Full title: Efficacy and safety of dapagliflozin in HFrEF according to age: insights from DAPA-HF

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ABSTRACT

Background: The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure trial (DAPA-HF), 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 (HFrEF). We examined the effects of dapagliflozin according to age, given potential concerns about efficacy and safety of therapies in the elderly.

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

Results: 4744 patients aged 22-94 years were randomized (mean age was 66.3 [SD 10.9] years). 636 patients were aged <55 years (13.4%), 1242 aged 55-64 (26.2%), 1717 aged 65-74 (36.2%) and 1149 ≥75 years (24.2%). 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 (13.2-18.7), 15.1 (13.1-17.5) and 18.0 (15.2-21.4) with corresponding dapagliflozin/placebo hazard ratios (95% CI): 0.87 (0.60-1.28), 0.71 (0.55-0.93), 0.76 (0.61-0.95), and 0.68 (0.53-0.88), P-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.

Conclusion: 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.

Clinical Trial Registration:

URL: https://clinicaltrials.gov/ct2/show/NCT03036124; ClinicalTrials.gov Unique Identifier: NCT03036124.

CLINICAL PERSPECTIVE

What is new?

- In the placebo-controlled Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure trial (DAPA-HF), 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 (HFrEF)
- The effects of dapagliflozin were consistent across the spectrum of age studied (22-94 years), both in terms of efficacy and safety.

What are the clinical implications?

- The benefit of dapagliflozin is consistent in older as well as younger patients, including in individuals aged ≥75 years.
- This risk adverse events with dapagliflozin was not greater in older, compared to younger patients.
- Advanced age *per se* is not a reason to withhold treatment with dapagliflozin in patients with HFrEF.

INTRODUCTION

As populations in many countries age rapidly, the number of elderly patients with heart failure is increasing steeply. However, in other regions, such as Latin America, Africa and parts of Asia, individuals with heart failure 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 Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure trial (DAPA-HF), 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 (HFrEF) [8]. The average age of patients randomized in DAPA-HF was 66 years and 36% of patients were aged 66 to 75 years and 21% were >75 years. 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, which 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 aged ≥18 years with HF were eligible if they were in New York Heart Association (NYHA) functional class ≥II, had a left ventricular ejection fraction (LVEF) ≤40%, and were optimally treated with pharmacological and device therapy for HF. Participants were also required to have a N-terminal pro-B-type natriuretic peptide (NT-proBNP) 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 a NT-proBNP level ≥900 pg/mL, irrespective of history of HF hospitalization. Key exclusion criteria included: symptoms of hypotension or systolic blood pressure <95 mmHg, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 (or rapidly declining renal function), type 1 diabetes mellitus, and another condition likely to prevent patient participation in the trial or greatly limit life expectancy. A full list of exclusion criteria is provided in the design paper [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 were collected. Visit 2 was the randomization visit and randomization was stratified based on diagnosis of type 2 diabetes (defined as an established diagnosis or a glycated haemoglobin level of ≥6.5% [≥48 mmol per mole]) at screening. After randomization, follow-up visits took place at 14 and 60 days, and then at 120, 240, 360 days and every four months thereafter. The visit early after randomization (14 days) was included to check renal function and blood pressure (as well as for symptoms of hypotension); this visit also allowed for adjustment of back-ground diuretic or other non-essential therapies. Dose reduction to 5 mg of 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 up-titration (or re-initiation) was encouraged thereafter in all cases, where possible.

Study outcomes

The primary outcome was the composite of an episode of worsening heart failure (HF hospitalization or urgent HF visit) or cardiovascular (CV) death, whichever occurred first. Secondary endpoints were the occurrence of HF hospitalization or CV death; HF hospitalizations (first and recurrent) and cardiovascular deaths; 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 (a) ≥50% sustained decline in eGFR, (b) end-stage renal disease (defined as sustained eGFR<15 mL/min/1.73 m^2, chronic dialysis treatment or renal transplantation) or (c) renal death; and death from any cause. Prespecified safety analyses included serious adverse events, adverse events leading to discontinuation of trial treatment, adverse events of interest (i.e.,

volume depletion, renal events, major hypoglycemic events, bone fractures, diabetic ketoacidosis, amputation) and any diagnosis of Fournier's gangrene, as well as laboratory findings of note.

Statistical analysis

In the present study, patients were divided into four age categories: (i) <55 years, (ii) 55–64 years, (iii) 65–74 years, and (iv) ≥75 years. Baseline characteristics were summarized as means and standard deviations, 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 status, with a history of HF hospitalization and treatment-group assignment as fixed-effect factors. We used Cox models to calculate hazard ratios, 95% confidence intervals, and two-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 one 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 modelled 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 using the "mfpi" command in STATA [14]. The interaction between age and treatment on the occurrence of the pre-specified 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 S1 and Figure S1, supplementary appendix). Additional exploratory analyses were conducted in very elderly patients i.e. those aged 75-80 and 80-85 years; we have provided these two categories, along with the categories ages ≥80 and ≥85 years. All analyses were

conducted using STATA version 15.1 (College Station, TX, USA). A P-value of 0.05 was considered statistically significant.

RESULTS

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

Patient characteristics

Compared to younger participants, older patients were more often women, white, and enrolled in Western 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 NYHA 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 76/75) in the <55 years and 55–64 years groups, but higher (mean 79) among patients in the two older age categories (65–74 and the ≥75 years) i.e. older patients had less severe symptoms. With respect to background heart failure medications, patients in the older groups were less frequently treated with beta-blockers, mineralocorticoid receptor antagonists (MRAs), diuretics, and digitalis than younger patients. Baseline use of angiotensin receptor neprilysin inhibitors (ARNI) was generally low but similar across age groups. The proportion of patients treated with cardiac resynchronization therapy increased with age, but patients aged ≥75 years were less likely to receive an implantable cardioverter-defibrillator (ICD) compared to those aged 55-64 or 65-74 years. Use of oral anticoagulant therapy increased with age while antiplatelet use was higher in patients aged 55-64 years.

Primary composite outcome

The unadjusted incidence of the primary composite outcome of a first episode of worsening HF or CV death, according to age is shown in Table 2 and Figure 1. The incidence of this endpoint in the placebo group was relatively similar in the age categories 55-64 and 65–74 years but was higher in those aged 75 years or older and lower in those aged <55 years. The hazard ratio (HR) 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 aged ≥75 years 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 aged <55 years was estimated as 35 fewer patients per 1000 person years of follow-up.

Cardiovascular death

As shown in Table 2 and Figure 2B, the rate of CV 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-value for interaction = 0.97).

Worsening heart failure events

By 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 (Table 2 and Figure 2C). Applying

the overall relative risk reduction (30%) to placebo group event rate in those aged ≥75 years, gave an absolute risk reduction of 36 per 1000 person years of follow-up. The equivalent absolute risk reduction in patients aged <55 years 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 from any cause increased steadily across age categories, with the highest rate in patients ≥75 years. The effect of dapagliflozin compared with placebo was consistent across the spectrum of age (Table 2 and Figure 2D; P-value for interaction 0.93). Applying the overall relative risk reduction (17%) to placebo group event rate in those aged ≥75 years, gave an absolute risk reduction of 19 fewer deaths per 1000 person years of follow-up. The equivalent absolute risk reduction in patients aged <55 years was estimated as 13 fewer deaths per 1000 person years.

Composite of recurrent heart failure hospitalization and cardiovascular death

As for the other endpoints, we observed a consistent effect of dapagliflozin on the occurrence of first and recurrent HF hospitalization and CV death across age categories (Table 2) (P-value for interaction =0.72).

Effect of dapagliflozin compared to placebo with age as a continuous variable

Figure 3 provides an alternative illustration of the effects of dapagliflozin compared with placebo, for the four outcomes described above, using fractional polynomial analysis. Each panel shows a continuous HR (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 for the possibility of a

non-linear effect of treatment by age to be modeled. As in the categorical analysis, the effect of dapagliflozin, compared with placebo, was consistent across the entire spectrum of age. The continuous HR was linear (Figure 3). Similar findings were also observed after adjusting for differences in baseline characteristics (Figure S1, supplementary appendix).

Change in Kansas City Cardiomyopathy Questionnaire at 8 months

As shown in Table 2, patients treated with dapagliflozin, overall, had a greater increase (improvement) in the KCCQ-TSS between baseline and 8 months and this benefit of dapagliflozin was consistent across age categories (P-value 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 to patients treated with placebo. Conversely, the proportion of patients with a decrease in KCCQ-TSS of ≥5 points (i.e. a clinically meaningful deterioration) was smaller in those treated with dapagliflozin. The benefit of dapagliflozin over placebo in both improving KCCQ-TSS, and in preventing deterioration, was consistent across age groups (P-value for each interaction=0.96). The numbers needed to treat (NNT) for one patient to have a clinically meaningful improvement in symptoms over 8 months was 14 overall, ranging from 10 to 29 across age groups; the NNT for 8 months to prevent one patient having a clinically important deterioration was 13 overall, ranging from 9 to 22, across age groups.

Additional exploratory analyses were carried out to evaluate safety in very elderly patients; these are provided in the Supplementary Appendix (Tables S2 and Table S3).

Pre-specified safety assessments

Table 3 shows the occurrence of the pre-specified adverse events of interest, according to age category. The proportion of patients stopping 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-value 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 aged ≥75 years (5.9% compared with 3.4% in the <55 years group). Discontinuation of study drug due to adverse events was similar in the two treatment arms (dapagliflozin and placebo) in each age category. For example, in the ≥75 years 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 pre-specified 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 aged ≥75 years 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 aged ≥75 years. *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 signification interaction between age category and the effect of dapagliflozin (P for interaction =0.002). Specifically, in patients ≥75 years, the incidence of serious renal adverse events was 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-value for interaction =0.78) and relatively few patients in any age group (and either treatment group) experienced a doubling of serum creatinine.

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

Additional exploratory analyses were carried out to evaluate safety in very elderly patients; these are provided in the Supplementary Appendix (Tables S2 and Table S3).

DISCUSSION

Patients enrolled in the DAPA-HF trial were older than in most previous HFrEF trials [15–17], and had a mean age close to that reported in contemporary registries [18]. Dapagliflozin reduced worsening heart failure 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, compared with younger patients.

We found, predictably, that baseline characteristic differed substantially across age categories. As observed in previous trials [15,19], older patients were more often women, 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 [20], non-white 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 life-saving medications (i.e. mineralocorticoid receptor antagonists and beta-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 CV death. The high rate of use of disease-modifying drugs at baseline may have contributed to the attenuated age-related gradient in CV 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 four 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), with 47 few patients in this age group, per 1000 treated, experiencing a primary endpoint over the duration of the trial. In addition to their higher baseline risk, older patients received slightly less conventional disease-modifying therapy which may also 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 comprised 28% of the oldest group in the present analysis [7]. Our data clearly show that dapagliflozin has substantial, clinically important, benefits in older as well as younger patients.

For older patients, improvement, or at least prevention of deterioration, in symptoms may be as important as extending life and it is also important to note that the overall improvement in KCCQ-TSS was as large in older individuals as it was in younger patients. Indeed, the NNTs to achieve a clinically important improvement, or to prevent a significant deterioration, in symptoms were small and as favourable in older patients as 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. Importantly, renal dysfunction which can be a particular problem in older individuals 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 prior SGLT2 inhibitor trials as 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 use of 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 heart failure (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 African American 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 enrolment of very high-risk patients. These limitations could affect the generalizability of our results.

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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TABLES AND FIGURES LEGENDS

TABLE 1. Baseline Characteristics According to Age Categories. **Glycated hemoglobin values are listed only for the patients with diabetes. †the numbers are relative to patients with type II diabetes history at baseline. ACE denotes 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, GFR Glomerular Filtration Rate, GLP-1 Glucagon-like Peptide 1, ICD Implantable Cardioverter-Defibrillator, MI Myocardial Infarction, NYHA New York Heart Association, KCCQ Kansas City Cardiomyopathy Questionnaire, PCI Percutaneous Coronary Intervention.*

TABLE 2. **Clinical Outcomes According to Age Categories.** *CV death denotes cardiovascular death, HF heart failure. *P value are for interaction between baseline age categories and treatment effect.*

TABLE 3. Occurrence of Adverse Events According to Age Categories (patients receiving at least one dose of study drug). **P value is for interaction between age categories and treatment effect on the occurrence of adverse events. †P value not provided because of few events. AE denotes Adverse Event, SBP Systolic Blood Pressure.*

FIGURE 1. Cumulative Incidence of the Primary Outcome according to Age Categories.

FIGURE 2. Effect of Dapagliflozin according to Age Categories. Panel A shows Occurrence of Primary Outcome, panel B shows Cardiovascular Death, panel C shows HF Hospitalization/Urgent Visit and panel D shows All-Cause Death. *P values are for interaction between baseline age categories and treatment effect. CV Death denotes Cardiovascular Death, HF heart failure. P value are for interaction between baseline age categories and treatment effect. CV Death denotes Cardiovascular Death, HF heart failure.*

FIGURE 3. Effect of Dapagliflozin on the Occurrence of Outcomes by Age. *CV Death denotes Cardiovascular Death, HF heart failure.*

TABLE 1 – Baseline Characteristics According to Age Categories.

Variable	<55 years (n=636)	55–64 years (n=1242)	65-74 years (n=1717)	≥75 years (n=1149)	P for trend
Age - years	47.1 (6.3)	59.9 (2.8)	69.4 (2.8)	79.4 (3.6)	
Female - no. (%)	120 (18.9)	265 (21.3)	403 (23.5)	321 (27.9)	**<0.001**
Race - no. (%)					**<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 – no. (%)					**<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)	
Systolic blood pressure - mmHg	117.7 ± 17.1	121.0 ± 16.1	122.9 ± 15.8	123.4 ± 16.5	**<0.001**
Diastolic blood pressure - mmHg	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**
Estimated GFR - mL/min/1.73m^2	83.0 ± 20.5	71.5 ± 18.3	62.0 ± 16.5	55.6 ± 15.2	**<0.001**
Median NTproBNP - pg/ml (IQR)	1107 (648, 2241)	1332 (813, 2394)	1453 (881, 2644)	1737 (1068, 3161)	**<0.001**
Heart failure etiology - no. (%)					**<0.001**
Ischemic etiology	258 (40.6)	660 (53.1)	1053 (61.3)	703 (61.2)	
Non-ischemic etiology	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 – no. (%)					**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 total symptoms score at baseline (IQR)	76 (52, 92)	75 (57, 92)	79 (60, 93)	79 (60, 92)	**<0.001**
Medical history – no (%)					
Hypertension	343 (53.9)	871 (70.1)	1357 (79.0)	951 (82.8)	**<0.001**
Type 2 Diabetes	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 Heart Failure	317 (49.8)	596 (48.0)	824 (48.0)	514 (44.7)	**0.042**
Prior MI	198 (31.1)	535 (43.1)	833 (48.5)	526 (45.8)	**<0.001**
Prior PCI	139 (21.9)	410 (33.0)	655 (38.1)	420 (36.6)	**<0.001**
Prior CABG	42 (6.6)	173 (13.9)	358 (20.9)	226 (19.7)	**<0.001**
Treatment – no (%)					

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**
Beta-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 treatment – no (%)†					
	<55 years (n=215)	**55–64 years (n=564)**	**65-74 years (n=758)**	**≥75 years (n=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

*Glycated hemoglobin values are listed only for the patients with diabetes. †the numbers are relative to patients with type II diabetes history at baseline. ACE denotes 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, GFR Glomerular Filtration Rate, GLP-1 Glucagon-like Peptide 1, ICD Implantable Cardioverter-Defibrillator, MI Myocardial Infarction, NYHA New York Heart Association, KCCQ Kansas City Cardiomyopathy Questionnaire, PCI Percutaneous Coronary Intervention.

TABLE 2. Clinical Outcomes According to Age Categories.

	<55 years (n=636)		55–64 years (n=1242)		65-74 years (n=1717)		≥75 years (n=1149)		P value for interaction*
Outcome	**Placebo (n=296)**	**Dapagliflozin (n=340)**	**Placebo (n=630)**	**Dapagliflozin (n=612)**	**Placebo (n=887)**	**Dapagliflozin (n=830)**	**Placebo (n=558)**	**Dapagliflozin (n=591)**	
CV death or HF hospitalization/urgent HF visit									0.76
No. (%)	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	0.87 (0.60-1.28), P=0.49		0.71 (0.55-0.93), P=0.012		0.76 (0.61-0.95), P=0.015		0.68 (0.53-0.88), P=0.003		
CV death									0.97
No. (%)	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	0.85 (0.51-1.43), P=0.54		0.87 (0.62-1.23), P=0.45		0.78 (0.58-1.04), P=0.089		0.83 (0.58-1.17), P=0.29		
HF hospitalization/urgent HF visit									0.18
No. (%)	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	1.05 (0.64-1.72), P=0.85		0.56 (0.40-0.78), P=0.001		0.76 (0.58-1.01), P=0.056		0.64 (0.47-0.88), P=0.006		
All-cause death									0.93
No. (%)	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	0.81 (0.49-1.35), P=0.43		0.91 (0.66-1.25), P=0.57		0.80 (0.62-1.05), P=0.10		0.79 (0.58-1.08), P=0.14		
CV death/HF hospitalization recurrent events									0.72
No. of events	81	80	198	134	268	202	195	151	
HR	0.89 (0.57-1.41), P=0.63		0.68 (0.51-0.91), P=0.010		0.80 (0.62-1.02), P= 0.076		0.70 (0.53-0.94), P=0.016		
KCCQ									
Change in KCCQ TSS score at 8 months	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 points improvement in	52.9	56.4	53.3	59.5	50.5	60.4	48.0	55.2	0.96

KCCQ at 8 months - %									
Patients with ≤5 points decrease in KCCQ at 8 months - %	30.2	25.7	31.3	25.7	34.2	23.3	33.9	27.6	0.96

CV death denotes cardiovascular death, HF heart failure. *P value are for interaction between baseline age categories and treatment effect.

TABLE 3. Occurrence of Adverse Events According to Age Categories (patients receiving at least one dose of study drug).

	<55 years (n=634)		55–64 years (n=1240)		65-74 years (n=1716)		⩾75 years (n=1146)		P value for interaction*
Adverse event	**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 adverse event	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 adverse event	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 adverse event (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 at 8 months	30 (10.2)	43 (12.7)	79 (12.5)	57 (9.3)	98 (11.1)	77 (9.3)	68 (12.2)	61 (10.4)	0.31
Change in creatinine with dapagliflozin (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 (mmHg)	-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

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

FIGURE 1. Cumulative Incidence of the Primary Outcome according to Age Categories.

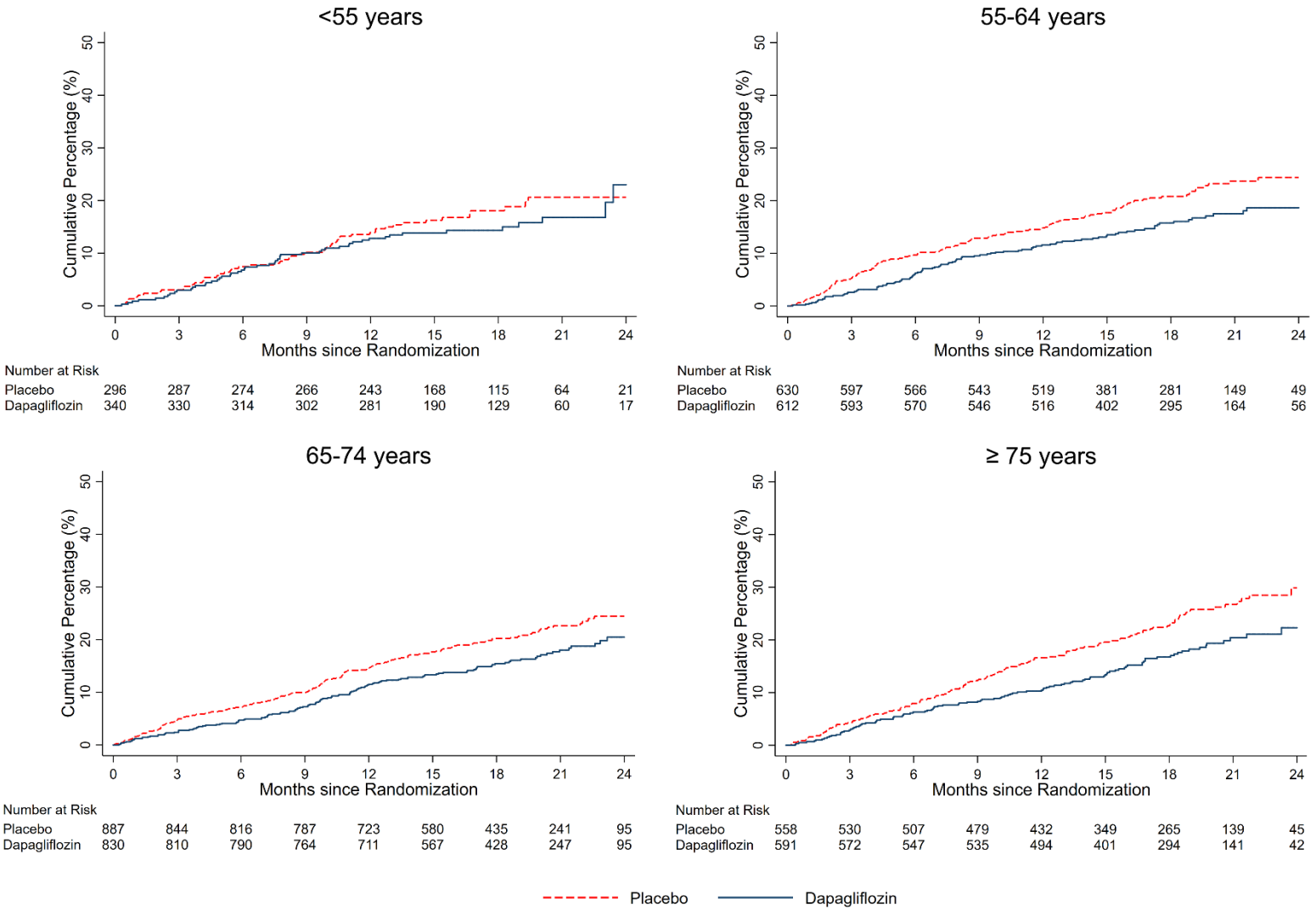
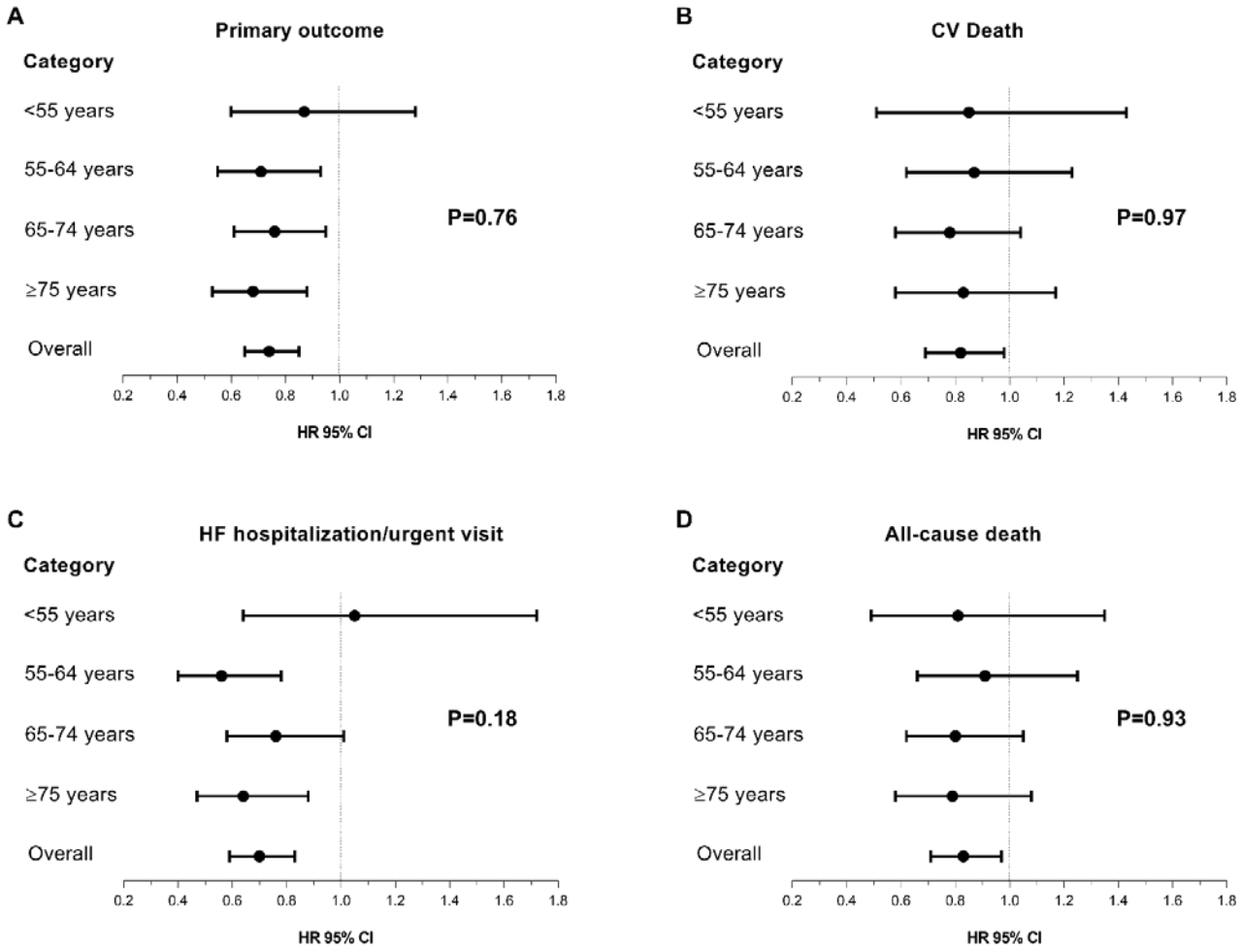
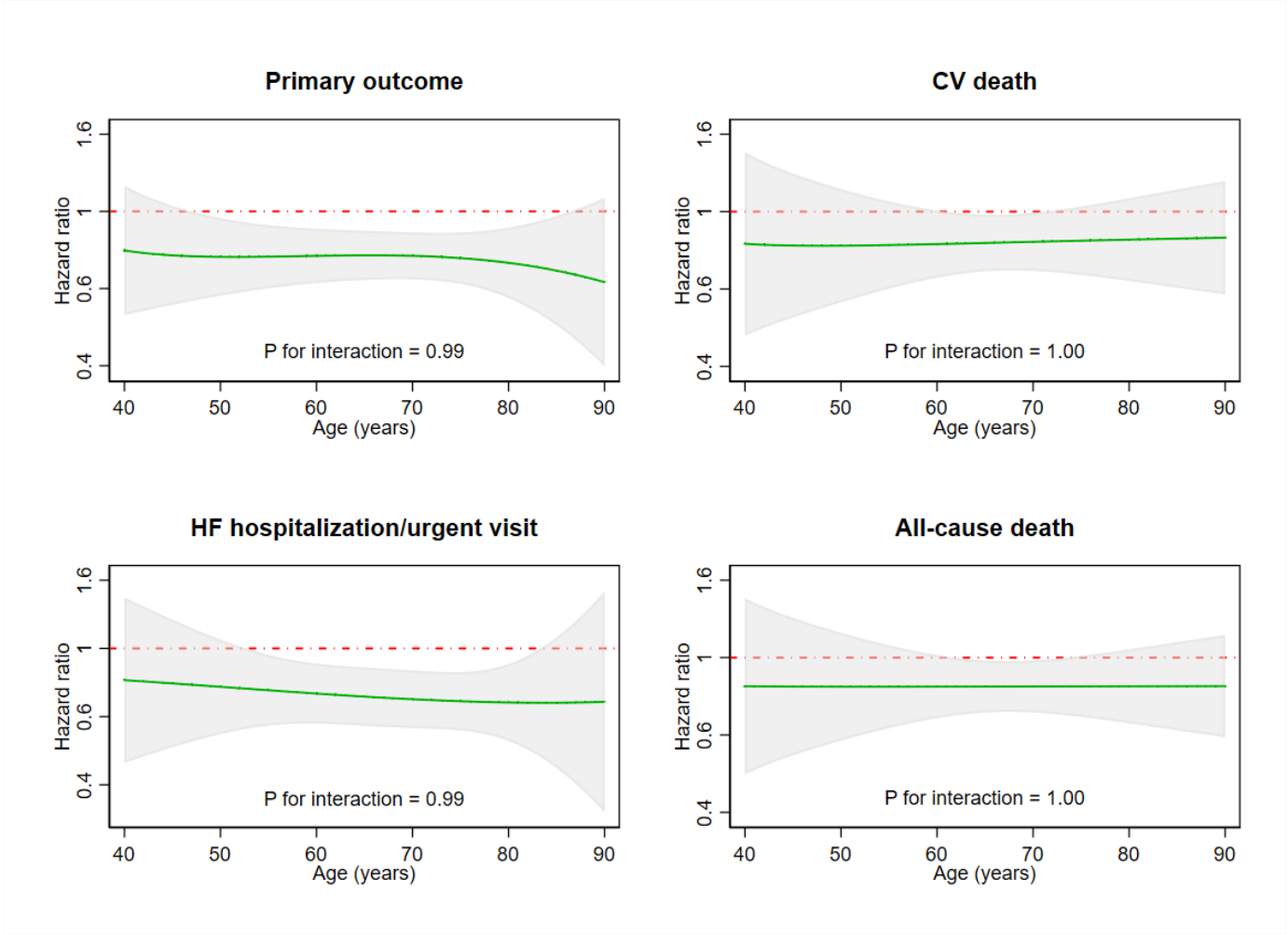


FIGURE 2. Effect of Dapagliflozin according to Age Categories. Panel A shows Occurrence of Primary Outcome, panel B shows Cardiovascular Death, panel C shows HF Hospitalization/Urgent Visit and panel D shows All-Cause Death.



P value are for interaction between baseline age categories and treatment effect. CV Death denotes Cardiovascular Death, HF heart failure.

FIGURE 3. Effect of Dapagliflozin on the Occurrence of Outcomes by Age.



CV Death denotes Cardiovascular Death, HF heart failure.