but not in patients withdrawn from placebo (17.0 [95% CI, 12.6–22.1] versus 14.1 [95% CI, 10.1–18.8] events per 100 patient-years for empagliflozin and placebo, respectively; between-group hazard ratio 1.18 [95% CI, 0.78–1.80]). The change in the annualized risk in the patients withdrawn from empagliflozin (from the on-treatment period to the off-treatment period) was significant (HR 1.75 [95% CI, 1.20–2.54], $P=0.0034$), whereas the change in the annualized risk in patients withdrawn from placebo was not significant (HR 1.12 [95% CI, 0.76–1.66]); $P=0.068$) for the time-period-by-treatment interaction, which compared between-group differences before and after planned end of treatment (Figure 1A). These findings were driven primarily by hospitalizations for heart failure (Table 2). The number of events during the withdrawal phase was small (49 versus 40 events in the empagliflozin and placebo groups), as shown in Table 2. Time-to-event plots for the prewithdrawal and postwithdrawal periods are shown in Figure S1. The patterns were similar when the 2 trials were analyzed separately (Table S3).

When double-blind therapy was withdrawn, we observed a 1.6±0.4 (adjusted mean±SE) greater decline in the KCCQ-CSS score at 30 days in the patients who had been withdrawn from treatment with empagliflozin compared with those withdrawn from treatment with placebo ($P<0.0001$; Figure 1B). The magnitude of this decline was similar to the magnitude of improvement that had been observed in these same patients after the first postrandomization assessment of KCCQ-CSS performed at the 12-week study visit.[16,17]

Table 1. Clinical Characteristics of Patients in Placebo and Empagliflozin Groups Before the Withdrawal of Double-Blind Therapy (Last Value on Double-Blind Treatment)

Characteristics	Placebo (n=2020)	Empagliflozin (n=1961)	*P* value
Age at baseline, y, mean±SD	70.3±9.7	70.3±9.6	0.993
Women, n (%)	789 (39.1)	770 (39.3)	0.894
Race and ethnicity, n (%)			0.664
Asian	389 (19.3)	377 (19.2)	
Black or African American	83 (4.1)	76 (3.9)	
White	1424 (70.5)	1406 (71.7)	
Other including mixed race*	122 (6.0)	102 (5.2)	
Geographic region, n (%)			0.499
Asia	367 (18.2)	354 (18.1)	
Europe	906 (44.9)	882 (45.0)	
North America	177 (8.8)	197 (10.0)	
Latin America	472 (23.4)	449 (22.9)	
Estimated glomerular filtration rate, mL·min^{-1}·1.73 m^{-2}, mean±SD	57.7 (20.2)	57.5 (20.0)	0.697
Body weight, kg, mean±SD	80.6 (19.5)	79.6 (19.3)	0.126
Ischemic pathogenesis, n (%)	796 (39.4)	786 (40.1)	0.663
Ejection fraction, n (%)			
≤40%	471 (23.3)	464 (23.7)	0.844
41% to <50%	500 (24.8)	470 (24.0)	
≥50%	1049 (51.9)	1027 (52.4)	
New York Heart Association class I or II, n (%)	1792 (88.7)	1758 (89.6)	0.456
Kansas City Cardiomyopathy Questionnaire, mean±SD	77.1 (19.5)	78.5 (19.7)	0.029
NT-proBNP, pg/mL	1017 (473–1864)	894 (418–1673)	0.002
Systolic blood pressure, mm Hg, mean±SD	130.9 (18.3)	129.7 (17.4)	0.038
Serum sodium, mmol/L, mean±SD	140.4 (3.1)	140.6 (3.1)	0.032
Serum potassium, mmol/L, mean±SD	4.49 (0.47)	4.47 (0.50)	0.304
Serum albumin, g/dL, mean±SD	4.36 (0.34)	4.39 (0.33)	0.004
Hemoglobin, g/dL, mean±SD	13.3 (1.7)	14.2 (1.8)	<0.001
Hematocrit, %, mean±SD	40.8 (4.9)	43.6 (5.2)	<0.001
Serum bicarbonate, mmol/L, mean±SD	23.1 (2.8)	22.9 (2.9)	0.009
Serum uric acid, mg/dL, mean±SD	6.5 (1.9)	5.6 (1.7)	<0.001
Hemoglobin A1c, %, mean±SD	6.4 (1.3)	6.3 (1.2)	0.129
Angiotensin converting-enzyme inhibitor or angiotensin receptor blocker, n (%)	1523 (75.4)	1488 (75.9)	0.722
Angiotensin receptor neprilysin inhibitor, n (%)	155 (7.7)	124 (6.3)	0.095
β-Blocker, n (%)	1760 (87.1)	1718 (87.6)	0.649
Mineralocorticoid receptor antagonist, n (%)	934 (46.2)	856 (43.7)	0.101

Values for age, sex, race, geographical region, pathogenesis, and ejection fraction represent values measured before randomization at the start of the trial. All other variables were assessed as the last value on double-blind treatment in those patients with valid data after withdrawal (except hemoglobin A1c, which was not measured after withdrawal). *P* value for NT-proBNP is based on log transformed data. For continuous variables, values are means±SD, except for NT-proBNP where medians and interquartile ranges are shown. NT-proBNP indicates N-terminal prohormone B-type natriuretic peptide.

*Data points were based on patient self-identification.

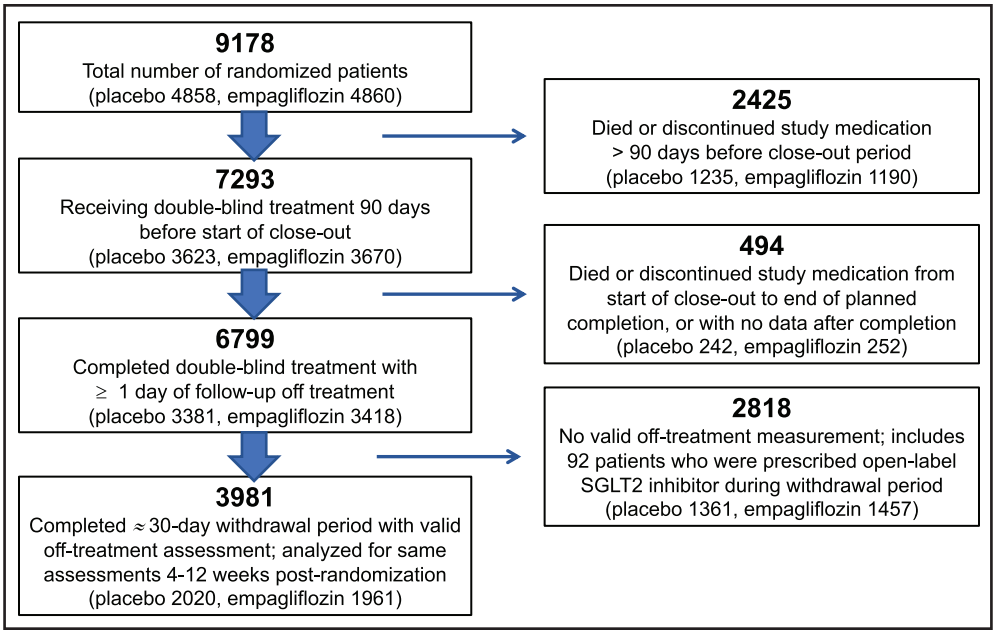

Figure 1. CONSORT diagram.
Source and disposition of randomized patients included in current analysis. Boldface number refers to total number of patients. The 3981 patients who completed the last-value-on-treatment and withdrawal period were also assessed (with respect to clinical, physiological, and laboratory variables) at baseline, 4 weeks after randomization, and 12 weeks after randomization. These data are shown in Figure 2B, Figure 3, and Table 3. SGLT2 indicates sodium-glucose cotransporter 2.

Physical Examination and Laboratory Assessments

At the start of randomized treatment, compared with placebo, initiation of therapy with empagliflozin was accompanied by decreases in body weight (adjusted mean difference±SE, −0.7±0.1 kg), systolic blood pressure (−1.8±0.4 mm Hg), eGFR (−3.0±0.3 mL·min^{-1}·1.73 m^{-2}), NT-proBNP (geometric mean ratio 0.93 [95% CI, 0.90–0.97]), and serum bicarbonate (−0.4±0.1 mg/dL), all P<0.001. Fasting glucose was not measured at 4 weeks after randomization. At the end of the trial, compared with placebo, the withdrawal of empagliflozin was accompanied by increases in fasting glucose (+4.0±1.3 mg/dL), body weight (+0.5±0.1 kg), systolic blood pressure (+2.3±0.5 mm Hg), eGFR (+2.7±0.3 mL·min^{-1}·1.73 m^{-2}), NT-proBNP (geometric mean ratio 1.07 [95% CI, 1.03–1.11]), and serum bicarbonate (+0.3±0.1 mg/dL), all P<0.01. The magnitude of the effects of empagliflozin during the initiation and withdrawal periods (which were separated by ≈1–3 years) were similar (Table 3 and Figure 2). The pattern of responses was similar in the 2 trials (Table S4).

At the start of the trial, compared with placebo, initiation of therapy with empagliflozin was accompanied by increases in hemoglobin and hematocrit at 4 weeks (adjusted mean difference±SE, hemoglobin +0.3±0.0 g/L and hematocrit +1.1±0.1%, both P<0.001, and these effects became larger after 12 weeks of double-blind therapy. At the end of the trial, compared with placebo, the withdrawal of empagliflozin was accompanied by significant decreases in hemoglobin (adjusted mean difference±SE, −0.4±0.0 g/L) and hematocrit (−1.5±0.1%). The magnitude of these changes was similar to those at 4 weeks but meaningfully smaller than those after 12 weeks of randomized treatment (Figure 2). Compared with placebo, uric acid decreased by −1.0±0.0 mg/dL at 4 weeks after the initiation of empagliflozin (P<0.001) and rose by +0.6±0.0 mg/dL (P<0.001) during the withdrawal period; the magnitude of latter effect was smaller than that observed at the start of randomized treatment (Table 3 and Figure 2). For all changes in physiological and laboratory variables, the pattern of responses was similar in the 2 trials (Table S4).

Although the mean changes during the withdrawal period were often similar to the mean changes during the first 4 weeks of double-blind therapy, there was no meaningful correlation between changes during the 2 time periods in individual patients for any variable, except for a modest correlation for uric acid (ρ −0.26). During the first 4 weeks of double-blind therapy, changes in hematocrit were not meaningfully correlated with changes in NT-proBNP (ρ −0.11 for placebo and −0.21 for empagliflozin) or with changes in body weight (ρ −0.18 for placebo and −0.18 for empagliflozin) but were modestly correlated with changes in serum albumin (ρ 0.46 for placebo and 0.42 for empagliflozin). Likewise, during the 30-day withdrawal period, changes in hematocrit were not meaningfully correlated with changes in NT-proBNP (ρ −0.20 for placebo and −0.23 for empagliflozin) or

Table 2. Cardiovascular Death or Heart Failure Hospitalization During the On-Treatment Period (90 Days From Start of Closeout to the End of Double-Blind Treatment) and During the Off-Treatment Withdrawal Period (From End of Double-Blind Treatment to End of Withdrawal Period ≈30 Days Later) For Both Trials Combined

Cardiac death or hospitalization	Placebo	Empagliflozin
Cardiovascular death or hospitalization for heart failure (both trials combined)		
On-treatment (90 days from start of closeout to end of double-blind treatment)		
Number of analyzed patients	3623	3670
Number of patients with event	163	132
Time at risk for event, years	1209.7	1229.5
Incidence rate (events per 100 patient-years at risk)	13.47 (11.48–15.62)	10.74 (8.98–12.64)
Hazard ratio	0.76 (0.60–0.96)	
Off-treatment (≈30 days from end of double-blind treatment to end of withdrawal period)		
Number of analyzed patients	3381	3418
Number of patients with event	40	49
Time at risk for event, y	283.5	287.6
Incidence rate (events per 100 patient-years at risk)	14.11 (10.08–18.81)	17.04 (12.61–22.13)
Hazard ratio	1.18 (0.78–1.80)	
Time to first hospitalization for heart failure (both trials combined)		
On-treatment (90 days from start of closeout to end of double-blind treatment)		
Number of analyzed patients	3623	3670
Number of patients with event	107	97
Time at risk for event, y	1209.7	1229.5
Incidence rate (events per 100 patient-years at risk)	8.84 (7.25–10.60)	7.89 (6.40–9.53)
Hazard ratio	0.84 (0.64–1.11)	
Off-treatment (≈30 days from end of double-blind treatment to end of withdrawal period)		
Number of analyzed patients	3381	3418
Number of patients with event	31	39
Time at risk for event, y	283.5	287.6
Incidence rate (events per 100 patient-years at risk)	10.94 (7.43–15.11)	13.56 (9.64–18.14)
Hazard ratio	1.21 (0.76–1.95)	

Also shown is the principal driving component of the primary end point: time to first heart failure hospitalization. Hazard ratios for EMPEROR Pooled (combined analysis of EMPEROR-Reduced [Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction] and EMPEROR-Preserved [Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction]) estimated from Cox regression models, adjusting for baseline values age, estimated glomerular filtration rate, left ventricular ejection fraction, log troponin T, log N-terminal prohormone B-type natriuretic peptide, diabetes status, sex, region, and study, and use of mineralocorticoid receptor antagonists and angiotensin receptor neprilysin inhibition, as well, at the start of the relevant time period.

with changes in body weight (ρ −0.11 for placebo and −0.18 for empagliflozin) but were modestly correlated with changes in serum albumin (ρ 0.39 for placebo and 0.37 for empagliflozin). These relationships were similar whether patients were withdrawn from placebo or from empagliflozin.

Additional information on the effects of initiation and withdrawal of treatment are shown in Table 3. Serum albumin increased after the start of empagliflozin and decreased after the withdrawal of the drug, but the changes were very small. Serum sodium and potassium concentrations did not change after 4 weeks of empagliflozin and showed minimal changes after withdrawal of empagliflozin.

DISCUSSION

In a preplanned protocol-specified manner, we withdrew double-blind randomized therapy with placebo or empagliflozin for ≈30 days in ≈7000 patients with heart failure and a preserved or reduced ejection fraction, who in general had been taking the 2 study drugs for periods typically exceeding 1 to 2 years. Before the planned withdrawal, the annualized rate of cardiovascular death or hospitalization for heart failure was lower in the empagliflozin group compared with the placebo group. However, when the study drugs were withdrawn for ≈30 days, the rate of cardiovascular death or hospitalization for heart failure increased in the patients who were withdrawn from empagliflozin, but not in those withdrawn from placebo. The hazard ratio for the effect of empagliflozin (versus placebo) changed from 0.76 (95% CI, 0.60–0.96) while patients were taking their study medications to 1.18 (95% CI, 0.78–1.80) while patients were not taking their study drugs (time period-by-treatment interaction P=0.068; Figure S1). The risk of a major heart failure event was numerically higher after the withdrawal of empagliflozin than in the placebo group before withdrawal (17.0 versus 13.5 events per 100 patient-years). It should be noted that the total number of events during the withdrawal period was <100; thus, the off-treatment observations for major heart failure outcomes should be viewed with considerable caution.

Nevertheless, worsening of clinical status after withdrawal of empagliflozin was evident not only with respect to change in the rate of major heart failure events, but also with respect to changes in health status, which was assessed in ≈4000 patients. When double-blind therapy was withdrawn, we observed a greater decline in the KCCQ-CSS score within 30 days in the patients who had been withdrawn from treatment with empagliflozin compared with those withdrawn from treatment with placebo (P<0.0001). The magnitude of this decline was similar to the magnitude of improvement that had been in these same patients after the first postrandomization assessment of KCCQ-CSS performed 12 weeks after

Table 3. Effect of Empagliflozin on Clinical and Laboratory Variables After Initiation of Treatment at the Start of the Trials and After Withdrawal of Treatment at the End of the Trials

Variables	4 weeks after initiation of study medications at start of trial (changes from prerandomization baseline value)			≈30 days after withdrawal of study medications at end of trial (changes from last value on double-blind treatment)		
	Placebo (n=2020)	Empagliflozin (n=1961)	Treatment effect	Placebo (n=2020)	Empagliflozin (n=1961)	Treatment effect
Systolic blood pressure, mm Hg	−0.8±0.3	−2.6±0.3	−1.8±0.4*	−1.1±0.3	+1.3±0.3	+2.3±0.5*
Body weight, kg	+0.1±0.1	−0.5±0.1	−0.7±0.1*	+0.0±0.1	+0.5±0.1	+0.5±0.1*
eGFR, mL·min^{-1}·1.73 m^{-2}	−0.8±0.2	−3.8±0.2	−3.0±0.3*	+0.3±0.2	+3.0±0.2	+2.7±0.3*
NT-proBNP, pg/mL	0.95 (0.92–0.97)	0.88 (0.86–0.91)	0.93* (0.90–0.97)	1.01 (0.98–1.03)	1.08 (1.05–1.10)	1.07* (1.03–1.11)
Serum albumin, g/L	−0.03±0.01	+0.01±0.01	+0.04±0.01*	−0.01±0.01	− 0.05±0.01	−0.05±0.01*
Hemoglobin, g/L	−0.1±0.0	+0.2±0.0	+0.3±0.0*	+0.0±0.0	−0.4±0.0	−0.4±0.0*
Hematocrit, %	−0.6±0.1	+0.6±0.1	+1.1±0.1*	−0.1±0.1	−1.6±0.1	−1.5±0.1*
Serum sodium, mmol/L	0.0±0.1	0.0±0.1	0.0±0.1	−0.1±0.1	−0.1±0.1	−0.1±0.1
Serum potassium, mmol/L	−0.03±0.01	−0.02±0.01	+0.01±0.01	+0.01±0.01	−0.01±0.01	−0.03±0.01‡
Serum bicarbonate, mmol/L	−0.0±0.1	−0.4±0.1	−0.4±0.1*	+0.1±0.1	+0.4±0.1	+0.3±0.1*
Fasting glucose, mg/dL				+0.5±0.9	+4.5±0.9	+4.0±1.3†
Serum uric acid, mg/dL	−0.0±0.0	−1.1±0.0	−1.0±0.0*	−0.0±0.0	+0.5±0.0	+0.6±0.0*
KCCQ-CSS	+3.4±0.3	+4.6±0.3	+1.3±0.4†	−0.4±0.3	−2.0±0.3	−1.6±0.4*

Results from mixed model for repeated measures model including changes from baseline at week 4, week 12, last value on treatment, and ≈30 days after treatment discontinuation. Shown are between-group differences for (1) the change from baseline at week 4 for physiological and laboratory variables and from baseline to week 12 for KCCQ; and (2) the change from the value at the end of the withdrawal period compared with last value on treatment. All analyses conducted in a single cohort of patients that provided withdrawal data. Shown are adjusted means±SE or adjusted geometric mean ratio (95% CI) for NT-proBNP. (Models for NT-proBNP are based on log transformed data.) The precise number of patients with available data for each physiological or laboratory assessment varied slightly, but, in general, was ≈1850 to 2000 for each visit in each treatment group. Symbols indicate level of significance for between-group differences: *P<0.001; †P<0.01; and ‡P<0.05. eGFR indicates estimated glomerular filtration rate; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire; and NT-proBNP, N-terminal prohormone B-type natriuretic peptide.

the initiation of double-blind therapy, ≈1 to 3 years earlier. Although changes in KCCQ-CSS score of 1 to 2 points represent a small difference when assessed in individual patients, these represent a 15% to 30% higher likelihood of a meaningful improvement on a population basis.[26,27]

Our laboratory assessments can provide insights into the durability of the effects of empagliflozin in the kidney, where it inhibits both SGLT2 and sodium-hydrogen exchanger 3 in the proximal renal tubule.[28–30] SGLT2 inhibition lowers blood glucose by promoting glycosuria, and our observation that blood glucose increased after discontinuation of treatment is consistent with a durable effect on urinary glucose excretion. Glycosuria is an important driver of the increase in uric acid excretion and the decrease in serum uric acid during SGLT2 inhibition,[31] and uric acid increased after withdrawal of empagliflozin. Sodium-hydrogen exchanger 3 inhibition induces a modest bicarbonaturia,[29,30] and serum bicarbonate decreases after SGLT2 inhibition.[32] We observed a decrease in serum bicarbonate at the start of the trials that persisted for the duration of the trials; this effect was reversed ≈30 days after withdrawal of the drug. Last, sodium-hydrogen exchanger 3 inhibition enhances sodium delivery to the macula densa, activating tubuloglomerular feedback and resulting in a decline in glomerular filtration rate.[33,34] We observed a decrease in eGFR during the first 4 weeks of randomized therapy, which was fully reversed during the withdrawal period. Taken collectively, these observations suggest that, during long-term treatment with SGLT2 inhibitors, tolerance does not develop to the effect of these drugs to inhibit SGLT2 and sodium-hydrogen exchanger 3 in the proximal tubule.

After discontinuation of empagliflozin, we observed small increases in body weight, systolic blood pressure, and NT-proBNP, which were accompanied by small decreases in hemoglobin, hematocrit, and serum albumin. These findings were the inverse of the changes seen after 4 weeks of double-blind treatment at the start of the trial. These observations might suggest a small increase in total body sodium stores and plasma volume after the withdrawal of therapy. However, increases in weight may have been (in part) related to the cessation of glycosuria, which (by itself) would have yielded a gain of 1.0 to 1.5 kg over the 30-day withdrawal period.[35] Furthermore, decreased erythropoietin stimulation and reduced erythrocytosis after the withdrawal of SGLT2 inhibitors may have contributed to the decreases in hemoglobin and hematocrit.[36,37] We found no or modest correlations between changes in hematocrit and changes in NT-proBNP, changes in body weight or changes in serum albumin during the 30-day withdrawal phase, with similar correlations in both the placebo and empagliflozin groups, suggesting that sodium retention did not selectively occur in one of the treatment groups.[38]

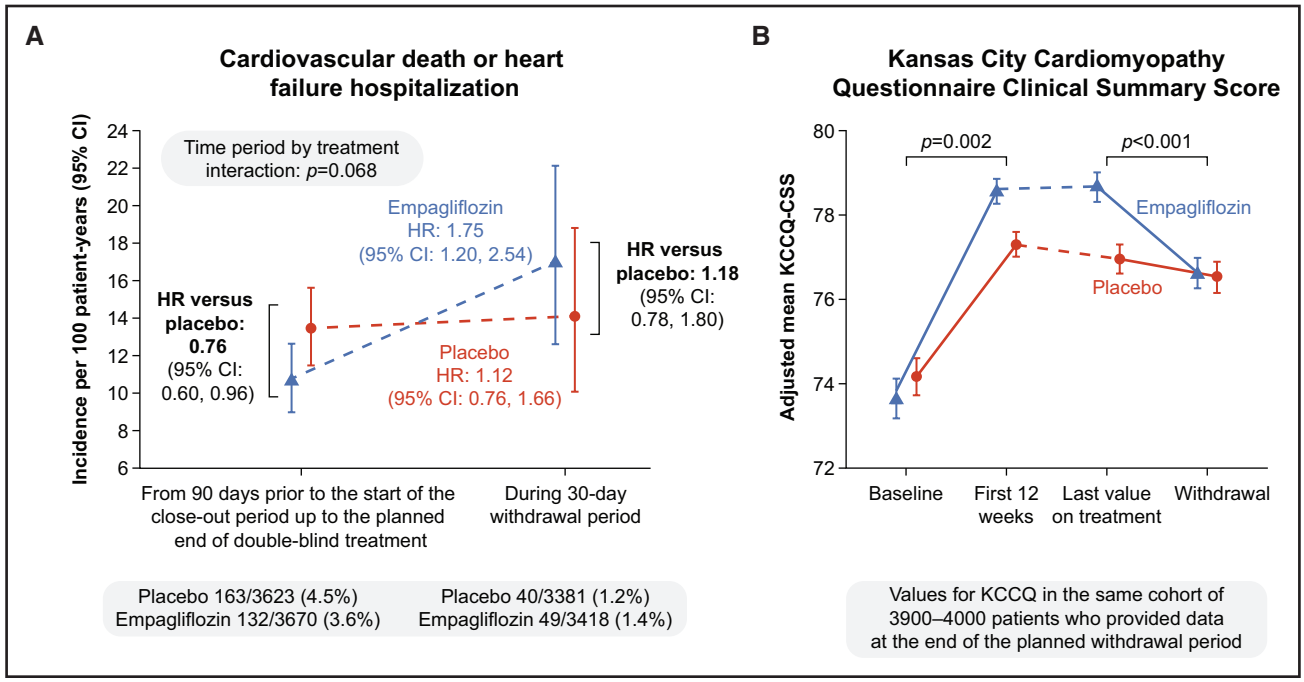

Figure 2. Effect of empagliflozin on clinical efficacy measures during initiation of double-blind therapy and after planned withdrawal of double-blind treatment.

A, The incidence of cardiovascular death or hospitalization for heart failure from 90 days before the start of the closeout period to the end of the double-blind treatment period and during the ≈30-day withdrawal period. Shown in black are the between-group differences, expressed as hazard ratio (HR) and 95% CIs. Within-group differences for the 2 treatment periods are shown in red for the placebo group and blue for the empagliflozin group. Time-to-event plots for these data are shown in Figure S1. **B**, Values for KCCQ-CSS (±SE) at baseline, 12 weeks after randomization, the last value on double-blind treatment and at the end of the 30-day withdrawal period in the same cohort of 3928 patients who provided KCCQ-CSS data at the end of the planned withdrawal period. *P* values show the between-group difference between empagliflozin versus placebo (1) during initiation of treatment ("on-treatment effect," assessed as between-group difference in the changes from baseline at 12 weeks of randomized treatment) and (2) at the end of the trial ("off-treatment effect," assessed as between-group difference at the end of the withdrawal period compared with last value on double-blind treatment), on the basis of mixed model for repeated measures analyses. KCCQ-CSS indicates Kansas City Cardiomyopathy Questionnaire Clinical Summary Score.

Our findings should be considered in light of certain strengths and limitations. In a large-scale trial, double-blind therapy was withdrawn by protocol design from patients who completed the treatment period, thus minimizing the confounding of previous observational studies.[7–11] Our approach was similar to that in another large-scale trial.[12] The group entering the withdrawal phase represented a less impaired subset of our original randomly assigned patients, because these patients were required to have survived and maintained double-blind treatment. Even at the end of the trial, the groups fortunately were well-balanced with respect to assignment to placebo or empagliflozin, because treatment with empagliflozin did not influence the rates of discontinuation of randomized therapy due to death or other causes. Nevertheless, the analyses performed in the patients included in our withdrawal analyses did not have the protection of randomization; however, we made every effort to adjust for all relevant prognostic variables. To address these potential issues and ensure balance between placebo and empagliflozin groups, we would have needed to perform a trial of several thousand patients who had been taking empagliflozin for years and who would be randomly assigned to continue the drug or be withdrawn into treatment with placebo for a period of several months or longer. Such a design has been carried in the past to evaluate the long-term efficacy of digoxin.[13]

Furthermore, it should be emphasized that the withdrawal of therapy was abrupt (as per protocol) and the period of follow-up off-treatment was brief (≈30 days). The proximal tubular effect of SGLT2 inhibitors elicits compensatory downstream antinatriuretic and antiaquaretic mechanisms that truncate any expected changes in urinary sodium and water excretion.[15–19] Abrupt withdrawal allows these counterregulatory mechanisms to become apparent as rebound phenomena, which have been reported when diuretics and vasodilator drugs are used for the treatment of heart failure.[39–41] Given the numerically higher event rate after the withdrawal of empagliflozin than in the placebo group before withdrawal, it is reasonable to postulate that a short-term rebound effect may have amplified the magnitude of the changes that we observed after the withdrawal of empagliflozin,[42] thus enhancing estimates of an on-treatment

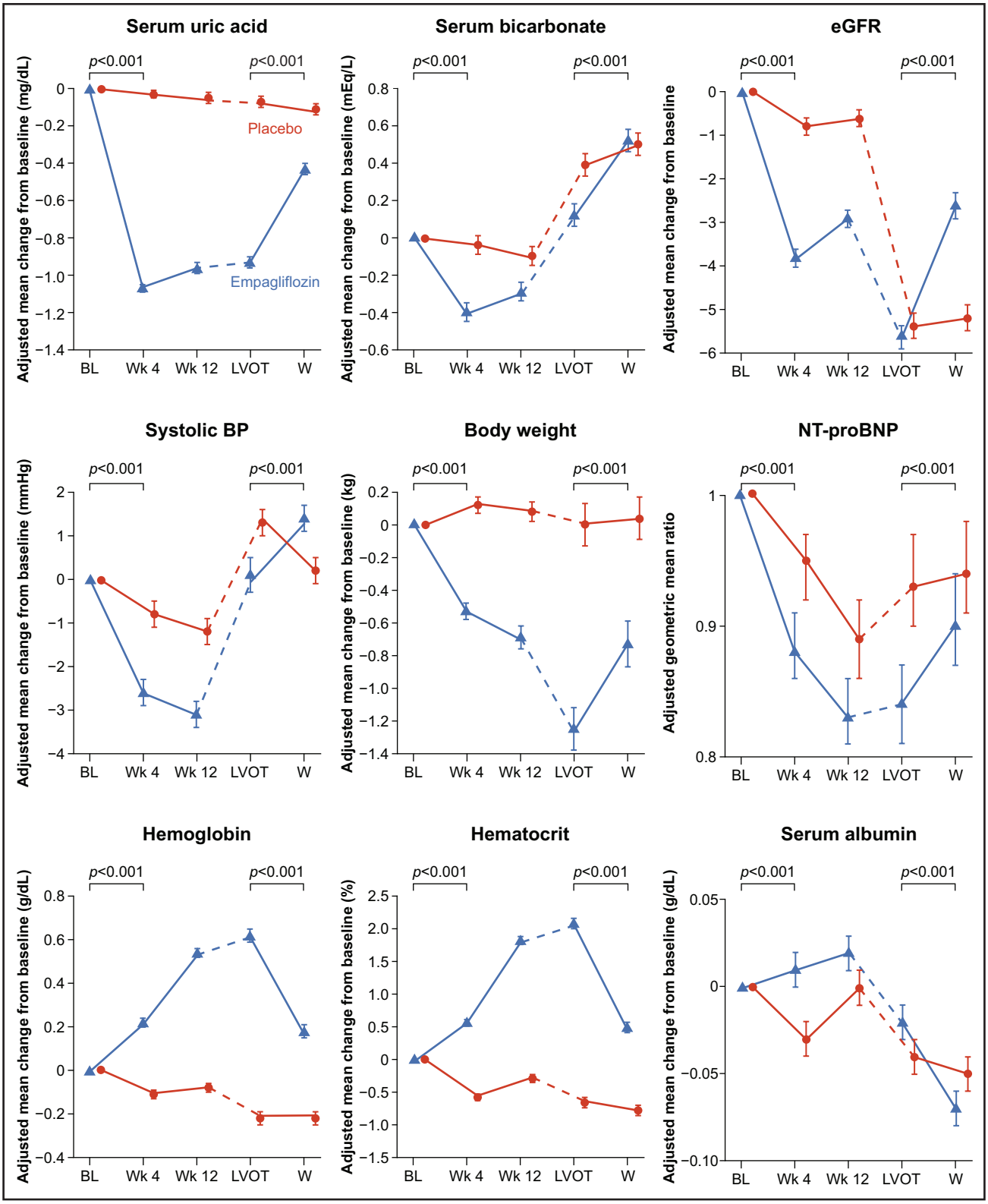

Figure 3. Effect of empagliflozin on physiological and laboratory assessments during initiation of double-blind therapy and after planned withdrawal of double-blind treatment.

Values at baseline (BL), 4 and 12 weeks after randomization, the last value on double-blind treatment (LVOT), and at the end of the 30-day withdrawal period (W) in the cohort of 3981 patients who provided data during the withdrawal period. Shown are adjusted mean changes from baseline±SE for all variables except for NT-proBNP, for which adjusted geometric mean ratio (95% CI) is displayed. *P* values on the left side of each graft represent the significance of between-group changes at 4 weeks from baseline, and *P* values on the right side of each graft represent the significance of between-group changes at the end of withdrawal compared with LVOT, on the basis of mixed model for repeated (*Continued*)

Figure 3 Continued. measures analyses. For NT-proBNP the analyses were performed on log-transformed values. The precise number of patients with available data for each physiological and laboratory assessment varied slightly but, in general, was ≈1850 to 2000 for each visit in each treatment group. BP indicates blood pressure; eGFR, estimated glomerular filtration rate; and NT-proBNP, N-terminal prohormone B-type natriuretic peptide.

effect. Conversely, our ability to assess the full effect of the discontinuation of treatment on clinical events may have been limited by the brevity of our withdrawal period, which was shorter than that in other drug withdrawal trials in patients with heart failure.[14,43,44] With additional time off-treatment, we would have observed more events, thus allowing us to define the between-group differences with greater certainty.

In conclusion, in 2 large-scale trials in which we withdrew randomized double-blind treatment with placebo or empagliflozin in patients with heart failure with a reduced or preserved ejection fraction, we demonstrated a persistent clinical benefit of empagliflozin even after years of treatment, which dissipated after withdrawal. Maintenance of the clinical effect of the drug was accompanied by persistence of the physiological and laboratory changes that are characteristic of SGLT2 inhibition. These findings indicate that tolerance does not develop during long-term treatment with empagliflozin in patients with heart failure and that cessation of treatment even for short periods of time may have deleterious consequences.

ARTICLE INFORMATION

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Supplemental Material

Figure S1

Tables S1–S4

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