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Efficacy and Safety of Dapagliflozin in Heart Failure With Reduced Ejection Fraction According to Age

Insights From DAPA-HF

Editorial, see p XXX

BACKGROUND: The DAPA-HF trial (Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure) showed that dapagliflozin added to other guideline-recommended therapies reduced the risk of mortality and heart failure hospitalization and improved symptoms in patients with heart failure and reduced ejection fraction. We examined the effects of dapagliflozin according to age, given potential concerns about the efficacy and safety of therapies in the elderly.

METHODS: Patients in New York Heart Association functional class II or greater with a left ventricular ejection fraction ≤40% and a modest elevation of NT-proBNP (N-terminal pro-B-type natriuretic peptide) were eligible. Key exclusion criteria included systolic blood pressure <95 mm Hg and estimated glomerular filtration rate <30 mL·min^{-1}·1.73 m^{-2}. The primary outcome was the composite of an episode of worsening heart failure (heart failure hospitalization or urgent heart failure visit) or cardiovascular death, whichever occurred first.

RESULTS: A total of 4744 patients 22 to 94 years of age (mean age, 66.3 [SD 10.9] years) were randomized: 636 patients (13.4%) were <55 years of age, 1242 (26.2%) were 55 to 64 years of age, 1717 (36.2%) were 65 to 74 years of age, and 1149 (24.2%) were ≥75 years of age. The rate of the primary outcome (per 100 person-years, placebo arm) in each age group was 13.6 (95% CI, 10.4–17.9), 15.7 (95% CI, 13.2–18.7), 15.1 (95% CI, 13.1–17.5), and 18.0 (95% CI, 15.2–21.4) with corresponding dapagliflozin/placebo hazard ratios of 0.87 (95% CI, 0.60–1.28), 0.71 (95% CI, 0.55–0.93), 0.76 (95% CI, 0.61–0.95), and 0.68 (95% CI, 0.53–0.88; *P* for interaction=0.76). Consistent benefits were observed for the components of the primary outcome, all-cause mortality, and symptoms. Although adverse events and study drug discontinuation increased with age, neither was significantly more common with dapagliflozin in any age group.

CONCLUSIONS: Dapagliflozin reduced the risk of death and worsening heart failure and improved symptoms across the broad spectrum of age studied in DAPA-HF. There was no significant imbalance in tolerability or safety events between dapagliflozin and placebo, even in elderly individuals.

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Clinical Perspective

What Is New?

- In the placebo-controlled DAPA-HF trial (Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure), dapagliflozin added to other guideline-recommended therapies reduced the risk of mortality and heart failure hospitalization and improved symptoms in 4744 patients with heart failure and reduced ejection fraction.
- The effects of dapagliflozin were consistent across the spectrum of age studied (22–94 years) in terms of both efficacy and safety.

What Are the Clinical Implications?

- The benefit of dapagliflozin is consistent in older and younger patients, including in individuals ≥75 years of age.
- The risk of adverse events with dapagliflozin was not greater in older compared with younger patients.
- Advanced age per se is not a reason to withhold treatment with dapagliflozin in patients with heart failure and reduced ejection fraction.

As populations in many countries age rapidly, the number of elderly patients with heart failure (HF) is increasing steeply. However, in other regions such as Latin America, Africa, and parts of Asia, individuals with HF are typically younger than those in, for example, North America and Western Europe.[1–4] It is therefore very important to understand the efficacy and safety of new treatments in all age groups, although tolerability may be a particular concern in the elderly, not just because of advanced age but also because of polypharmacy. The benefit of therapy may also be questioned in the elderly.[5–7]

In the placebo-controlled DAPA-HF trial (Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure), dapagliflozin added to other guideline-recommended therapies reduced the risk of mortality and HF hospitalization and improved symptoms in 4744 patients with HF and reduced ejection fraction (HFrEF).[8] The average age of patients randomized in DAPA-HF was 66 years; 36% of patients were 66 to 75 years of age, and 21% were >75 years of age. We have examined the efficacy and safety of dapagliflozin according to age in a post hoc analysis of DAPA-HF.

METHODS

DAPA-HF was a randomized, double-blind, controlled trial in patients with HFrEF that evaluated the efficacy and safety of dapagliflozin 10 mg once daily compared with matching placebo added to standard care. The design, baseline characteristics, and primary results of the trial have been published.[8–10] The Ethics Committee of each of the 410 participating institutions (in 20 countries) approved the protocol, and all patients gave written informed consent. The corresponding author had full access to all of the trial data and takes responsibility for its integrity and the data analysis. The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Patients

Men and women ≥18 years of age with HF were eligible if they were in New York Heart Association functional class II or greater, had a left ventricular ejection fraction ≤40%, and were optimally treated with pharmacological and device therapy for HF. Participants were also required to have an NT-proBNP (N-terminal pro-B-type natriuretic peptide) concentration ≥600 pg/mL (≥400 pg/mL if hospitalized for HF within the previous 12 months). Patients with atrial fibrillation or atrial flutter were required to have an NT-proBNP level ≥900 pg/mL, regardless of history of HF hospitalization. Key exclusion criteria included symptoms of hypotension or systolic blood pressure <95 mm Hg, estimated glomerular filtration rate (eGFR) <30 mL·min^{-1}·1.73 m^{-2} (or rapidly declining renal function), type 1 diabetes mellitus, and another condition likely to prevent patient participation in the trial or to greatly limit life expectancy. A full list of exclusion criteria is provided in the design article.[9]

Study Procedures

After the provision of informed consent, visit 1 started a 14-day screening period during which the trial inclusion and exclusion criteria were checked and baseline information was collected. Visit 2 was the randomization visit, and randomization was stratified on the basis of diagnosis of type 2 diabetes mellitus (defined as an established diagnosis or a glycated hemoglobin level ≥6.5% [≥48 mmol/mol]) at screening. After randomization, follow-up visits took place at 14 and 60 days and then at 120, 240, and 360 days and every 4 months thereafter. The visit early after randomization (14 days) was included to check renal function and blood pressure (as well as to check for symptoms of hypotension); this visit also allowed adjustment of background diuretic or other nonessential therapies. Dose reduction to 5 mg dapagliflozin or matching placebo (or discontinuation of study drug) was to be considered in case of an acute unexpected decline in eGFR, volume depletion, or hypotension (or to avoid these conditions); however, dose uptitration (or reinitiation) was encouraged thereafter in all cases when possible.

Study Outcomes

The primary outcome was the composite of an episode of worsening HF (HF hospitalization or urgent HF visit) or cardiovascular death, whichever occurred first. Secondary end points were the occurrence of HF hospitalization or cardiovascular death; HF hospitalizations (first and recurrent) and cardiovascular death; change from baseline to 8 months in the total symptom score of the Kansas City Cardiomyopathy Questionnaire (KCCQ)[11]; the incidence of a composite worsening renal function outcome, consisting of ≥50% sustained decline in eGFR, end-stage renal disease (defined

as sustained eGFR<15 mL·min^{-1}·1.73 m^{-2}, chronic dialysis treatment, or renal transplantation), or renal death; and death resulting from any cause. Prespecified safety analyses included serious adverse events, adverse events leading to discontinuation of trial treatment, adverse events of interest (ie, volume depletion, renal events, major hypoglycemic events, bone fractures, diabetic ketoacidosis, amputation), and any diagnosis of Fournier gangrene, as well as laboratory findings of note.

Statistical Analysis

In the present study, patients were divided into 4 age categories: <55, 55 to 64, 65 to 74, and ≥75 years. Baseline characteristics were summarized as means and SDs, medians and interquartile ranges, or percentages. Time-to-event data were evaluated with the use of Kaplan–Meier estimates and Cox proportional-hazards models, stratified according to diabetes mellitus status, with history of HF hospitalization and treatment group assignment as fixed-effect factors. We used Cox models to calculate hazard ratios, 95% confidence intervals, and 2-sided *P* values and used a semiparametric proportional-rates model to calculate total (including recurrent) events.[12] We analyzed the change in total symptom score on the KCCQ from baseline to 8 months in surviving patients. Safety analyses were performed in patients who had undergone randomization and received at least 1 dose of dapagliflozin or placebo (a total of 8 patients were excluded). The effect of dapagliflozin compared with placebo on each outcome was also examined across the spectrum of age in a Cox regression model in which age was modeled as a continuous variable. A fractional polynomial was constructed of age and entered into the model as an interaction term with treatment.[13] The results of the interaction were displayed graphically with the mfpi command in Stata (StataCorp, College Station, TX).[14] The interaction between age and treatment on the occurrence of the prespecified safety outcomes was tested in a logistic regression model with an interaction term between age and treatment. The effect of differences in baseline characteristics was examined by adjustment of the model in sensitivity analysis (Table I and Figure I in the online-only Data Supplement). Additional exploratory analyses were conducted in very elderly patients, that is, those 75 to 79 and 80 to 84 years of age; we have provided these 2 categories, along with the categories ≥80 and ≥85 years of age, in Tables II and III in the online-only Data Supplement. All analyses were conducted with Stata version 15.1. A value of *P*<0.05 was considered statistically significant.

RESULTS

Overall, 4744 patients between 22 and 94 years of age were randomized. The mean age was 66.3 years (SD, 10.9 years). The number and proportion of patients in the different age categories analyzed are shown in Table 1. There were 636 patients <55 years of age (13.4%; median age, 49 [44–52] years), 1242 participants between 55 and 64 years of age (26.2%; median age, 60 [58–62] years), 1717 patients 65 to 74 years of age (36.2%; median age, 69 [67–72] years), and 1149 individuals ≥75 years of age (24.2%; median age, 79 [76–82] years).

Patient Characteristics

Compared with younger participants, older patients were more often women, white, and enrolled in Europe and North America. Older patients also had a higher average systolic blood pressure, serum creatinine, and natriuretic peptide levels, as well as a higher average ejection fraction (Table 1). Older patients were also more likely than younger patients to be in New York Heart Association functional class III/IV than in class II and to have hypertension, coronary artery disease, and atrial fibrillation. Median baseline KCCQ total symptom score (KCCQ-TSS) was similar (mean, 76 and 75) in those <55 and 55 to 64 years of age but higher (mean 79) among patients in the 2 older age categories (65–74 and ≥75 years); that is, older patients had less severe symptoms. With respect to background HF medications, patients in the older groups were less frequently treated with β-blockers, mineralocorticoid receptor antagonists, diuretics, and digitalis than younger patients. Baseline use of angiotensin receptor neprilysin inhibitors was generally low but similar across the age groups. The proportion of patients treated with cardiac resynchronization therapy increased with age, but patients ≥75 years of age were less likely to receive an implantable cardioverter-defibrillator compared with those 55 to 64 or 65 to 74 years of age. Use of oral anticoagulant therapy increased with age, whereas antiplatelet use was higher in patients 55 to 64 years of age. The proportions of patients treated with guideline-recommended medications across age groups are presented in Table IV in the online-only Data Supplement.

Primary Composite Outcome

The unadjusted incidence of the primary composite outcome of a first episode of worsening HF or cardiovascular death according to age is shown in Table 2 and Figure 1. The incidence of this end point in the placebo group was relatively similar in the age categories of 55 to 64 and 65 to 74 years but was higher in those ≥75 years of age and lower in those <55 years of age. The hazard ratio for the effect of dapagliflozin compared with placebo on the primary outcome was consistent across the spectrum of age (Table 2 and Figure 2A), with a *P* value for interaction of 0.76.

Applying the overall relative risk reduction (26%) to the placebo group event rate in those ≥75 years of age gave an absolute risk reduction of 47 fewer patients experiencing a primary outcome per 1000 person-years of follow-up. The equivalent absolute risk reduction in patients <55 years of age was estimated as 35 fewer patients per 1000 person-years of follow-up.

Table 1. Baseline Characteristics According to Age Categories

Variable	Age <55 y (n=636)	Age 55–64 y (n=1242)	Age 65–74 y (n=1717)	Age ≥75 y (n=1149)	*P* for Trend
Age, y	47.1 (6.3)	59.9 (2.8)	69.4 (2.8)	79.4 (3.6)	
Female, n (%)	120 (18.9)	265 (21.3)	403 (23.5)	321 (27.9)	<0.001
Race, n (%)					<0.001
White	327 (51.4)	844 (68.0)	1280 (74.5)	882 (76.8)	
Black or African American	50 (7.9)	77 (6.2)	65 (3.8)	34 (3.0)	
Asian	243 (38.2)	297 (23.9)	352 (20.5)	224 (19.5)	
Other	16 (2.5)	24 (1.9)	20 (1.2)	9 (0.8)	
Region, n (%)					<0.001
North America	83 (13.1)	157 (12.6)	245 (14.3)	192 (16.7)	
South America	123 (19.3)	262 (21.1)	278 (16.2)	154 (13.4)	
Europe	188 (29.6)	530 (42.7)	852 (49.6)	584 (50.8)	
Asia/Pacific	242 (38.1)	293 (23.6)	342 (19.9)	219 (19.1)	
Physiologic measures					
Systolic blood pressure, mm Hg	117.7±17.1	121.0±16.1	122.9±15.8	123.4±16.5	<0.001
Diastolic blood pressure, mm Hg	75.0±11.2	74.9±10.4	73.4±10.0	71.4±10.5	<0.001
Heart rate, bpm	74.5±12.2	72.2±12.1	70.8±11.0	70.3±11.7	<0.001
BMI, kg/m^2	29.2±7.4	28.9±6.0	28.2±5.6	26.7±5.1	<0.001
Creatinine, mg/dL	1.08±0.31	1.14±0.36	1.21±0.34	1.24±0.33	<0.001
Creatinine, µmol/L	95.9±27.7	100.9±31.7	106.8±30.0	109.4±29.6	<0.001
Glycated hemoglobin,* %	7.8 (1.8)	7.7 (1.8)	7.3 (1.4)	7.0 (1.1)	<0.001
eGFR, mL·min^{-1}·1.73 m^{-2}	83.0±20.5	71.5±18.3	62.0±16.5	55.6±15.2	<0.001
Median NT-proBNP (IQR), pg/mL	1107 (648, 2241)	1332 (813, 2394)	1453 (881, 2644)	1737 (1068, 3161)	<0.001
HF type, n (%)					<0.001
Ischemic	258 (40.6)	660 (53.1)	1053 (61.3)	703 (61.2)	
Nonischemic	316 (49.7)	478 (38.5)	536 (31.2)	357 (31.1)	
Unknown	62 (9.7)	104 (8.4)	128 (7.5)	89 (7.7)	
Ejection fraction, %	29.2±7.2	30.5±6.9	31.3±6.6	32.3±6.5	<0.001
NYHA class, n (%)					0.018
II	442 (69.5)	860 (69.2)	1153 (67.2)	748 (65.1)	
III	184 (28.9)	368 (29.6)	553 (32.2)	393 (34.2)	
IV	10 (1.6)	14 (1.1)	11 (0.6)	8 (0.7)	
KCCQ-TSS at baseline (IQR)	76 (52, 92)	75 (57, 92)	79 (60, 93)	79 (60, 92)	<0.001
Medical history, n (%)					
Hypertension	343 (53.9)	871 (70.1)	1357 (79.0)	951 (82.8)	<0.001
Type 2 diabetes mellitus	215 (33.8)	564 (45.4)	758 (44.1)	446 (38.8)	0.50
Atrial fibrillation	118 (18.6)	401 (32.3)	718 (41.8)	581 (50.6)	<0.001
Hospitalization for HF	317 (49.8)	596 (48.0)	824 (48.0)	514 (44.7)	0.042
Previous MI	198 (31.1)	535 (43.1)	833 (48.5)	526 (45.8)	<0.001
Previous PCI	139 (21.9)	410 (33.0)	655 (38.1)	420 (36.6)	<0.001
Previous CABG	42 (6.6)	173 (13.9)	358 (20.9)	226 (19.7)	<0.001
Treatment, n (%)					
ACE inhibitor	393 (61.8)	720 (58.0)	958 (55.8)	590 (51.3)	<0.001
ARB	143 (22.5)	323 (26.0)	477 (27.8)	364 (31.7)	<0.001
ARNI	70 (11.0)	141 (11.4)	181 (10.5)	116 (10.1)	0.37
Diuretic	611 (96.1)	1183 (95.2)	1598 (93.1)	1041 (90.6)	<0.001
Digitalis	146 (23.0)	245 (19.7)	313 (18.2)	183 (15.9)	<0.001

(*Continued*)

Table 1. Continued

Variable	Age <55 y (n=636)	Age 55–64 y (n=1242)	Age 65–74 y (n=1717)	Age ≥75 y (n=1149)	*P* for Trend
β-Blocker	624 (98.1)	1211 (97.5)	1642 (95.6)	1081 (94.1)	<0.001
Mineralocorticoid antagonist	527 (82.9)	939 (75.6)	1192 (69.4)	712 (62.0)	<0.001
Oral anticoagulant	162 (25.5)	465 (37.4)	769 (44.8)	573 (49.9)	<0.001
Antiplatelet	324 (50.9)	711 (57.2)	961 (56.0)	596 (51.9)	0.61
Statin	342 (53.8)	836 (67.3)	1222 (71.2)	776 (67.5)	<0.001
ICD	116 (18.2)	265 (21.3)	388 (22.6)	184 (16.0)	0.15
CRT-D	19 (3.0)	68 (5.5)	121 (7.0)	81 (7.0)	<0.001
ICD or CRT-D	135 (21.2)	333 (26.8)	509 (29.6)	265 (23.1)	0.51
CRT-P/CRT-D	23 (3.6)	83 (6.7)	142 (8.3)	106 (9.2)	<0.001
Diabetes mellitus treatment, n (%)†					
No. of patients	215	564	758	446	
Biguanide	117 (54.4)	315 (55.9)	392 (51.7)	192 (43.0)	<0.001
Sulfonylurea	50 (23.3)	131 (23.2)	168 (22.2)	89 (20.0)	0.22
DPP-4 inhibitor	21 (9.8)	71 (12.6)	127 (16.8)	91 (20.4)	<0.001
GLP-1 receptor agonist	5 (2.3)	1 (0.2)	12 (1.6)	3 (0.7)	0.61
Insulin	57 (26.5)	161 (28.5)	228 (30.1)	94 (21.1)	0.085

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; CABG, coronary artery bypass grafting; CRT-D, cardiac resynchronization therapy–defibrillator; CRT-P, cardiac resynchronization therapy–pacemaker; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and PCI, percutaneous coronary intervention.

*Glycated hemoglobin values are listed only for the patients with diabetes mellitus.

†Glucose-lowering medications are listed only for the patients with a history of type II diabetes mellitus at baseline.

Cardiovascular Death

As shown in Table 2 and Figure 2B, the rate of cardiovascular death in the placebo group did not vary greatly across age categories. The effect of dapagliflozin compared with placebo was consistent across the spectrum of age (Table 2 and Figure 2B). The *P* value for interaction was not significant (*P* for interaction=0.97).

Worsening HF Events

In contrast, there was more evidence of an increasing rate of worsening HF events in the placebo group with increasing age (Table 2 and Figure 2C). The effect of dapagliflozin compared with placebo was consistent across all age groups, including in patients ≥75 years of age (Table 2 and Figure 2C). Applying the overall relative risk reduction (30%) to the placebo group event rate in those ≥75 years of age gave an absolute risk reduction of 36 per 1000 person-years of follow-up. The equivalent absolute risk reduction in patients <55 years of age was estimated as 23 per 1000 person-years of follow-up.

All-Cause Mortality

As shown in Table 2 and Figure 2D, the rate of death resulting from any cause increased steadily across age categories, with the highest rate in patients ≥75 years of age. The effect of dapagliflozin compared with placebo was consistent across the spectrum of age (*P* for interaction=0.93; Table 2 and Figure 2D). Applying the overall relative risk reduction (17%) to the placebo group event rate in those ≥75 years of age gave an absolute risk reduction of 19 fewer deaths per 1000 person-years of follow-up. The equivalent absolute risk reduction in patients <55 years of age was estimated as 13 fewer deaths per 1000 person-years.

Composite of Recurrent HF Hospitalization and Cardiovascular Death

As for the other end points, we observed a consistent effect of dapagliflozin on the occurrence of first and recurrent HF hospitalization and cardiovascular death across age categories (*P* for interaction=0.72; Table 2).

Effect of Dapagliflozin Compared With Placebo With Age as a Continuous Variable

Figure 3 provides an alternative illustration of the effects of dapagliflozin compared with placebo for the 4 outcomes described above using fractional polynomial analysis. Each panel shows a continuous hazard ratio (with 95% CI) for dapagliflozin compared with placebo across the spectrum of age (age shown as a continuous variable on the *x* axis). The polynomial allows the possibility of a nonlinear effect of treatment by age to be modeled.

Table 2. Clinical Outcomes According to Age Categories

Outcome	Age <55 y (n=636)		Age 55–64 y (n=1242)		Age 65–74 y (n=1717)		Age ≥75 y (n=1149)		*P* for Interaction*
	Placebo (n=296)	Dapagliflozin (n=340)	Placebo (n=630)	Dapagliflozin (n=612)	Placebo (n=887)	Dapagliflozin (n=830)	Placebo (n=558)	Dapagliflozin (n=591)	
Cardiovascular death or HF hospitalization/urgent HF visit									0.76
n (%)	53 (17.9)	52 (15.3)	131 (20.8)	96 (15.7)	184 (20.7)	135 (16.3)	134 (24.0)	103 (17.4)	
Rate (95% CI)	13.6 (10.4–17.9)	11.8 (9.0–15.5)	15.7 (13.2–18.7)	11.4 (9.3–13.9)	15.1 (13.1–17.5)	11.4 (9.6–13.5)	18.0 (15.2–21.4)	12.6 (10.4–15.3)	
HR (95% CI), *P* value	0.87 (0.60–1.28), 0.49		0.71 (0.55–0.93), 0.012		0.76 (0.61–0.95), 0.015		0.68 (0.53–0.88), 0.003		
Cardiovascular death									0.97
n (%)	29 (9.8)	28 (8.2)	70 (11.1)	60 (9.8)	107 (12.1)	79 (9.5)	67 (12.0)	60 (10.2)	
Rate (95% CI)	7.0 (4.9–10.1)	6.0 (4.1–8.6)	7.8 (6.2–9.9)	6.8 (5.3–8.8)	8.3 (6.9–10.0)	6.4 (5.1–8.0)	8.3 (6.5–10.6)	7.0 (5.5–9.1)	
HR (95% CI), *P* value	0.85 (0.51–1.43), 0.54		0.87 (0.62–1.23), 0.45		0.78 (0.58–1.04), 0.089		0.83 (0.58–1.17), 0.29		
HF hospitalization/urgent HF visit									0.18
n (%)	29 (9.8)	34 (10.0)	90 (14.3)	52 (8.5)	117 (13.2)	86 (10.4)	90 (16.1)	65 (11.0)	
Rate (95% CI)	7.5 (5.2–10.7)	7.7 (5.5–10.8)	10.8 (8.8–13.3)	6.2 (4.7–8.1)	9.6 (8.0–11.5)	7.3 (5.9-–9.0)	12.1 (9.9–14.9)	8.0 (6.2–10.1)	
HR (95% CI), *P* value	1.05 (0.64–1.72), 0.85		0.56 (0.40–0.78), 0.001		0.76 (0.58–1.01), 0.056		0.64 (0.47–0.88), 0.006		
All-cause death									0.93
n (%)	31 (10.5)	29 (8.5)	80 (12.7)	72 (11.8)	129 (14.5)	99 (11.9)	89 (16.0)	76 (12.9)	
Rate (95% CI)	7.5 (5.3–10.7)	6.2 (4.3–8.9)	8.9 (7.2–11.1)	8.2 (6.5–10.3)	10.0 (8.4–11.9)	8.0 (6.6–9.7)	11.0 (9.0–13.6)	8.9 (7.1–11.1)	
HR (95% CI), *P* value	0.81 (0.49–1.35), 0.43		0.91 (0.66–1.25), 0.57		0.80 (0.62-–1.05), 0.10		0.79 (0.58–1.08), 0.14		
Cardiovascular death/HF hospitalization recurrent events									0.72
No. of events	81	80	198	134	268	202	195	151	
RR (95% CI), *P* value	0.89 (0.57–1.41), 0.63		0.68 (0.51–0.91), 0.010		0.80 (0.62–1.02), 0.076		0.70 (0.53–0.94), 0.016		
KCCQ									
Change in KCCQ-TSS score at 8 mo	5.1 (20.4)	6.7 (19.8)	4.7 (19.0)	6.8 (20.6)	3.0 (19.1)	6.3 (17.2)	1.2 (19.0)	4.9 (17.8)	0.65
Patients with ≥5-point improvement in KCCQ-TSS at 8 mo, %	52.9	56.4	53.3	59.5	50.5	60.4	48.0	55.2	0.96
Patients with ≥5-point decrease in KCCQ-TSS at 8 mo, %	30.2	25.7	31.3	25.7	34.2	23.3	33.9	27.6	0.96

HF indicates heart failure; HR, hazard ratio; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; and RR, rate ratio.
**P* values are for interaction between baseline age categories and treatment effect.

As in the categorical analysis, the effect of dapagliflozin compared with placebo was consistent across the entire spectrum of age. The continuous hazard ratio was linear (Figure 3). Similar findings were also observed after adjustment for differences in baseline characteristics (Figure I in the online-only Data Supplement).

Change in KCCQ at 8 months

As shown in Table 2, patients treated with dapagliflozin overall had a greater increase (improvement) in KCCQ-TSS between baseline and 8 months, and this benefit of dapagliflozin was consistent across age categories (*P* for interaction=0.65).

The proportion of patients with an improvement of KCCQ-TSS of ≥5 points was greater in patients treated with dapagliflozin compared with patients treated with placebo. Conversely, the proportion of patients with a decrease in KCCQ-TSS of ≥5 points (ie, a clinically meaningful deterioration) was smaller in those treated with dapagliflozin. The benefit of dapagliflozin over placebo both in improving KCCQ-TSS and in preventing deterioration was consis-

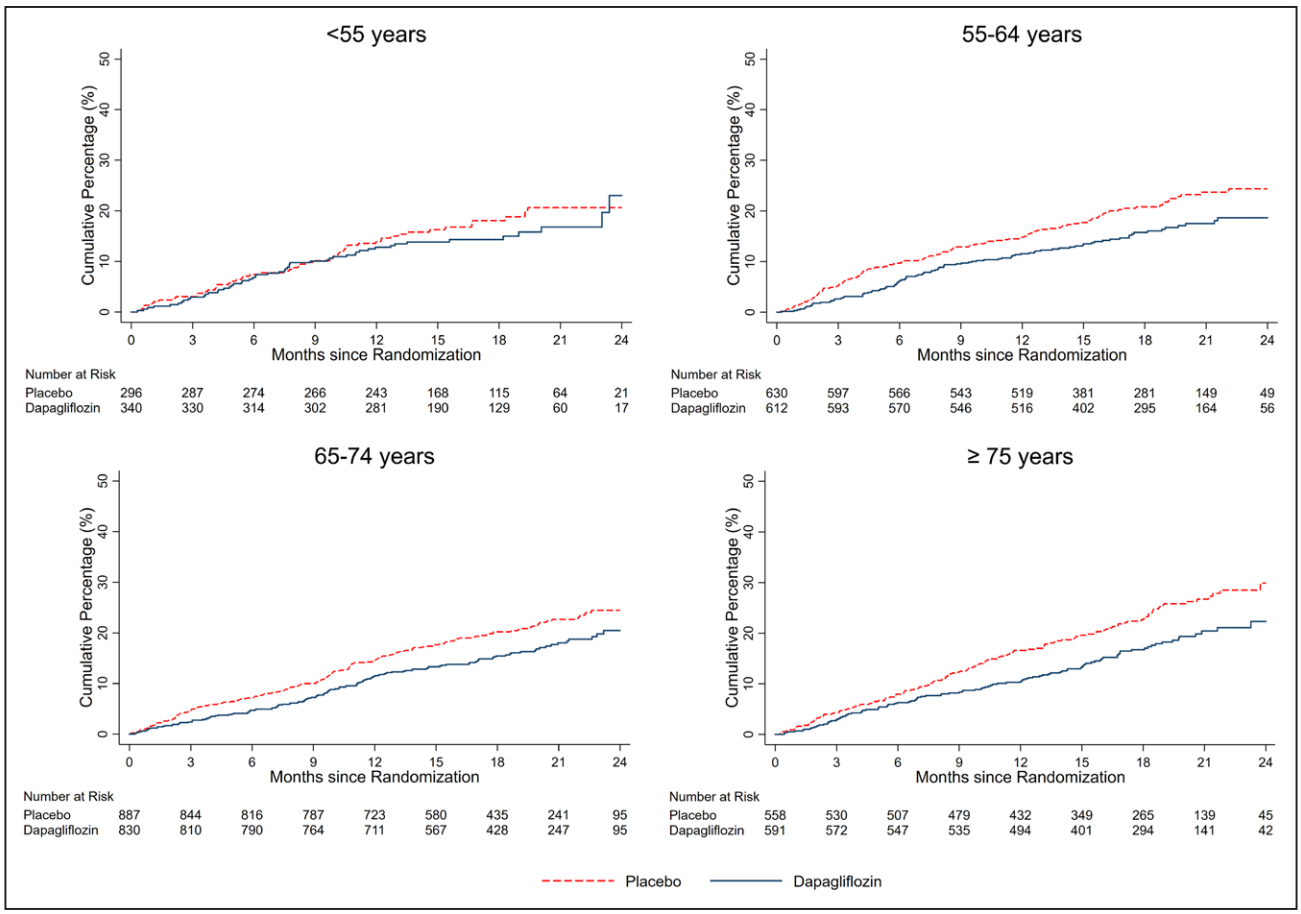

Figure 1. Cumulative incidence of the primary outcome according to age categories.

tent across age groups (*P* for each interaction=0.96). The numbers needed to treat for 1 patient to have a clinically meaningful improvement in symptoms over 8 months was 14 overall, ranging from 10 to 29 across age groups; the number needed to treat for 8 months to prevent 1 patient from having a clinically important deterioration was 13 overall, ranging from 9 to 22 across age groups.

Additional exploratory analyses were carried out to evaluate efficacy in very elderly patients. These analyses are provided in Table II in the online-only Data Supplement.

Prespecified Safety Assessments

Table 3 shows the occurrence of the prespecified adverse events of interest according to age category. The proportion of patients stopping the study drug for any reason increased with increasing age in the placebo group. However, the rate of discontinuation was similar between dapagliflozin and placebo, with no interaction between age category and the effect of treatment (*P* for interaction=0.38). The incidence of any adverse event leading to permanent treatment discontinuation increased with increasing age in the placebo group, with the highest incidence in patients ≥75 years of age (5.9% compared with 3.4% in those <55 years of age). Discontinuation of study drug because of adverse events was similar in the 2 treatment arms (dapagliflozin and placebo) in each age category. For example, in the ≥75-year-old group, discontinuation for an adverse event occurred in 5.8% of patients randomized to dapagliflozin compared with 5.9% randomized to placebo.

A similar age-related pattern was observed for adverse events and serious adverse events overall. The most common of the prespecified safety outcomes of interest were adverse events related to volume depletion and renal adverse events. Volume depletion adverse events were reported in 10.1% of the placebo group ≥75 years of age and in 10.5% in the dapagliflozin group. Renal adverse events were reported in 6.8% of the dapagliflozin and 10.6% of the placebo group ≥75 years of age. Serious adverse events related to volume depletion occurred overall in 29 patients (1.2%) in the dapagliflozin group and 40 patients (1.7%) in the placebo group, without any interaction between age categories and treatment effect (*P* for interaction=0.15). Serious renal adverse events occurred in 38 patients (1.6%) in the dapagliflozin group and 65 patients (2.7%) in the placebo group, with a significant interaction between age category and the effect of dapagliflozin (*P* for interaction=0.002). Specifically, in patients ≥75 years of age, the incidence of serious renal adverse events was

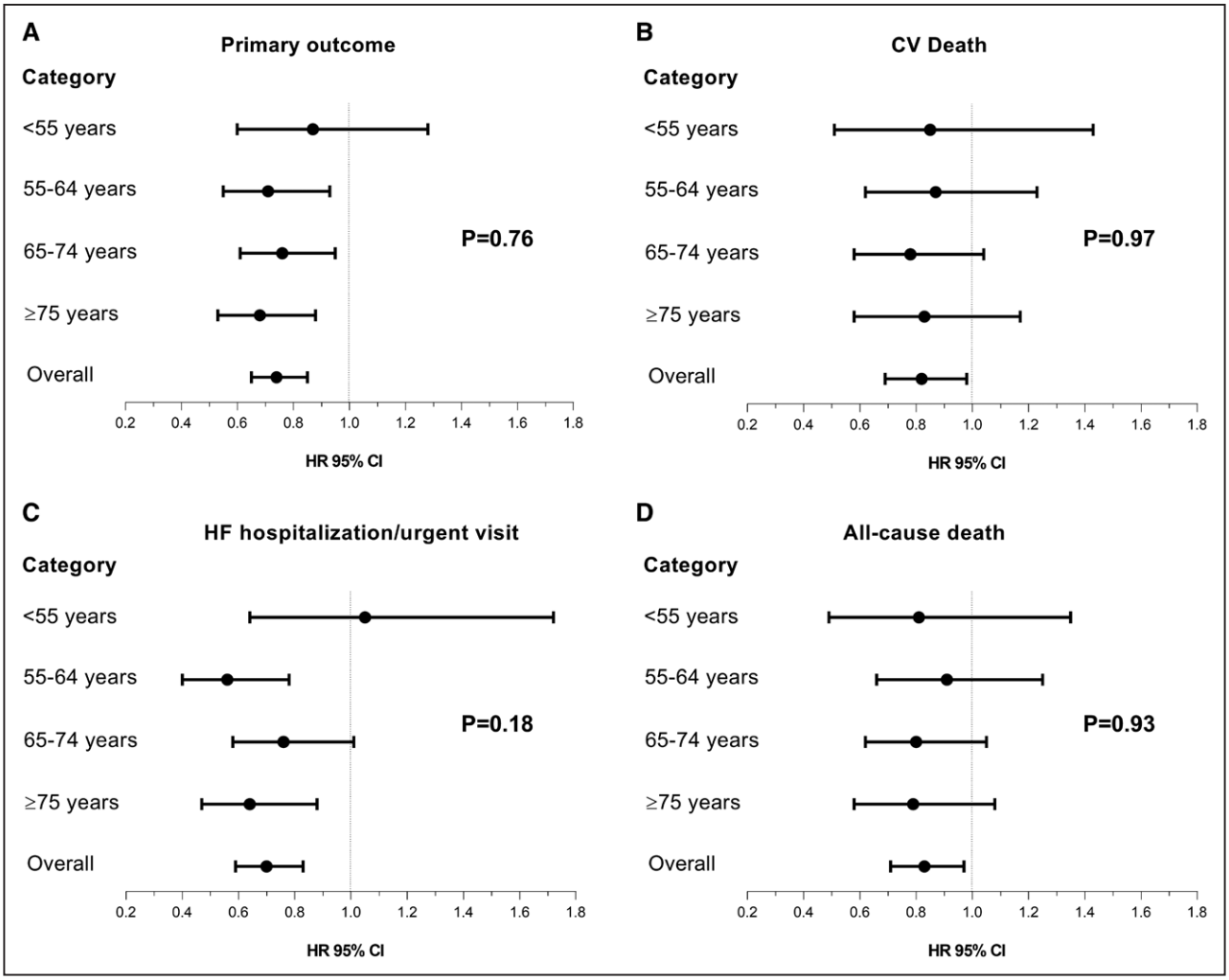

Figure 2. Effect of dapagliflozin according to age categories.
A, Occurrence of the primary outcome. **B**, Cardiovascular (CV) death. **C**, Heart failure (HF) hospitalization/urgent visit. **D**, All-cause death. *P* values are for interaction between baseline age categories and treatment effect. HR indicates hazard ratio.

0.5% in the dapagliflozin group compared with 5.4% in the placebo group, although it should be noted that the number of these events was small. The mean change in serum creatinine with dapagliflozin at 8 months was minimal across each age category (*P* for interaction=0.78), and relatively few patients in any age group (and either treatment group) experienced a doubling of serum creatinine over the duration of the trial.

The mean change in systolic blood pressure with dapagliflozin at 8 months was small and similar in each age category (*P* for interaction=0.97).

Additional exploratory analyses were carried out to evaluate safety in very elderly patients; these analyses are provided in Table III in the online-only Data Supplement.

DISCUSSION

Patients enrolled in the DAPA-HF trial were older than the patients in most previous HFrEF trials[15–17] and had a mean age close to that reported in contemporary registries.[18] Dapagliflozin reduced worsening HF events and death across all age categories, with larger absolute benefits in older patients. Dapagliflozin also improved symptoms in each age group, with no heterogeneity of treatment effect. Dapagliflozin was well tolerated, with no significant difference between dapagliflozin and placebo in any age group. Indeed, serious renal adverse events were less frequent with dapagliflozin in the oldest age category. Therefore, the benefit/risk profile of dapagliflozin was as favorable in older as in younger patients.

We found, predictably, that baseline characteristics differed substantially across age categories. As observed in previous trials,[15,19] older patients were more often women and hypertensive and had a higher prevalence of atrial fibrillation and impaired renal function compared with younger participants. Older patients had higher NT-proBNP levels than younger patients. As reported in the PARADIGM-HF trial (Prospective Com-

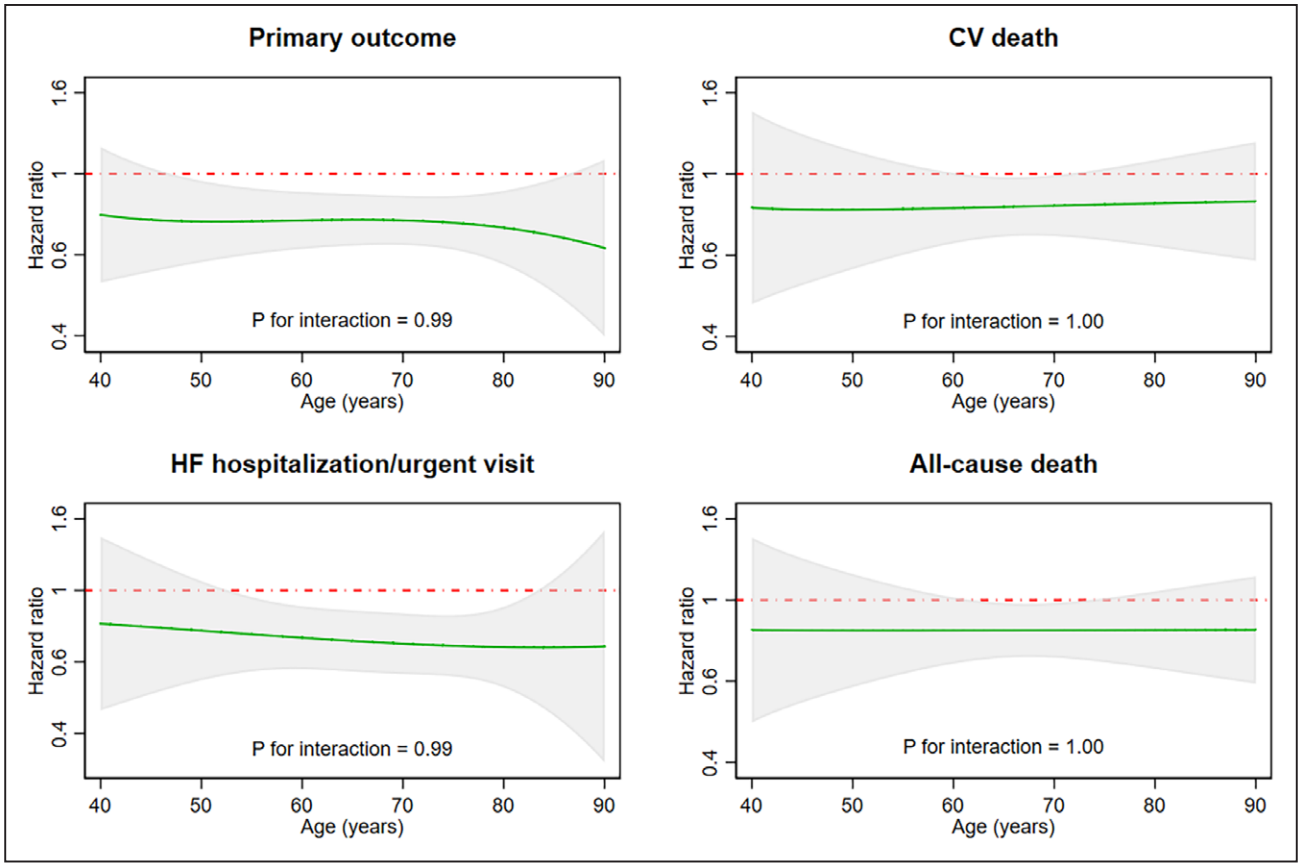

Figure 3. Effect of dapagliflozin on the occurrence of outcomes by age.
P values are for interaction between baseline age and treatment effect. CV indicates cardiovascular; and HF, heart failure.

parison of ARNI [Angiotensin Receptor Neprilysin Inhibitors] With ACEi [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure),[20] nonwhite individuals and patients from the Asia-Pacific region were younger than white participants. In DAPA-HF overall, a larger proportion of patients were receiving guideline-recommended lifesaving medications (ie, mineralocorticoid receptor antagonists and β-blockers) compared with previous trials, and this was also true for patients in the oldest age group.

We observed a higher rate of events as age increased, although this gradient was clearer for worsening HF events than for cardiovascular death. The high rate of use of disease-modifying drugs at baseline may have contributed to the attenuated age-related gradient in cardiovascular death, which, as in PARADIGM-HF, was less steep than in historical trials.[21]

As clearly shown in Figures 2 and 3, the benefit of dapagliflozin on each of the 4 mortality/hospitalization outcomes examined was consistent across the whole age range studied. Because older patients were at higher absolute risk, the absolute benefit of dapagliflozin was greatest in the most elderly participants (≥75 years of age), with 47 fewer patients in this age group per 1000 person-years experiencing a primary end point. In addition to their higher baseline risk, older patients received slightly less conventional disease-modifying therapy, which also may have amplified the benefit of dapagliflozin. Whatever the precise explanation, the benefits observed emphasize the importance of overcoming the therapeutic nihilism that often characterizes the management of older patients with many diseases and, above all, older women who made up 28% of the oldest group in the present analysis.[7] Our data clearly show that dapagliflozin has substantial, clinically important benefits in older and younger patients.

For older patients, improvement, or at least prevention of deterioration, in symptoms may be as important as extending life, and it is important to note that the overall improvement in KCCQ-TSS was as large in older individuals as it was in younger patients. Indeed, the numbers needed to treat to achieve a clinically important improvement or to prevent a significant deterioration in symptoms were small and as favorable in older patients as in younger patients.

Our analyses of safety and tolerability were also reassuring. Although adverse events and study drug discontinuation increased with age (in the placebo group), neither was common, and more relevantly, they did not differ by treatment group. Renal dysfunction, which can be a particular problem in older indi-

Table 3. Occurrence of Adverse Events According to Age Categories (Patients Receiving at Least 1 Dose of Study Drug)

Adverse event	Age <55 y (n=634)		Age 55–64 y (n=1240)		Age 65–74 y (n=1716)		Age ≥75 y (n=1146)		*P* for Interaction*
	Placebo (n=295)	Dapagliflozin (n=339)	Placebo (n=630)	Dapagliflozin (n=610)	Placebo (n=886)	Dapagliflozin (n=830)	Placebo (n=557)	Dapagliflozin (n=589)	
Volume depletion	14 (4.7)	23 (6.8)	35 (5.6)	36 (5.9)	57 (6.4)	57 (6.9)	56 (10.1)	62 (10.5)	0.86
Serious volume depletion	3 (1.0)	1 (0.3)	12 (1.9)	5 (0.8)	11 (1.2)	15 (1.8)	14 (2.5)	8 (1.4)	0.15
Renal AE	11 (3.7)	14 (4.1)	33 (5.2)	48 (7.9)	67 (7.6)	51 (6.1)	59 (10.6)	40 (6.8)	0.031
Serious renal AE	4 (1.4)	3 (0.9)	9 (1.4)	13 (2.1)	22 (2.5)	19 (2.3)	30 (5.4)	3 (0.5)	0.002
Fracture	0 (0.0)	1 (0.3)	11 (1.7)	11 (1.8)	24 (2.7)	13 (1.6)	15 (2.7)	24 (4.1)	†
Amputation	0 (0.0)	2 (0.6)	2 (0.3)	4 (0.7)	5 (0.6)	6 (0.7)	5 (0.9)	1 (0.2)	†
Major hypoglycemia	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.2)	3 (0.5)	1 (0.2)	†
Diabetic ketoacidosis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	†
AE leading to permanent treatment discontinuation	10 (3.4)	10 (2.9)	23 (3.7)	25 (4.1)	50 (5.6)	42 (5.1)	33 (5.9)	34 (5.8)	0.93
AE leading to temporary treatment discontinuation	34 (11.5)	29 (8.6)	75 (11.9)	73 (12.0)	133 (15.0)	112 (13.5)	107 (19.2)	70 (11.9)	0.09
AE leading to treatment dose reduction	4 (1.4)	9 (2.7)	7 (1.1)	7 (1.1)	8 (0.9)	13 (1.6)	6 (1.1)	14 (2.4)	0.75
Any serious AE (including death)	101 (34.2)	111 (32.7)	252 (40.0)	213 (34.9)	366 (41.3)	319 (38.4)	275 (49.4)	252 (42.8)	0.61
Discontinuation of study drug for any reasons	22 (7.5)	37 (10.9)	57 (9.0)	50 (8.2)	104 (11.7)	90 (10.8)	75 (13.5)	72 (12.2)	0.38
Doubling of serum creatinine	7 (2.4)	5 (1.5)	17 (2.7)	14 (2.3)	24 (2.7)	20 (2.4)	29 (5.2)	4 (0.7)	0.011
Change in creatinine with dapagliflozin at 8 mo, mg/dL	0.04 (-0.01 to 0.09), *P*=0.096		–0.01 (–0.04 to 0.02), *P*=0.49		0.03 (0.01 to 0.06), *P*=0.017		0.03 (–0.01 to 0.06), *P*=0.10		0.78
Change in SBP with dapagliflozin at 8 mo, mm Hg	–1.97 (–4.29 to 0.35), *P*=0.095		–0.36 (–2.06 to 1.34), *P*=0.68		–1.97 (–3.40 to -0.54), P=0.007		–1.42 (–3.26 to –0.42), *P*=0.13		0.97

AE indicates adverse event; and SBP, systolic blood pressure.
**P* value is for interaction between age categories and treatment effect on the occurrence of adverse events.
†*P* value is not provided because of few events.

viduals with HFrEF, was not more common with dapagliflozin, and serious renal adverse events were actually less common in the dapagliflozin group. It is difficult to make direct comparisons of safety outcomes with previous sodium-glucose cotransporter 2 inhibitor trials because the patients included in DAPA-HF were at much higher cardiovascular risk, had more underlying renal dysfunction, and were receiving quite different background therapy, particularly renin-angiotensin system blockers and diuretics. Collection of safety information was also different, with targeted identification of specific adverse effects, especially those related to concerns in patients with HF (volume depletion and renal dysfunction).

As with other similar studies, there are some obvious limitations. This is a post hoc analysis, and the age categories chosen were arbitrary (although commonly used in similar studies). The number of black patients was relatively small, although similar to other global HFrEF trials.[15,22] As in other trials, the prespecified inclusion and exclusion criteria will have reduced the enrollment of very high-risk patients. These limitations could affect the generalizability of our results.

Conclusions

Dapagliflozin reduced the risk of death and worsening HF and improved symptoms across the broad spectrum of age studied in DAPA-HF. There was no significant imbalance in tolerability or safety events between dapagliflozin and placebo, even in elderly individuals.

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