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ORIGINAL INVESTIGATIONS

Empagliflozin Improves Outcomes in Patients With Heart Failure and Preserved Ejection Fraction Irrespective of Age

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ABSTRACT

BACKGROUND Empagliflozin reduces cardiovascular death (CVD) or heart failure (HF) hospitalization (HFH) in patients with HF and preserved ejection fraction. Treatment effects and safety in relation to age have not been studied.

OBJECTIVES The purpose of this study was to evaluate the interplay of age and empagliflozin effects in EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction).

METHODS We grouped patients (n = 5,988) according to their baseline age (<65 years [n = 1,199], 65-74 years [n = 2,214], 75-79 years [n = 1,276], ≥80 years [n = 1,299]). We explored the influence of age on empagliflozin effects on CVD or HFH (primary outcome), total HFH, rate of decline in estimated glomerular filtration rate, health-related quality of life with the Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score, and frequency of adverse events.

RESULTS Considering only patients on placebo, the incidence of primary outcomes (*P* trend = 0.02) and CVD (*P* trend = 0.003) increased with age. Empagliflozin reduced primary outcomes (*P* trend = 0.33), first HFH (*P* trend = 0.22), and first and recurrent HFH (*P* trend = 0.11) across all age groups with an effect being similar at ≥75 years (*P* interaction = 0.22) or >80 years (*P* interaction = 0.51). Empagliflozin improved Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score at week 52 and attenuated the decline of estimated glomerular filtration rate without age interaction (*P* = 0.48 and *P* = 0.32, respectively). There were no clinically relevant differences in adverse events between empagliflozin and placebo across the age groups.

CONCLUSIONS Empagliflozin reduced primary outcomes and first and recurrent HFH and improved symptoms across a broad age spectrum. High age was not associated with reduced efficacy or meaningful intolerability. (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction [EMPEROR-Preserved]; NCT03057951) (J Am Coll Cardiol 2022;80:1-18) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

eGFR = estimated glomerular filtration rate

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

HRQoL = health-related quality of life

KCCQ = Kansas City Cardiomyopathy Questionnaire

KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score

SGLT2 = sodium-glucose cotransporter-2

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors reduce cardiovascular death and heart failure (HF) hospitalization in patients with diabetes,[1-3] in patients with HF with reduced ejection fraction (HFrEF),[4,5] and in patients with HF with preserved ejection fraction (HFpEF).[6] Hence, they are recommended in recent guidelines with a Class IA evidence for treatment of HFrEF.[7] We studied the interplay of age with the efficacy and safety of empagliflozin in patients enrolled in the EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction) trial. HFpEF patients are usually older than HFrEF patients[8] and have a higher mortality risk associated with older age, while the risk for cardiovascular death is lower than in HFrEF and HFrEF.[9] Although the relative treatment effects at different ages of sacubitril/valsartan,[10] beta-blockers,[11] and dapagliflozin[12] are similar in patients with HFrEF, no such data exist for SGLT2 inhibition in HFpEF. Because there may be concerns that with advanced age, treatment effects may be decreased and adverse events may be increased,[13] we conducted the present prespecified analysis on the outcomes and safety of empagliflozin in EMPEROR-Preserved.

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METHODS

STUDY DESIGN. The design, baseline characteristics,[14] and results[6] of the EMPEROR-Preserved trial have been published previously. The ethical committees of each of the participating 622 institutions in 23 countries approved the protocol, and all patients gave written informed consent. The registration identifier at clinicaltrials.gov is NCT03057951.

STUDIED PATIENTS AND PROCEDURES. Patients with HF and ejection fraction of >40% were screened, and those fulfilling eligibility criteria were randomized in a double-blind, 1:1 fashion to receive placebo or empagliflozin 10 mg daily in addition to their usual therapy. EMPEROR-Preserved randomized 5,988 patients with New York Heart Association functional class II-IV HF and an ejection fraction of >40% to receive empagliflozin 10 mg once daily or placebo in addition to standard therapy. Patients were required to have elevated N-terminal pro-B-type natriuretic peptide levels (>900 pg/mL or >300 pg/mL in patients with or without atrial fibrillation, respectively) and have evidence of structural heart disease (left ventricular hypertrophy or left atrial enlargement) or a documented hospitalization for HF within the 12 months before enrollment. 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 discretion of the investigator.

Patients were assessed at study visits for major outcomes, vital signs, estimated glomerular filtration rate (eGFR) by the Chronic Kidney Disease Epidemiology Collaboration, adverse events, and changes in medications or clinical status that reflected changes in the course of HF. All randomized individuals were followed up for the occurrence of prespecified 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 the 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 ANALYSES. Patients were grouped according to their age at baseline (<65 years, 65-74 years, 75-79 years, ≥80 years). We evaluated the risk of serious HF events and eGFR decline treated with placebo, and we compared the effects of empagliflozin vs placebo. We examined the influence of age on the occurrence of adverse events in the placebo and empagliflozin groups.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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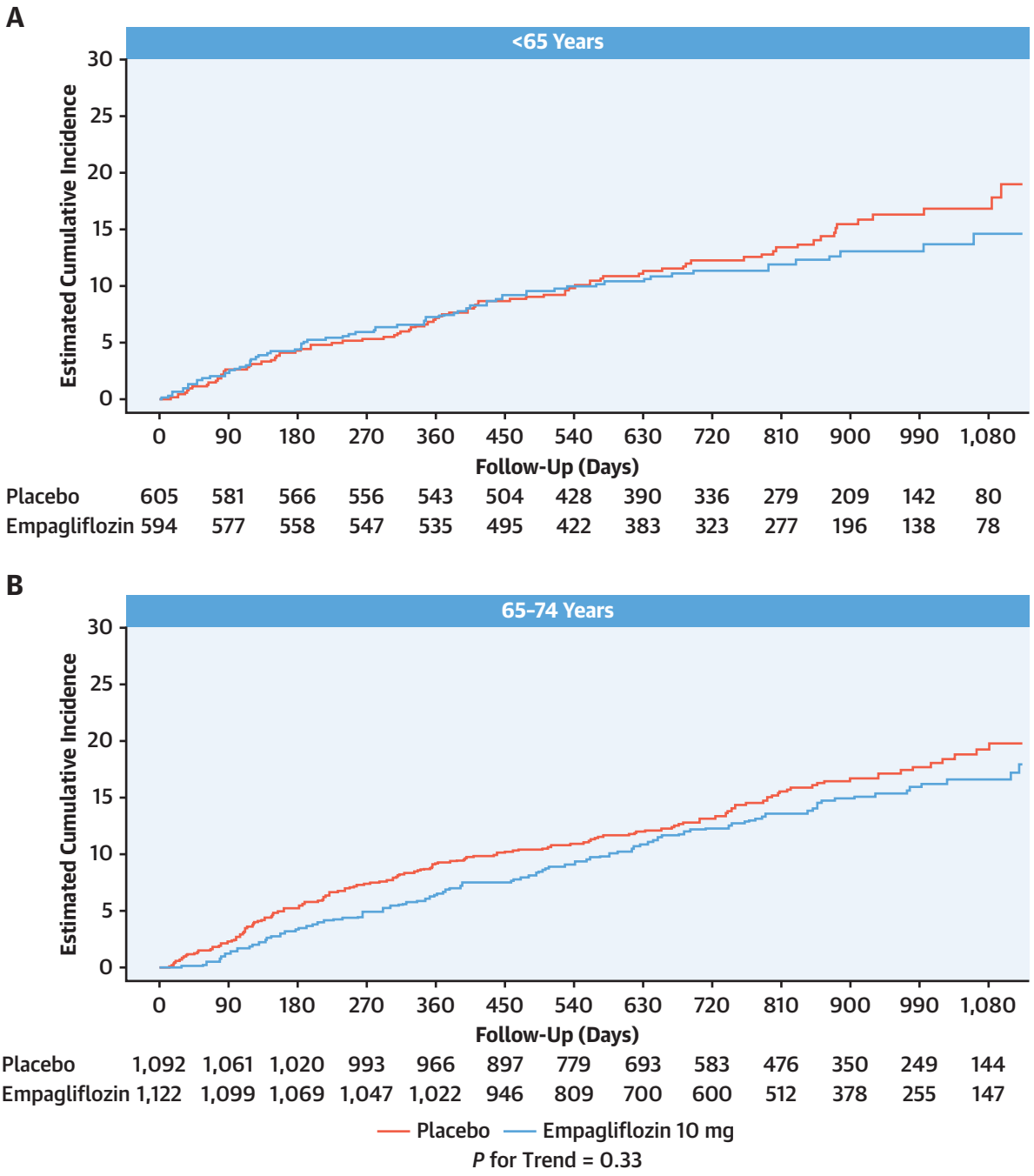
TABLE 1 Baseline Characteristics by Age Groups

	Age Group, y				*P* Value for Trend
	<65 (n = 1,199)	65-74 (n = 2,214)	75-79 (n = 1,276)	≥80 (n = 1,299)	
Sex					<0.0001
Male	760 (63.4)	1,277 (57.7)	657 (51.5)	618 (47.6)	
Female	439 (36.6)	937 (42.3)	619 (48.5)	681 (52.4)	
Race					<0.0001
White	802 (66.9)	1,694 (76.5)	1,022 (80.1)	1,024 (78.8)	
Black/African American	98 (8.2)	93 (4.2)	34 (2.7)	33 (2.5)	
Asian	183 (15.3)	300 (13.6)	165 (12.9)	176 (13.5)	
Other, including mixed race	114 (9.5)	127 (5.7)	55 (4.3)	66 (5.1)	
Missing	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	
Region					<0.0001
North America	139 (11.6)	249 (11.2)	137 (10.7)	194 (14.9)	
Latin America	439 (36.6)	556 (25.1)	273 (21.4)	247 (19.0)	
Europe	381 (31.8)	1,028 (46.4)	649 (50.9)	631 (48.6)	
Asia	122 (10.2)	249 (11.2)	152 (11.9)	163 (12.5)	
Other	118 (9.8)	132 (6.0)	65 (5.1)	64 (4.9)	
LVEF, %	52.3 ± 8.6	54.1 ± 8.6	54.7 ± 8.7	56.2 ± 8.8	<0.0001
Baseline NT-proBNP, pg/mL	721.0 (397-1,481)	893.0 (467-1,607)	1,077.0 (535-1,845)	1,285.0 (685-2,121)	<0.0001
Baseline BP, mm Hg					<0.0001
SBP <140 and DBP <90	809 (67.5)	1,465 (66.2)	749 (58.7)	803 (61.8)	
SBP ≥140 or DBP ≥90	390 (32.5)	749 (33.8)	527 (41.3)	496 (38.2)	
Baseline heart rate, beats/min	71.3 ± 11.5	69.9 ± 11.8	70.0 ± 12.1	70.6 ± 12.0	0.2249
Baseline weight, kg	87.82 ± 21.34	84.63 ± 19.48	79.75 ± 17.51	73.53 ± 15.8	<0.0001
Baseline BMI, kg/m^2	31.14 ± 6.35	30.57 ± 5.87	29.38 ± 5.5	27.83 ± 5.13	<0.0001
Baseline eGFR according to CKD-EPI, mL/min/1.73 m^2	72.4 ± 22.5	62.3 ± 18.3	56.1 ± 16.5	51.3 ± 16.4	<0.0001
Baseline eGFR according to CKD-EPI, mL/min/1.73 m^2					<0.0001
≥60	850 (70.9)	1,232 (55.6)	525 (41.1)	391 (30.1)	
<60	348 (29.0)	981 (44.3)	751 (58.9)	908 (69.9)	
Missing	1 (0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	
Baseline urine albumin-to-creatinine ratio, mg/g					<0.0001
Normal (<30)	680 (56.7)	1,297 (58.6)	773 (60.6)	724 (55.7)	
Microalbuminuria (30-≤300)	322 (26.9)	676 (30.5)	400 (31.3)	462 (35.6)	
Macroalbuminuria (>300)	195 (16.3)	231 (10.4)	98 (7.7)	105 (8.1)	
Missing	2 (0.2)	10 (0.5)	5 (0.4)	8 (0.6)	
Baseline hemoglobin, g/dL	13.64 ± 1.66	13.46 ± 1.58	13.21 ± 1.48	12.9 ± 1.47	<0.0001
History of atrial fibrillation or atrial flutter[a]					<0.0001
No	813 (67.8)	1,057 (47.7)	486 (38.1)	488 (37.6)	
Yes	384 (32.0)	1,154 (52.1)	788 (61.8)	809 (62.3)	
Missing	2 (0.2)	3 (0.1)	2 (0.2)	2 (0.2)	
Baseline HS troponin T, ng/L	22.31 ± 27.03	21.98 ± 31.15	23.89 ± 28.22	27.83 ± 31.91	<0.0001
History of HHF (in the last 12 months)[b]	319 (26.6)	472 (21.3)	284 (22.3)	294 (22.6)	<0.0001
Cause of HF					<0.0001
Ischemic	451 (37.6)	837 (37.8)	426 (33.4)	403 (31.0)	
Nonischemic	748 (62.4)	1,376 (62.1)	850 (66.6)	896 (69.0)	
Missing	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	
Diabetes at baseline					<0.0001
Diabetic	656 (54.7)	1,171 (52.9)	607 (47.6)	504 (38.8)	
Nondiabetic	543 (45.3)	1,043 (47.1)	669 (52.4)	795 (61.2)	
NYHA functional class at baseline					0.0088
I	0 (0.0)	2 (0.1)	1 (0.1)	1 (0.1)	
II	987 (82.3)	1,841 (83.2)	1,051 (82.4)	1,004 (77.3)	
III	208 (17.3)	364 (16.4)	222 (17.4)	289 (22.2)	
IV	4 (0.3)	7 (0.3)	2 (0.2)	5 (0.4)	

Values are n (%), mean ± SD, or median (IQR). [a]Defined as atrial fibrillation or atrial flutter reported in any electrocardiogram before treatment intake or history of atrial fibrillation or atrial flutter reported in the medical history. [b]Reported either on heart failure history and diagnosis or Health Care Resource Utilization form.

BMI = body mass index; BP = blood pressure; CKD-EPI = Chronic Kidney Disease-Epidemiology Collaboration; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HF = heart failure; HFH = heart failure hospitalization; HS = high-sensitivity; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure.

FIGURE 1 **Primary Outcome by Age Groups**



Cumulative incidence function for the effect of empagliflozin **(blue)** and placebo **(red)** on the primary outcome (composite of first heart failure hospitalization or cardiovascular death) by age groups of **(A)** <65 years, **(B)** 65-74 years, **(C)** 75-79 years, and **(D)** ≥80 years. No corrections for multiple testing were applied.

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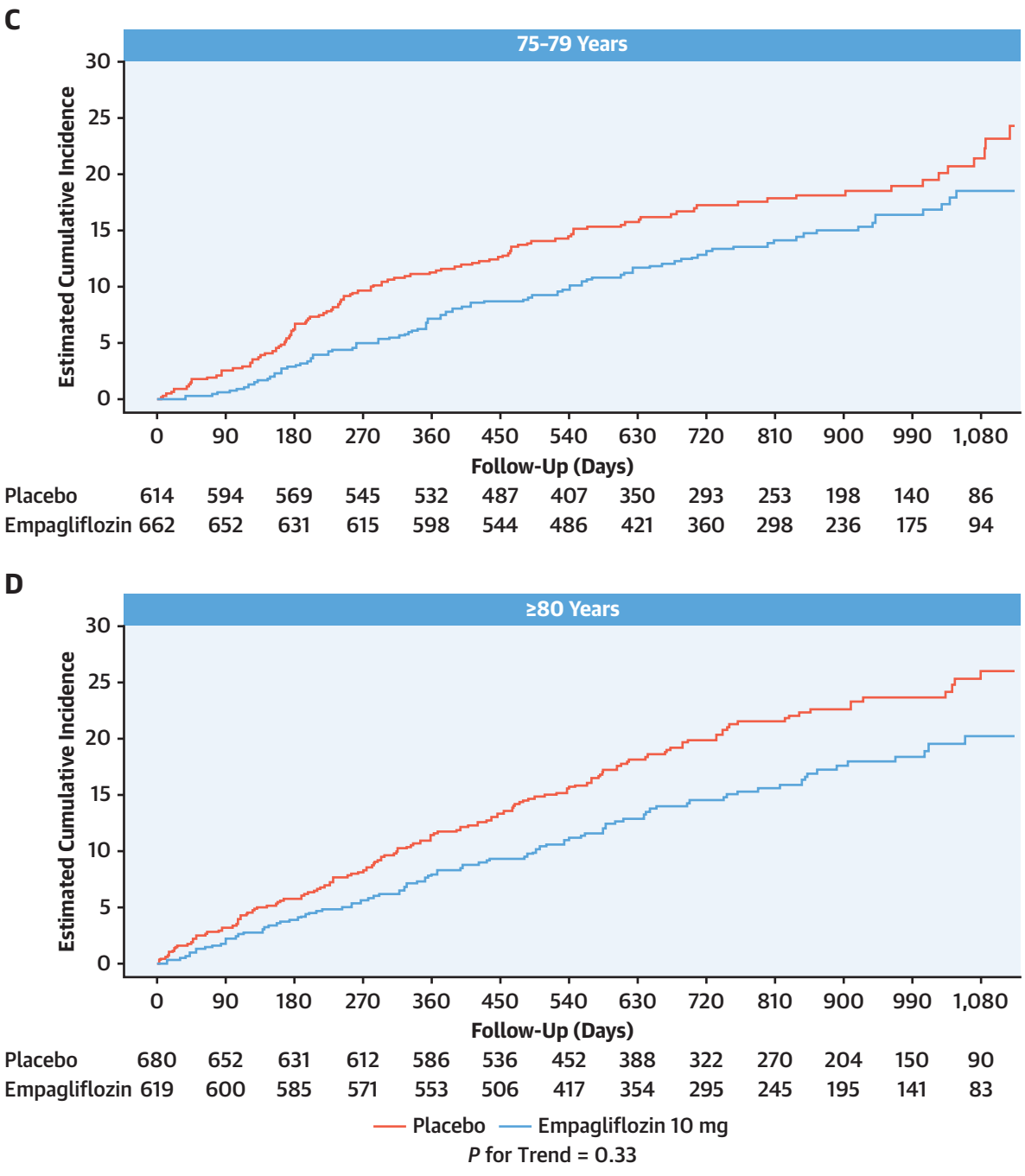
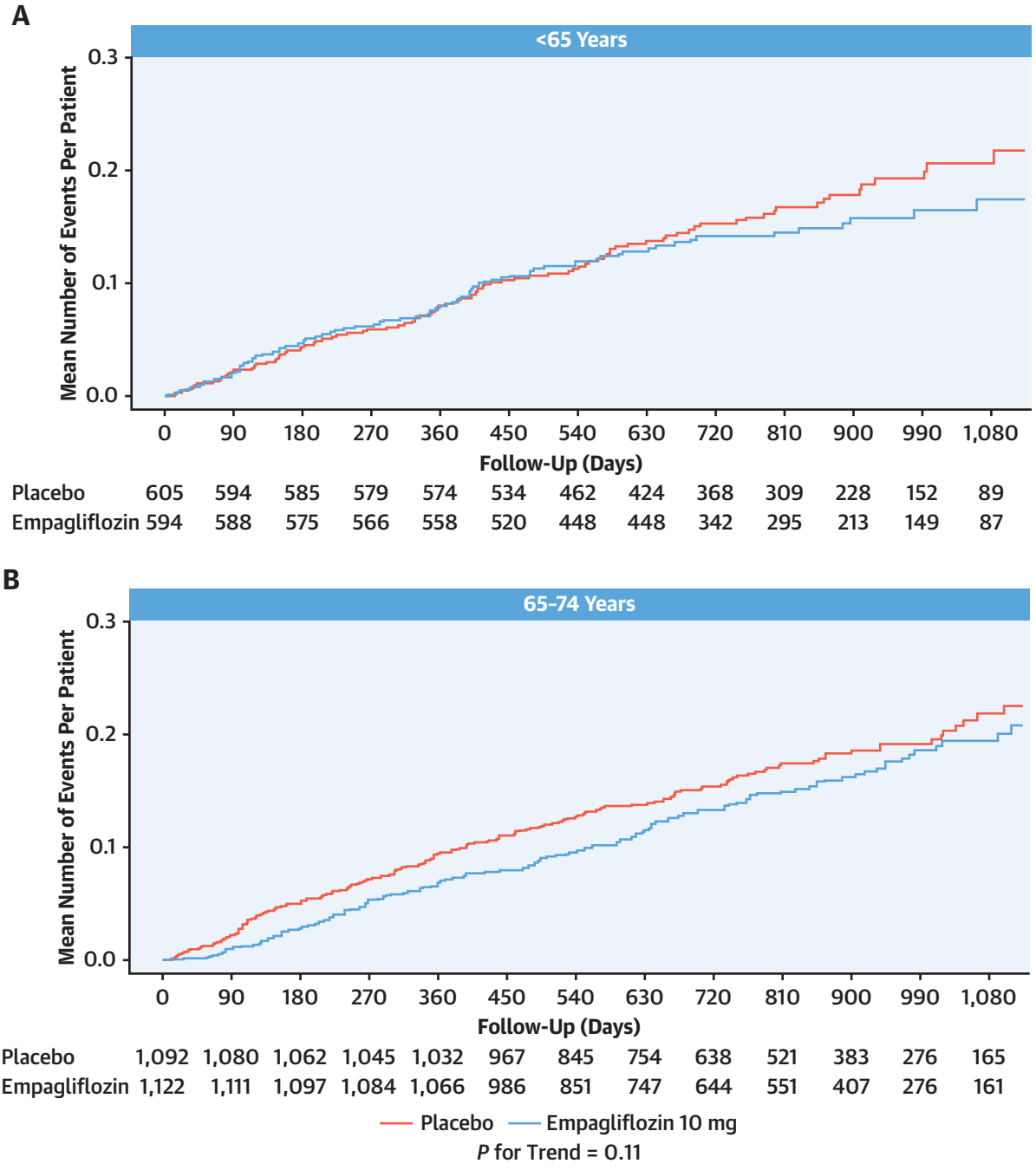
FIGURE 1 Continued



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

QUALITY OF LIFE OUTCOME ASSESSMENT. Health-related quality of life (HRQoL) was assessed using the Kansas City Cardiomyopathy Questionnaire

FIGURE 2 Recurrent Heart Failure Hospitalization by Age Groups



Mean cumulative function for the effect of empagliflozin **(blue)** and placebo **(red)** on recurrent heart failure hospitalization by age groups of **(A)** <65 years, **(B)** 65-74 years, **(C)** 75-79 years, and **(D)** ≥80 years. No corrections for multiple testing were applied.

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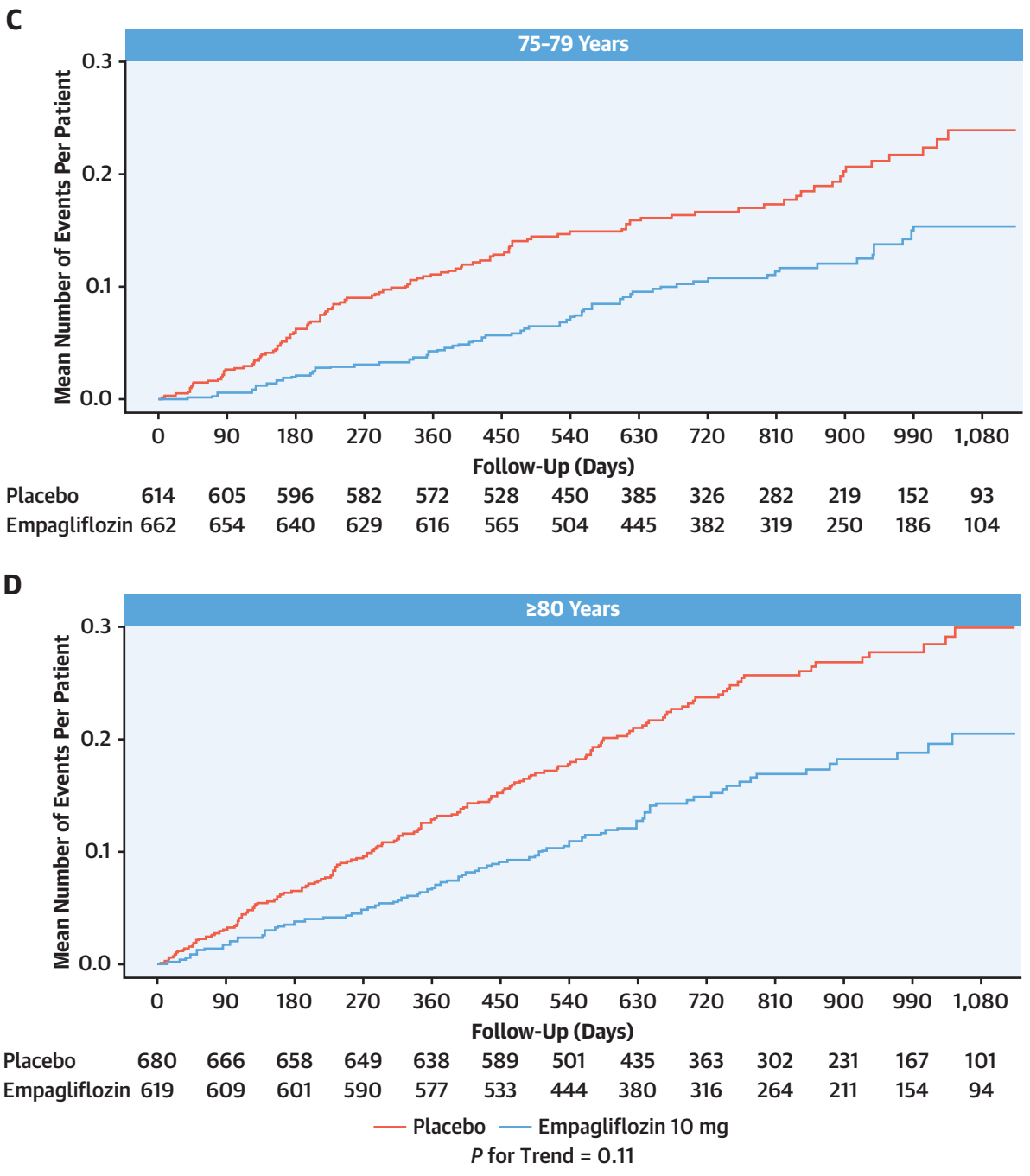
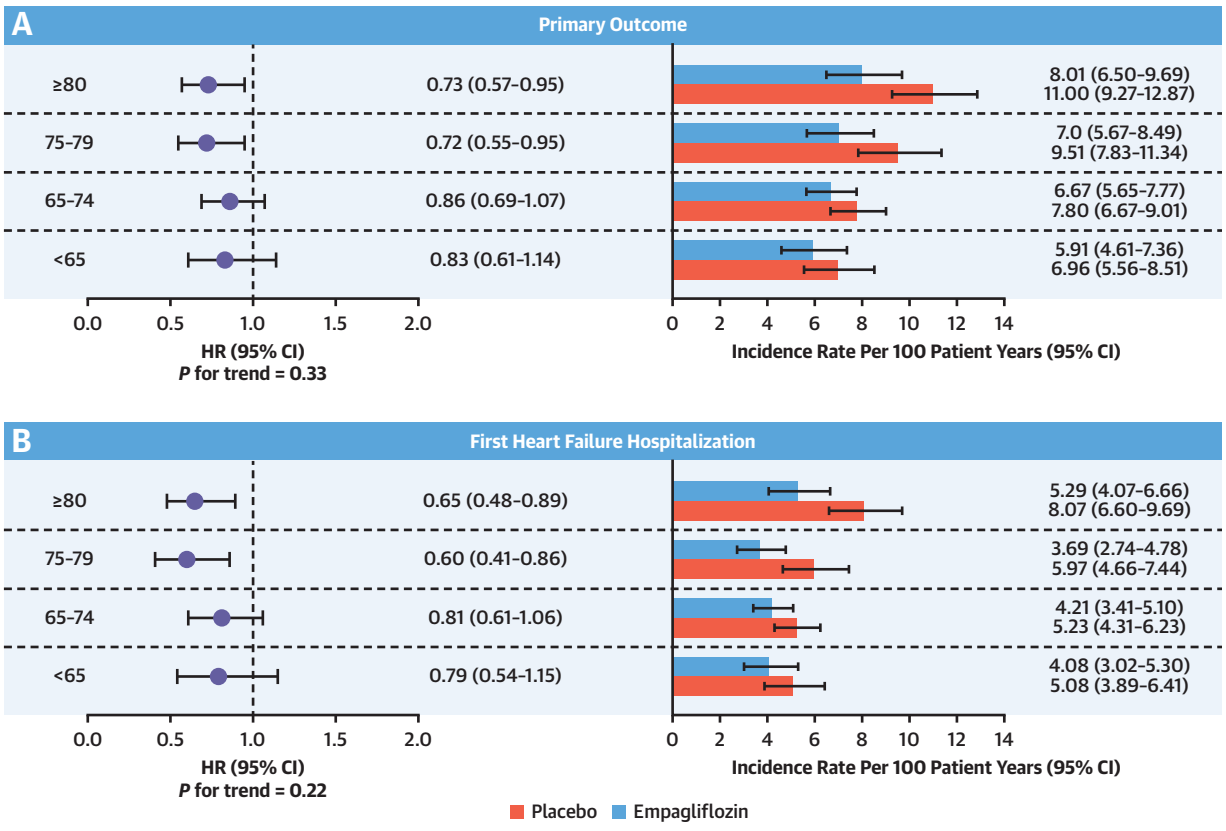
(KCCQ)-23, which includes 23 items that map to 7 domains: symptom frequency, symptom burden, symptom stability, physical limitations, social limitations, quality of life, and self-efficacy. The KCCQ scores are summarized as: 1) a total symptom score, which consists of the symptom frequency and symptom burden domains; 2) a clinical summary score (CSS) consisting of the physical limitation

FIGURE 2 Continued



domain and total symptom score; and 3) an overall summary score, which is formed by combining the CSS and the quality of life and social limitation domains. The scores range from 0 to 100, with 100 being the best possible score. Herein, the data of the CSS are presented. The KCCQ was completed by patients at baseline and at 3, 8, and 12 months postrandomization. The complete HRQoL of EMPEROR-Preserved data have been published elsewhere.[15]

FIGURE 3 Treatment Effects by Age Groups



HR **(left)** and incidence rate per 100 patient-years **(right)** for empagliflozin compared to placebo according to age for the **(A)** primary outcome (composite of first heart failure hospitalization or cardiovascular death) and **(B)** first heart failure hospitalization. **Red** represents placebo, and **blue** represents empagliflozin. No corrections for multiple testing were applied.

STATISTICAL ANALYSES. The effect of empagliflozin compared with placebo on the time to first event analyses was examined across the age groups using Cox proportional hazard regression models with prespecified covariates of sex, geographic region, diabetes status at baseline, left ventricular ejection fraction, and eGFR at baseline. The interaction between categorical age and treatment group on the occurrence of the prespecified outcomes was tested using a treatment-by-age interaction trend test. The interaction between categorical age and treatment group on the occurrence of the prespecified outcomes was tested using a treatment-by-age interaction trend test assuming ordered age categories. The first secondary outcome of total (first and recurrent) HF hospitalizations was evaluated with the use of the joint frailty model that accounted for informative censoring because of cardiovascular death. Between-group differences in the slope of change in eGFR were analyzed using a random-intercept, random-slope model using on-treatment data. The slope and the joint frailty models included the same covariates as the Cox model. We assessed the influence of empagliflozin on HRQoL differences between treatments groups in KCCQ-CSS at baseline and at 3, 8, and 12 months using a mixed model for repeated measures and the least-squares mean difference between treatment groups as estimated following adjustment for baseline CSS, eGFR, region, sex, diabetes status, and left ventricular ejection fraction. Responder analysis was performed to study the proportion of patients with an improvement or deterioration in CSS at 12 months postrandomization using established clinically meaningful thresholds for CSS (≥5, ≥10, and ≥15 points). Multiple imputation to account for missing CSS value estimates was combined using Rubin's rules.[16] Odd ratios with 95% CIs were calculated for a logistic regression model, which included baseline CSS, eGFR, region, diabetes status, and left ventricular ejection fraction. Patients who

died before the timepoints were accounted as not improved in the improvement analysis and deteriorated in the deterioration analysis. Missing scores are imputed for surviving patients. Ceiling effects were managed as follows: if a patient had a baseline value of ≤5 points, he or she was defined as having a 5-point deterioration if the value was ≤5 points at 52 weeks; conversely, if a patient had a baseline value of ≥95 points, he or she was defined as having a 5-point improvement if the value was ≥95 points at 52 weeks. The relationship of age with outcomes was analyzed by the incidence rates in patients treated with placebo using a Poisson model for primary outcome, time to first HF hospitalization, and cardiovascular death and using a negative binomial model for first and recurrent HF hospitalizations adjusted with the same covariates as the Cox model. The frequencies of the prespecified safety outcomes were investigated in a logistic regression model adjusted with the same covariates as the Cox model. *P* values and 95% CIs presented in this report have not been adjusted for multiplicity, and therefore inferences drawn from these statistics may not be reproducible.

All analyses were performed using SAS, version 9.4 (SAS Institute). All *P* values reported are 2 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.

DATA SHARING STATEMENT. Data will be made available upon request in adherence with transparency conventions in medical research and through requests to the executive committee. The executive committee of EMPEROR-Preserved has developed a comprehensive analysis plan and numerous prespecified analyses that will be presented in future scientific meetings and publications. At a later timepoint, the full database will be made available in adherence with the transparency policy of the sponsor.[17]

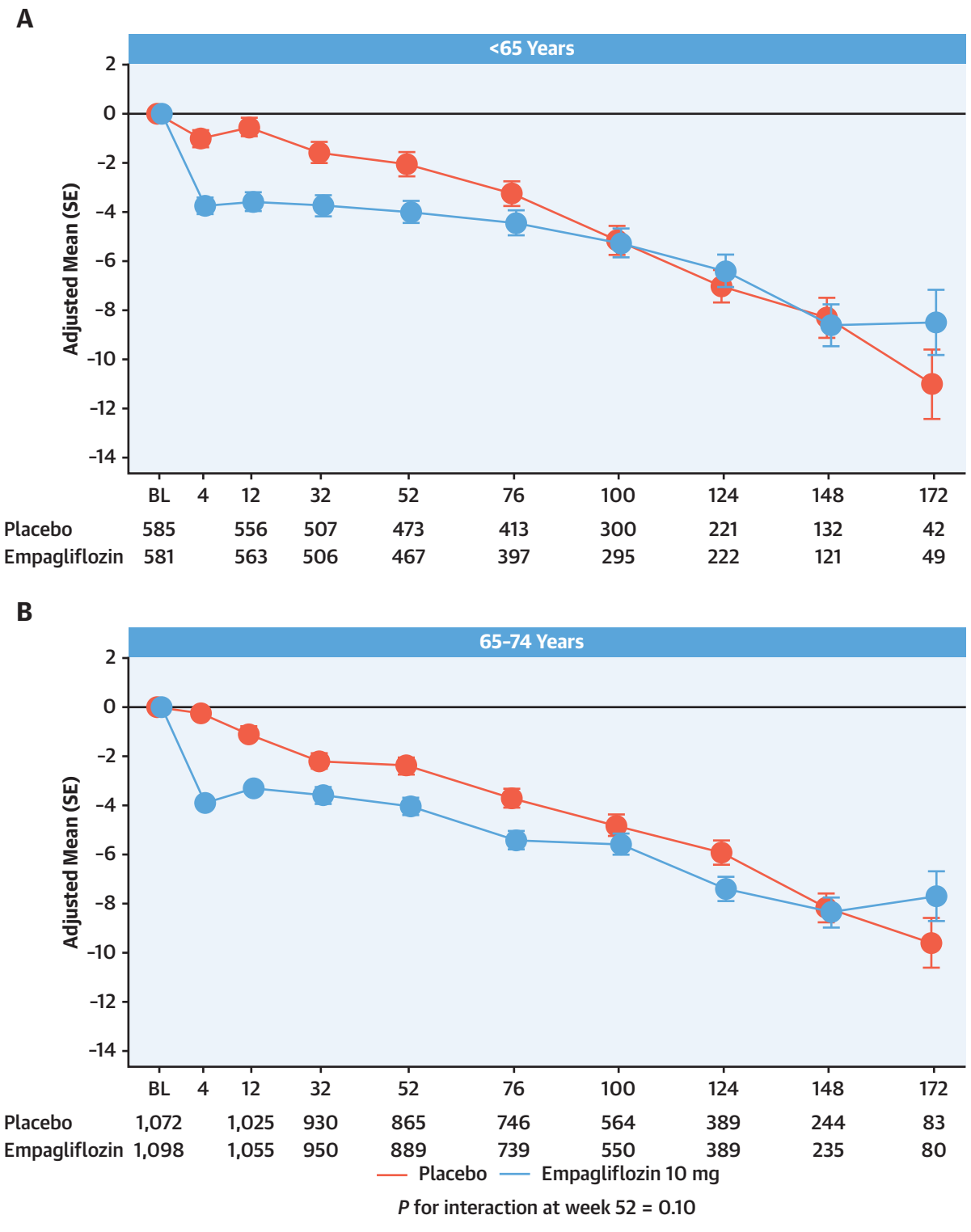
RESULTS

PATIENT CHARACTERISTICS. A total of 5,988 patients were randomly assigned to receive either empagliflozin (n = 2,997 patients, 10 mg once daily) or placebo (2,991 patients). The flow is summarized in Supplemental Figure 1. **Table 1** shows the baseline characteristics of patients according to age. Those with older age were more likely to be female and to have higher ejection fraction, higher N-terminal pro-B-type natriuretic peptide plasma concentrations, lower eGFR, more frequently atrial fibrillation or flutter, and higher blood pressure.

ASSOCIATION OF AGE WITH OUTCOMES. The relationship of age with outcomes was investigated by calculating the incidence rates for major endpoints in patients treated with placebo. The incidence rate for the primary outcome was 6.96 (95% CI: 5.56-8.51) at <65 years, 7.80 (95% CI: 6.67-9.01) at 65-74 years, 9.51 (95% CI: 7.83-11.34) at 75-79 years, and 11.00 (95% CI: 9.27-12.87) at ≥80 years per 100 patient-years (*P* for trend = 0.02). Differences were not significant for first HF hospitalization (*P* for trend = 0.26) but were significant for cardiovascular death (*P* for trend = 0.003). Noncardiovascular death was more prominent compared to cardiovascular death at ≥80 years (34.2% vs 25.3%) and increased across the age groups (*P* for trend = 0.02).

EFFECT OF EMPAGLIFLOZIN ON EFFICACY OUTCOMES. The cumulative incidence function of the primary outcome (cardiovascular death or HF hospitalization) according to age is shown in **Figure 1**. The relative risk reduction of the primary outcome of empagliflozin was similar across the age groups (*P* for trend = 0.33). Supplemental Figure 2 summarizes the cumulative incidence function for first HF hospitalization, which showed similar results, with an interaction trend *P* of 0.22 (nonsignificant) at ≥80 years. **Figure 2** depicts the effect of empagliflozin on first and recurrent HF hospitalizations by age. There was a *P* for interaction trend of 0.11 with a similar risk reduction at ≥80 years. **Figure 3** summarizes the HRs for the primary outcome (left) and the incidence rates (right) of the primary outcome (**Figure 3A**) and the first HF hospitalization (**Figure 3B**). Age did not significantly modify the magnitude of risk reduction by empagliflozin on the primary outcome (*P* for interaction trend = 0.33) and first HF hospitalization (*P* for interaction trend = 0.22). HR modeled as a continuous variable is shown in Supplemental Figure 3A for the primary outcome and for the first HF hospitalization (Supplemental Figure 3B). The cumulative incidence event function for cardiovascular death (Supplemental Figure 4) and all-cause death (Supplemental Figure 5) is shown in the Appendix. There was neither a significant treatment effect nor an interaction by age on mortality outcomes. As a sensitivity analysis, we grouped all patients <75 years and ≥75 years (Supplemental Figures 6A and 6B) as well as <80 years and ≥80 years (Supplemental Figures 6C and 6D). The treatment effect of the primary outcome was maintained at ≥75 years (Supplemental Figure 6B) (*P* for interaction = 0.22) and ≥80 years (Supplemental Figure 6D) (*P* for interaction = 0.51) compared to <75 years and <80 years (Supplemental Figures 6A and 6C, respectively).

FIGURE 4 **eGFR Change From Baseline by Age Group**



The eGFR adjusted mean differences (mL/1.73 m^2/year) change over time in patients treated with empagliflozin (10 mg) **(blue)** or placebo **(red)** in patients **(A)** <65 years, **(B)** 65-74 years, **(C)** 75-79 years, and **(D)** ≥80 years. The eGFR was determined by using the chronic kidney disease epidemiology collaboration equation. No corrections for multiple testing were applied. eGFR = estimated glomerular filtration rate.

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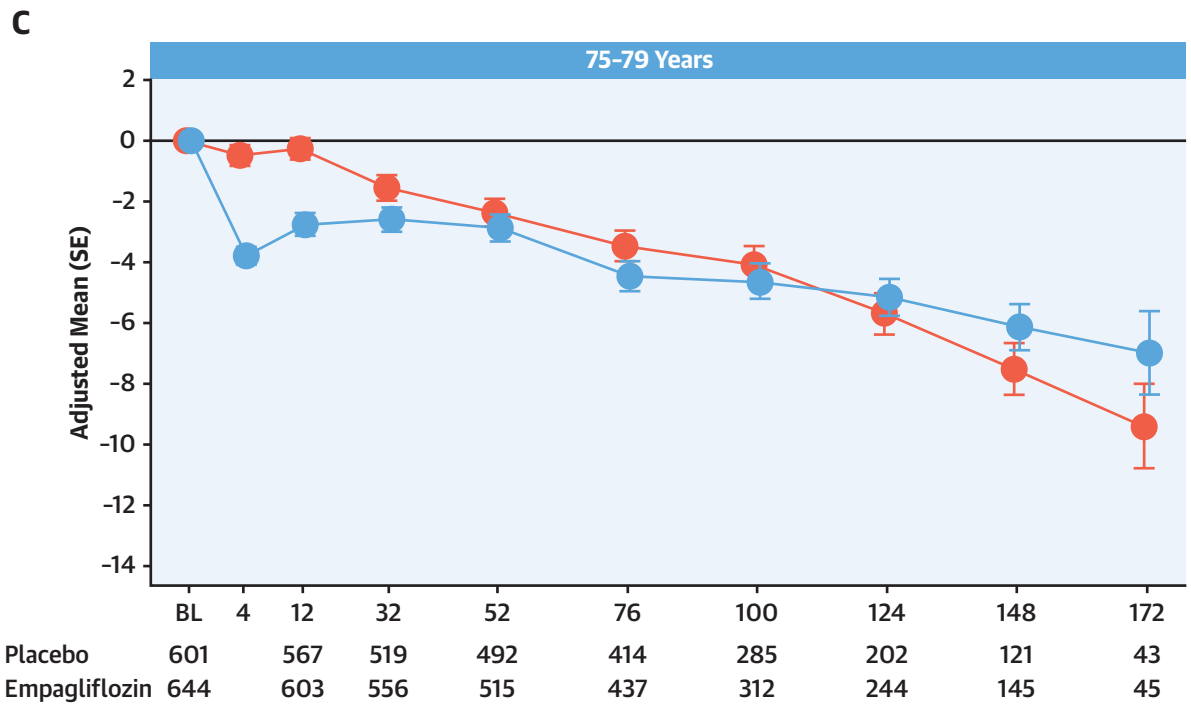
FIGURE 4 Continued



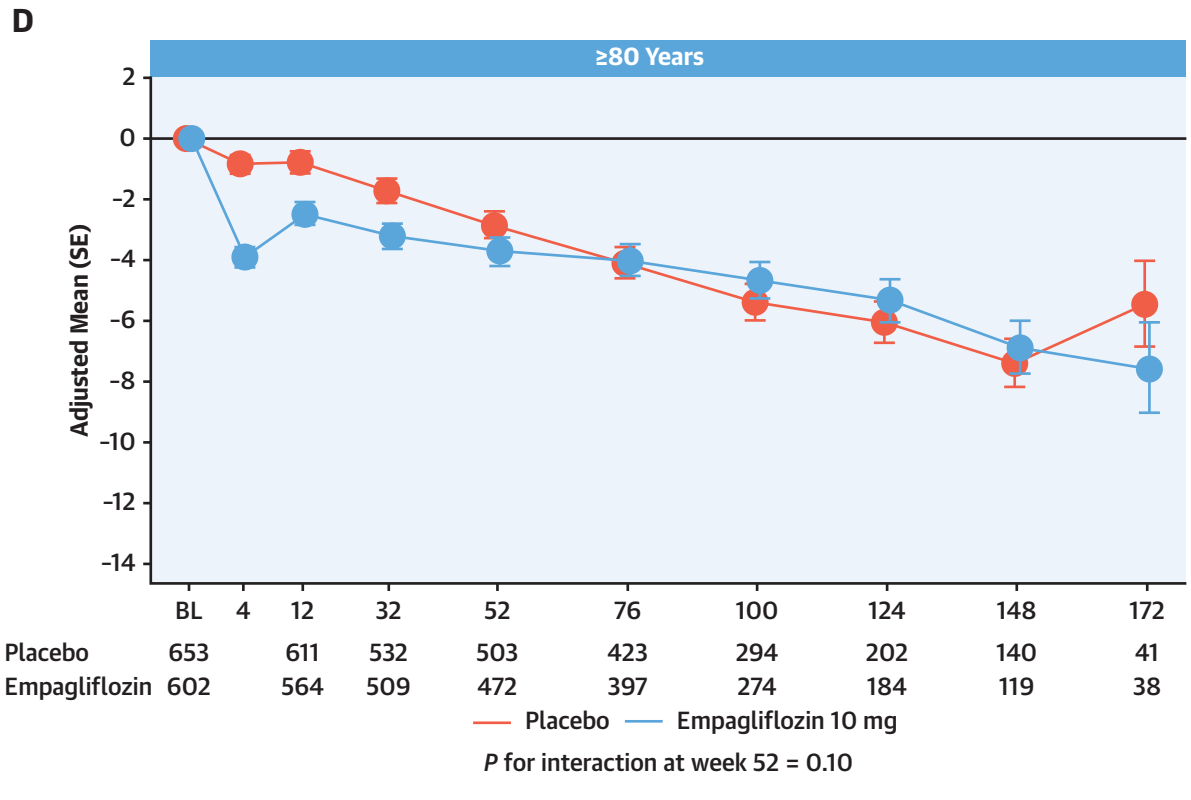
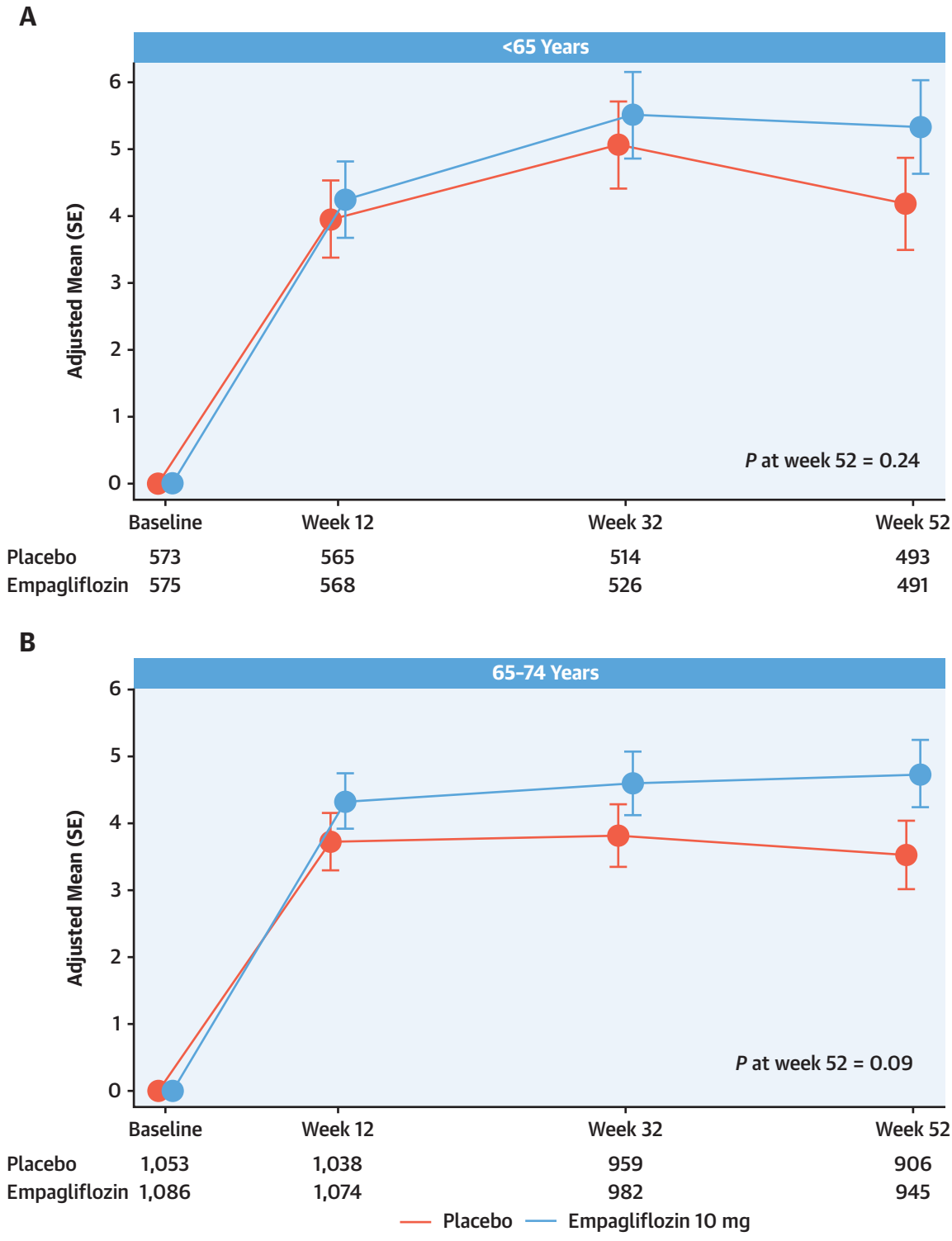


FIGURE 5 KCCQ-CSS Change From Baseline by Age Group



Effect of empagliflozin **(blue)** and placebo **(red)** on mean KCCQ-CSS in patients **(A)** <65 years, **(B)** 65-74 years, **(C)** 75-79 years, and **(D)** ≥80 years. No corrections for multiple testing were applied. KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score.

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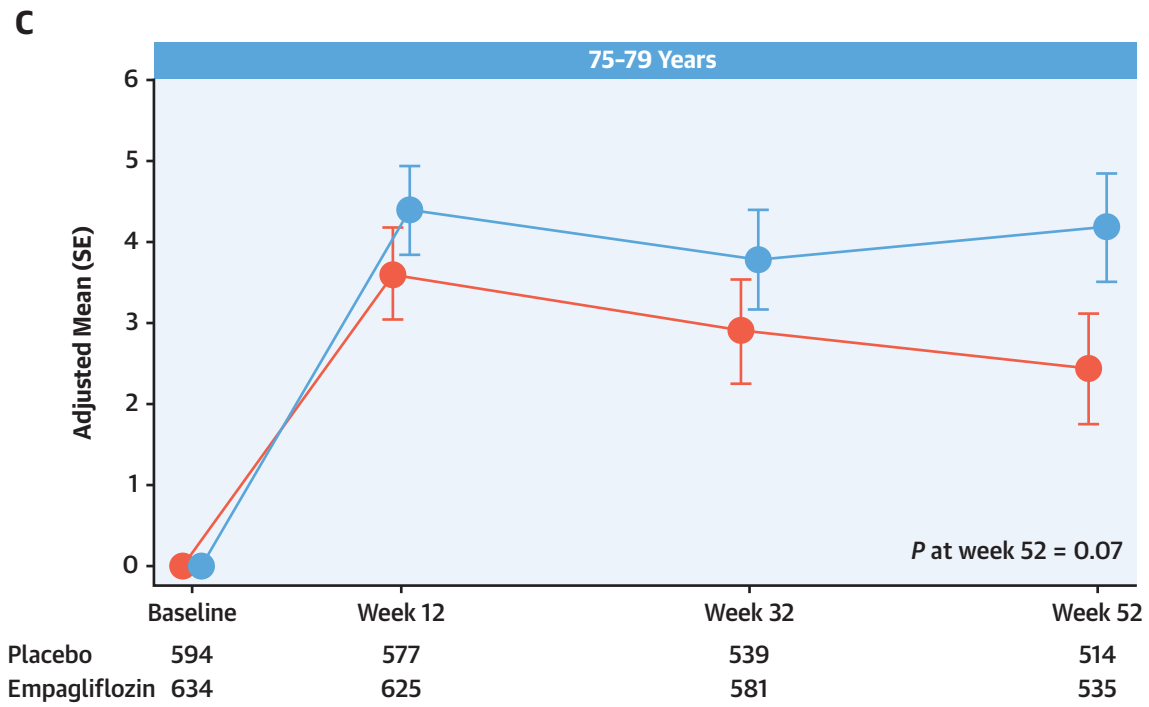
FIGURE 5 Continued



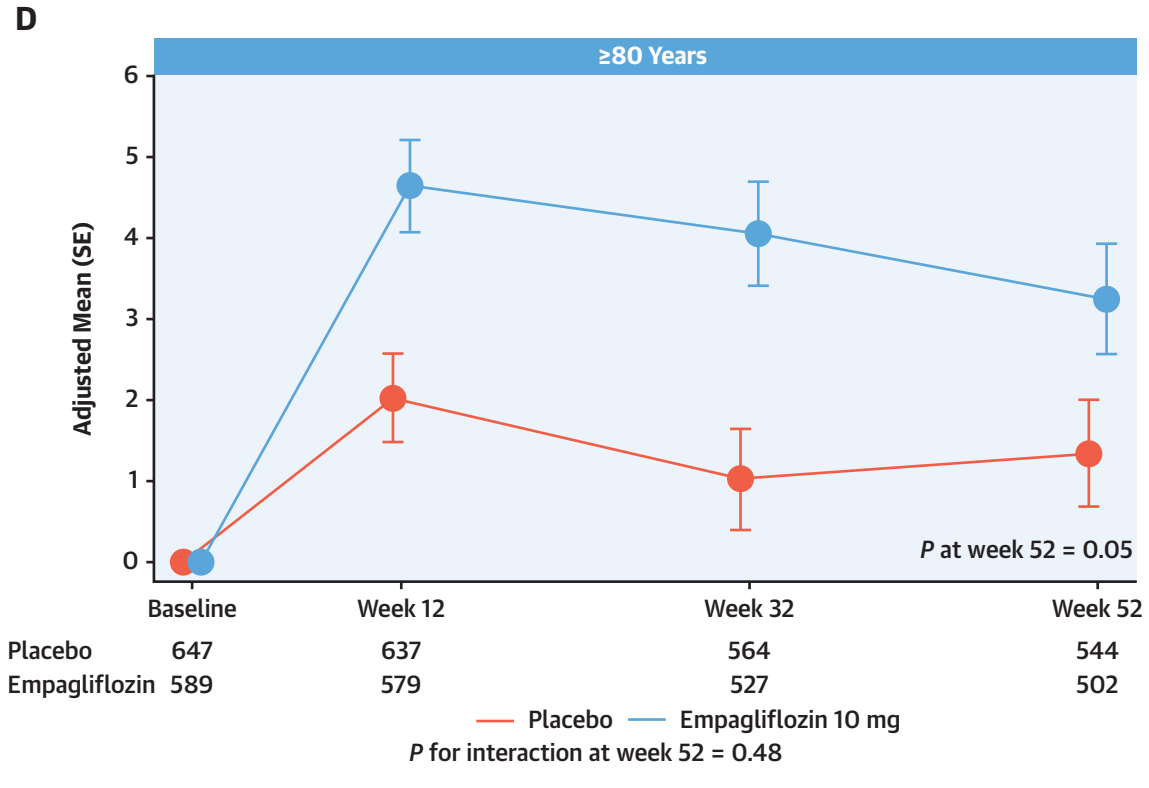


TABLE 2 Adverse Events

	<65 y					65-74 y				
	Placebo		Empagliflozin			Placebo		Empagliflozin		
Category of AEs	n = 605	Incidence Rate per 100 PY	n = 594	Incidence Rate per 100 PY	*P* Value	n = 1,092	Incidence Rate per 100 PY	n = 1,121	Incidence Rate per 100 PY	*P* Value
Patients with any AEs	513 (84.8)	140.06	491 (82.7)	115.94	0.28	926 (84.8)	134.08	951 (84.8)	128.65	0.89
AEs leading to treatment discontinuation	97 (16.0)	8.43	91 (15.3)	8.03	0.69	179 (16.4)	8.56	198 (17.7)	9.35	0.42
Serious AEs	279 (46.1)	32.87	258 (43.4)	30.37	0.32	528 (48.4)	34.61	513 (45.8)	31.79	0.26
Hypotension	33 (5.5)	2.95	44 (7.4)	4.02	0.18	87 (8.0)	4.33	114 (10.2)	5.72	0.07
Acute renal failure	72 (11.9)	6.57	60 (10.1)	5.58	0.24	146 (13.4)	7.43	137 (12.2)	6.83	0.45
Confirmed hypoglycemic events	15 (2.5)	1.32	15 (2.5)	1.34	0.95	26 (2.4)	1.26	26 (2.3)	1.24	0.99
Urinary tract infections	32 (5.3)	2.87	48 (8.1)	4.39	0.06	89 (8.2)	4.44	96 (8.6)	4.72	0.67
Genital infections	6 (1.0)	0.52	14 (2.4)	1.25	0.09	8 (0.7)	0.38	22 (2.0)	1.04	0.01
Symptomatic hypotension	20 (3.3)	1.77	27 (4.5)	2.43	0.28	54 (4.9)	2.63	75 (6.7)	3.67	0.08

	75-79 y					≥80 y					
	Placebo		Empagliflozin			Placebo		Empagliflozin			
	n = 613	Incidence Rate per 100 PY	n = 662	Incidence Rate per 100 PY	*P* Value	n = 679	Incidence Rate per 100 PY	n = 619	Incidence Rate per 100 PY	*P* Value	*P* for Interaction Trend Between Age Groups
Patients with any AEs	548 (89.4)	162.05	579 (87.5)	143.48	0.22	598 (88.1)	172.57	553 (89.3)	165.58	0.44	0.39
AEs leading to treatment discontinuation	125 (20.4)	10.97	141 (21.3)	11.33	0.69	150 (22.1)	12.45	141 (22.8)	12.67	0.72	0.73
Serious AEs	337 (55.0)	44.41	336 (50.8)	37.08	0.10	399 (58.8)	49.90	329 (53.2)	40.34	0.04	0.37
Hypotension	59 (9.6)	5.42	80 (12.1)	6.88	0.17	78 (11.5)	6.88	73 (11.8)	7.02	0.88	0.28
Acute renal failure	72 (11.7)	6.58	79 (11.9)	6.79	0.95	94 (13.8)	8.29	87 (14.1)	8.38	0.90	0.31
Confirmed hypoglycemic events	19 (3.0)	1.69	15 (2.3)	1.21	0.33	18 (2.7)	1.51	17 (2.7)	1.54	0.98	0.78
Urinary tract infections	44 (7.2)	3.99	65 (9.8)	5.47	0.07	78 (11.5)	6.81	88 (14.2)	8.58	0.20	0.87
Genital infections	5 (0.8)	0.44	24 (3.6)	1.96	0.002	3 (0.4)	0.25	7 (1.1)	0.63	NA[a]	0.56
Symptomatic hypotension	34 (5.5)	3.06	50 (7.6)	4.19	0.15	48 (7.1)	4.12	45 (7.3)	4.19	0.87	0.38

Values are n (%) unless otherwise indicated. Statistical testing for subgroups with <14 events was not calculated.
AE = adverse event; NA = not applicable; PY = person-years.

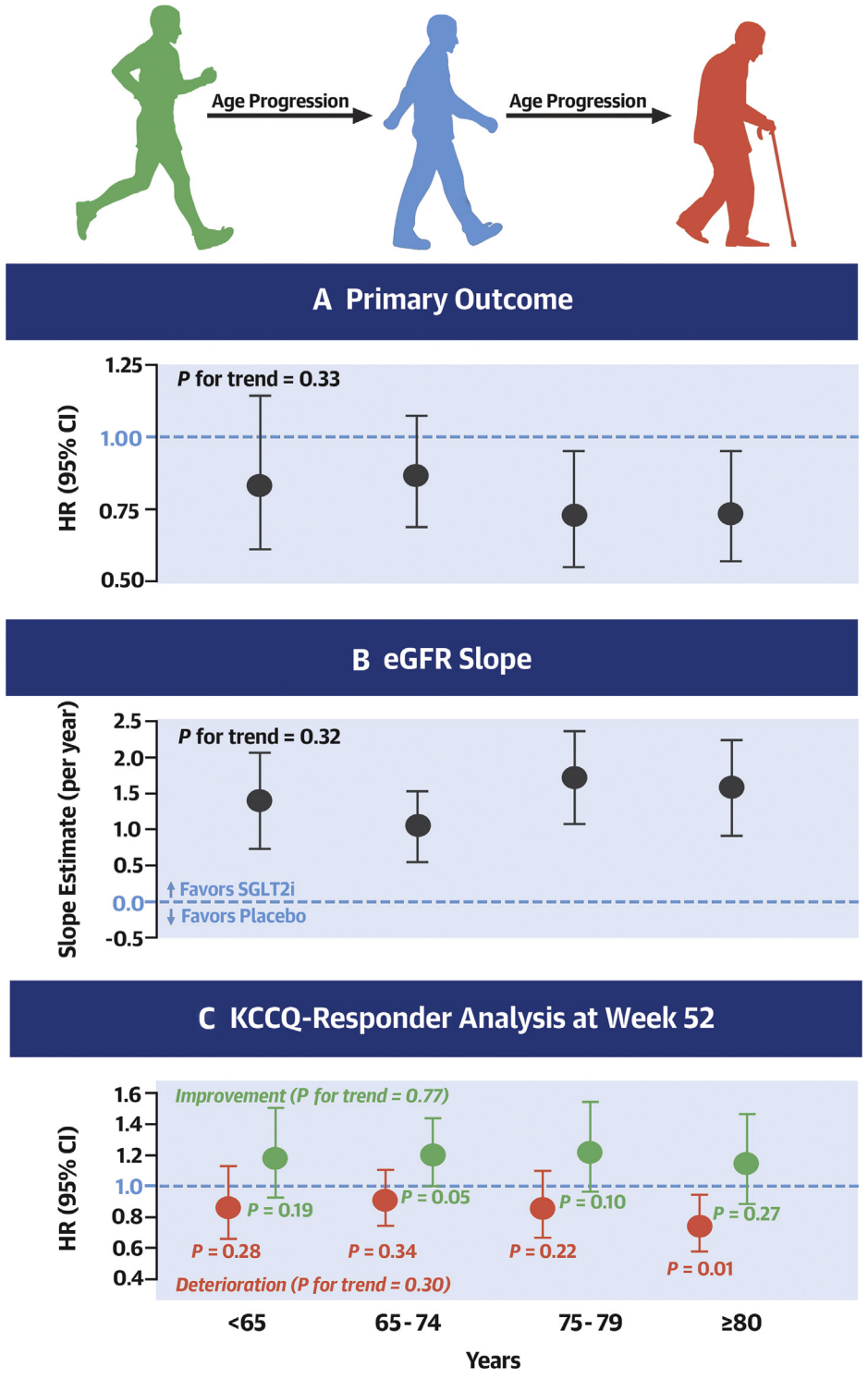
Similar results were observed for the first HF hospitalization (Supplemental Figures 7A and 7C) and recurrent HF hospitalization (Supplemental Figures 7B and 7D).

EFFECTS ON eGFR DECLINE. Empagliflozin reduced the slope of eGFR decline from week 4 to the end of follow-up (**Figure 4**). Overall, the difference of the mean slope of change compared to placebo (95% CI) was 1.36 (1.06-1.66) mL/min/1.73 m^2/year ($P = 0.0001$). The effect was similar in all age groups from <65 to ≥80 years (*P* for interaction trend = 0.32).

EFFECTS ON HRQoL. The mean change of the KCCQ-CSS by treatment arms over time is presented in **Figure 5**. Compared to placebo, patients treated with empagliflozin showed greater improvement in mean KCCQ with no significant differences between the age groups (*P* for interaction at week 52 = 0.48). The responder analysis with the effect of empagliflozin is shown in Supplemental Figure 8. Patients in the empagliflozin arm were more likely to show an improvement of ≥5 points, ≥10 points, and ≥15 points and were less likely to show deterioration. There was no significant interaction between the response to empagliflozin of CSS and age. In the sensitivity analysis, we looked at the change of KCCQ-CSS in patients <75 and ≥75 years and <80 and ≥80 years. There was no heterogeneity of KCCQ-CSS and between older and younger individuals (≥75, Supplemental Figures 9A and 9B) and ≥80 years (Supplemental Figures 9C and 9D) compared to <75 (Supplemental Figure 9A) and <80 years (Supplemental Figure 9C), respectively. Similar results were obtained by looking at the responder rate in individuals ≥75 years (Supplemental Figure 10B) and ≥80 years (Supplemental Figure 10D) compared to <75 years (Supplemental Figure 10A) and <80 years (Supplemental Figure 10C).

SAFETY ASSESSMENTS. The number of patients with any adverse event leading to discontinuation of study medication was not increased across age and was not meaningfully different between the empagliflozin and placebo groups. There was no increase in adverse events including serious adverse events with

CENTRAL ILLUSTRATION **Effect of Empagliflozin According to Age**



Böhm M, et al. J Am Coll Cardiol. 2022;80(1):1-18.

The effects of empagliflozin on **(A)** the primary outcome over the spectrum of age, **(B)** decline of estimated glomerular filtration rate (slope) according to age groups, and **(C)** Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score response according to age. eGFR = estimated glomerular filtration rate; KCCQ-Responder = Kansas City Cardiomyopathy Questionnaire Responder; SGLT2i = sodium-glucose cotransporter-2 inhibitor.

increasing age, which was also observed for hypotension and acute renal failure. The differences between placebo and empagliflozin remained not significant over the age spectrum. Similar results were observed for hypoglycemic events, urinary tract infections, genital infections, bone fractures, and symptomatic hypotension, with these events occurring rarely. Acute renal injury episodes were less likely at <65 and 65 to <74 years on empagliflozin and similar at higher ages (**Table 2**).

DISCUSSION

We show a clinically meaningful efficacy of empagliflozin across all age groups for cardiovascular death and HF hospitalization, first HF hospitalization, and first and recurrent HF hospitalization. In addition, an improvement of KCCQ-CSS and a slowing of eGFR decline across all age categories were demonstrated. As there was no significant statistical interaction with age, the effects on HF outcomes were similar in aging individuals at >75 years. Age was associated with an increased rate of adverse events without meaningful alteration by empagliflozin, including in the elderly. Serious acute renal adverse events were less likely at <65 years and 65-74 years and similar at older ages with empagliflozin (**Central Illustration**).

Patients with HFpEF are usually older than patients with HFrEF,[8,9] and several pharmacologic treatments have not shown significant benefit in HFpEF.[18] Empagliflozin has shown a significant reduction of the composite of cardiovascular death and HF hospitalization in HFpEF patients.[6] In the population of EMPEROR-Preserved, we found that patients in the higher age category were more often female, had higher blood pressure and higher left ventricular ejection fraction at baseline, but had lower eGFR. Therefore, concerns have been expressed in elderly HF patients and, particularly, in patients with higher age and HFpEF[9,19] that treatment effects across the age spectrum are diminished and that benefits come at a high cost of impairment of quality of life and tolerability of the drug.[19,20] Herein, we provide clear evidence that the efficacy of empagliflozin on HF outcomes is maintained over the full age spectrum. The effectiveness is not vanishing in patients ≥75 years and ≥85 years. In patients with HFrEF, treatment effects are also similar across the age spectrum for sacubitril/valsartan,[10] beta blockers,[11] dapagliflozin,[12] and ivabradine.[20]

Interestingly, similar results on improvement of KCCQ-CSS were also shown. Patients along the age spectrum had similar increases of KCCQ-CSS at different ages and also in individuals ≥75 years or ≥80 years. Here, the results were similar to those of dapagliflozin treatment in HFrEF, showing comparable improvements in KCCQ-CSS scores over 32 weeks in older compared to younger patients. This finding is of particular importance because in elderly patients, the improvement of quality of life and symptoms may be as important as prolonging the lifetime. Importantly, the preserved outcome improvement does not come at a cost of significantly impaired quality of life or increased adverse drug-induced events. The changes reported herein are most likely clinically meaningful because a significant portion of patients increased by 5 points in the KCCQ-CSS, which is considered a significant threshold for well-being and outcome prediction.[21] In EMPEROR-Preserved, patients were more likely to have higher blood pressure and impaired kidney function, which were further accounted for at increasing ages of individuals in this trial. Reassuringly, empagliflozin did not have heterogeneous effects over the spectrum of blood pressure[22] and impaired kidney function in HFrEF.[23]

Impaired kidney function is one predictor of outcomes in HFpEF.[8,9] Herein, the eGFR was lower in more advanced age. Nevertheless, the mitigation of eGFR decline by empagliflozin was maintained across the entire age spectrum. In this respect, it is interesting that SGLT2 inhibition reduces cellular senescence in the kidneys[24] related to the attenuation of vascular aging[25] and endothelial senescence, protecting from vascular dysfunction by angiotensin II-induced stimulation of toxic microparticles.[26] The mechanisms might be similar to those of ketone body accumulation[24] or calory restrictions[27] and also affect, in addition to the kidney, the senescence of cardiac stromal cells[28] and could involve the activation of longevity gene programs and the activation of autophagic flux.[29] These mechanisms, although speculative, might provide a common soil hypothesis for the broad beneficial effects of SGLT2 inhibition on HF outcomes, renal protection, and finally quality of life.

STUDY LIMITATIONS. As a prespecified analysis of a randomized controlled trial, this analysis has some limitations. Age categorization was predefined; nevertheless, treatment was not randomized to age groups and may have been subject to unidentified confounders. Separating this population by age resulted in smaller age groups and event numbers, rendering some of the results nonsignificant because of limited power. Still, to our knowledge, this is the largest population and study to date across the age spectrum in patients with HFpEF.

CONCLUSIONS

Empagliflozin reduced the risk of HF and renal outcomes as well as improved HRQoL in patients with HFpEF across the age spectrum, and elderly patients tolerated empagliflozin well.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with HFpEF, empagliflozin reduces major adverse cardiovascular events and worsening of renal dysfunction independent of age.

TRANSLATIONAL OUTLOOK: Dedicated studies of older cohorts are needed to better define the role of empagliflozin in the management of HFpEF in elderly patients.

REFERENCES

1. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. 2019;393:31–39.

2. Kato ET, Silverman MG, Mosenzon O, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. *Circulation*. 2019;139:2528–2536.

3. Fitchett D, Inzucchi SE, Cannon CP, et al. Empagliflozin reduced mortality and hospitalization for heart failure across the spectrum of cardiovascular risk in the EMPA-REG OUTCOME trial. *Circulation*. 2019;139:1384–1395.

4. McMurray JJV, Solomon SD, Inzucchi SE, et al. DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008.

5. Packer M, Anker SD, Butler J, et al. EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383:1413–1424.

6. Anker SD, Butler J, Filippatos G, et al. EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385:1451–1461.

7. McDonagh TA, Metra M, Adamo M, et al, ESC Scientific Document Group. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599–3726.

8. Lam CS, Donal E, Kraigher-Krainer E, et al. Epidemiology and clinical course of heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2011;13:18–28.

9. Chen X, Savarese G, Dahlström U, et al. Age-dependent differences in clinical phenotype and prognosis in heart failure with mid-range ejection compared with heart failure with reduced or preserved ejection fraction. *Clin Res Cardiol*. 2019;108:1394–1405.

10. Jhund PS, Fu M, Bayram E, et al. PARADIGM-HF Investigators and Committees. Efficacy and safety of LCZ696 (sacubitril-valsartan) according to age: insights from PARADIGM-HF. *Eur Heart J*. 2015;36:2576–2584.

11. Kotecha D, Manzano L, Krum H, et al. Beta-Blockers in Heart Failure Collaborative Group. Effect of age and sex on efficacy and tolerability of β blockers in patients with heart failure with reduced ejection fraction: individual patient data meta-analysis. *BMJ*. 2016;353:i1855.

12. Martinez FA, Serenelli M, Nicolau JC, et al. Efficacy and safety of dapagliflozin in heart failure with reduced ejection fraction according to age: insights from DAPA-HF. *Circulation*. 2020;141:100–111.

13. Ali Raza J, Movahed A. Use of cardiovascular medications in the elderly. *Int J Cardiol*. 2002;85:203–215.

14. Anker SD, Butler J, Filippatos G, et al. EMPEROR-Preserved Trial Committees and Investigators. Baseline characteristics of patients with heart failure with preserved ejection fraction in the EMPEROR-Preserved trial. *Eur J Heart Fail*. 2020;22:2383–2392.

15. Butler J, Filippatos G, Siddiqi TJ, et al. Empagliflozin, health status, and quality of life in patients with heart failure and preserved ejection fraction: the EMPEROR-Preserved Trial. *Circulation*. 2022;145:184–193.

16. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. New York: John Wiley and Sons; 2004.

17. Boehringer Ingelheim Clinical study results for you. Accessed May 10, 2022. https://trials.boehringer-ingelheim.com/transparency_policy.html

18. Wintrich J, Kindermann I, Ukena C, et al. Therapeutic approaches in heart failure with preserved ejection fraction: past, present, and future. *Clin Res Cardiol*. 2020;109:1079–1098.

19. Tromp J, Shen L, Jhund PS, et al. Age-related characteristics and outcomes of patients with heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2019;74:601–612.

20. Tavazzi L, Swedberg K, Komajda M, et al. SHIFT Investigators. Efficacy and safety of ivabradine in chronic heart failure across the age spectrum: insights from the SHIFT study. *Eur J Heart Fail*. 2013;15:1296–1303.

21. Butler J, Khan MS, Mori C, et al. Minimal clinically important difference in quality of life scores for patients with heart failure and reduced ejection fraction. *Eur J Heart Fail*. 2020;22:999–1005.

22. Böhm M, Anker SD, Butler J, et al, EMPEROR-Reduced Trial Committees and Investigators. Empagliflozin improves cardiovascular and renal outcomes in heart failure irrespective of systolic blood pressure. *J Am Coll Cardiol*. 2021;78:1337–1348.

23. Zannad F, Ferreira JP, Pocock SJ, et al. Cardiac and kidney benefits of empagliflozin in heart failure across the spectrum of kidney function: insights from EMPEROR-Reduced. *Circulation*. 2021;143:310–321.

24. Kim MN, Moon JH, Cho YM. Sodium-glucose cotransporter-2 inhibition reduces cellular senescence in the diabetic kidney by promoting ketone body-induced NRF2 activation. *Diabetes Obes Metab*. 2021;23:2561–2571.

25. Liu L, Ni YQ, Zhan JK, et al. The role of SGLT2 inhibitors in vascular aging. *Aging Dis*. 2021;12:1323–1336.

26. Park SH, Belcastro E, Hasan H, et al. Angiotensin II-induced upregulation of SGLT1 and 2 contributes to human microparticle-stimulated endothelial senescence and dysfunction: protective effect of gliflozins. *Cardiovasc Diabetol*. 2021;20:65–72.

27. Hoong CWS, Chua MWJ. SGLT2 inhibitors as calorie restriction mimetics: insights on longevity pathways and age-related diseases. *Endocrinology*. 2021;162:bqab079.

28. Madonna R, Doria V, Minnucci I, et al. Empagliflozin reduces the senescence of cardiac stromal cells and improves cardiac function in a murine model of diabetes. *J Cell Mol Med*. 2020;24:12331–12340.

29. Packer M. Longevity genes, cardiac ageing, and the pathogenesis of cardiomyopathy: implications for understanding the effects of current and future treatments for heart failure. *Eur Heart J*. 2020;41:3856–3861.

KEY WORDS age, cardiovascular outcomes, empagliflozin, heart failure, kidney function

APPENDIX For supplemental figures, please see the online version of this paper.

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