The Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure Trial (DAPA-HF)

Results in Nondiabetic Patients

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On behalf of the DAPA-HF Committees and Investigators

University of Glasgow

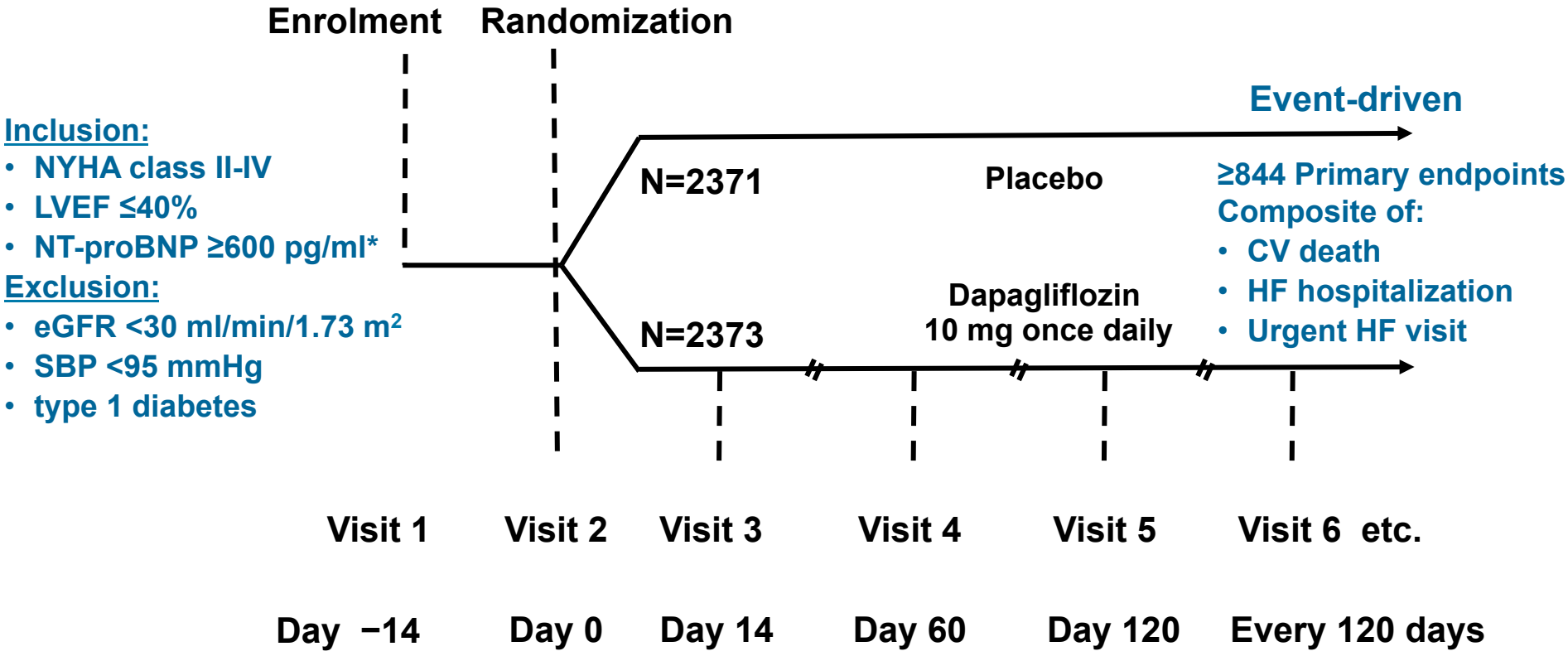
DAPAHF

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

DAPA-HF Design

4,744 patients 20 countries



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

Key baseline characteristics

Characteristic	Diabetes (n=2139)*	No diabetes (n=2605)
Mean age (yr)	67	66
Male (%)	78	76
NYHA class II/III/IV (%)	**64/35/1**	**71/29/1**
Mean LVEF (%)	31	31
Median NT-proBNP (pg/ml)	1484	1413
Mean systolic BP (mmHg)	123	121
Ischaemic aetiology (%)	**62**	**51**
Mean eGFR (ml/min/1.73m^2)	63	68
eGFR <60 ml/min/1.73m^2 (%)	**46**	**36**
Prior heart failure hospitalization (%)	49	46

*includes 156 patients with previously undiagnosed diabetes i.e. two HbA1c ≥6.5% (≥48 mmol/mol)

Baseline treatment

Treatment (%)	Diabetes (n=2139)	No diabetes (n=2605)
Diuretic	95	92
ACE-inhibitor/ARB/ARNI[+]	93	94
ACE inhibitor	55	57
ARB	29	27
Sacubitril/valsartan	11	11
Beta-blocker	97	96
MRA	72	71
ICD*	27	26
CRT**	7	8

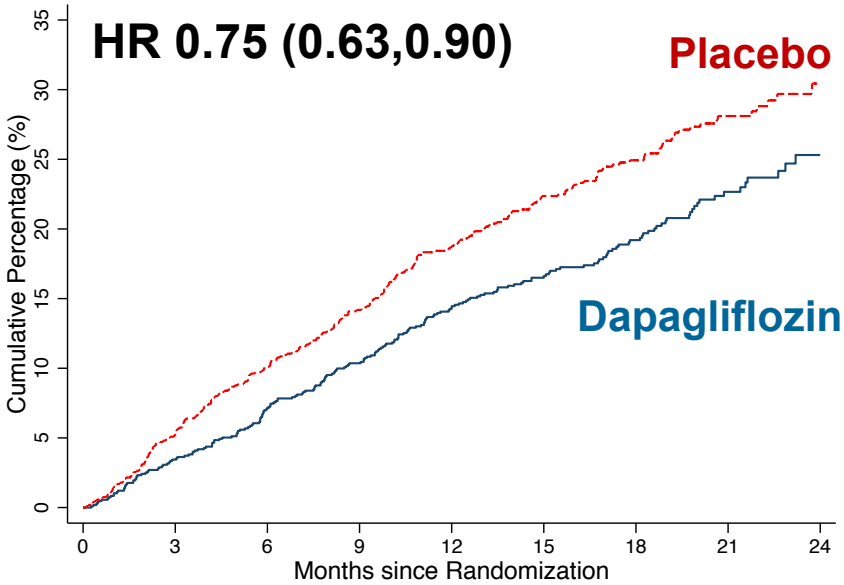
[+]ARNI = angiotensin receptor neprilysin inhibitor
*ICD or CRT-D **CRT-P or CRT-D

Primary outcome

Primary composite outcome

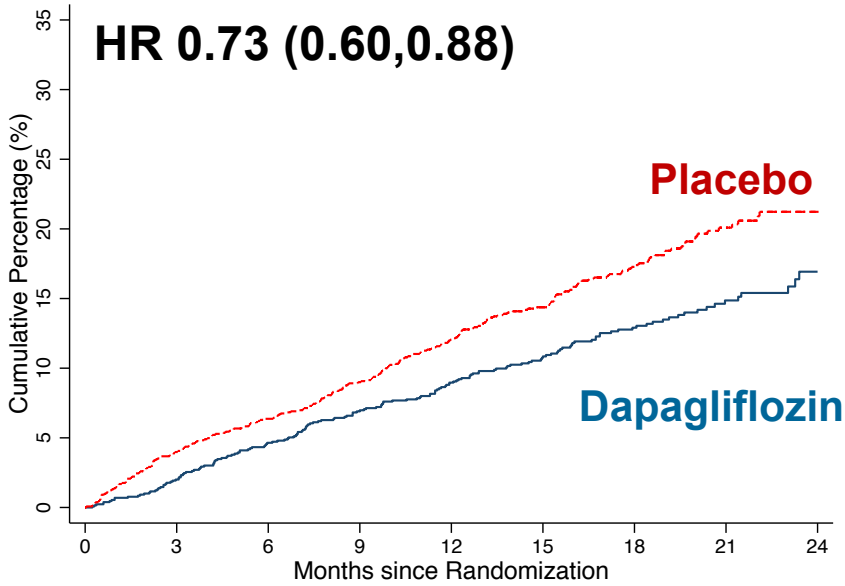
CV Death/HF hospitalization/Urgent HF visit

Diabetes



Number at Risk									
Dapagliflozin	1075	1037	994	955	876	678	500	259	88
Placebo	1064	1005	949	899	816	630	469	253	89

No Diabetes



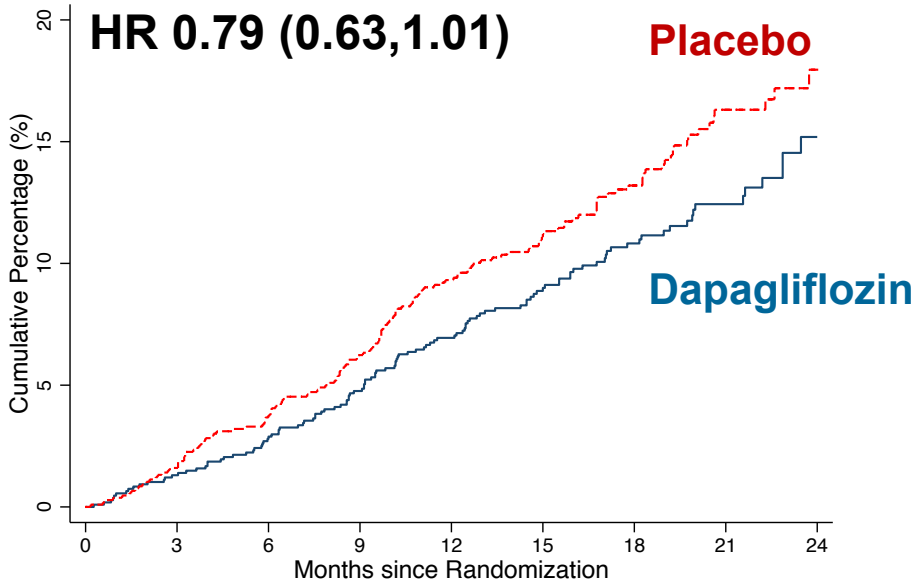
Number at Risk									
Dapagliflozin	1298	1268	1227	1192	1126	882	646	353	122
Placebo	1307	1253	1214	1176	1101	848	627	340	121

P interaction 0.80

Components of primary outcome

Cardiovascular death

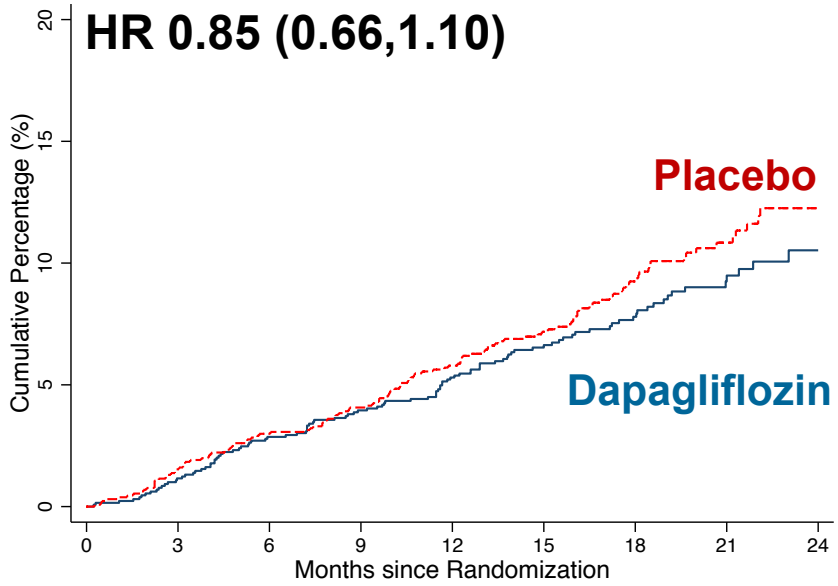
Diabetes



Number at Risk

Dapagliflozin	1075	1060	1041	1015	951	739	552	295	104
Placebo	1064	1044	1019	985	910	717	534	286	102

No Diabetes



Number at Risk

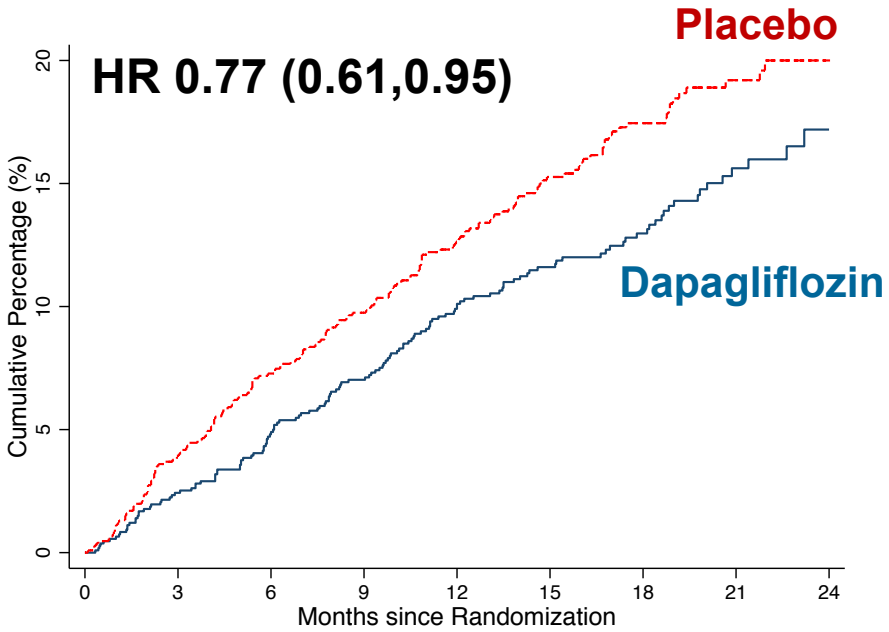
Dapagliflozin	1298	1279	1252	1233	1176	925	690	376	128
Placebo	1307	1286	1260	1245	1181	919	685	378	132

P interaction 0.70

Components of primary outcome

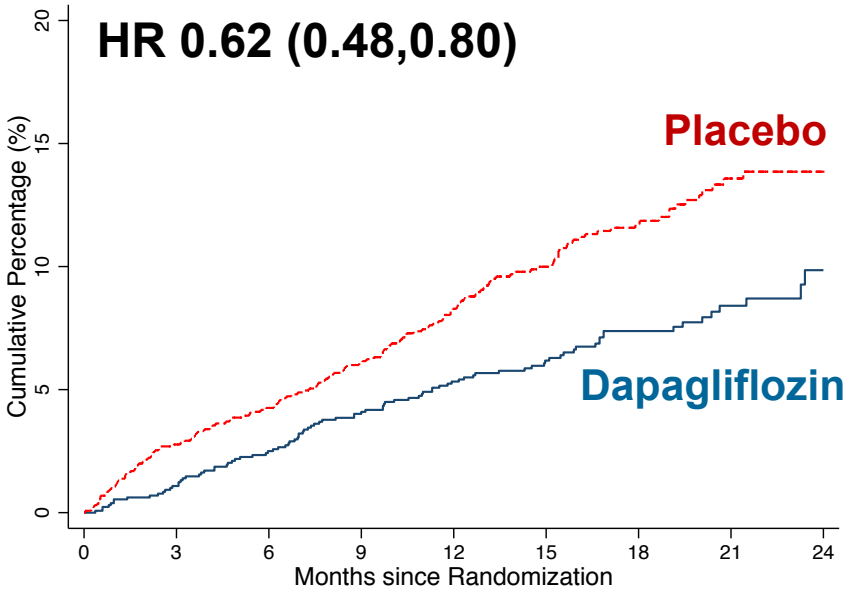
Worsening HF event

Diabetes



Number at Risk									
Dapagliflozin	1075	1037	994	955	876	678	500	259	88
Placebo	1064	1005	949	899	816	630	469	253	89

No Diabetes



Number at Risk									
Dapagliflozin	1298	1268	1227	1192	1126	882	646	353	122
Placebo	1307	1253	1214	1176	1101	848	627	340	121

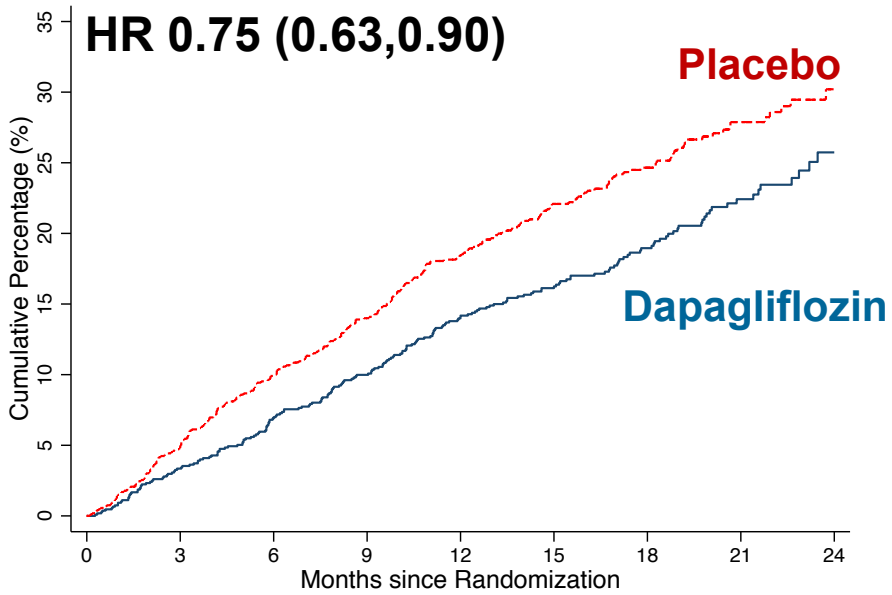
P interaction 0.23

Secondary outcomes

In order of hierarchical testing

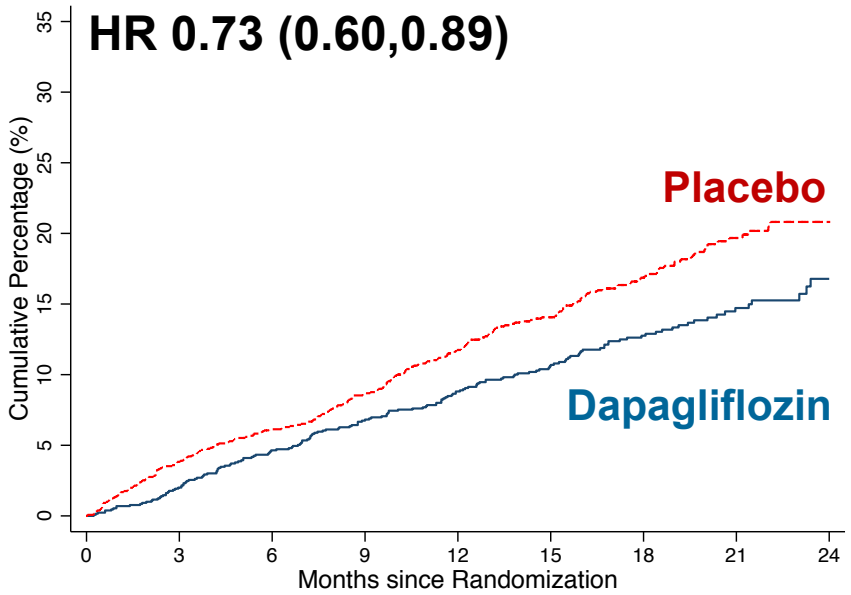
CV death or HF hospitalization

Diabetes



Number at Risk									
Dapagliflozin	1075	1038	996	959	879	681	501	260	88
Placebo	1064	1009	951	901	819	632	470	254	90

No Diabetes



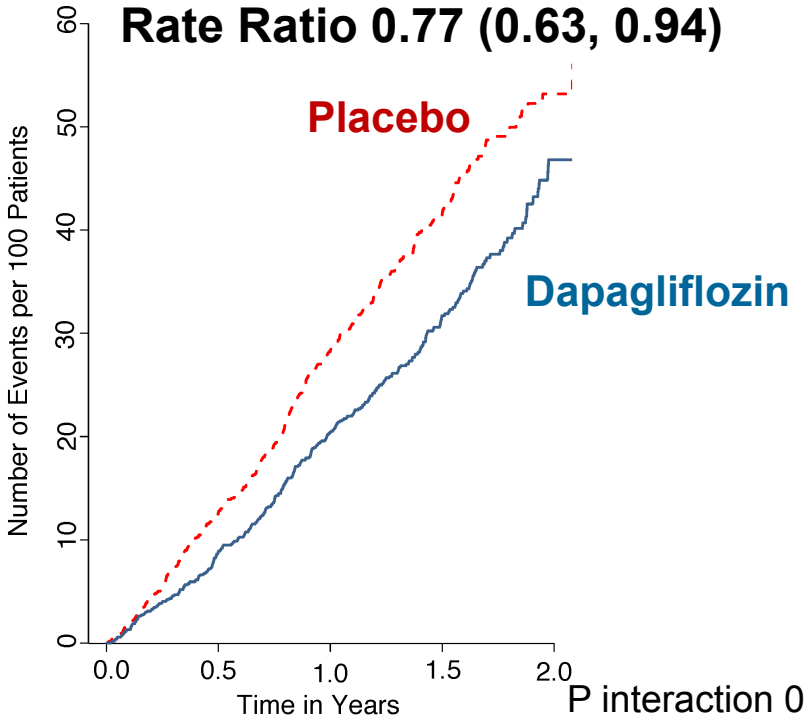
Number at Risk									
Dapagliflozin	1298	1268	1227	1194	1128	882	646	353	122
Placebo	1307	1255	1217	1181	1105	851	631	342	122

P interaction 0.83

Total HF hospitalizations and CV death

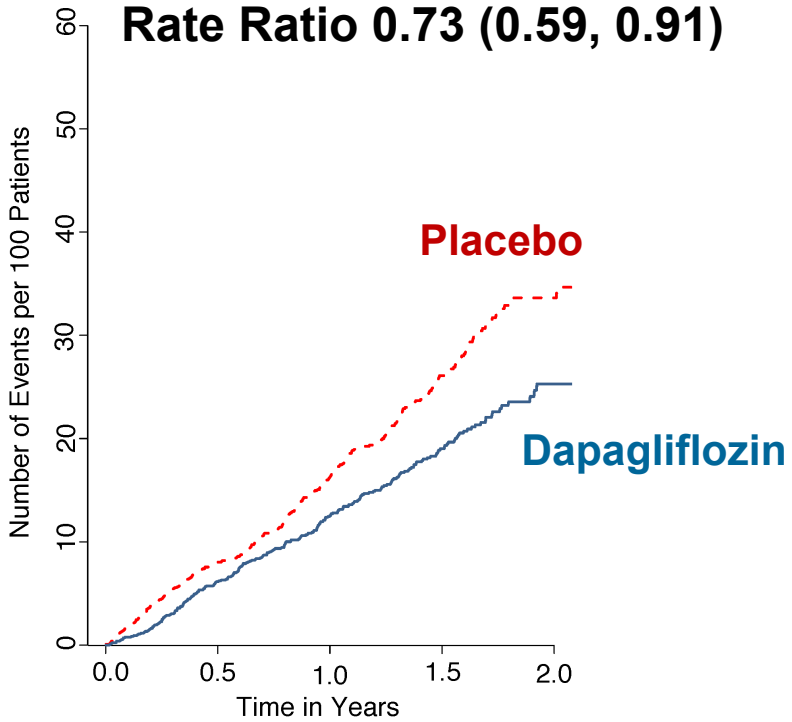
Including first and repeat hospitalizations

Diabetes

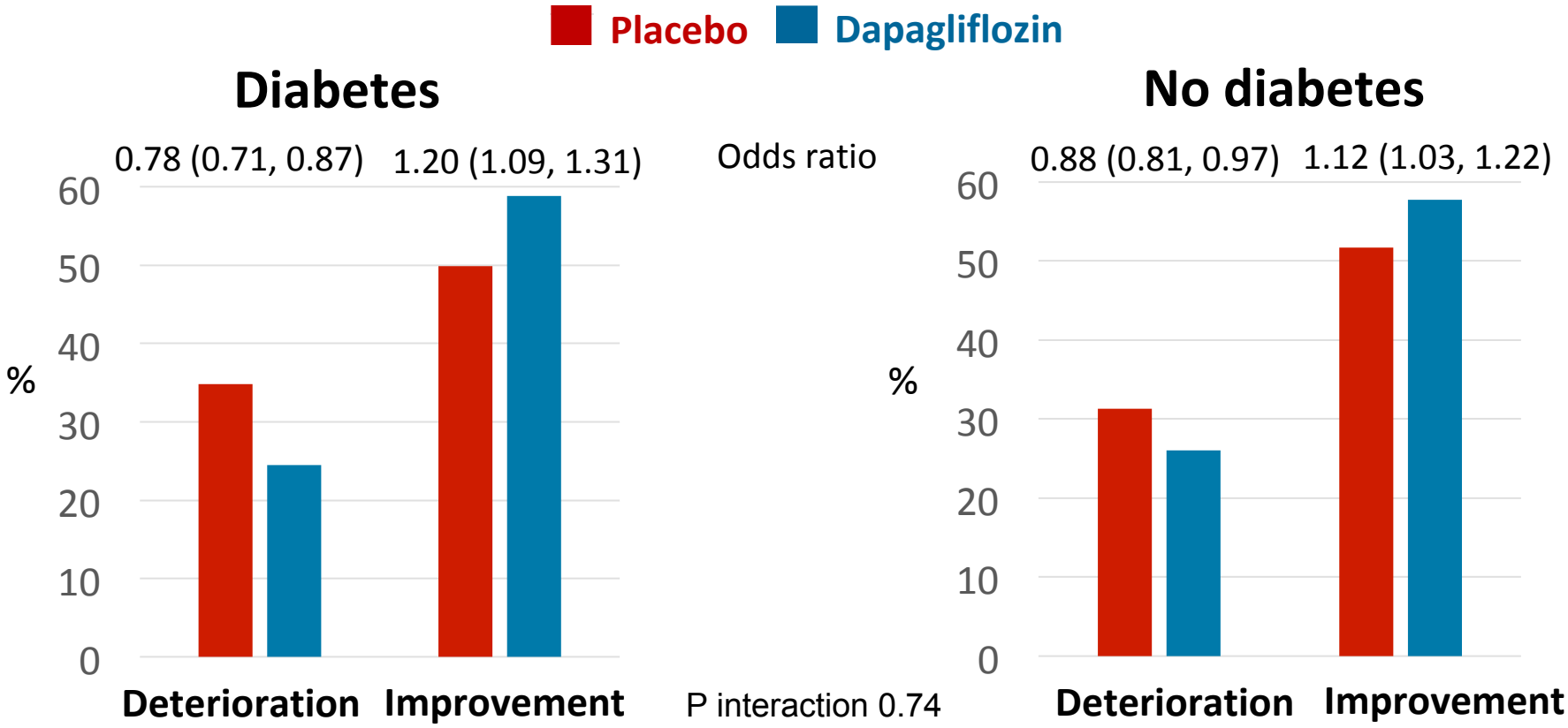


P interaction 0.74

No Diabetes



Clinically meaningful change (≥5 points) in KCCQ-TSS



Worsening renal function endpoint

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

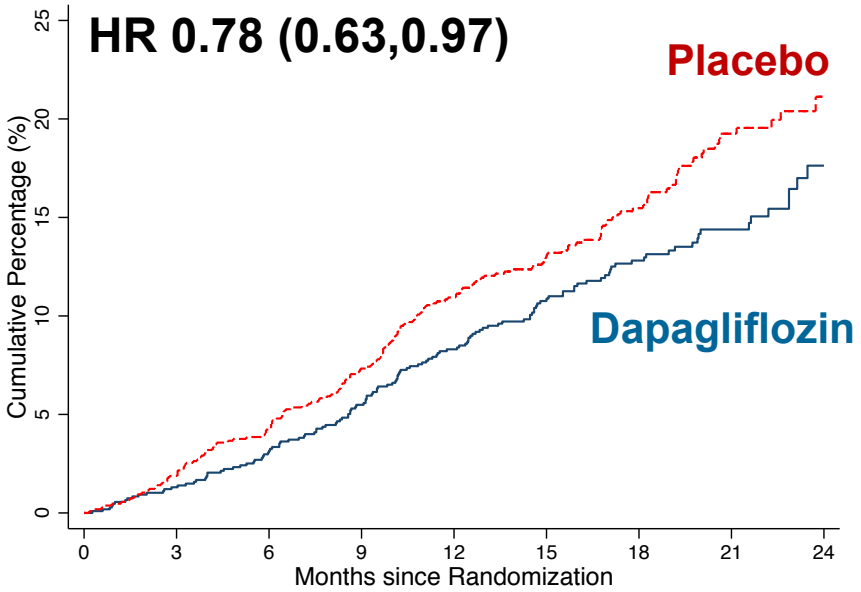
	Placebo No. (%)	Dapagliflozin No. (%)	Hazard ratio (95%CI)
Diabetes (n=2139)	24 (2.3)	18 (1.7)	0.73 (0.39, 1.34)
No diabetes (n=2605)	15 (1.2)	10 (0.8)	0.67 (0.30, 1.49)

P interaction 0.86

ESRD consisted of sustained eGFR below 15 ml/min/1.73m^2, sustained dialysis or kidney transplantation *Sustained = 28 days or more

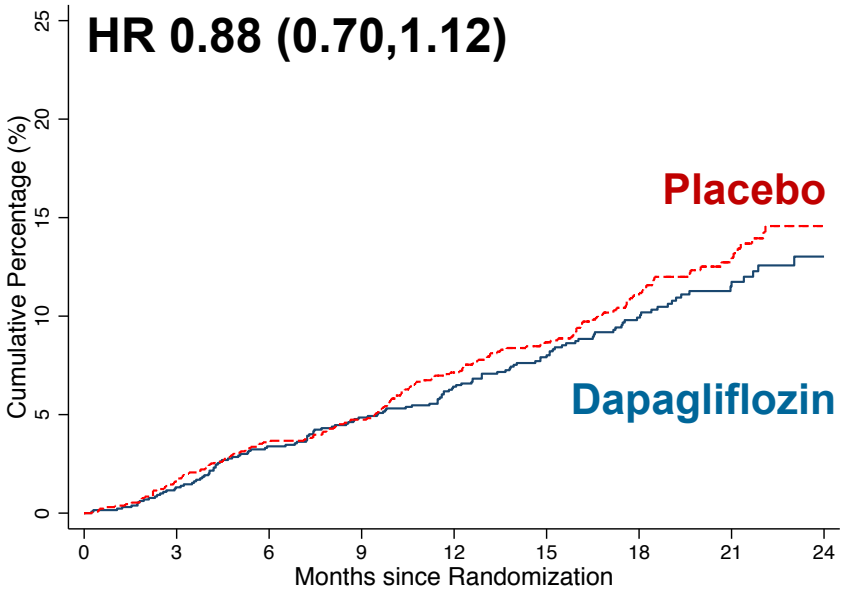
All-cause death

Diabetes



Number at Risk									
Dapagliflozin	1075	1061	1042	1016	952	740	552	295	104
Placebo	1064	1044	1019	986	911	718	535	286	102

No Diabetes



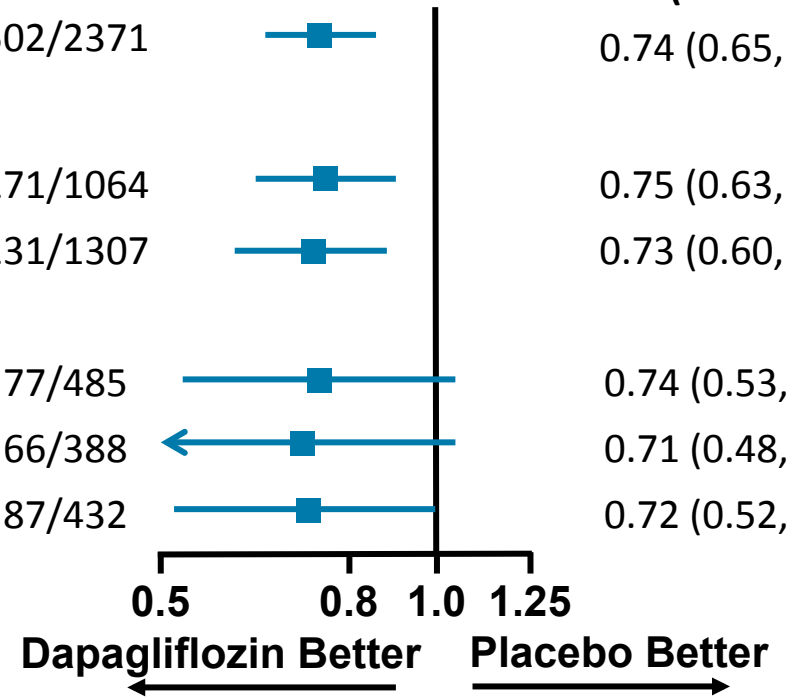
Number at Risk									
Dapagliflozin	1298	1281	1254	1235	1178	926	691	377	129
Placebo	1307	1286	1260	1245	1181	920	686	379	133

P interaction 0.45

Treatment effect by diabetes status and HbA1c

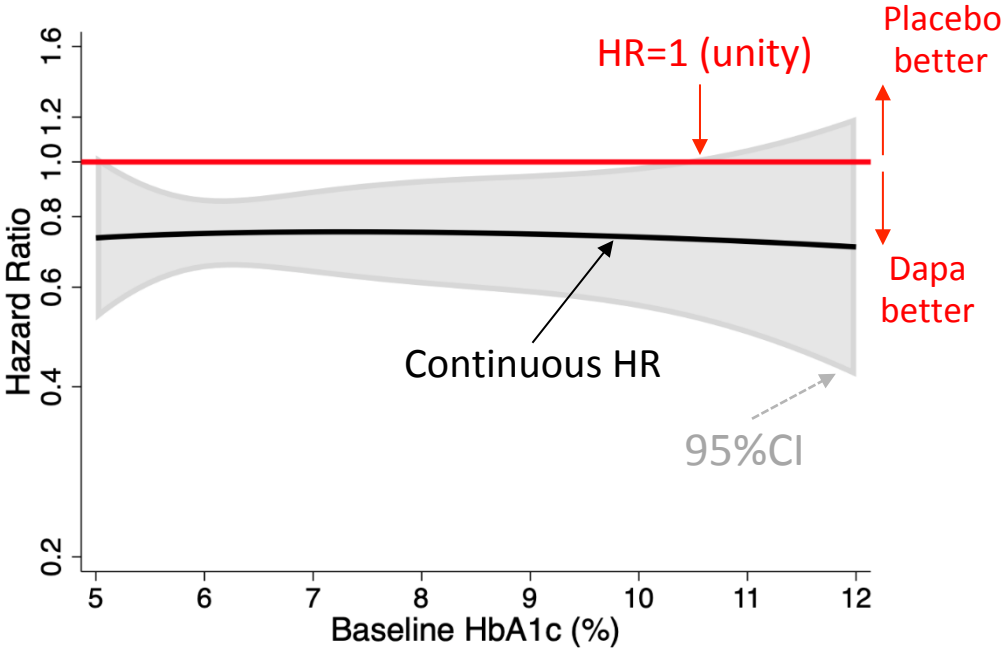
Primary endpoint

	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)
HbA1c tertiles in patients without T2D at baseline			
≤5.6%	65/521	77/485	0.74 (0.53,1.04)
5.7-5.9%	44/365	66/388	0.71 (0.48,1.04)
≥6.0%	62/408	87/432	0.72 (0.52,1.00)

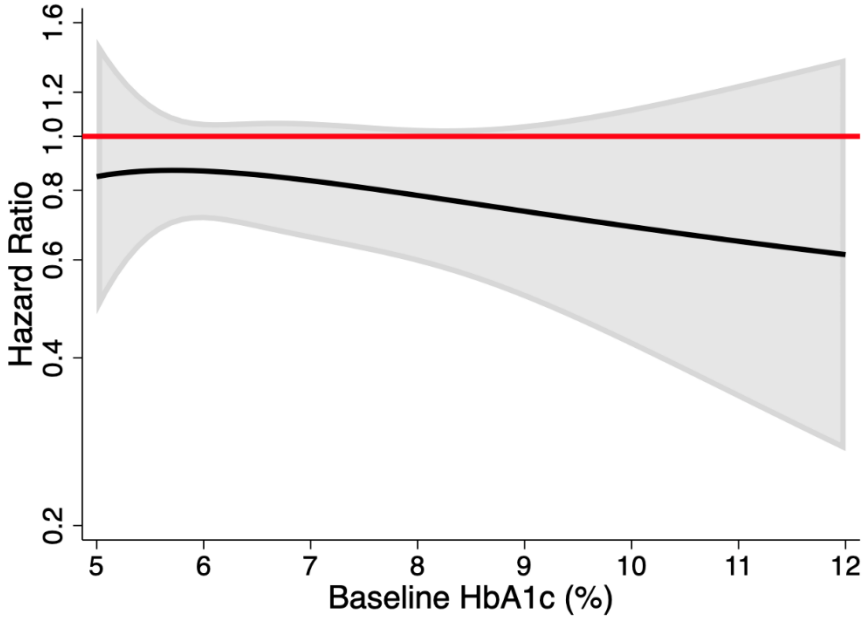


Treatment effect according to baseline HbA1c (All patients)

Primary endpoint



Cardiovascular death



Safety and tolerability

Safety/adverse events (AEs)

Patients exposed to at least one dose of study drug*	Diabetes			No diabetes		
	Placebo	Dapa	*P-value*	Placebo	Dapa	*P-value*
AE of interest (%)						
Volume depletion	7.8	7.8	*1.00*	6.1	7.3	*0.24*
Renal AE	8.7	8.5	*0.94*	6.0	4.8	*0.19*
Fracture	2.4	2.1	*0.66*	1.9	2.1	*0.78*
Amputation	0.8	1.1	*0.66*	0.2	0.1	*N/A*
Major hypoglycaemia[+]	0.4	0.4	*N/A*	0	0	*N/A*
Diabetic ketoacidosis	0	0.3	*N/A*	0	0	*N/A*
AE leading to treatment discontinuation (%)	5.4	4.0	*0.15*	4.5	5.3	*0.41*
Any serious AE (incl. death) (%)	48.3	41.7	*0.002*	36.9	34.6	*0.24*

*The safety population included patients receiving ≥1 dose of trial medication: dapagliflozin n= 2368 and placebo n=2368. [+]Major hypoglycemia defined as hypoglycemia requiring the assistance of another person to actively administer carbohydrates, glucagon, or take other corrective action.

Summary and conclusions

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