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

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DAPAHF

Disclosure

Dr Martinez reports personal fees from AstraZeneca during the conduct of the study.

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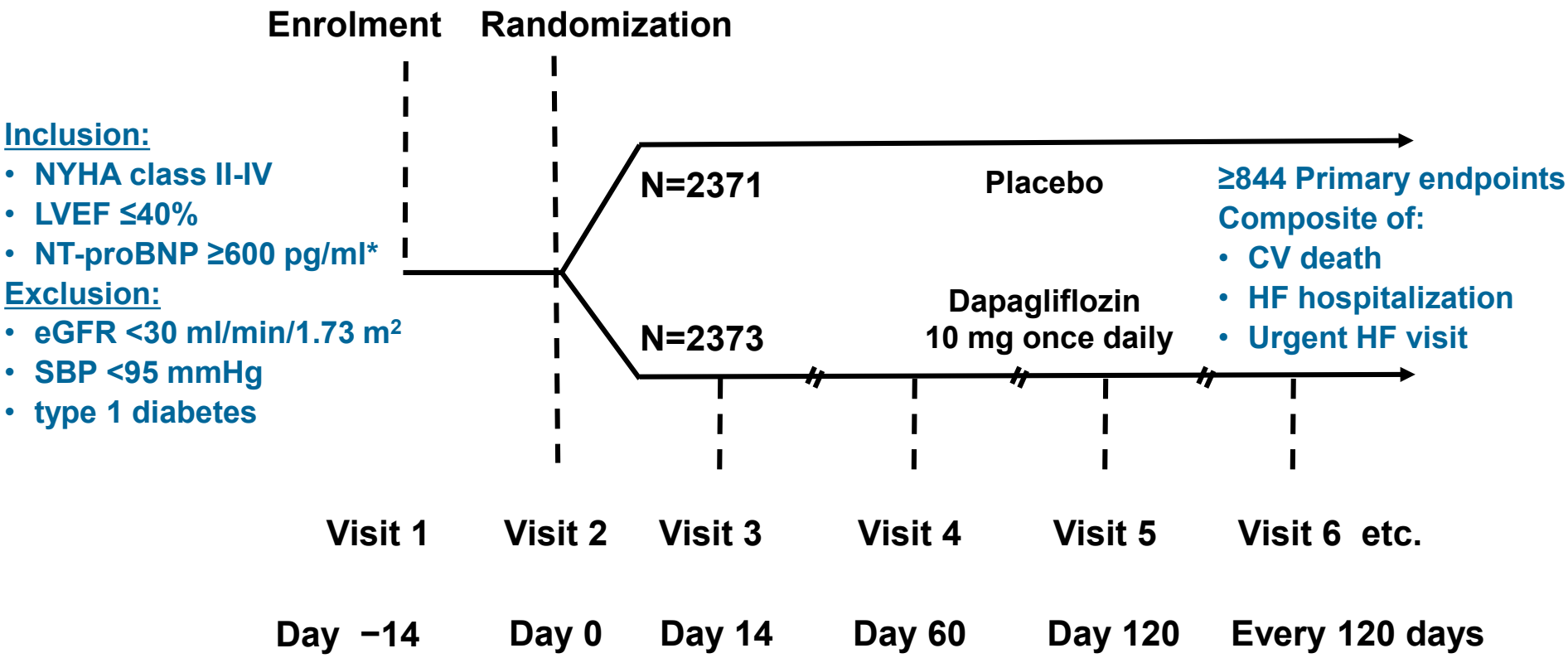
Background (1)

- In many countries, the number of elderly patients with heart failure (HF) is increasing.
- In other geographic regions (such as Latin America, Africa and Asia), people with HF are often younger than those in North America and Western Europe.
- Therefore, it is very important to understand the efficacy and safety of new treatments in all age groups.

Background (2)

- Tolerability is a particular concern in the elderly, not only because of advanced age and comorbidity, but also because of polypharmacy.
- The benefit of therapy may also be questioned in the elderly.
- We examined the efficacy and safety of dapagliflozin according to age in a *post hoc* analysis of DAPA-HF, a placebo-controlled trial in which dapagliflozin was added to other guideline-recommended therapies in patients with HF and reduced ejection fraction (HFrEF).

DAPA-HF Design



*≥400 pg/ml if HF hospitalization within ≤12 months; ≥900 pg/ml if atrial fibrillation/flutter

Statistical methods

- Age considered as both a categorical (<55, 55–64, 65–74, ≥75 years) and continuous variable.
- Time-to-event data analysed using Kaplan–Meier estimates and Cox proportional-hazards models.
- A semiparametric proportional-rates model (LWYY) used to calculate total (including recurrent) events.
- A fractional polynomial was constructed with age and entered into the model as an interaction term with treatment.
- The interaction between age & treatment for the pre-specified safety outcomes was tested in a logistic regression model.

Results

Key baseline characteristics according to age

Median age 67 (range 22-94) years, 36% of patients were aged 66–75 years and 21% were >75 years

Characteristic	<55 years (n=636)	55–64 years (n=1242)	65–74 years (n=1717)	≥75 years (n=1149)	*P for trend*
Age, years	47	60	69	79	-
Female, n (%)	19	21	24	28	*<0.001*
Atrial fibrillation n (%)	19	32	42	51	*<0.001*
Prior MI, n (%)	31	43	49	46	*<0.001*
Hypertension, n (%)	54	70	79	83	*<0.001*
Type 2 diabetes, n (%)	34	45	44	39	*0.50*
eGFR, mL/min/1.73 m^2	83	72	62	56	*<0.001*
eGFR <60 mL/min/1.73 m^2, n (%)	14	27	46	62	*<0.001*
SBP, mmHg	118	121	123	123	*<0.001*

Data are mean or n (%); eGFR, estimated glomerular filtration rate; MI, myocardial infarction; SBP, systolic blood pressure.

Heart failure characteristics according to age

Variable	<55 years (n=636)	55–64 years (n=1242)	65–74 years (n=1717)	≥75 years (n=1149)	*P for trend*
Ischemic etiology, n (%)	41	53	61	61	*<0.001*
NYHA class, n (%)					*0.018*
II	70	69	67	65	
III	29	30	32	34	
IV	1.6	1.1	0.6	0.7	
KCCQ-TSS (score out of 100)	76	75	79	79	*<0.001*
Prior HF hospitalization, n (%)	50	48	48	45	*0.042*
Ejection fraction, %	29	31	31	32	*<0.001*
NTproBNP, pg/mL	1107	1332	1453	1737	*<0.001*

Data are mean KCCQ and NT-proBNP median) or n (%); HF, heart failure; NTproBNP, N-terminal pro B-type natriuretic peptide; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire –Total Symptom Score; NYHA, New York Heart Association

Baseline treatment according to age

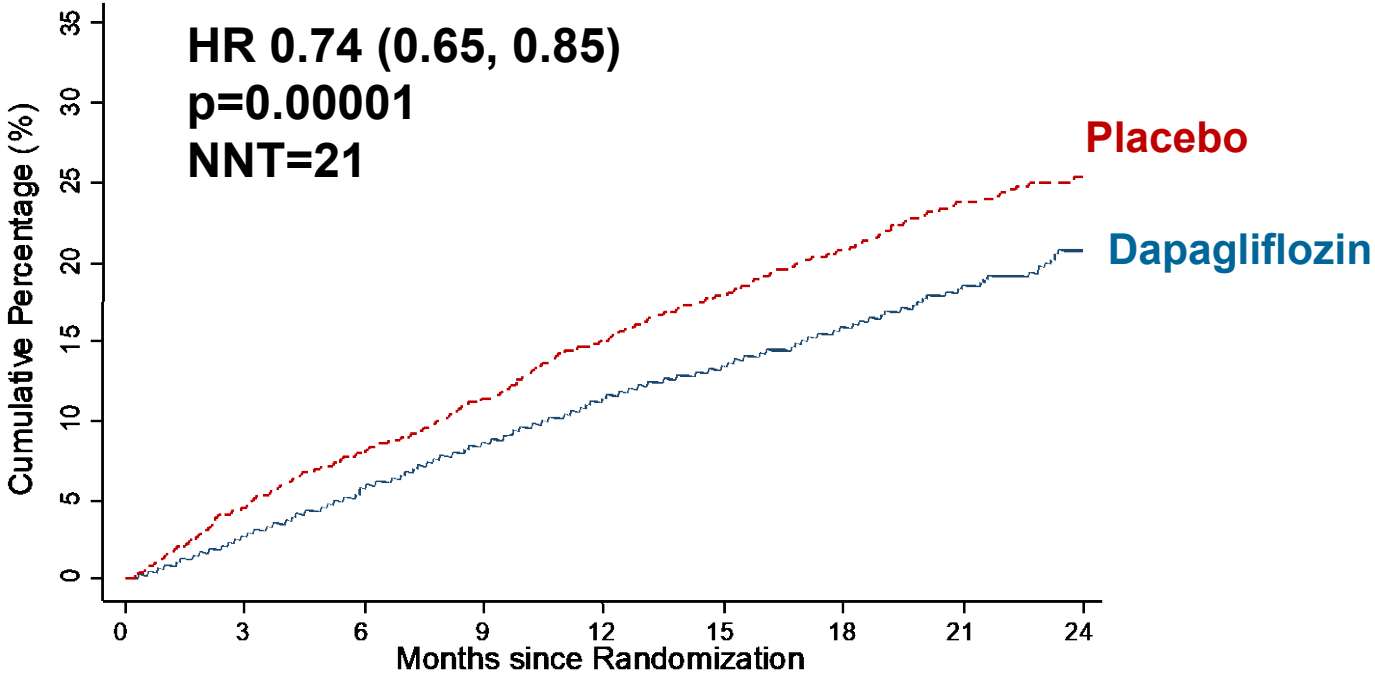
Treatment	<55 years (n=636)	55–64 years (n=1242)	65–74 years (n=1717)	≥75 years (n=1149)	*P for trend*
ACE inhibitor	62	58	56	51	*<0.001*
ARB	23	26	28	32	*<0.001*
ARNI	11	11	11	10	*0.37*
Diuretic	96	95	93	91	*<0.001*
Digitalis	23	20	18	16	*<0.001*
Beta-blocker	98	98	96	94	*<0.001*
MRA	83	76	69	62	*<0.001*
ICD or CRT-D	21	27	30	23	*0.51*
CRT-P/CRT-D	4	7	8	9	*<0.001*

Data are n (%); ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CRT, Cardiac Resynchronization Therapy, D, Defibrillator; ICD, Implantable Cardioverter-Defibrillator; MRA, mineralocorticoid receptor antagonist; P, Pacemaker.

Efficacy outcomes

Overall: Primary composite outcome

CV Death/HF hospitalization/Urgent HF visit



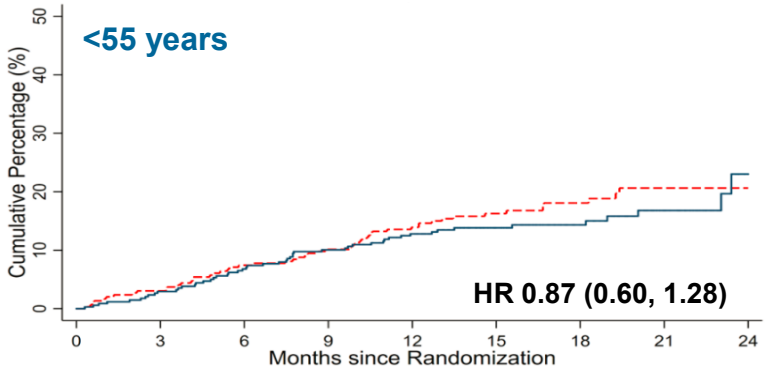
Number at Risk

Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

McMurray JJV et al N Engl J Med. 2019 Sep 19. doi:10.1056/NEJMoa1911303

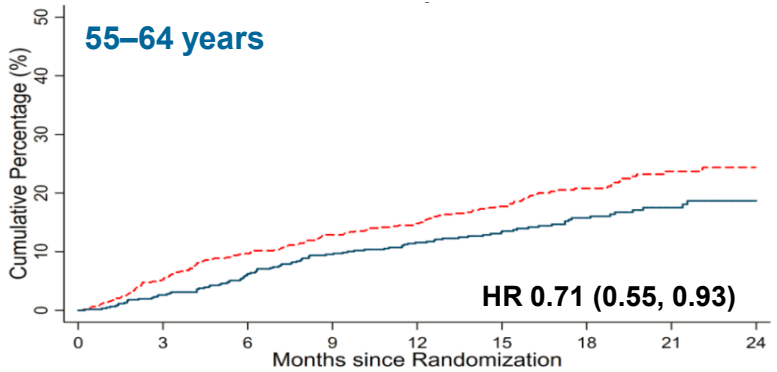
Primary outcome according to age

Placebo — Dapagliflozin — P interaction = 0.76



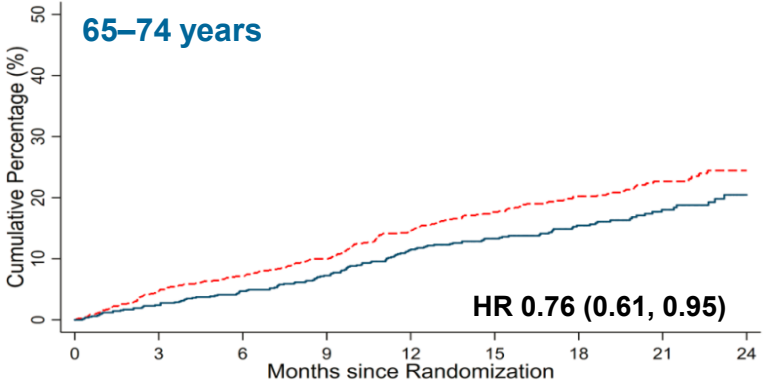
Number at Risk

Placebo	296	287	274	266	243	168	115	64	21
Dapagliflozin	340	330	314	302	281	190	129	60	17



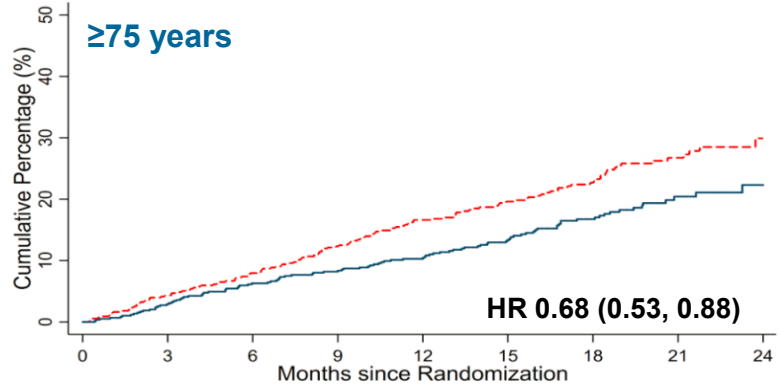
Number at Risk

Placebo	630	597	566	543	519	381	281	149	49
Dapagliflozin	612	593	570	546	516	402	295	164	56



Number at Risk

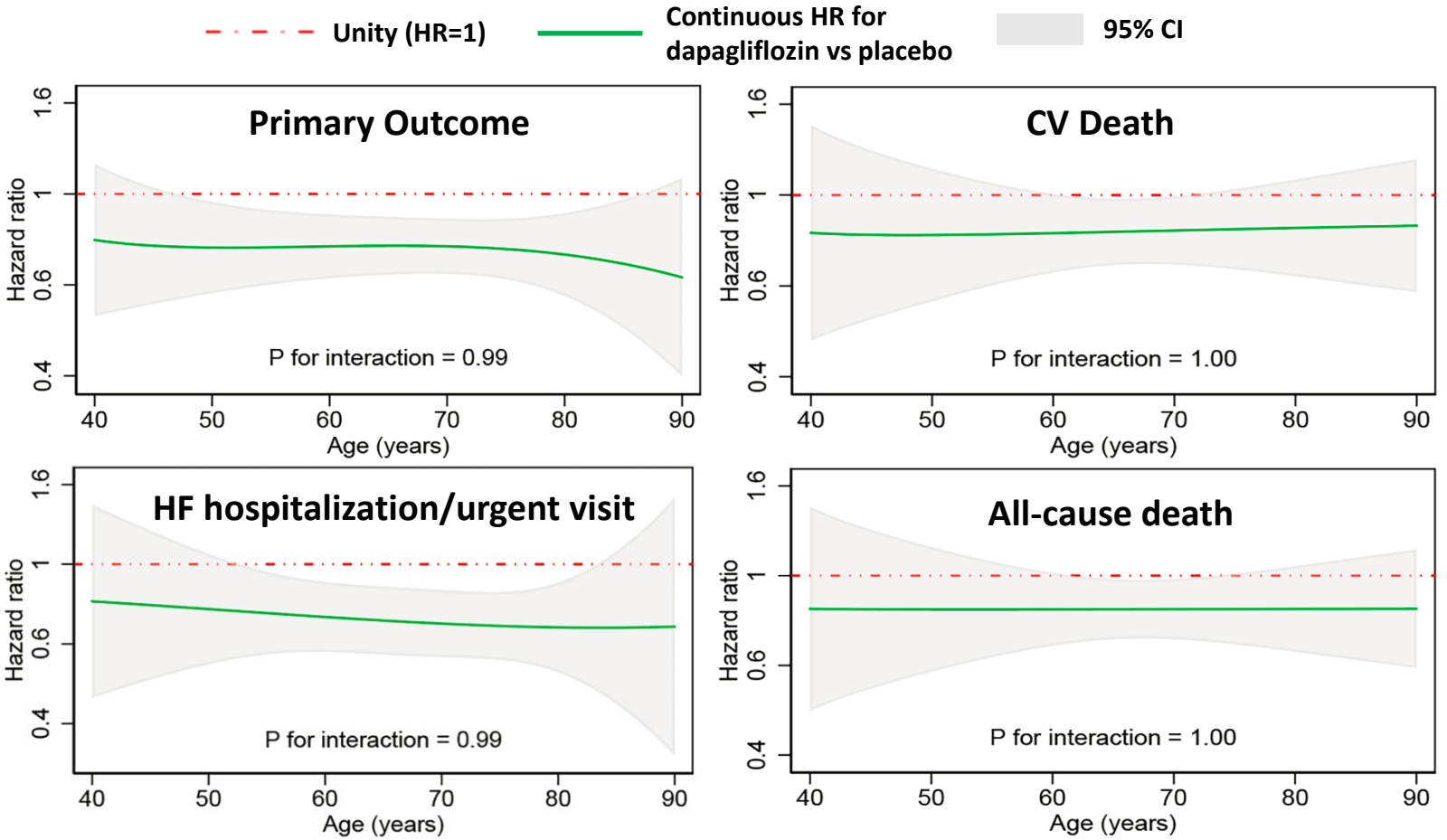
Placebo	887	844	816	787	723	580	435	241	95
Dapagliflozin	830	810	790	764	711	567	428	247	95



Number at Risk

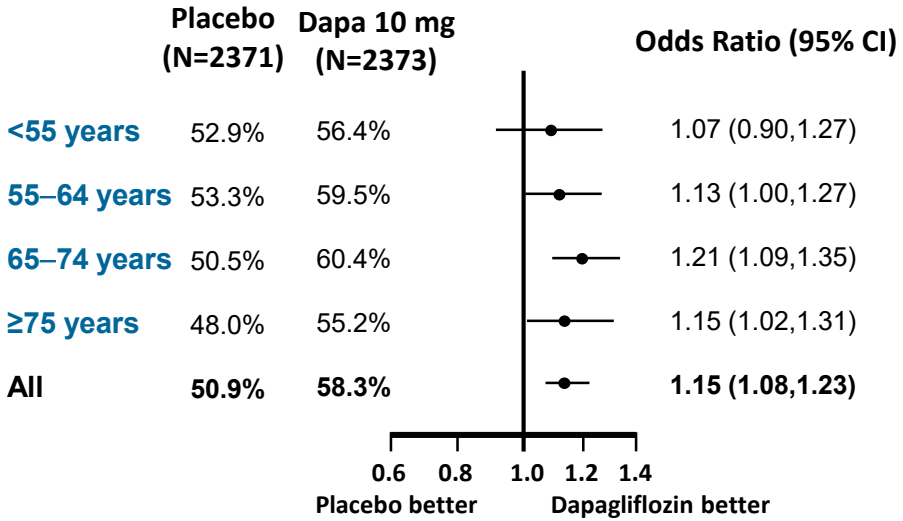
Placebo	558	530	507	479	432	349	265	139	45
Dapagliflozin	591	572	547	535	494	401	294	141	42

Outcomes according to age (continuous variable)

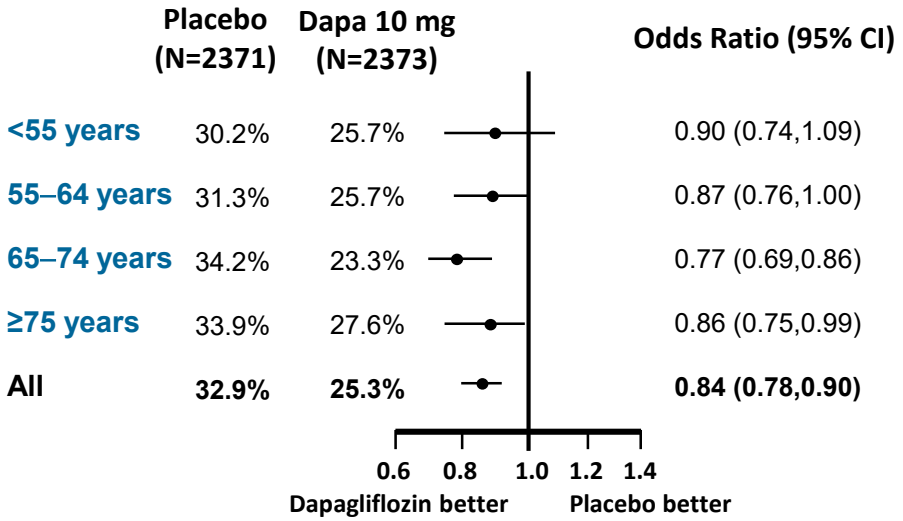


Clinically meaningful change (≥5 points) in KCCQ-TSS from baseline to 8 months

Improvement



Deterioration



CI = Confidence Interval, Dapa = Dapagliflozin

Tolerability and safety

Adverse events related to volume depletion according to age

	<55 years (n=634)		55–64 years (n=1240)		65–74 years (n=1716)		≥75 years (n=1146)		*P value**
% of patients	**Placebo (n=295)**	Dapa (n=339)	**Placebo (n=630)**	Dapa (n=610)	**Placebo (n=886)**	Dapa (n=830)	**Placebo (n=557)**	Dapa (n=589)	
Volume depletion	**5**	7	**6**	6	**6**	7	**10**	11	*0.86*
Volume depletion (serious)	**1**	0.3	**2**	0.8	**1**	2	**3**	1	*0.15*

*P-value is for interaction between age categories and treatment effect on the occurrence of adverse events; Data are n (%); Includes patients receiving at least one dose of study drug

Renal safety according to age

	<55 years (n=634)		55–64 years (n=1240)		65–74 years (n=1716)		≥75 years (n=1146)		*P value**
% of patients	**Placebo (n=295)**	Dapa (n=339)	**Placebo (n=630)**	Dapa (n=610)	**Placebo (n=886)**	Dapa (n=830)	**Placebo (n=557)**	Dapa (n=589)	
Renal AE	**4**	4	**5**	8	**8**	6	**11**	7	*0.031*
Serious renal AE	**1**	0.9	**1**	2	**3**	2	**5**	0.5	*0.002*
Doubling of serum creatinine	**2**	2	**3**	2	**3**	2	**5**	0.7	*0.011*

*P-value is for interaction between age categories and treatment effect on the occurrence of adverse events; Data are n (%); Includes patients receiving at least one dose of study drug

Treatment reduction/discontinuation and serious AEs according to age

	<55 years (n=634)		55–64 years (n=1240)		65–74 years (n=1716)		≥75 years (n=1146)		*P value**
% of patients	**Placebo (n=295)**	Dapa (n=339)	**Placebo (n=630)**	Dapa (n=610)	**Placebo (n=886)**	Dapa (n=830)	**Placebo (n=557)**	Dapa (n=589)	
AE → permanent treatment discontin.	**3**	3	**4**	4	**6**	5	**6**	6	*0.93*
Any serious AE (including death)	**34**	33	**40**	35	**41**	38	**49**	43	*0.61*
Any discontin. of study treatment	**8**	11	**9**	8	**12**	11	**14**	12	*0.38*

*P-value is for interaction between age categories and treatment effect on the occurrence of adverse events; Data are n (%); Includes patients receiving at least one dose of study drug; Discontin., discontinuation

Summary and conclusions

- Dapagliflozin reduced the risk of worsening HF events and CV death, and improved symptoms, in patients with HFrEF, when added to standard therapy. *These benefits were consistent across the range of ages studied.*
- The relative and absolute risk reductions in death and hospitalization were substantial and clinically important. *The absolute benefits in older patients were large because they were at higher risk than younger patients.*
- Dapagliflozin was well tolerated, and the rate of treatment discontinuation was low, *in all age groups.*
- Dapagliflozin offers a new approach to the treatment of HFrEF, *irrespective of age*.

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