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Efficacy and Safety of Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction According to Age: The DELIVER Trial

Running Title: *Peikert, Martinez, Vaduganathan, et al.; Dapagliflozin in HFpEF According to Age*

Alexander Peikert, MD[1*]; Felipe A. Martinez, MD[2*]; Muthiah Vaduganathan, MD, MPH[1*]; Brian L. Claggett, PhD[1]; Ian J. Kulac, MS[1]; Akshay S. Desai, MD, MPH[1]; Pardeep S. Jhund, MBChB, MSc, PhD[3]; Rudolf A. de Boer, MD[4]; David DeMets, PhD[5]; Adrian F. Hernandez, MD[6]; Silvio E Inzucchi, MD[7]; Mikhail N. Kosiborod, MD[8]; Carolyn S.P. Lam, MD[9]; Sanjiv J. Shah, MD[10]; Tsvetana Katova, MD[11]; Béla Merkely, MD[12]; Orly Vardeny, PharmD, MS[13]; Ulrica Wilderäng, PhD[14]; Daniel Lindholm, MD[14]; Magnus Petersson, MD[14]; Anna Maria Langkilde, MD[14]; John J.V. McMurray, MD[3], Scott D. Solomon, MD[1]

[*]These authors contributed equally

[1]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [2]Universidad Nacional de Córdoba, Córdoba, Argentina; [3]BHF Cardiovascular Research Centre, University of Glasgow, UK; [4]University of Groningen, University Medical Center Groningen, Department of Cardiology, Groningen, the Netherlands; [5]University of Wisconsin, Madison, WI; [6]Duke University Medical Center, Durham, NC; [7]Yale School of Medicine, New Haven, CT; [8]Saint Luke's Mid America Heart Institute and University of Missouri-Kansas City, Kansas City, MO; [9]National Heart Centre Singapore & Duke-National University of Singapore, Singapore; [10]Northwestern University Feinberg School of Medicine, Chicago, IL; [11]Department of Noninvasive Cardiology, National Cardiology Hospital, Sofia, Bulgaria; [12]Heart and Vascular Center, Semmelweis University, Budapest, Hungary; [13]Minneapolis VA Center for Care Delivery and Outcomes Research, University of Minnesota, Minneapolis, MN; [14]Late-Stage Development, Cardiovascular, Renal, and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden

Address for Correspondence:
Scott D. Solomon, MD
The Edward D. Frohlich Distinguished Chair
Professor of Medicine
Harvard Medical School, Brigham and Women's Hospital
Department of Medicine, Cardiovascular Division
75 Francis Street, Boston, MA 02115
Telephone: +1 (857) 307-1960
Fax: +1 (857) 307-1944
Email: ssolomon@bwh.harvard.edu

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Abstract

Background: The prevalence of heart failure (HF) with mildly reduced or preserved ejection fraction (EF) markedly increases with age, with older individuals disproportionately facing excess risk for mortality and hospitalization.
Methods: The DELIVER trial (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure) randomized patients with New York Heart Association functional class II-IV and left ventricular EF >40% to either dapagliflozin or placebo for a median follow-up period of 2.3 years. We examined efficacy and safety outcomes by age categories (<55, 55-64, 65-74 and ≥75 years) and across age as a continuous measure.
Results: Among 6,263 randomized patients (aged 40-99 years, mean age 71.7 ± 9.6 years), 338 (5.4%) were <55 years, 1,007 (16.1%) were 55-64 years, 2,326 (37.1%) were 65-74 years, and 2,592 (41.4%) were ≥75 years. Dapagliflozin reduced the risk of the primary composite outcome compared with placebo in all age categories ($p_{interaction}$=0.95) and across the age spectrum as a continuous function ($p_{interaction}$=0.76). Similar benefits were observed for the components of the primary outcome, with no significant interaction between randomized treatment and age category. Adverse events occurred more frequently with increasing age, but there were no significant differences in predefined safety outcomes between patients randomized to dapagliflozin and placebo across all age categories.
Conclusions: In patients with HF and mildly reduced or preserved EF enrolled in DELIVER, Dapagliflozin reduced cardiovascular death or HF events across the spectrum of age, with a consistent safety profile, including among the traditionally under-treated older segment of patients ≥75 years.

Clinical Trial Registration: URL: https://www.clinicaltrials.gov Unique identifier: NCT03619213

Key Words: aging; heart failure with preserved ejection fraction; heart failure with mildly reduced ejection fraction; dapagliflozin; SGLT2 inhibitors

Non-standard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
AE	adverse events
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor neprilysin inhibitor
ARR	absolute rate reduction
DAE	adverse events leading to treatment discontinuation
DELIVER	Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure
eGFR	estimated glomerular filtration rate
HFpEF	heart failure with preserved ejection fraction
HFmrEF	heart failure with mildly reduced ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
ICD	implantable cardioverter-defibrillator
IQR	interquartile range

KCCQ-TSS	Kansas City Cardiomyopathy Questionnaire Total Symptom Score
MRA	mineralocorticoid receptor antagonist
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
OR	Odd ratio
RR	rate ratio
SAE	serious adverse events
SGLT2	sodium–glucose co-transporter 2

What Is New?

- Dapagliflozin was similarly efficacious across the spectrum of age in DELIVER (40-99 years), with a consistent safety profile in all age categories.

What Are the Clinical Implications?

- The benefits of dapagliflozin extend across a broad spectrum of age, including those over 75 years.
- Older patients with heart failure with mildly reduced and preserved ejection fraction have an increased risk of mortality and hospitalizations and should therefore be considered for treatment with dapagliflozin.
- Patients with advanced age do not experience a higher risk of adverse events with dapagliflozin; the safety and tolerability profile appears comparable in older and younger patients.
- The results are consistent with those demonstrated among patients with heart failure and reduced ejection fraction in the DAPA HF trial, suggesting that clinical benefits of dapagliflozin are robust across the spectrum of age and ejection fraction in chronic HF.

Introduction

The prevalence of heart failure with preserved ejection fraction (HFpEF) or heart failure with mildly reduced ejection fraction (HFmrEF) increases substantially with age, and patients tend to be older than those with heart failure with reduced ejection fraction (HFrEF).[1] Although older adults with HFpEF and HFmrEF disproportionately face excess risks of mortality, hospitalization burden, and contribute to health system costs, this patient population is often underrepresented in modern cardiovascular trials.[2,3] Limited evidence and the high burden of comorbidity in older patients associated with frailty, polypharmacy, and increased mortality risk leads to physician concerns about attenuated treatment effects and reduced safety, together with substantial underutilization of guideline-recommended therapies in this population.[4,5] Reducing HF events in the older segment of the HFpEF and HFmrEF population is an unmet need, and represents a key measure of quality, performance, and reimbursement.

Sodium–glucose co-transporter 2 (SGLT2) inhibitors added to conventional therapy have been shown to reduce cardiovascular mortality and heart failure (HF) events in patients with reduced and preserved ejection fraction.[6-8] Dapagliflozin was recently demonstrated to be efficacious and safe across a broad spectrum of age in patients with heart failure with reduced ejection fraction (HFrEF).[9] Whether the observed benefits across the age spectrum extend to patients with heart failure with preserved or mildly reduced ejection fraction remains unknown.

The DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure) trial compared dapagliflozin to placebo in patients with preserved or mildly reduced ejection fraction (LVEF >40%).[10] The trial enrolled patients over a broad range of ages from 40 to 99 years. This pre-specified analysis takes an in-depth look

at the efficacy and safety of dapagliflozin in patients with HFpEF and HFmrEF across the age spectrum in the DELIVER trial, including among those who are above the age of 75 years.

Methods

Data Sharing

The sponsor of this trial is committed to sharing access to patient-level data and supporting clinical documents from eligible studies with qualified external researchers. These requests are reviewed and approved by an independent review panel based on scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The trial data availability is according to the criteria and process described.[11]

Study Design and Patients

The design and baseline characteristics of the DELIVER trial has been described previously.[12,13] Briefly, DELIVER was an international, randomized, double-blind, event-driven trial comparing dapagliflozin with placebo in patients with HFpEF or HFmrEF. Adults 40 years of age or older with or without diabetes, with an LVEF >40%, New York Heart Association functional class II-IV, evidence of structural heart disease (left atrial enlargement or left ventricular hypertrophy), and elevation in natriuretic peptides (N-terminal pro B-type natriuretic peptide ≥300 pg/mL or ≥600 pg/mL for patients in atrial fibrillation or flutter) were eligible. Qualifying LVEF measurements were based on documented echocardiography or cardiac magnetic resonance imaging within 12 months prior to enrolment. The trial enrolled both ambulatory and hospitalized patients. Key exclusion criteria included hypertension (systolic blood pressure ≥160 mmHg if not on ≥3 antihypertensive medications, or ≥180 mmHg regardless of number of

medications), estimated glomerular filtration rate (eGFR) <25 mL/min/1.73 m^2, type 1 diabetes, treatment with SGLT2 inhibitors within 4 weeks of randomization or intolerance of a SGLT2 inhibitor and probable alternative diagnoses potentially accounting for the patients' symptoms. The protocol was approved by institutional review boards or ethics committees at each individual study site, and each patient provided written informed consent. The trial is registered in ClinicalTrials.gov, NCT03619213.

Study Procedures

After informed consent and a 21-day screening period, patients were randomized to dapagliflozin10mg or placebo once daily. Randomization was stratified by type 2 diabetes status at baseline. Concomitant medical treatment of comorbidities was recommended according to local standard of care. Following randomization, study visits took place at 30, 120, 240, 360, and 480 days after randomization, and then every 120 days thereafter.

Study Outcomes

As in the primary study, the primary outcome of this analysis was the composite of worsening heart failure events (defined as either unplanned hospitalization or urgent heart failure visit requiring intravenous therapy) or cardiovascular death. Key secondary outcomes included the total number of heart failure events (hospitalization for heart failure, urgent heart failure visit) or cardiovascular death, cardiovascular death, all-cause mortality, and change from baseline in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS) at 8 months.[14] Pre-specified safety outcomes included serious adverse events, adverse events leading to treatment discontinuation, amputations, adverse events leading to amputation and potential risk factors for adverse events leading to amputations affecting the lower limbs.

Statistical Analyses

The patient population was divided into the following categories based on age at study entry: <55 years, 55-64 years, 65-74 years and ≥75 years. Baseline characteristics were compared across age categories using linear regression, Cuzick's non-parametric trend test, and chi-squared tests for trend. Event rates across the spectrum of age were assessed by Poisson regression using restricted cubic splines with knot placement at the 10th, 50th, and 90th percentiles. Treatment effects were examined by Cox proportional hazards models stratified by type 2 diabetes at baseline and interaction terms for effect modification by age categories, with separate models used for each age category. In additional models, treatment effects were analyzed with age modeled as continuous variable. Effect modification as a continuous function of age was further estimated by Poisson regression models with baseline age expressed by restricted cubic splines. Differences in KCCQ-TSS between baseline and 8 months across age categories were assessed using regression models for trends with interaction terms. Continuous KCCQ-TSS interactions were analyzed by linear regression models, using month 8 data, adjusted for baseline KCCQ-TSS values. Interactions pertaining to binary KCCQ-TSS outcomes were examined by logistic regression models. Safety outcomes according to age were analyzed using logistic regression models with interaction terms. Statistical analyses were conducted using STATA version 16.1 (StataCorp, College Station, TX, USA). P-values of <0.05 were considered statistically significant.

Results

Patient Characteristics

The DELIVER trial randomized a total of 6263 patients of ages from 40 to 99 years across 350 sites in 20 countries (mean age 71.7 ± 9.6). Baseline characteristics by age categories are shown in Table 1. Older patients were more frequently female and white. Systolic blood pressure, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in patients with atrial fibrillation were higher, and history of atrial fibrillation or flutter, hypertension, chronic obstructive pulmonary disease, and prior stroke were more common with higher age. Type 2 diabetes was more common among patients in the age categories 55-64 and 65-74 than in patients < 55 and ≥ 75 years of age. Mean left ventricular ejection was highest among participants ≥75 years, and this oldest segment was more likely to have left ventricular ejection fractions ≥60% compared with younger age groups (37% vs. 25%). Body mass index (BMI), heart rate, diastolic blood pressure, HbA1c levels, and eGFR tended to be lower with increasing age. The use of angiotensin-converting enzyme inhibitors, angiotensin receptor neprilysin inhibitors, mineralocorticoid receptor antagonists, and beta-blocker were lower among older patients, while loop diuretic and angiotensin receptor blocker use were higher. Treatment with pacemaker tended to be more frequent with increasing age. Patients were similar across all age categories with respect to geographic region, history of dyslipidemia, atherosclerotic cardiovascular disease, prior HF hospitalization, sleep apnea, NT-proBNP levels in patients without atrial fibrillation, New York Heart Association functional class, KCCQ-TSS, and implantable cardioverter-defibrillator therapy.

Clinical Outcomes and Efficacy of Dapagliflozin Compared With Placebo according to Age

Crude event rates for the primary composite outcome of worsening heart failure events or cardiovascular death and its components did not significantly differ between the age categories, while all-cause mortality rates increased by age (Supplemental Table 1).

Dapagliflozin consistently reduced the risk of the primary outcome compared with placebo across all age categories ($p_{interaction}$=0.95; Table 2, Figure 1). Similarly, the treatment effect of dapagliflozin compared with placebo on cardiovascular death, worsening HF events (HF hospitalization or urgent HF visit), and all-cause mortality did not significantly differ across the categories of age ($p_{interaction}$>0.7 for all; Table 2, Figure 1). Likewise, the benefit of dapagliflozin over placebo on the improvement and prevention of deterioration of KCCQ-TSS was similar independent of age (Table 2). Consistent with the categorical analysis, results were similar with age modeled as a continuous variable ($p_{interaction}$>0.50 for all). The effect modification of dapagliflozin as a continuous function of age for key outcomes is shown in Figure 2.

Safety Outcomes

Overall, adverse events (AE) and treatment discontinuation for any cause occurred more frequently with increasing age, although no significant differences were detected between patients receiving dapagliflozin and placebo. Rates of serious adverse events (SAE), adverse events leading to treatment discontinuation, amputations, adverse events leading to amputation, and potential risk factors for adverse events leading to lower limb amputations were similar between dapagliflozin and placebo within each age category, with no significant interaction between age and treatment effect (Table 3). There were no differences between dapagliflozin-

and placebo-treated patients in the percentage of diabetic ketoacidosis, major hypoglycemia, volume depletion, or renal events as a function of age (Table 3).

Discussion

In patients with HF with mildly reduced and preserved ejection fraction randomized in the DELIVER trial, dapagliflozin reduced cardiovascular mortality or worsening HF events across the spectrum of age. Although adverse events occurred more frequently with increasing age, safety outcomes did not vary by age between patients randomized to dapagliflozin and placebo, including in the oldest segment of the population ≥75 years.

The mean age in DELIVER was comparable to other recent trials in HFpEF and slightly older than historical studies in this type of heart failure with a majority (77%) of the total patients being older than 65 years of age, reflecting the aging of the population in most developed countries.[8,15,16] Consistent with previous randomized trials, patient characteristics varied between age categories, with no significant differences observed between patients randomized to dapagliflozin compared with those randomized to placebo. The baseline prevalence of atrial flutter and fibrillation was higher in older patients, with lower BMI, heart rate, diastolic blood pressure, and HbA1c levels observed with increasing age. As shown in other studies with similar populations, hypertension and parameters of renal dysfunction were more evident among older individuals.[8,17] Similar to observations from previous HF trials, the tendency of higher absolute baseline NT-proBNP levels in older age groups possibly reflect a greater burden of myocardial stress.[6,7,18] Cardiovascular medications use was lower with age, except for loop diuretics and angiotensin receptor blockers, which were prescribed more frequently in older patients. Possible explanations may include the general underutilization of guideline-recommended therapies in

older populations, potential adverse effects of compound groups, and in particular for the mineralocorticoid receptor antagonists, concerns about heightened vulnerability to hyperkalemia and worsening renal function.[19,20] As expected, the use of pacemakers was higher in older patients, who tend to be at a higher risk for cardiac conduction disorders.[21]

Many older patients with HF with preserved ejection fraction have smaller left ventricular sizes, higher estimated ejection fractions, and distinct patterns of cardiac remodeling compared with younger individuals. Indeed, in DELIVER, older participants had the highest average left ventricular ejection fraction and more patients had ejection fractions ≥60%. This unique cardiac structural profile may alter their responsiveness to medical therapies for HF. EMPEROR-Preserved raised the concern about attenuation of clinical benefit in patients in the highest range of left ventricular ejection. These data from DELIVER however suggest that neither age nor ejection fraction attenuates the benefits of SGLT2 inhibition.

While the risk for worsening HF events and CV death did not significantly differ across the age categories, crude event rates were comparable to other recent trials in HFpEF, although DAPA-HF and other previous trials observed a more prominent increase in risk with age.[9,22,23] It is conceivable that the broader study population, which included patients with improved LVEF who appear to experience relatively lower event rates, and disease-modifying therapies for comorbidities may have attenuated the age-related risk gradient in DELIVER.[24]

The benefits of dapagliflozin on the primary outcome and its components were consistent across the whole spectrum of age examined, including among those ≥75 years. Correspondingly, the study drug reduced the primary composite outcome (17% vs. 20%, p=0.029) and the incidence of worsening HF events (12% vs. 15%, p=0.029), supporting benefits even in the oldest patient segment. Because symptom improvement may have equal significance to higher

life expectancy, particularly in older patient groups, it is noteworthy that all age groups showed similar improvements in KCCQ-TSS. Overall, the results are consistent with those shown among patients with HFrEF in the DAPA-HF trial, implying that clinical benefits appear to extend across the spectrum of age over the whole range of ejection fraction in patients with chronic HF.[9,25]

Regarding measures of safety, adverse events occurred more frequently with increasing age, but all pre-specified safety outcomes were similar across all age categories between patients randomized to dapagliflozin and placebo, including serious adverse events. Similar proportions of patients discontinued their treatment with dapagliflozin and placebo, with no evidence of age-related differences. Although older individuals face a higher risk for renal impairment, the rates of serious renal adverse events were similar in patients who received dapagliflozin or placebo independent of age, even in those over 75 years of age. Despite the higher concomitant use of cardiovascular medications with diuretic effects in older patients, volume depletion was not more common in patients receiving dapagliflozin at all ages. Moreover, there was no increased risk of major hypoglycemic events or diabetic ketoacidosis with dapagliflozin. These findings demonstrate that dapagliflozin can be used in all age groups in patients with HF and mildly reduced and preserved EF without compromising safety. Importantly, a recent post hoc analysis of the EMPEROR Preserved trial showed a consistent risk-benefit profile across the age spectrum for the SGLT2 inhibitor empagliflozin among those with HF and EF >40%.[22] Previous safety by age analysis of dapagliflozin in patients with HFrEF observed a similar safety profile.[9]

Limitations

The age-categories are arbitrary, although the categories are commonly used in similar analyses and additional continuous analyses were performed showing consistent findings. As with other

randomized trials, the predefined inclusion and exclusion criteria may have affected the generalizability of the study population's characteristics, including medication.

Conclusions

Dapagliflozin reduced cardiovascular death or worsening HF events across the spectrum of age in patients with HF with mildly reduced and preserved ejection fraction, with an acceptable safety profile, including among the traditionally under-treated and most vulnerable older segment of patients ≥75 years. The results are consistent with those demonstrated among patients with heart failure and reduced ejection fraction in the DAPA-HF trial, implying that clinical benefits of dapagliflozin are robust across the spectrum of age over the whole range of ejection fraction in chronic HF.

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Supplemental Materials

Supplemental Table 1

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Table 1. Baseline Characteristics According to Age Categories.

Variable	Age < 55 (n=338)	Age 55-64 (n=1007)	Age 65-74 (n=2326)	Age ≥ 75 (n=2592)	*P*-value for Trend
Age	49.7 ± 3.9	60.6 ± 2.7	69.9 ± 2.8	80.5 ± 4.2	
Male, n (%)	230 (68.0%)	651 (64.6%)	1315 (56.5%)	1320 (50.9%)	<0.001
Race, n (%)					0.01
White	206 (60.9%)	697 (69.2%)	1702 (73.2%)	1834 (70.8%)	
Asian	89 (26.3%)	202 (20.1%)	453 (19.5%)	530 (20.4%)	
Black Or African American	24 (7.1 %)	40 (4.0 %)	58 (2.5 %)	37 (1.4 %)	
American Indian Or Alaska Native	10 (3.0 %)	29 (2.9 %)	55 (2.4 %)	95 (3.7 %)	
Other	9 (2.7 %)	39 (3.9 %)	58 (2.5 %)	96 (3.7 %)	
Geographic Region, n (%)					0.37
Europe and Saudi Arabia	135 (39.9%)	457 (45.4%)	1225 (52.7%)	1188 (45.8%)	
Asia	87 (25.7%)	194 (19.3%)	438 (18.8%)	507 (19.6%)	
Latin America	84 (24.9%)	244 (24.2%)	394 (16.9%)	459 (17.7%)	
North America	32 (9.5 %)	112 (11.1%)	269 (11.6%)	438 (16.9%)	
Medical history, n (%)					
Atrial Fibrillation/Flutter	90 (26.6%)	431 (42.8%)	1333 (57.3%)	1698 (65.5%)	<0.001
Prior stroke	21 (6.2 %)	86 (8.5 %)	226 (9.7 %)	264 (10.2%)	0.015
Hypertension	262 (77.5%)	869 (86.3%)	2080 (89.4%)	2342 (90.4%)	<0.001
Dyslipidemia	176 (52.1%)	669 (66.4%)	1482 (63.7%)	1663 (64.2%)	0.06
Type 2 Diabetes Mellitus	148 (43.8%)	497 (49.4%)	1136 (48.8%)	1025 (39.5%)	<0.001
Chronic Obstructive Pulmonary Disease	20 (5.9 %)	105 (10.4%)	273 (11.7%)	294 (11.3%)	0.026
Sleep Apnea	26 (7.7 %)	63 (6.3 %)	220 (9.5 %)	176 (6.8 %)	0.61
Prior Myocardial Infarction	99 (29.3%)	337 (33.5%)	654 (28.1%)	549 (21.2%)	<0.001
Atherosclerotic Cardiovascular Disease	169 (50.0%)	612 (60.8%)	1364 (58.6%)	1407 (54.3%)	0.09
Prior HF Hospitalization	155 (45.9%)	385 (38.2%)	962 (41.4%)	1037 (40.0%)	0.44
NYHA Class, n (%)					0.08
I	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	1 (0.0 %)	
II	259 (76.6%)	765 (76.0%)	1776 (76.4%)	1913 (73.8%)	
III	76 (22.5%)	240 (23.8%)	546 (23.5%)	669 (25.8%)	
IV	3 (0.9 %)	2 (0.2 %)	4 (0.2 %)	9 (0.3 %)	
KCCQ-TSS	70 ± 24	69 ± 23	71 ± 22	70 ± 22	0.85
LVEF(%)	51.0 ± 8.8	51.8 ± 8.2	53.9 ± 8.5	55.8 ± 8.8	<0.001
Physiologic measures					
Body Mass Index	31.2 ± 7.0	30.9 ± 6.5	30.5 ± 6.2	28.7 ± 5.5	<0.001
Median NT-proBNP with AF [IQR]	1062 [874, 1815]	1161 [858, 1993]	1310 [922, 1960]	1575 [1088, 2515]	<0.001
Median NT-proBNP without AF [IQR]	764 [502, 1280]	704 [450, 1355]	677 [451, 1161]	761 [482, 1370]	0.27
Systolic Blood Pressure (mmHg)	125.7 ± 17.3	127.3 ± 15.2	128.5 ± 15.6	128.6 ± 14.9	0.002
Diastolic Blood Pressure (mmHg)	77.0 ± 10.6	75.8 ± 10.2	74.6 ± 10.1	72.2 ± 10.3	<0.001
HbA1c (%)	6.9 ± 2.1	6.9 ± 1.8	6.7 ± 1.4	6.4 ± 1.1	<0.001
Heart rate (beats/min)	72.3 ± 11.5	72.3 ± 11.6	71.7 ± 11.7	70.9 ± 11.9	<0.001
Creatinine (umol/L)	99.4 ± 38.5	100.0 ± 31.4	101.6 ± 30.9	104.7 ± 29.9	<0.001
eGFR (mL/min/1.73m2)	78.0 ± 23.9	69.2 ± 19.3	62.1 ± 18.1	54.7 ± 16.3	<0.001
Treatment, n (%)					
Loop diuretics	246 (72.8%)	755 (75.0%)	1767 (76.0%)	2043 (78.8%)	<0.001

ACE inhibitor	128 (37.9%)	419 (41.7%)	903 (38.8%)	845 (32.6%)	<0.001
ARB	108 (32.0%)	329 (32.7%)	865 (37.2%)	970 (37.4%)	0.004
ARNI	40 (11.8%)	60 (6.0 %)	98 (4.2 %)	103 (4.0 %)	<0.001
Beta-blocker	288 (85.2%)	855 (85.0%)	1992 (85.6%)	2042 (78.8%)	<0.001
MRA	207 (61.2%)	499 (49.6%)	1010 (43.4%)	951 (36.7%)	<0.001
Pacemaker	12 (3.6 %)	47 (4.7 %)	214 (9.2 %)	389 (15.0%)	<0.001
ICD	8 (2.4 %)	17 (1.7 %)	53 (2.3 %)	35 (1.4 %)	0.12

Plus–minus values are mean ± standard deviation. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide and NYHA, New York Heart Association. *P*-values are reported for trends across age categories.

Table 2. Clinical Outcomes According to Age Categories

Outcome	Age < 55 (n=338)		Age 55-64 (n=1007)		Age 65-74 (n=2326)		Age ≥ 75 (n=2592)		$P_{interaction}$*
	Placebo (n=171)	Dapagliflozin (n=167)	Placebo (n=506)	Dapagliflozin (n=501)	Placebo (n=1190)	Dapagliflozin (n=1136)	Placebo (n=1265)	Dapagliflozin (n=1327)	
Primary composite									
n (%)	31(18%)	24 (14%)	90 (18%)	81 (16%)	234 (20%)	179 (16%)	255 (20%)	228 (17%)	0.95
Rate (per 100 pt-yrs)	8.9	7.1	8.9	7.7	9.5	7.5	10.1	8.3	
ARR (per 100 pt-yrs)	1.8		1.1		2.0		1.9		
HR (95% CI)	0.80 (0.47, 1.37)		0.88 (0.65, 1.19)		0.79 (0.65, 0.96)		0.82 (0.69, 0.98)		
CV death									
n (%)	9 (5%)	9 (5%)	37 (7%)	40 (8%)	94 (8%)	75 (7%)	121 (10%)	107 (8%)	0.74
Rate (per 100 pt-yrs)	2.4	2.5	3.3	3.6	3.5	3.0	4.4	3.7	
ARR (per 100 pt-yrs)	-0.1		-0.3		0.5		0.8		
HR (95% CI)	1.08 (0.43, 2.72)		1.08 (0.69, 1.69)		0.85 (0.62, 1.15)		0.83 (0.64, 1.07)		
HF Event									
n (%)	25 (15%)	20 (12%)	65 (13%)	53 (11%)	178 (15%)	134 (12%)	187 (15%)	161 (12%)	0.99
Rate (per 100 pt-yrs)	7.2	5.9	6.4	5.1	7.2	5.6	7.4	5.9	
ARR (per 100 pt-yrs)	1.3		1.3		1.6		1.6		
HR (95% CI)	0.83 (0.46, 1.49)		0.80 (0.56, 1.15)		0.78 (0.62, 0.97)		0.79 (0.64, 0.98)		
HF Hospitalization									
n (%)	21 (12%)	19 (11%)	58 (11%)	45 (9%)	166 (14%)	123 (11%)	173 (14%)	142 (11%)	0.94
Rate (per 100 pt-yrs)	5.9	5.6	5.6]	4.3	6.6	5.1	6.8	5.1	
ARR (per 100 pt-yrs)	0.4		1.3		1.6		1.7		
HR (95% CI)	0.95 (0.51, 1.76)		0.77 (0.52, 1.13)		0.77 (0.61, 0.97)		0.75 (0.60, 0.94)		
Urgent HF Visit									
n (%)	4 (2%)	4 (2%)	15 (3%)	8 (2%)	26 (2%)	20 (2%)	33 (3%)	28 (2%)	0.80
Rate (per 100 pt-yrs)	1.1	1.1	1.4	0.7	1.0	0.8	1.2	1.0	
ARR (per 100 pt-yrs)	0.1		0.7		0.2		0.3		
HR (95% CI)	1.05 (0.26, 4.21)		0.52 (0.22, 1.24)		0.81 (0.45, 1.45)		0.79 (0.48, 1.31)		
KCCQ-TSS									
Mean change at 8 months	4 ± 22	8 ± 19	7 ± 19	10 ± 19	6 ± 21	8 ± 20	4 ± 21	7 ± 20	0.51
Proportion with increase ≥5 in score at 8 months, n (%)	64 (46.4%)	67 (54.0%)	179 (50.9%)	196 (54.3%)	431 (49.2%)	428 (51.7%)	379 (45.2%)	444 (49.7%)	0.88
OR (95% CI)	1.36 (0.84, 2.21)		1.15 (0.86, 1.54)		1.10 (0.91, 1.34)		1.19 (0.99, 1.44)		
Proportion with decrease ≥5 in score at 8 months, n (%)	38 (27.5%)	22 (17.7%)	88 (25.0%)	66 (18.3%)	226 (25.8%)	179 (21.6%)	227 (27.1%)	205 (22.9%)	0.23
OR (95% CI)	0.57 (0.31, 1.03)		0.67 (0.47, 0.96)		0.79 (0.63, 0.99)		0.80 (0.64, 1.00)		

All-cause death									
n (%)	15 (9%)	14 (8%)	68 (13%)	68 (14%)	182 (15%)	156 (14%)	261 (21%)	259 (20%)	0.97
Rate (per 100 pt-yrs)	4.0	3.9	6.1	6.1	6.8	6.1	9.5	8.8	
ARR (per 100 pt-yrs)	0.0		0.0		0.6		0.7		
HR (95% CI)	1.00 (0.48, 2.06), 0.99		1.00 (0.71, 1.40), 1.00		0.91 (0.73, 1.13), 0.39		0.93 (0.78, 1.10), 0.39		

ARR indicates absolute rate reduction; CV, cardiovascular; HF, heart failure; HR, hazard ratio; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; OR, Odd ratio; pt-yrs, patient-years; and RR, rate ratio.

*$P_{\text{interaction}}$ values are reported for interaction between treatment effect and baseline age categories.

Table 3. Occurrence of Adverse Events According to Age Categories

Adverse Event	Age < 55 (n=338)		Age 55-64 (n=1007)		Age 65-74 (n=2326)		Age ≥ 75 (n=2592)		$P_{interaction}$*
	Placebo (n=171)	Dapagliflozin (n=167)	Placebo (n=506)	Dapagliflozin (n=501)	Placebo (n=1190)	Dapagliflozin (n=1136)	Placebo (n=1265)	Dapagliflozin (n=1327)	
Any serious AE (including death), n (%)	62 (36.3%)	69 (41.3%)	225 (44.6%)	217 (43.3%)	536 (45.1%)	482 (42.5%)	600 (47.5%)	593 (44.8%)	0.58
Any AE leading to treatment discontinuation, n (%)	2 (1.2 %)	5 (3.0 %)	24 (4.8 %)	29 (5.8 %)	65 (5.5 %)	52 (4.6 %)	90 (7.1 %)	96 (7.3 %)	0.43
Any AE leading to treatment interruption, n (%)	20 (11.7%)	24 (14.4%)	75 (14.9%)	58 (11.6%)	177 (14.9%)	158 (13.9%)	222 (17.6%)	196 (14.8%)	0.46
Treatment discontinuation for any reason, n (%)	18 (10.5%)	19 (11.4%)	61 (12.1%)	62 (12.4%)	142 (11.9%)	145 (12.8%)	221 (17.5%)	218 (16.5%)	0.81
Any amputation, n (%)	2 (1.2 %)	2 (1.2 %)	4 (0.8 %)	3 (0.6 %)	16 (1.3 %)	13 (1.1 %)	3 (0.2 %)	1 (0.1 %)	0.87
Any potential risk factor AE for amputation affecting lower limbs, n (%)	12 (7.0 %)	14 (8.4 %)	28 (5.6 %)	22 (4.4 %)	73 (6.1 %)	84 (7.4 %)	86 (6.8 %)	68 (5.1 %)	0.15
Any definite or probable diabetic ketoacidosis, n (%)	0 (0.0 %)	1 (0.6 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	1 (0.1 %)	0 (0.0 %)	0 (0.0 %)	†
Any major hypoglycemic event, n (%)	0 (0.0 %)	0 (0.0 %)	2 (0.4 %)	2 (0.4 %)	1 (0.1 %)	1 (0.1 %)	4 (0.3 %)	3 (0.2 %)	†
Any serious AE or DAE suggestive of volume depletion, n (%)	0 (0.0 %)	4 (2.4 %)	4 (0.8 %)	6 (1.2 %)	8 (0.7 %)	13 (1.1 %)	20 (1.6 %)	19 (1.4 %)	0.47
Any renal serious AE or DAE, n (%)	4 (2.3 %)	5 (3.0 %)	13 (2.6 %)	14 (2.8 %)	29 (2.4 %)	18 (1.6 %)	33 (2.6 %)	36 (2.7 %)	0.56

AE indicates adverse event; DAE, adverse events leading to treatment discontinuation; MI, myocardial infarction.

*$P_{interaction}$ values are reported for interaction between treatment effect and baseline age categories.

†$P_{interaction}$-value not reported due to low event numbers.

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Figure Legends

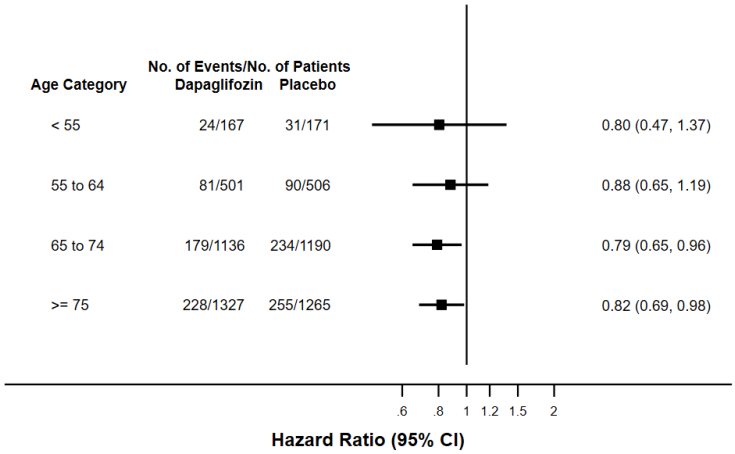
Figure 1. Effect of Dapagliflozin by Age Categories.

Treatment effect of dapagliflozin, compared with placebo, on the primary composite outcome (first occurrence CV death, HF hospitalization or urgent HF visit), cardiovascular death, heart failure events (HF hospitalization and urgent HF visit), and all-cause death according to age categories, based on Cox proportional hazards models. CV indicates cardiovascular; HF, heart failure; 95% CI, 95% confidence interval.

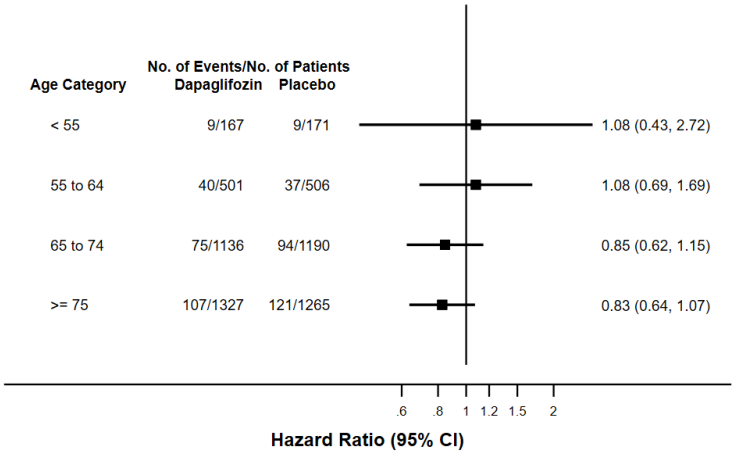
Figure 2. Effect of Dapagliflozin on the Occurrence of Key Outcomes According to Baseline Age.

Treatment effect of dapagliflozin, compared with placebo, on the primary composite outcome (first occurrence CV death, HF hospitalization or urgent HF visit), cardiovascular death, heart failure events, including its components HF hospitalization and urgent HF visit, and all-cause death across a range of baseline age. Estimated rate ratios and 95% confidence intervals were obtained from Poisson regression models with baseline age expressed via restricted cubic spline. CV indicates cardiovascular; and HF, heart failure.

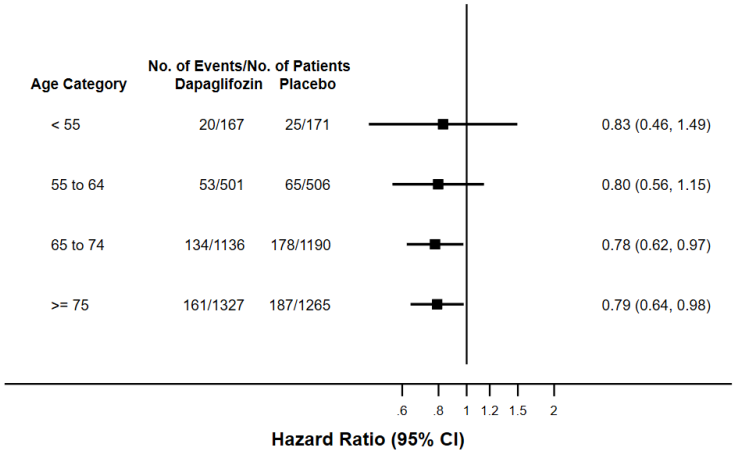
Primary composite



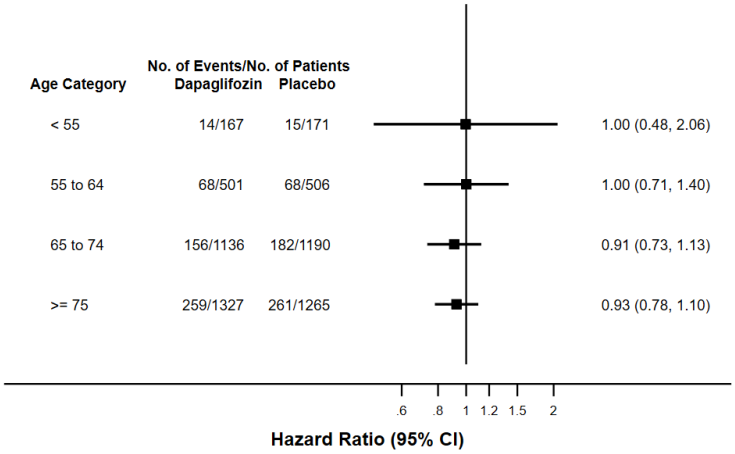
CV death

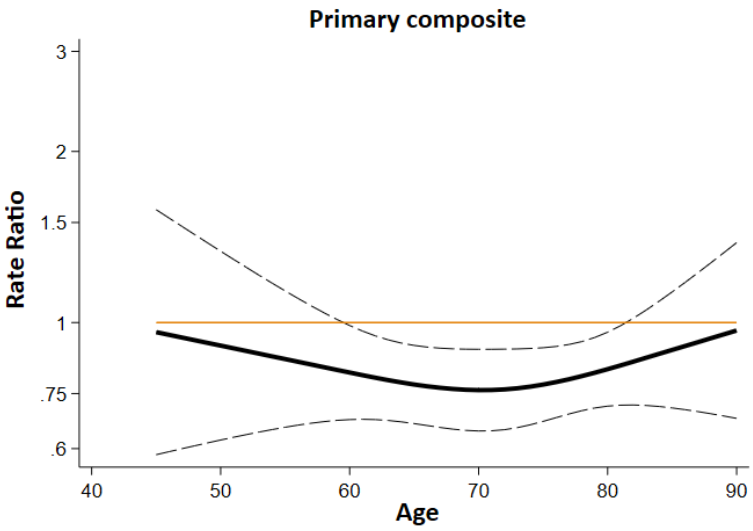


HF Event



All-cause death




Primary composite
Rate Ratio
3
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Age


CV death
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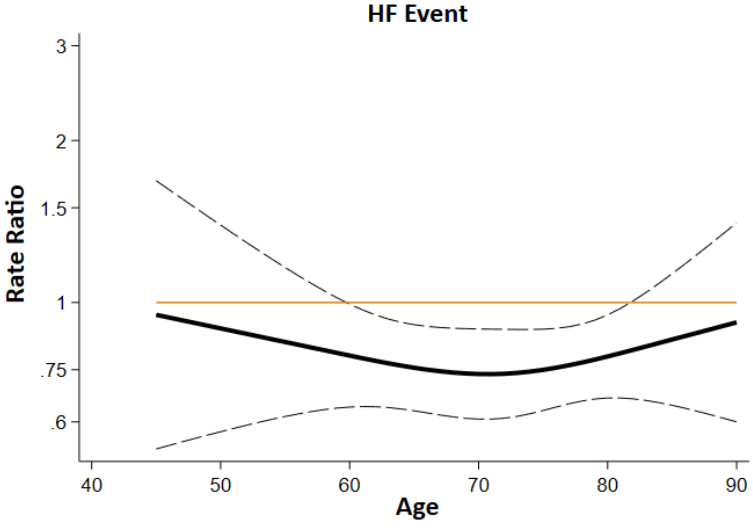
HF Event
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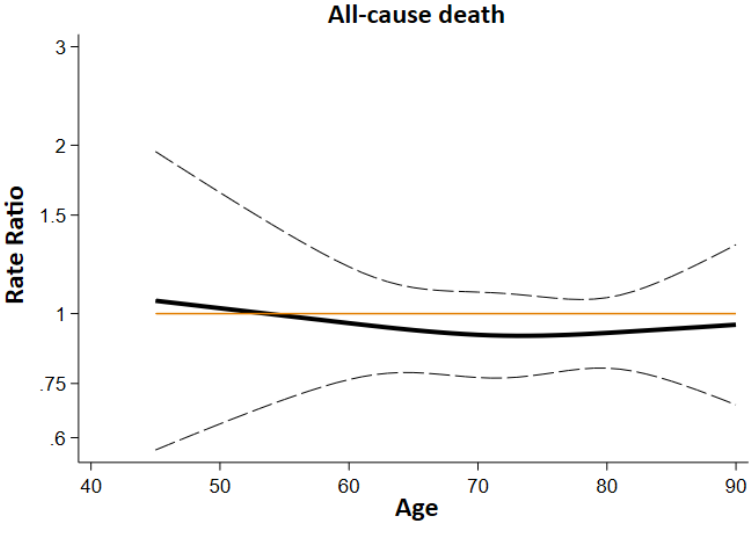
All-cause death
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