Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

John McMurray
BHF Cardiovascular Research Centre,
University of Glasgow & Queen Elizabeth
University Hospital, Glasgow

University of Glasgow

DAPAHF

AstraZeneca

Declaration of interest

- Others (My employer, Glasgow University, has been paid by AstraZeneca, for my role as Principal Investigator in the DAPA-HF trial with dapagliflozin)

Trial leadership and data analysis

Executive Committee

John J.V. McMurray MD (Chairman), David L. DeMets, Silvio E. Inzucchi, Lars Køber, Mikhail N. Kosiborod, Anna Maria Langkilde, Felipe A. Martinez, Piotr Ponikowski, Marc S. Sabatine, Mikaela Sjöstrand, Scott D. Solomon

AstraZeneca leadership

Anna Maria Langkilde, Olof Bengtsson, Mikaela Sjöstrand, Kinga Kazanowska, Mikael Forsby, Ywonne Fox

Data analysis

Olof Bengtsson, Folke Folkvaljon, Samvel Gasparyan (AstraZeneca); Pardeep Jhund, Kieran Docherty, Alice Jackson, Jim Lewsey (University of Glasgow)

Background

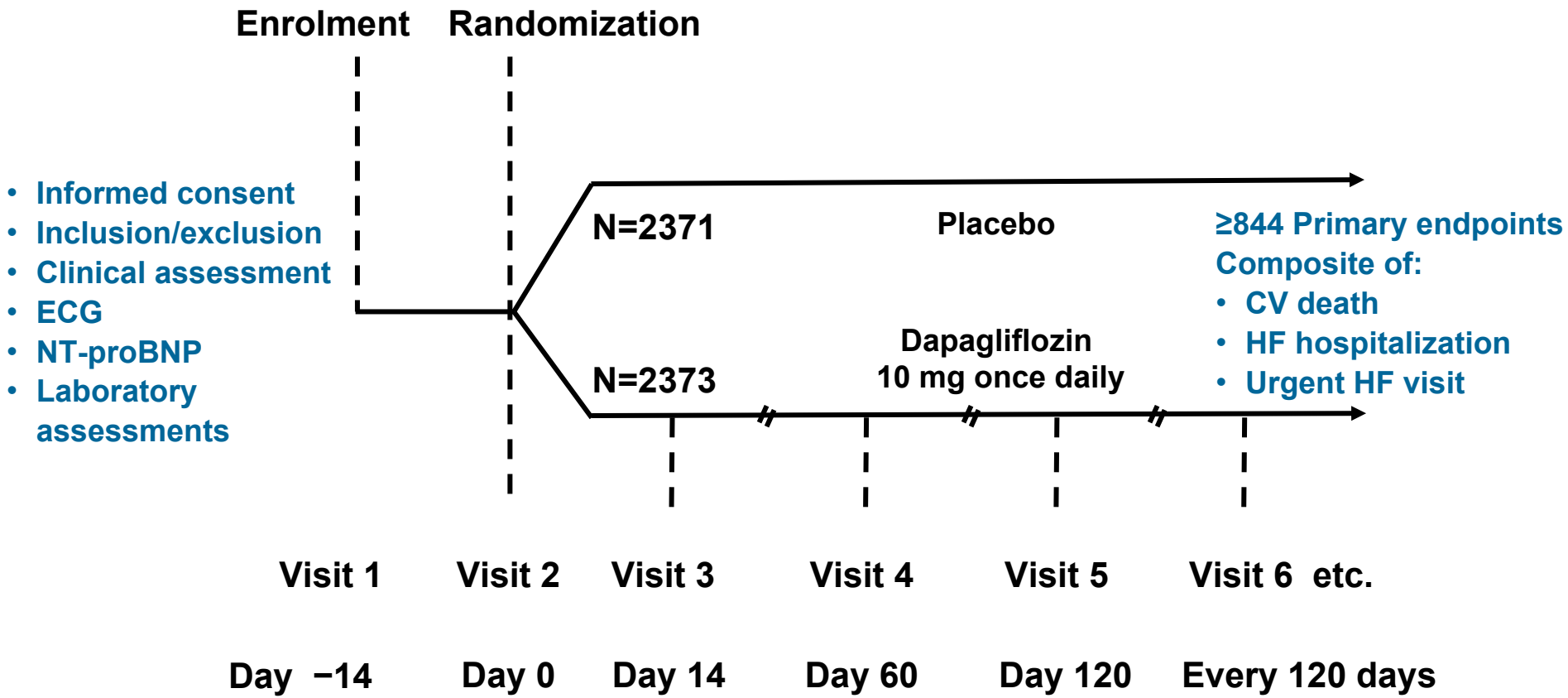
- Sodium-glucose co-transporter 2 (SGLT2) inhibitors ***prevent*** the development of heart failure in patients with type 2 diabetes (T2D). Can they be used to ***treat*** patients with established heart failure?
- The benefits of SGLT2 inhibitors may be glucose-independent. Can SGLT2 inhibitors be used to treat patients ***without*** T2D?
- We tested the SGLT2 inhibitor dapagliflozin,10 mg once daily, added to standard therapy, in patients with heart failure and reduced ejection fraction (HFrEF) both ***with and without*** T2D

Trial Design

- **Key inclusion criteria:** Symptomatic HF; EF ≤40%; NT-proBNP ≥600 pg/ml (if hospitalized for HF within last 12 months ≥400 pg/mL; if atrial fibrillation/flutter ≥900 pg/mL)
- **Key exclusion criteria:** eGFR <30 ml/min/1.73 m^2; symptomatic hypotension or SBP <95 mmHg; type 1 diabetes mellitus
- **Primary endpoint:** Worsening HF event or cardiovascular death (worsening HF event = unplanned HF hospitalization or an urgent heart failure visit requiring intravenous therapy)

For full details see McMurray JJV et al Eur J Heart Fail. 2019;21:665-675

DAPA-HF Design



DAPA-HF - A global trial

4,744 patients 20 countries

North America

Canada	223
USA	454

Western Europe

Denmark	99
Germany	186
Netherlands	135
Sweden	68
UK	62

Central/Eastern Europe

Bulgaria	266
Czech Rep.	210
Hungary	250
Poland	290
Slovakia	166
Russia	422

Latin America

Argentina	297
Brazil	520

Asia-Pacific

China	237
India	237
Japan	343
Taiwan	141
Vietnam	138

Key baseline characteristics

Characteristic	Dapagliflozin (n=2373)	Placebo (n=2371)
Mean age (yr)	66	67
Male (%)	76	77
NYHA class II/III/IV (%)	68/31/1	67/32/1
Mean LVEF (%)	31	31
Median NT pro BNP (pg/ml)	1428	1446
Mean systolic BP (mmHg)	122	122
Ischaemic aetiology (%)	55	57
Mean eGFR (ml/min/1.73m^2)	66	66
Prior diagnosis T2D (%)	42	42
Any baseline T2D (%)*	45	45

*includes 82 dapagliflozin and 74 placebo patients with previously undiagnosed diabetes i.e. two HbA1c ≥6.5% (≥48 mmol/mol)

Baseline treatment

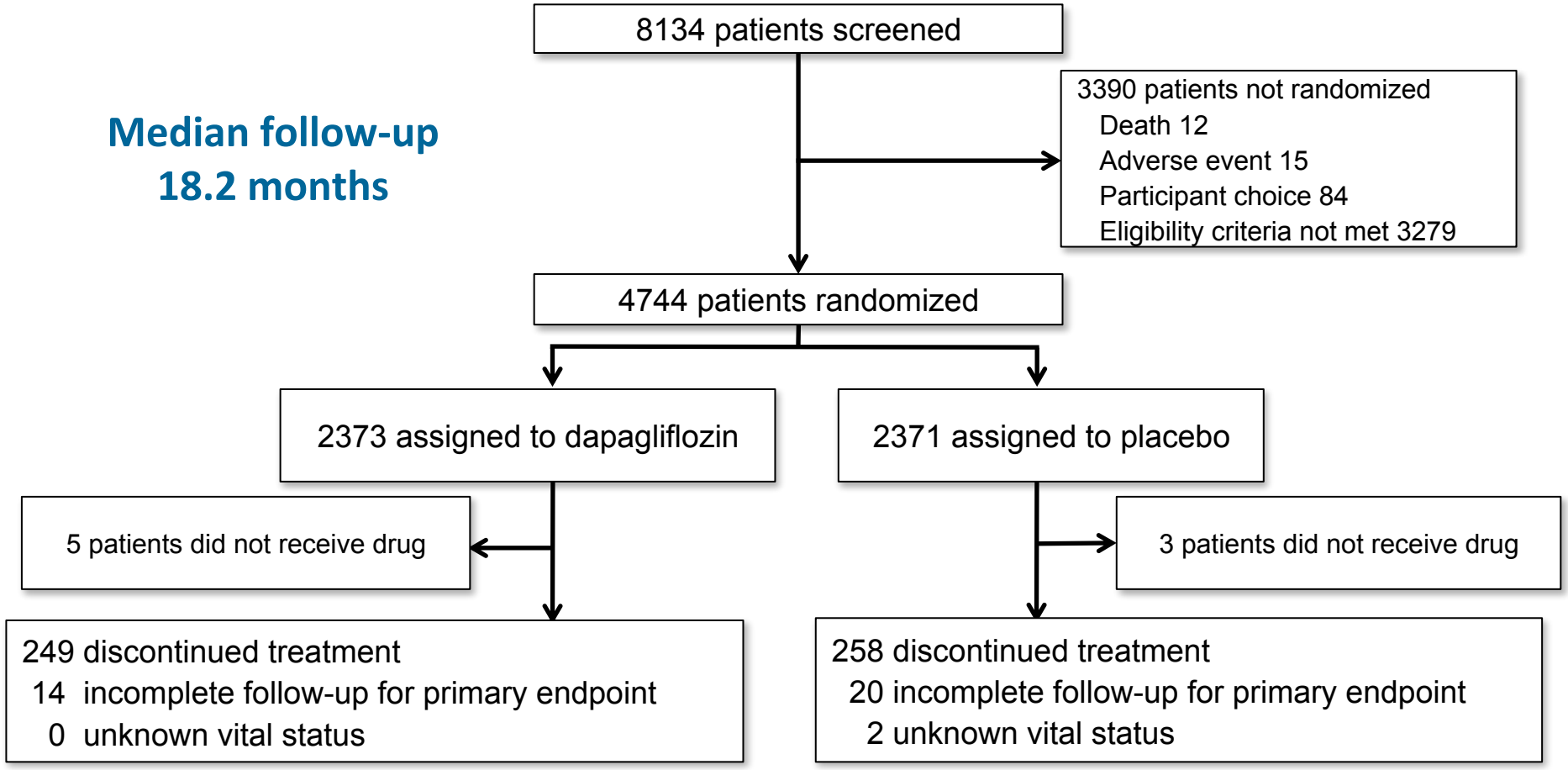
Treatment (%)	Dapagliflozin (n=2373)	Placebo (n=2371)
Diuretic	93	94
ACE-inhibitor/ARB/ARNI[+]	94	93
ACE inhibitor	56	56
ARB	28	27
Sacubitril/valsartan	11	11
Beta-blocker	96	96
MRA	71	71
ICD*	26	26
CRT**	8	7

[+]ARNI = angiotensin receptor neprilysin inhibitor
*ICD or CRT-D **CRT-P or CRT-D

For full details see McMurray JJV et al
Eur J Heart Fail.2019 Jul 15. doi: 10.1002/ejhf.1548

Patient disposition

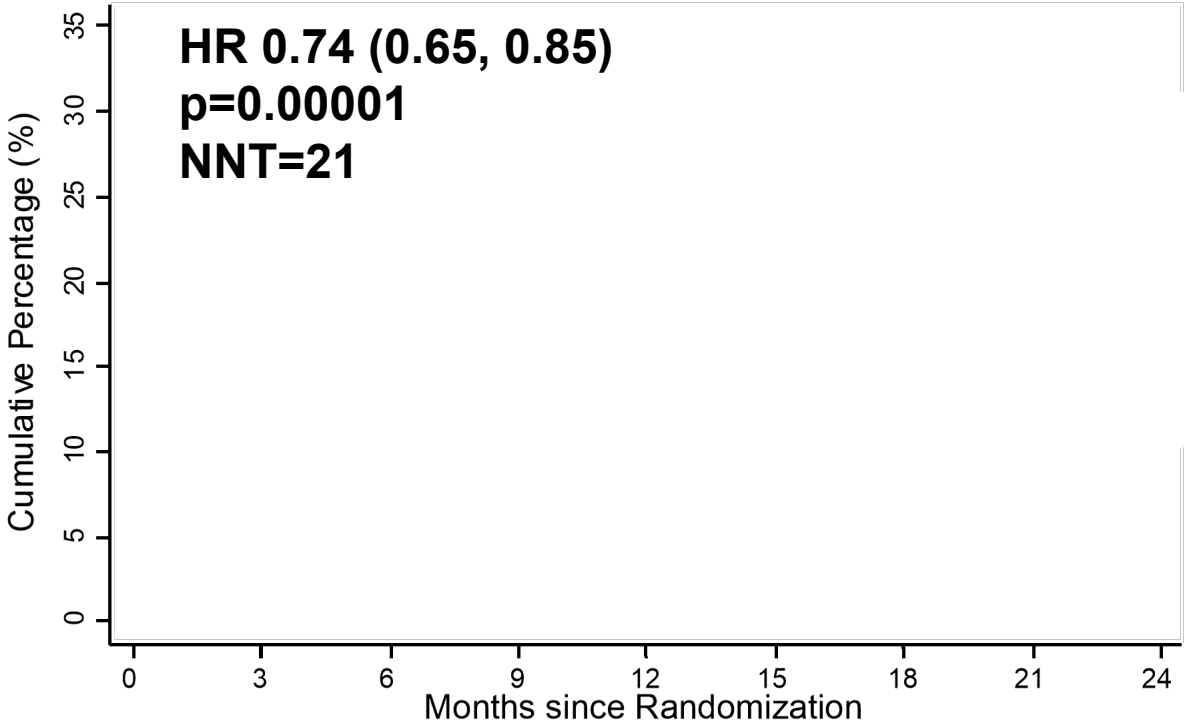
Median follow-up
18.2 months



Primary outcome

Primary composite outcome

CV Death/HF hospitalization/Urgent HF visit



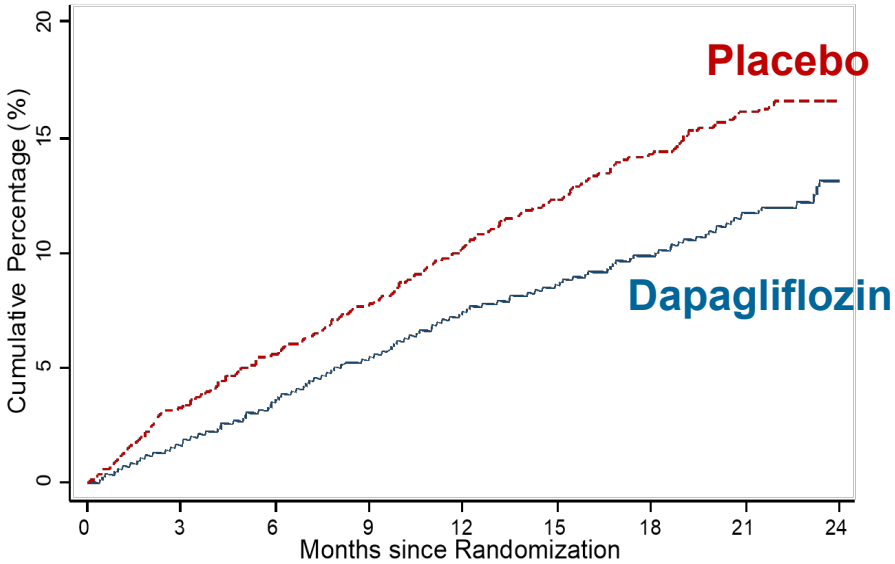
Number at Risk

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

Components of primary outcome

Worsening HF event

HR 0.70 (0.59, 0.83); p=0.00003

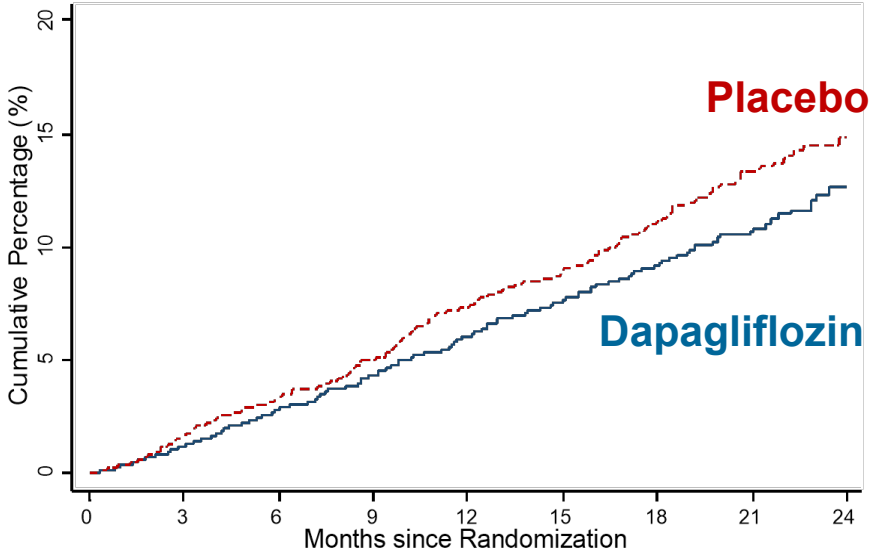


Number at Risk

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

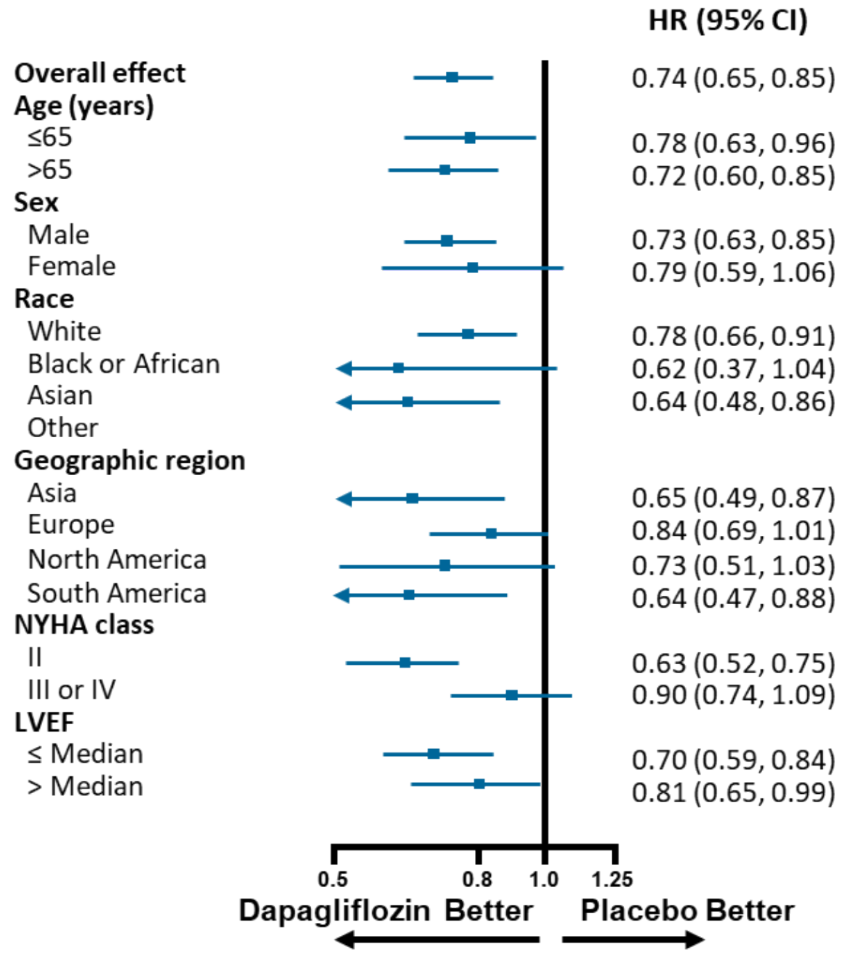
Cardiovascular death

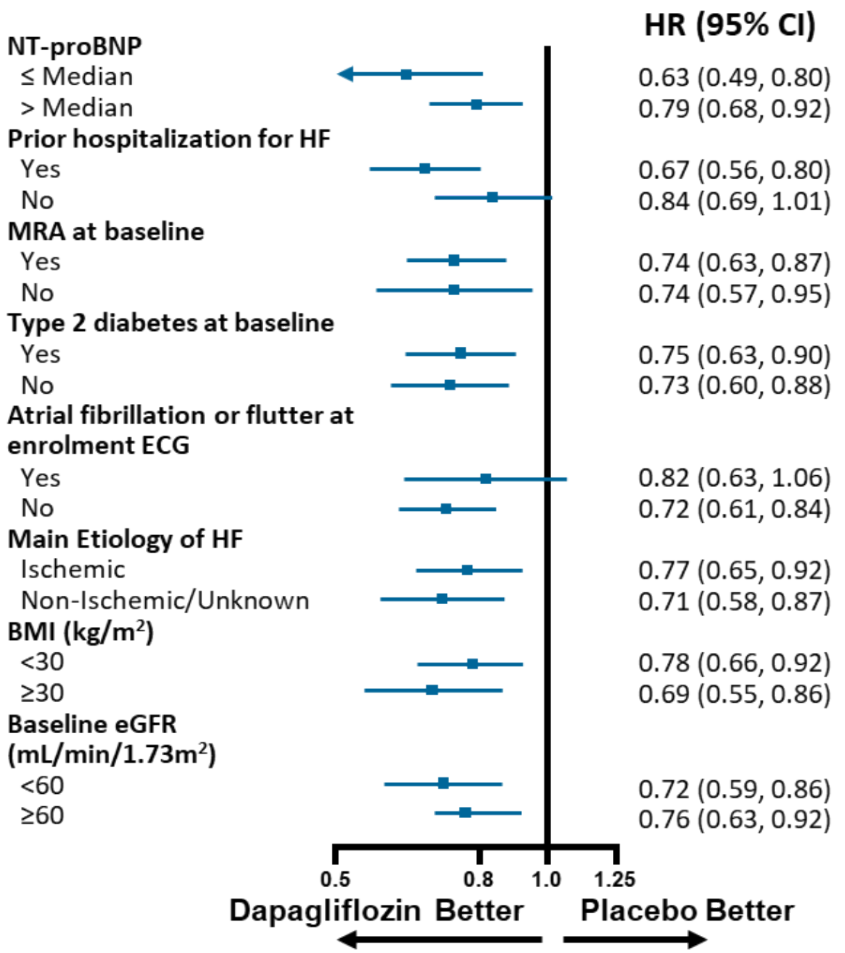
HR 0.82 (0.69, 0.98); p=0.029



	2373	2339	2293	2248	2127	1664	1242	671	232
	2371	2330	2279	2230	2091	1636	1219	664	234

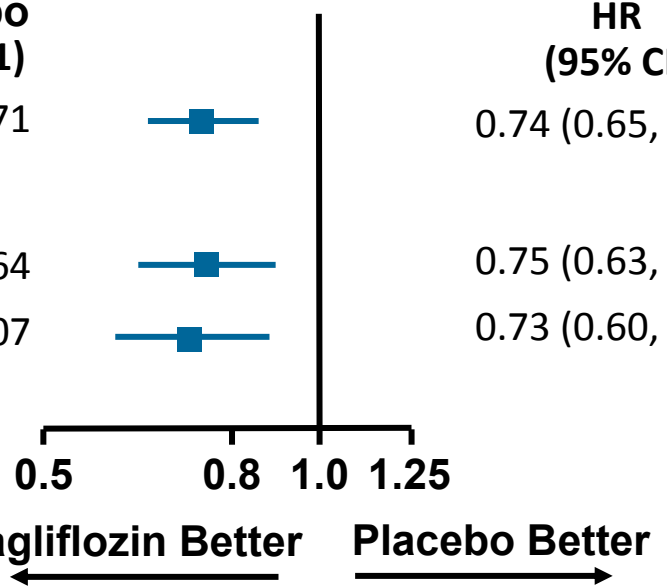
Primary Endpoint: Prespecified subgroups





No diabetes/diabetes subgroup: Primary endpoint

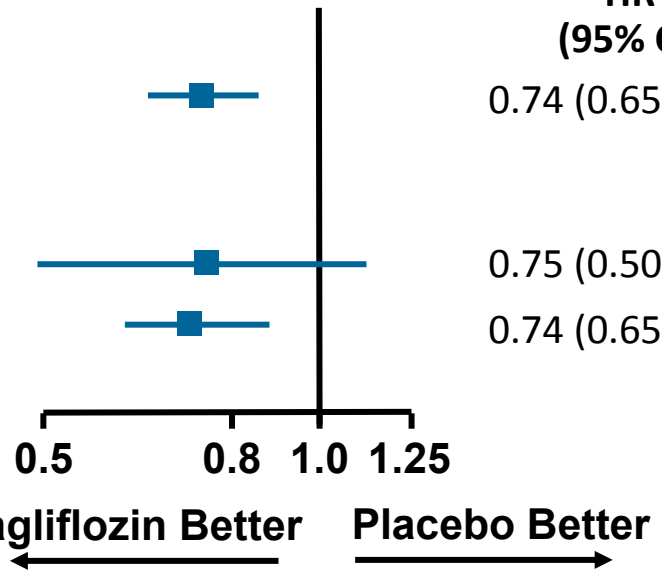
	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Type 2 diabetes at baseline*			
Yes	215/1075	271/1064	0.75 (0.63, 0.90)
No	171/1298	231/1307	0.73 (0.60, 0.88)



*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomization visits.

ARNI/no ARNI *post hoc* subgroup: Primary endpoint

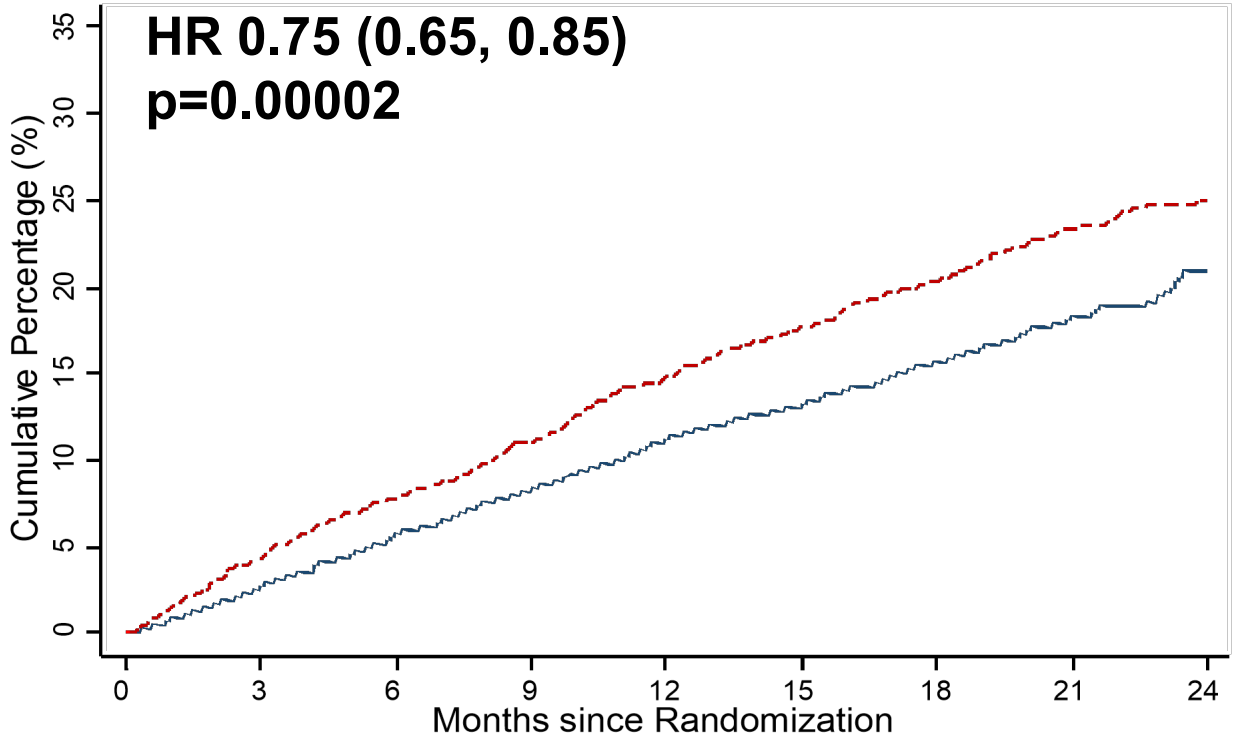
	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Angiotensin Receptor Neprilysin Inhibitor (ARNI)			
Yes	41/250	56/258	0.75 (0.50, 1.13)
No	345/2123	446/2113	0.74 (0.65, 0.86)



Secondary outcomes

In order of hierarchical testing

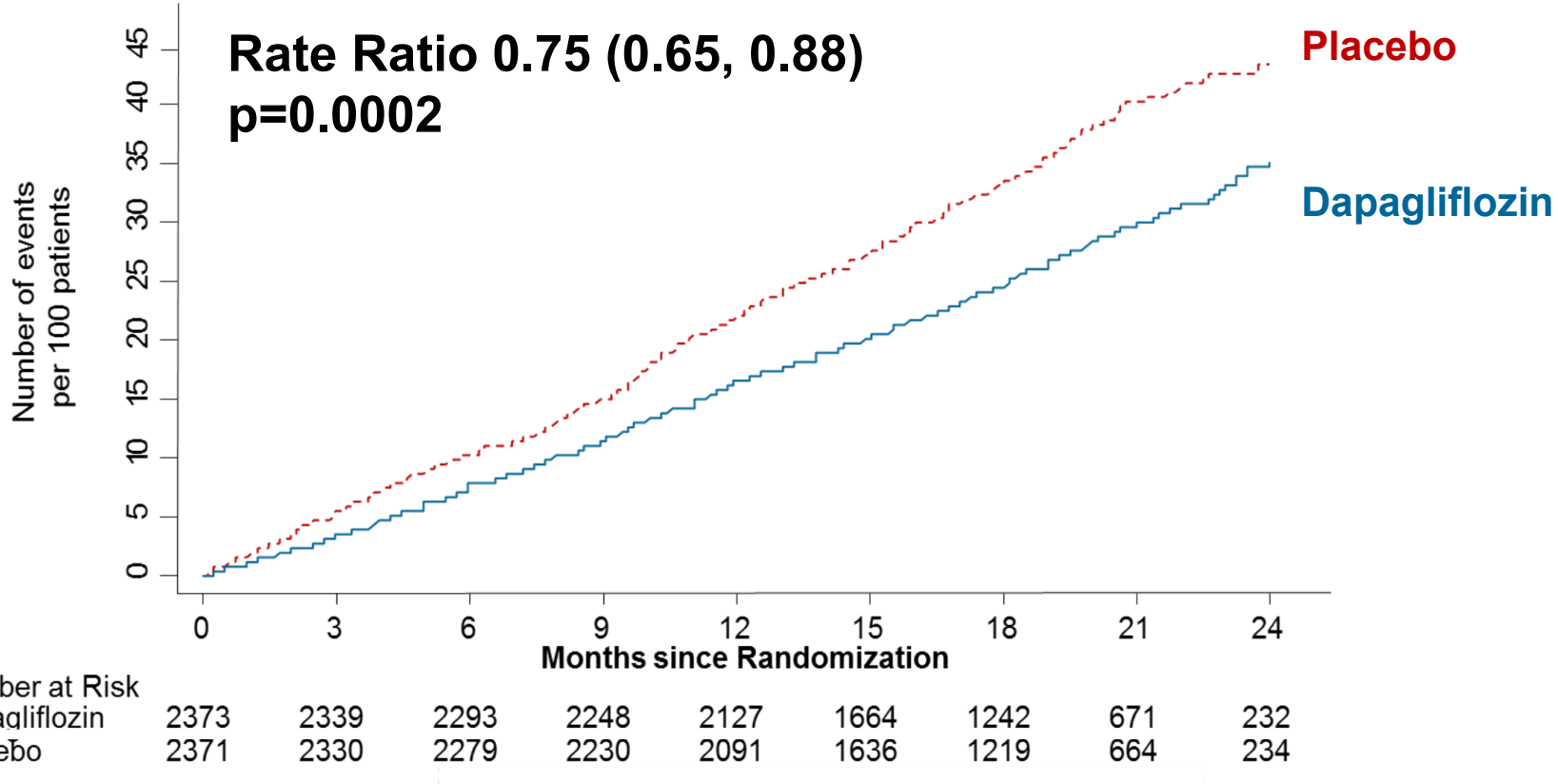
CV death or HF hospitalization



Number at Risk									
Dapagliflozin	2373	2306	2223	2153	2007	1563	1147	613	210
Placebo	2371	2264	2168	2082	1924	1483	1101	596	212

Total HF hospitalizations and CV death

Including first and repeat hospitalizations



Kansas City Cardiomyopathy Questionnaire (KCCQ)

Total Symptom Score (TSS): Change from baseline to 8 months

Treatment	Change
Dapagliflozin	**+6.1** ± 18.6
Placebo	**+3.3** ± 19.2

Difference

2.8 points (95% CI 1.6, 4.0)

p<0.001*

Increase in score indicates an improvement

*Calculated from win ratio, incorporating death. Win ratio = 1.18 (CI 1.11, 1.26). Win ratio >1 indicates superiority of dapagliflozin over placebo

Kansas City Cardiomyopathy Questionnaire (KCCQ)

Total Symptom Score: Proportion with ≥5 point change from baseline to 8 months*

Treatment	Dapagliflozin	Placebo	Odds ratio (95% CI)
≥5 point improvement	58%	51%	1.15 (1.08, 1.23) p<0.001
≥5 point deterioration	25%	33%	0.84 (0.78, 0.90) p<0.001

*Taking account of death

Worsening renal function endpoint

Composite of: Sustained* ≥50% reduction in eGFR, end-stage renal disease (ESRD) or death from renal causes

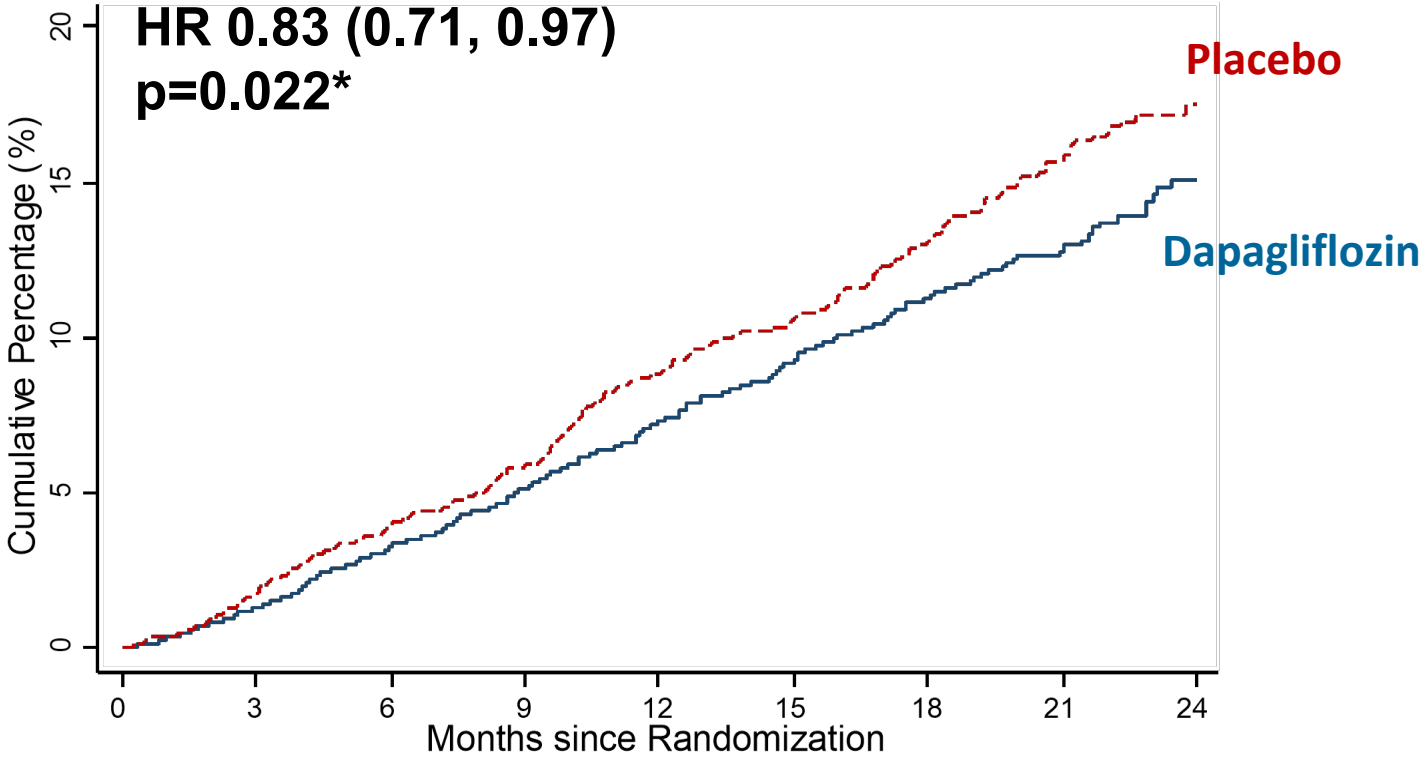
Treatment	No. (%)
Dapagliflozin	28 (1.2)
Placebo	39 (1.6)

Hazard ratio (95% CI)
0.71 (0.44, 1.16)
p=0.17

ESRD consisted of sustained eGFR below 15 ml/min/1.73m^2, sustained dialysis or kidney transplantation

*Sustained = 28 days or more

All-cause death



Number at Risk									
Dapagliflozin	2373	2342	2296	2251	2130	1666	1243	672	233
Placebo	2371	2330	2279	2231	2092	1638	1221	665	235

*Nominal p value

Safety/adverse events

Patients exposed to at least one dose of study drug	Dapagliflozin (n=2368)	Placebo (n=2368)	p-value
Adverse events (AE) of interest (%)			
Volume depletion[+]	7.5	6.8	0.40
Renal AE[‡]	6.5	7.2	0.36
Fracture	2.1	2.1	1.00
Amputation	0.5	0.5	1.00
Major hypoglycaemia	0.2	0.2	-
Diabetic ketoacidosis	0.1	0.0	-
AE leading to treatment discontinuation (%)	4.7	4.9	0.79
Any serious adverse event (incl. death) (%)	38	42	<0.01

[+] Volume depletion serious AEs in 29 dapagliflozin patients (1.2%) and 40 placebo patients (1.7%), p=0.23

[‡] Renal serious AEs in 38 dapagliflozin patients (1.6%) and 65 placebo patients (2.7%), p=0.009

Summary and conclusions

- Dapagliflozin reduced the risk of worsening heart failure events and cardiovascular death, and improved symptoms, in patients with HFrEF, when added to standard therapy
- The relative and absolute risk reductions in death and hospitalization were substantial, clinically important, and consistent across important subgroups, including patients ***without*** T2D
- Dapagliflozin was well tolerated and the rate of treatment discontinuation was low
- Dapagliflozin offers a new approach to the treatment of HFrEF

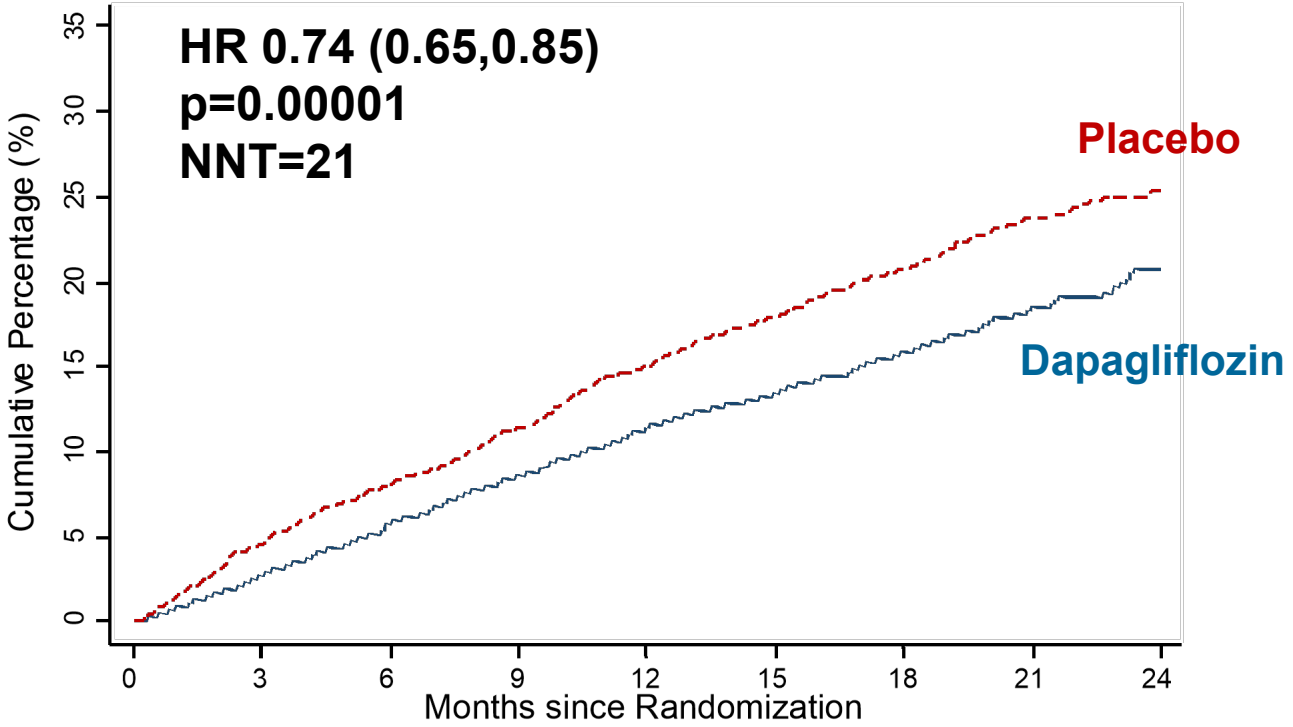
DAPA-HF

20 countries, 410 Sites, 8134 patients screened

Thank You

Primary composite outcome

CV Death/HF hospitalization/Urgent HF visit



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