Pooled analysis of DAPA-HF and DELIVER

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DAPAHF DELIVER

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DAPA-HF & DELIVER pooled analysis: Background

- When added to standard therapy, the SGLT2 inhibitor, dapagliflozin, reduced the risk of worsening heart failure (HF) or cardiovascular (CV) death in patients with HF and a left ventricular ejection fraction (LVEF) ≤40% in the DAPA-HF trial and >40% in the DELIVER trial
- DAPA-HF and DELIVER were not powered to test the effect of dapagliflozin on the components of the primary outcome or important secondary outcomes
- Prior to database lock of DELIVER, we planned an analysis of the pooled cohorts from DAPA-HF and DELIVER to examine the effect of dapagliflozin on key clinical outcomes

PROSPERO: CRD42022346524

DAPA-HF & DELIVER pooled analysis: Background

- In our analysis plan we specified a number of sub-groups that would be examined (age, sex, NYHA class, history of diabetes, LVEF [above and below 40%] and eGFR)
- However, an analysis of empagliflozin in the EMPEROR trials, suggested that there was attenuation of the effect of empagliflozin in patients with a higher LVEF
- Therefore, we updated our statistical analysis plan to examine additional LVEF subgroups (≤ 49%, 50 to 59%, ≥60%) and LVEF as a continuous variable

DAPA-HF & DELIVER pooled analysis: Aims

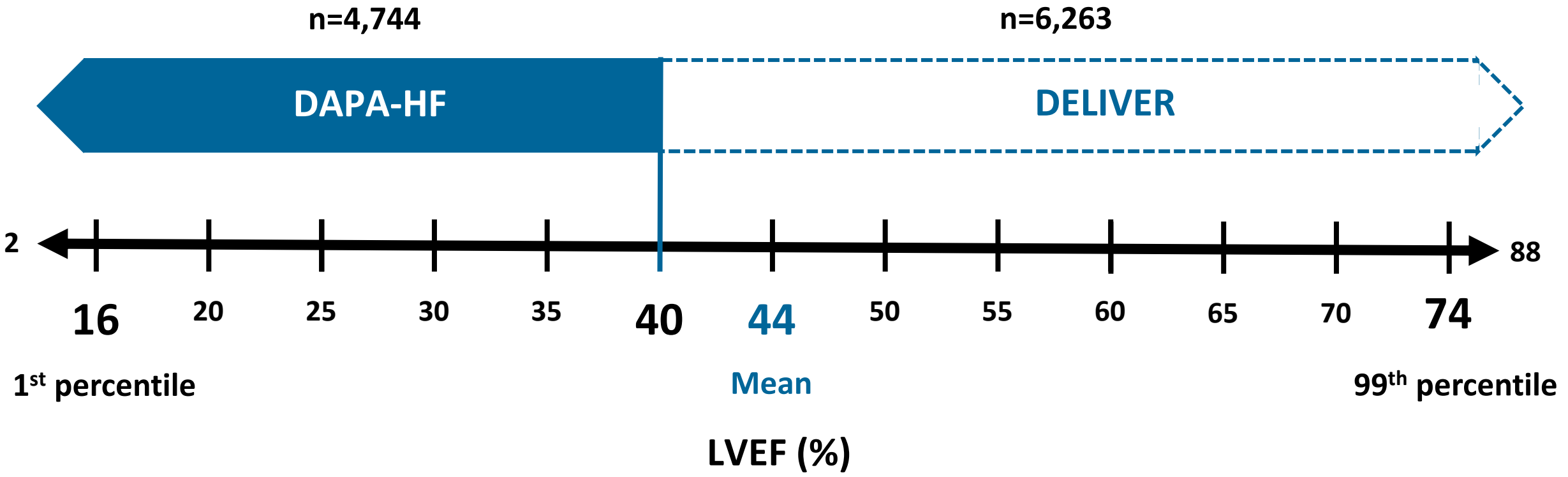
- The following endpoints were studied in this pre-specified hierarchy to control alpha:
  - **CV Death** (pre-specified to include undetermined deaths from both trials)
  - **All cause death**
  - **Total (i.e., first and repeat) hospitalisations for HF** (with an additional supportive analysis of time to the first occurrence of hospital admissions for heart failure, outside alpha control)
  - **CV death/ myocardial infarction/ stroke** (i.e., “major adverse cardiovascular events” - MACE)
- To compare our findings with the analysis of the EMPEROR trials we also examined the composite of CV death/ first HF hospitalisation

DAPA-HF and DELIVER pooled dataset

Dapagliflozin 10mg once daily vs placebo

Median follow-up = 22 (IQR 17-30) months

Pooled dataset n=11,007

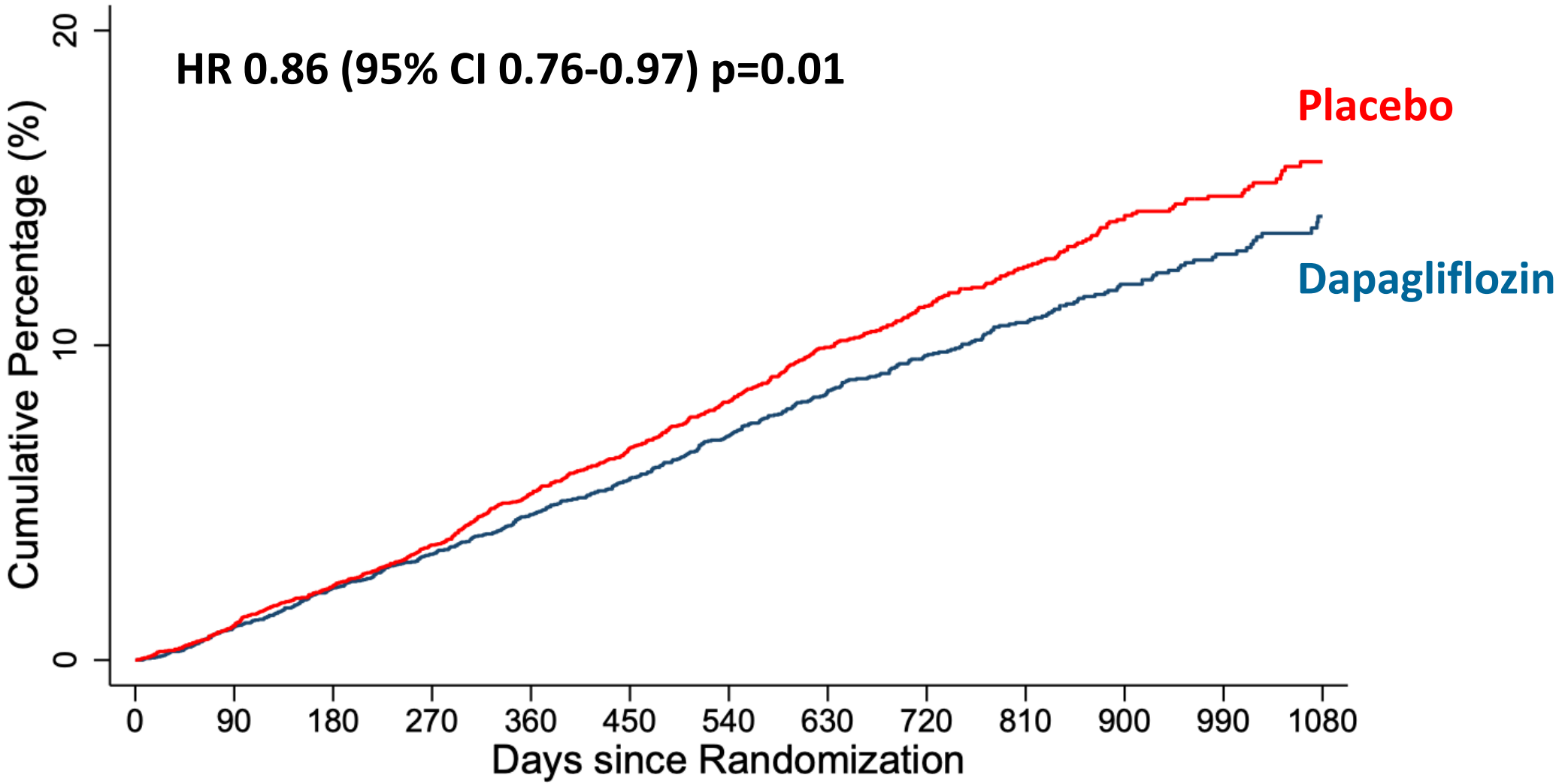


McMurray JJV et al Eur J Heart Fail. 2019;21:665-675 and Solomon SD et al Eur J Heart Fail 2021;23:1217-1225

DAPA-HF & DELIVER pooled: Key baseline characteristics

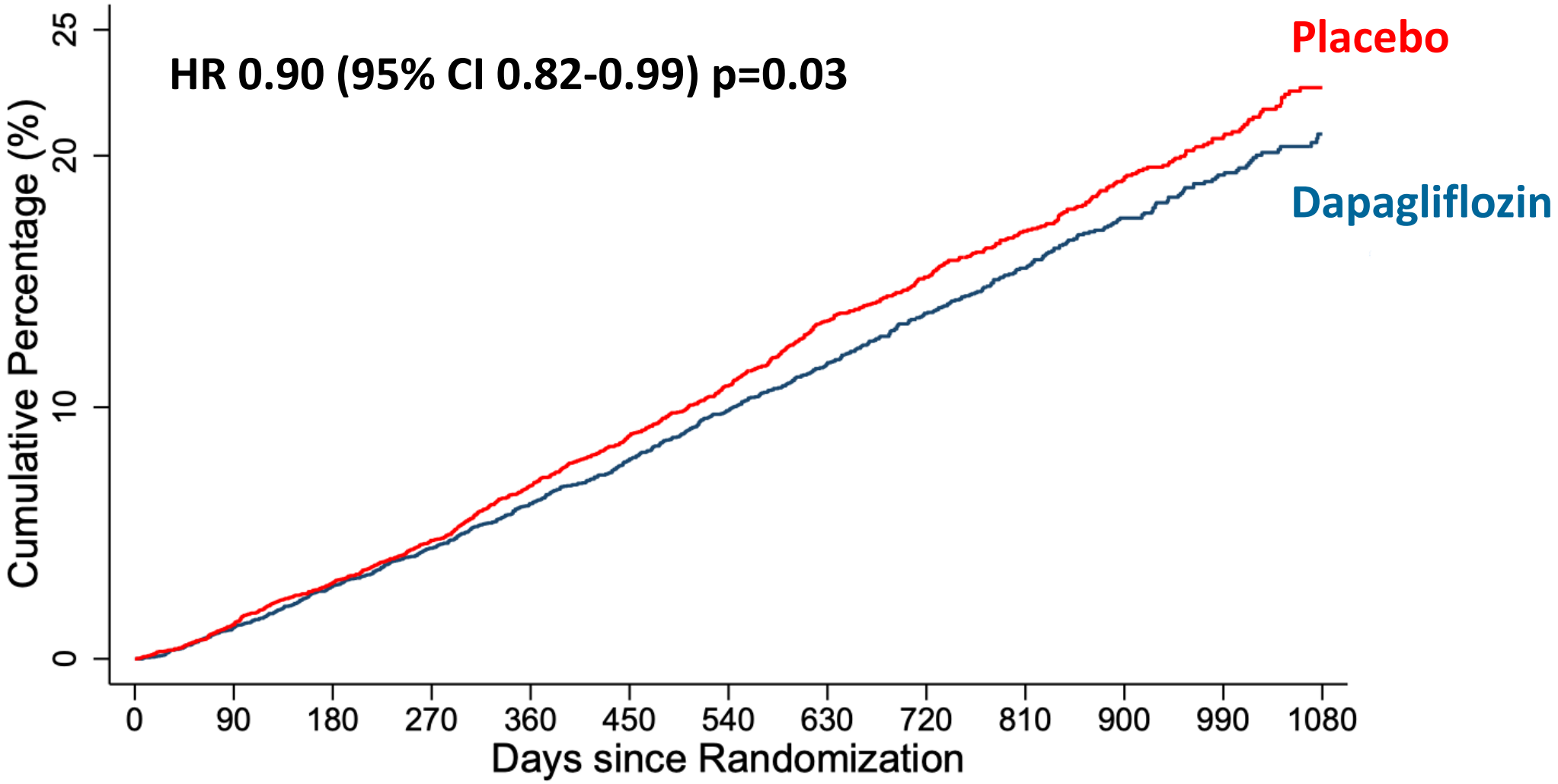
	LVEF ≤30% →	LVEF >60%	P for trend
Mean age (yr)	65±11	74±9	<0.001
Male (%)	79%	44%	<0.001
NYHA class III/IV (%)	32%	21%	<0.001
Mean Body Mass Index (%)	28±6	30±6	<0.001
Median NT pro BNP (pg/ml)	1680 (964-3163)	903 (542-1548)	<0.001
Mean systolic BP (mmHg)	118±15	129±15	<0.001
Prior HF Hospitalisation (%)	49%	33%	<0.001
Mean eGFR (ml/min/1.73m^2)	66±20	59±19	<0.001
Type 2 diabetes (%)	41%	44%	0.16
Atrial fibrillation (%)	34%	57%	<0.001

DAPA-HF & DELIVER pooled data: Cardiovascular death



Number at Risk													
Dapagliflozin	5504	5430	5339	5254	5087	4556	3826	3010	2403	1781	1312	903	441
Placebo	5503	5426	5333	5238	5048	4508	3789	2978	2391	1767	1306	910	451

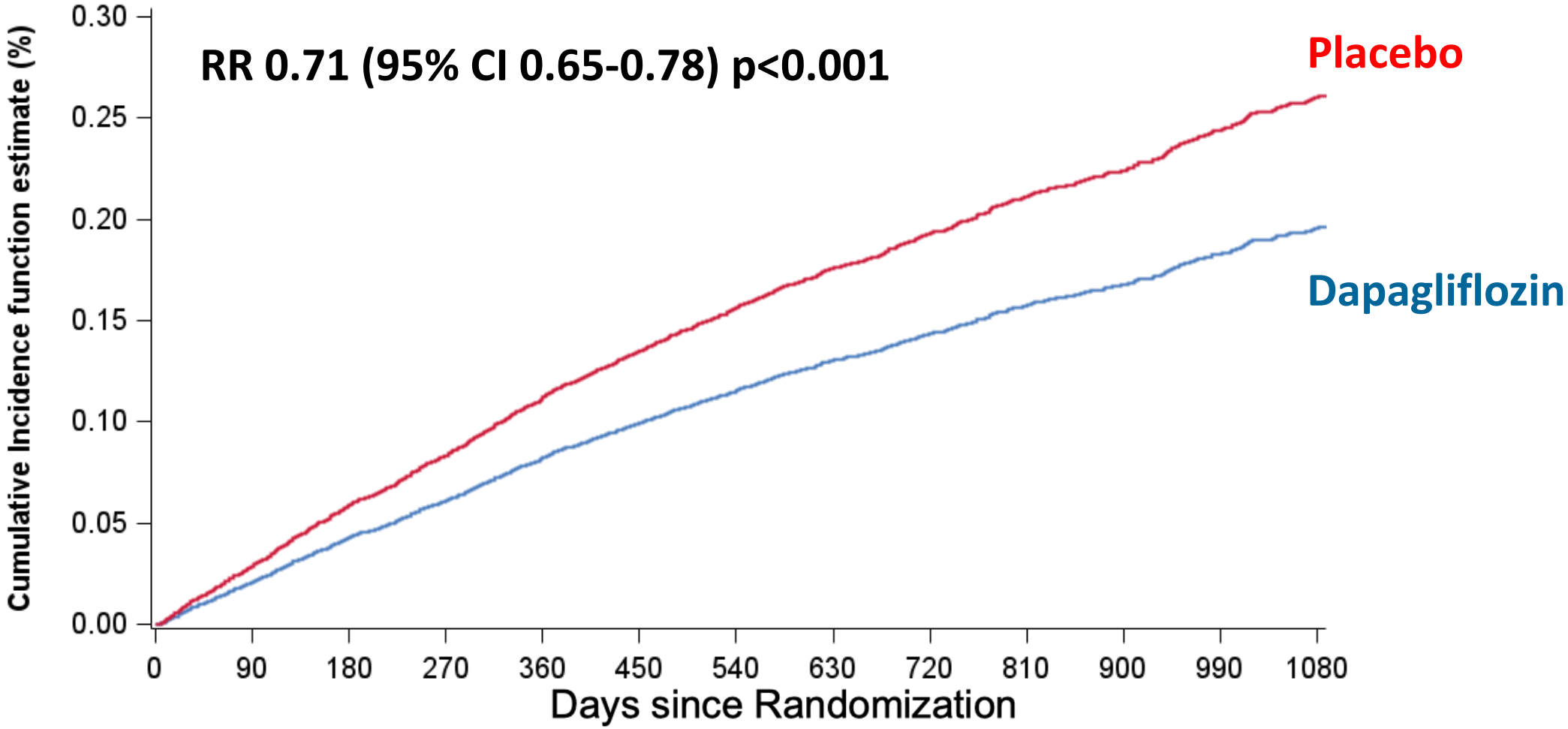
DAPA-HF & DELIVER pooled data: All-cause death



Number at Risk													
Dapagliflozin	5504	5435	5344	5260	5092	4561	3830	3014	2407	1784	1314	905	443
Placebo	5503	5427	5337	5243	5054	4515	3796	2984	2396	1770	1309	910	451

DAPA-HF & DELIVER pooled: Total HF hospitalisations

Ghosh and Lin method accounting for CV death



Number at Risk

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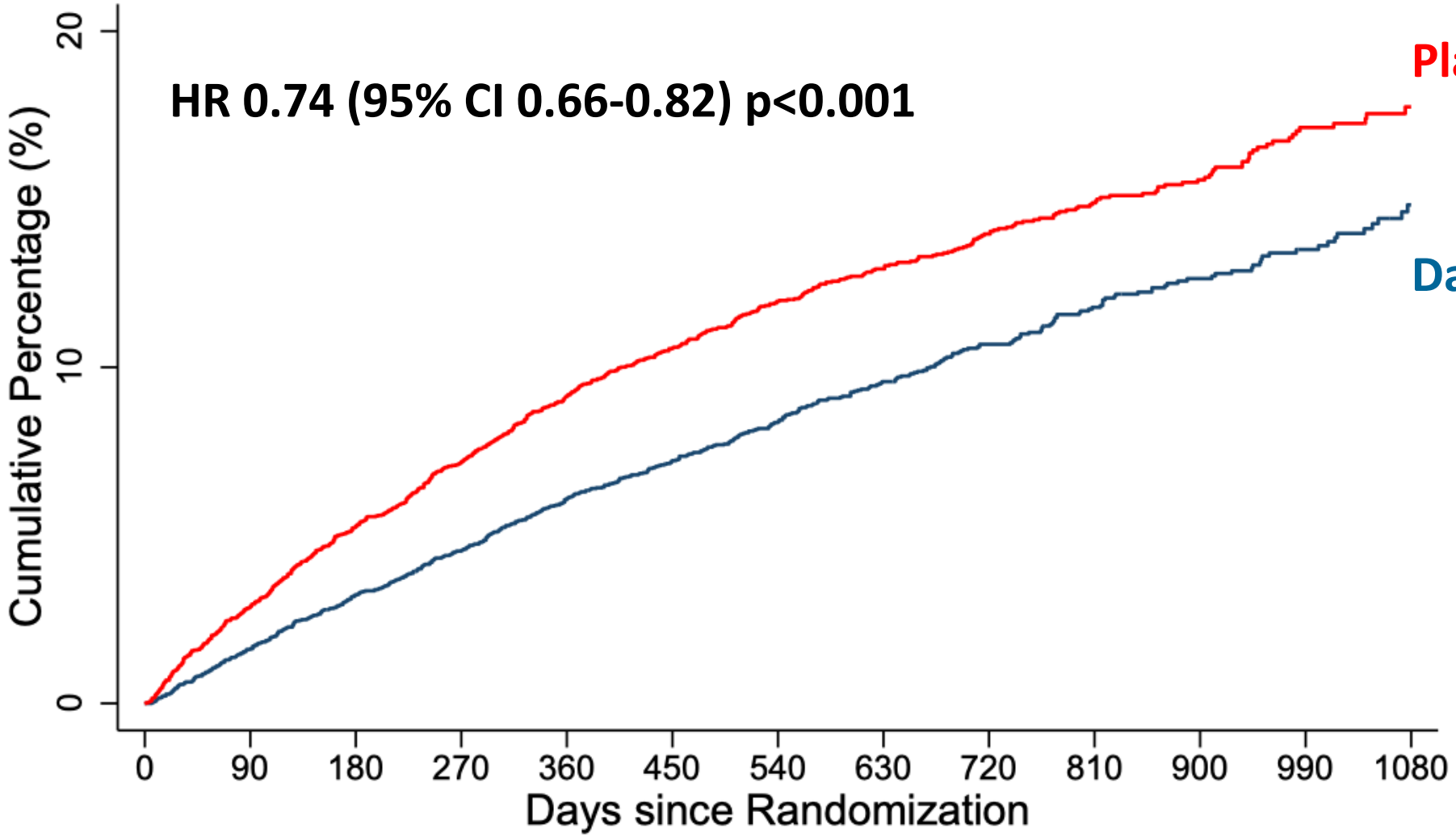
Placebo	5503	5427	5337	5243	5054	4515	3796	2984	2396	1770	1309	910	451

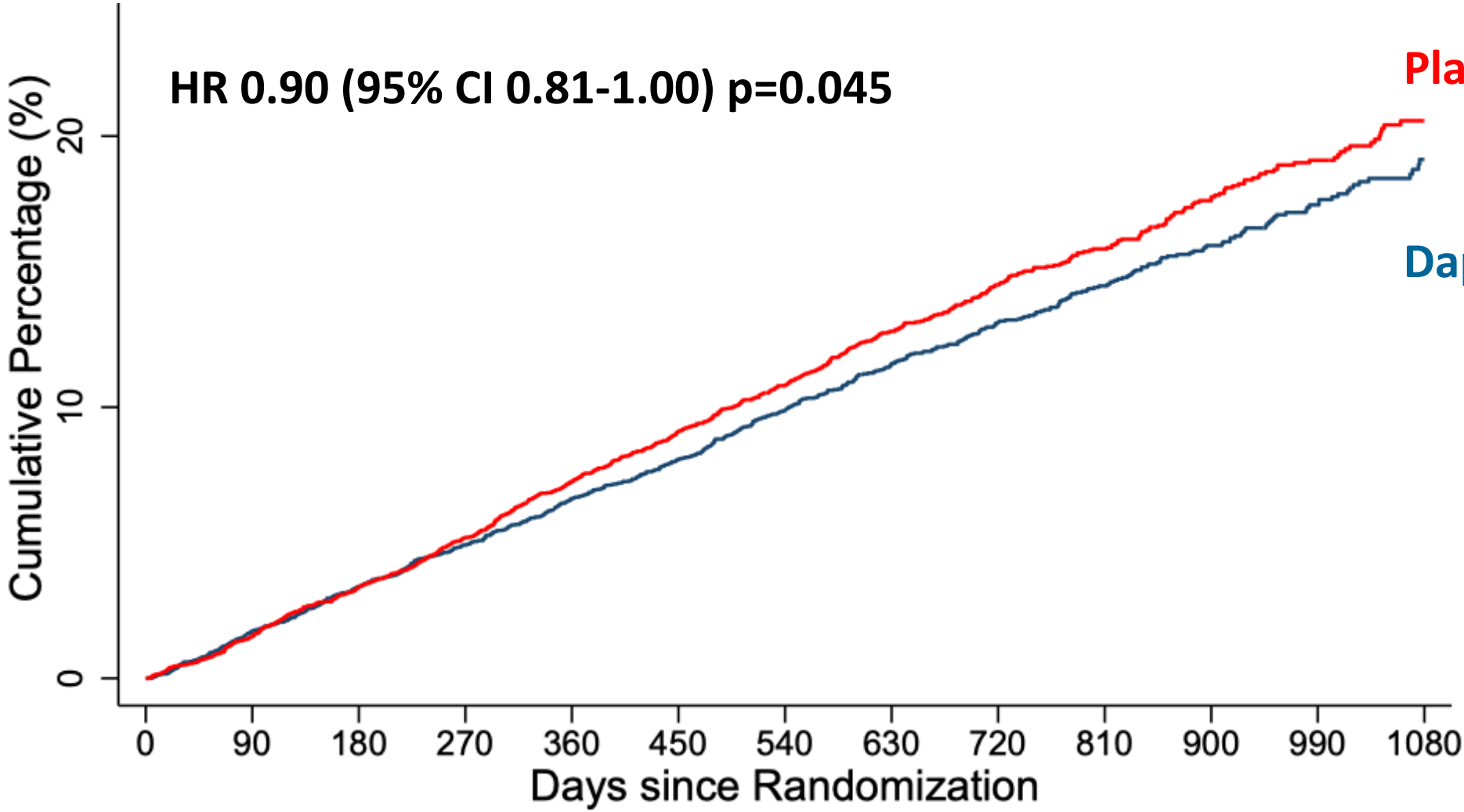
DAPA-HF & DELIVER pooled: First HF hospitalisation*



Number at Risk													
Dapagliflozin	5504	5351	5183	5053	4835	4302	3574	2787	2218	1633	1197	814	396
Placebo	5503	5282	5084	4907	4662	4121	3449	2707	2165	1586	1161	785	389

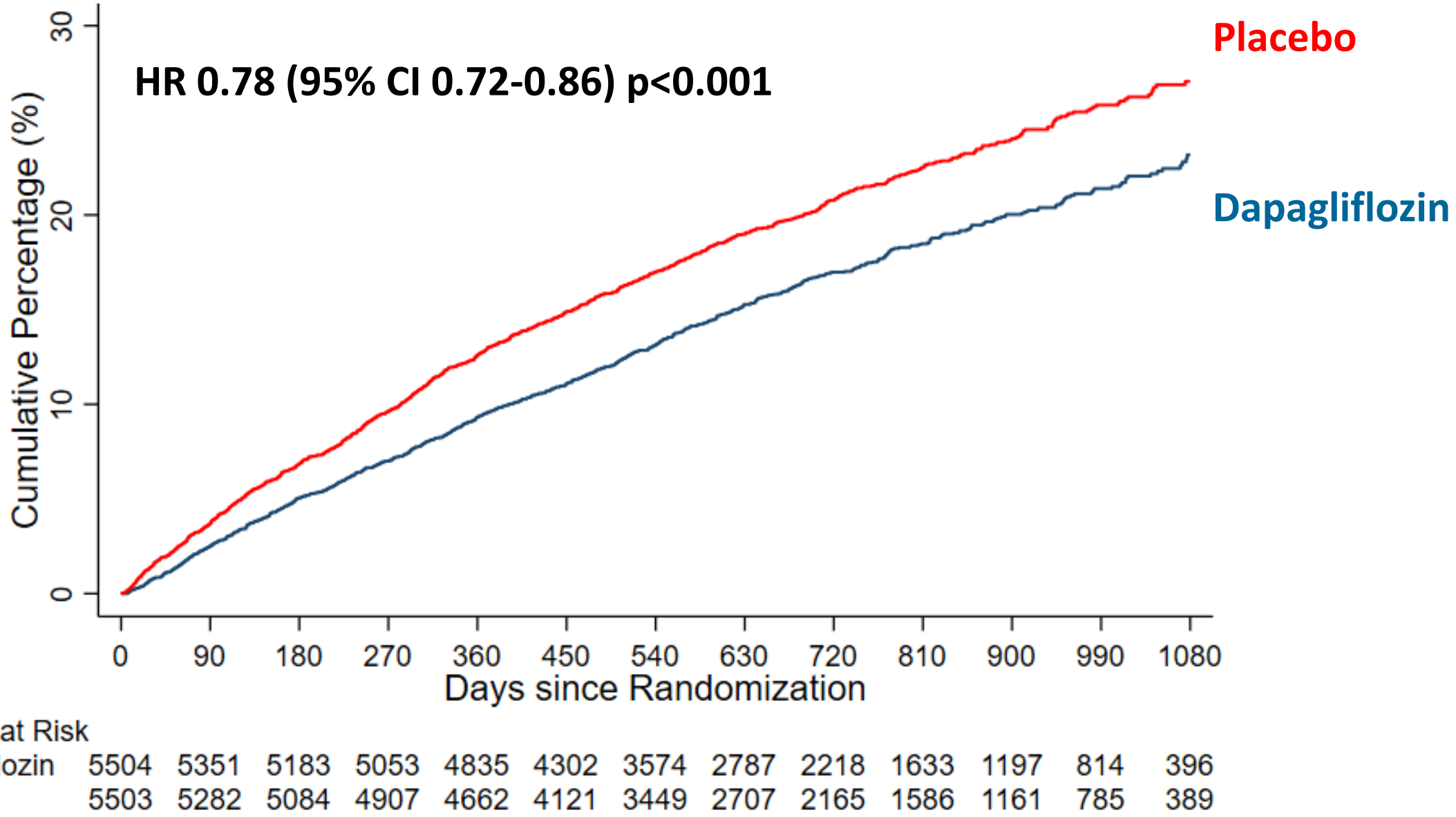
**supportive analysis - outside alpha control*

DAPA-HF & DELIVER pooled: CV death/MI/stroke



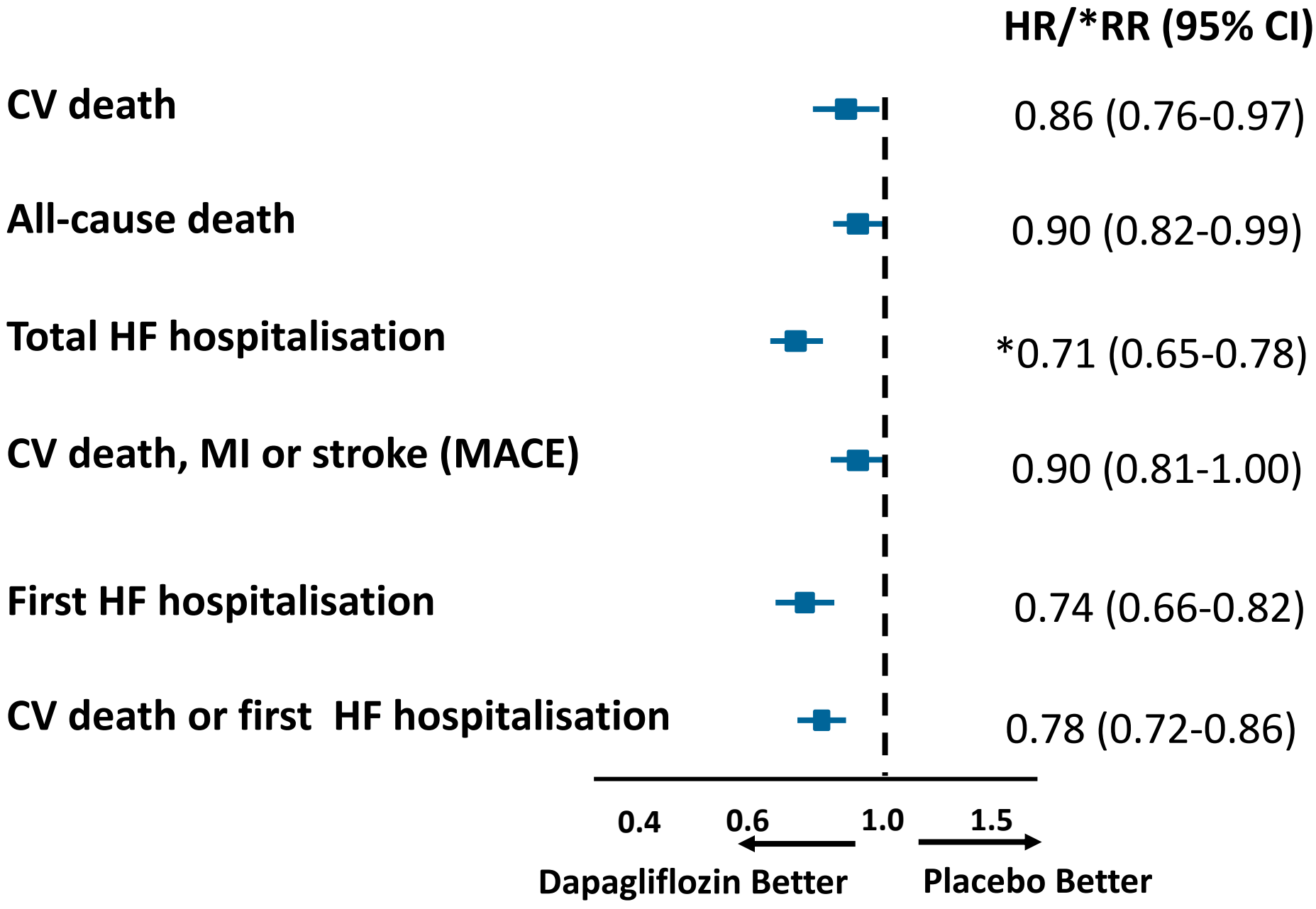
Number at Risk													
Dapagliflozin	5504	5389	5271	5158	4968	4432	3706	2904	2312	1706	1251	852	417
Placebo	5503	5396	5270	5144	4930	4381	3675	2872	2295	1692	1243	859	421

DAPA-HF & DELIVER: CV death/HF hospitalisation*

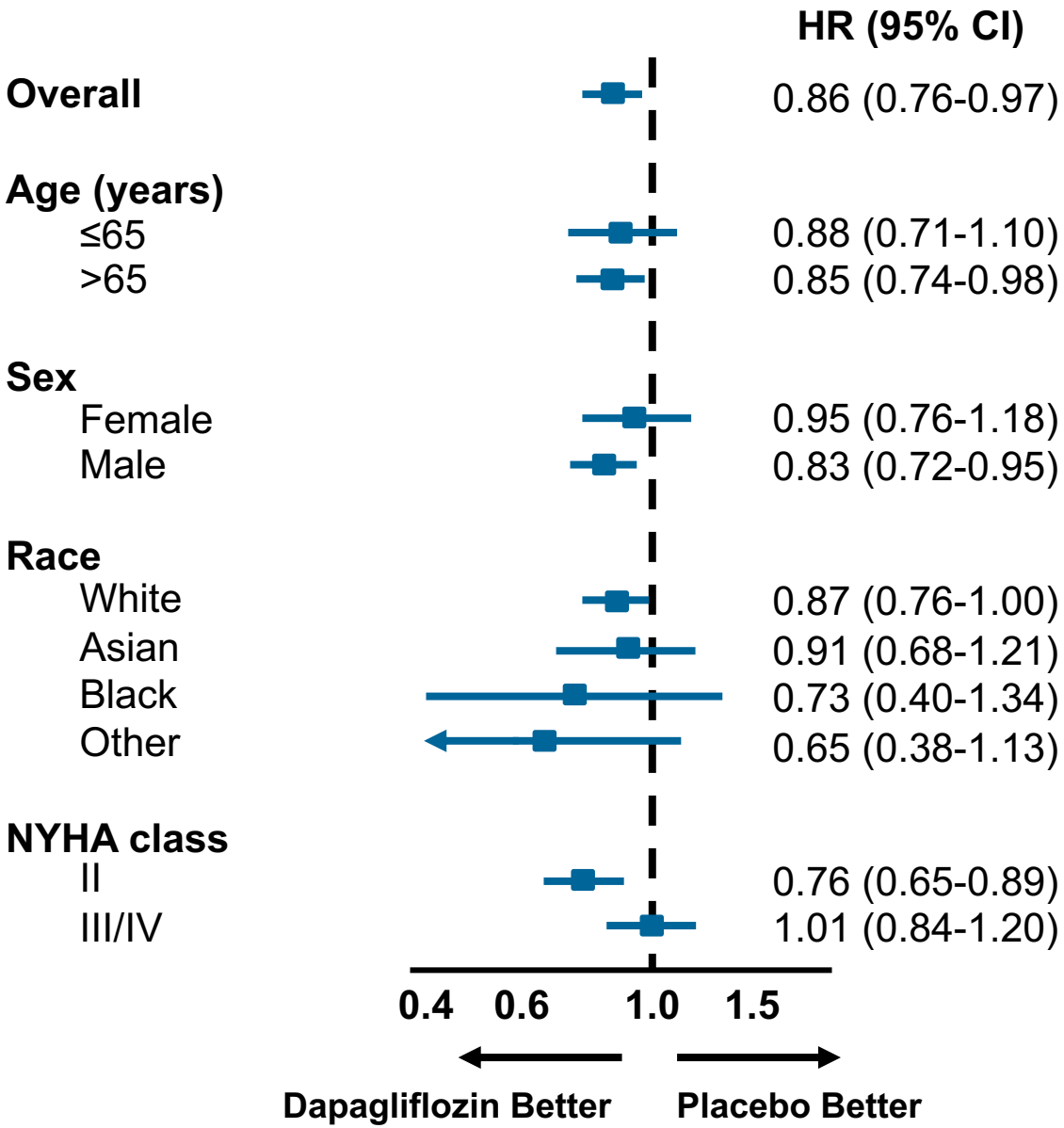


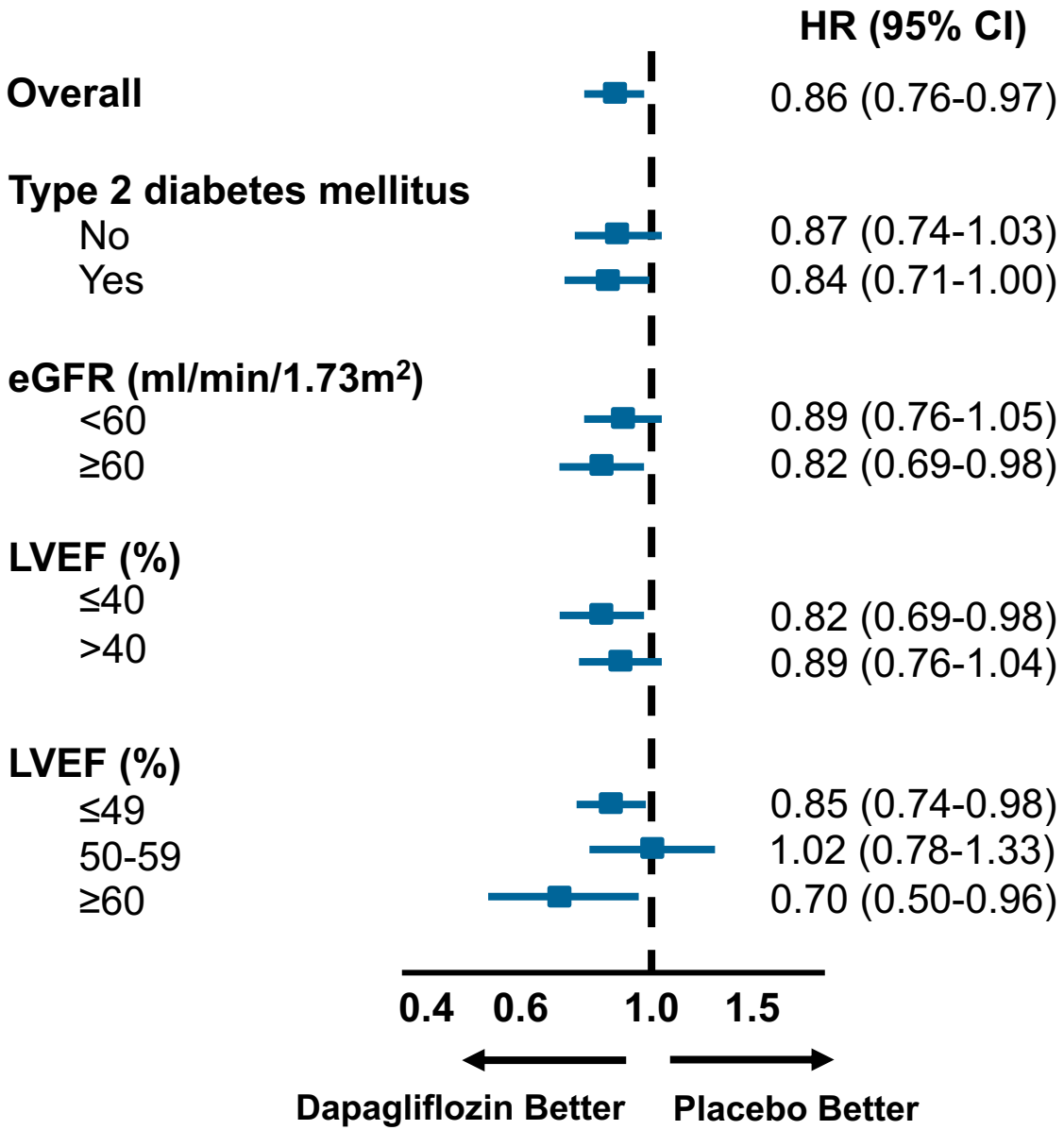
**supportive analysis - outside alpha control*

DAPA-HF & DELIVER pooled: Outcome hierarchy

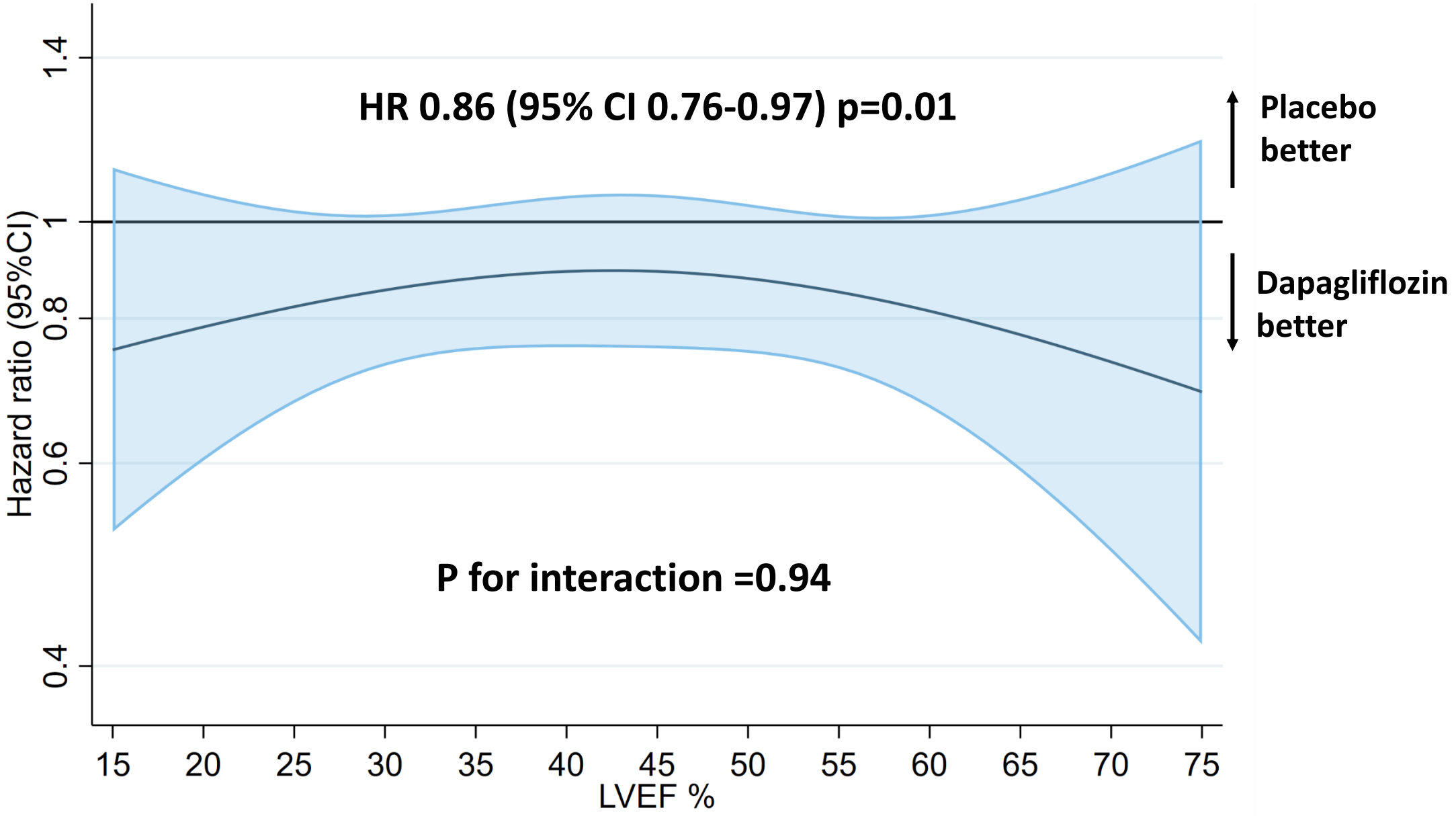


DAPA-HF & DELIVER pooled: Cardiovascular death in pre-specified subgroups

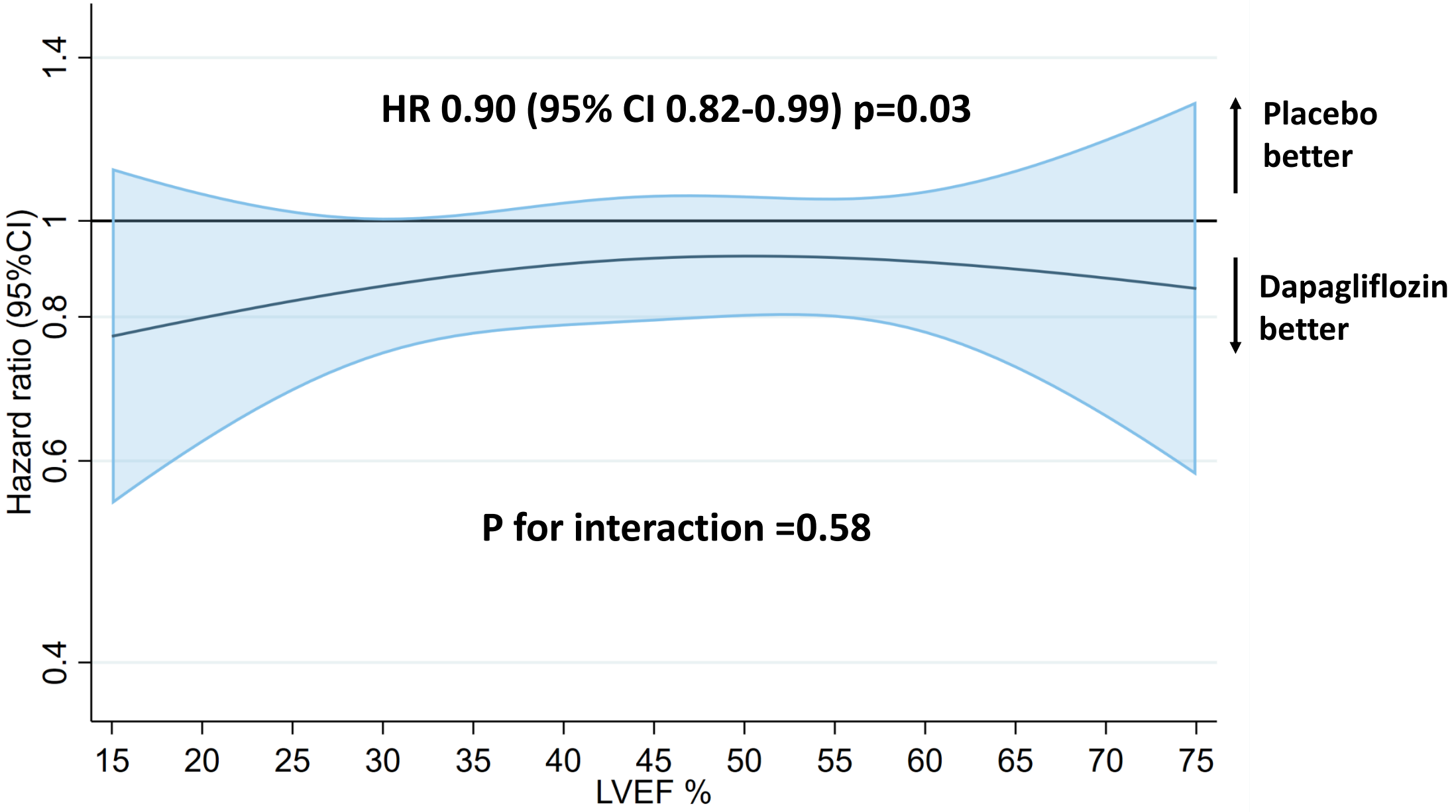




DAPA-HF & DELIVER pooled: Cardiovascular death



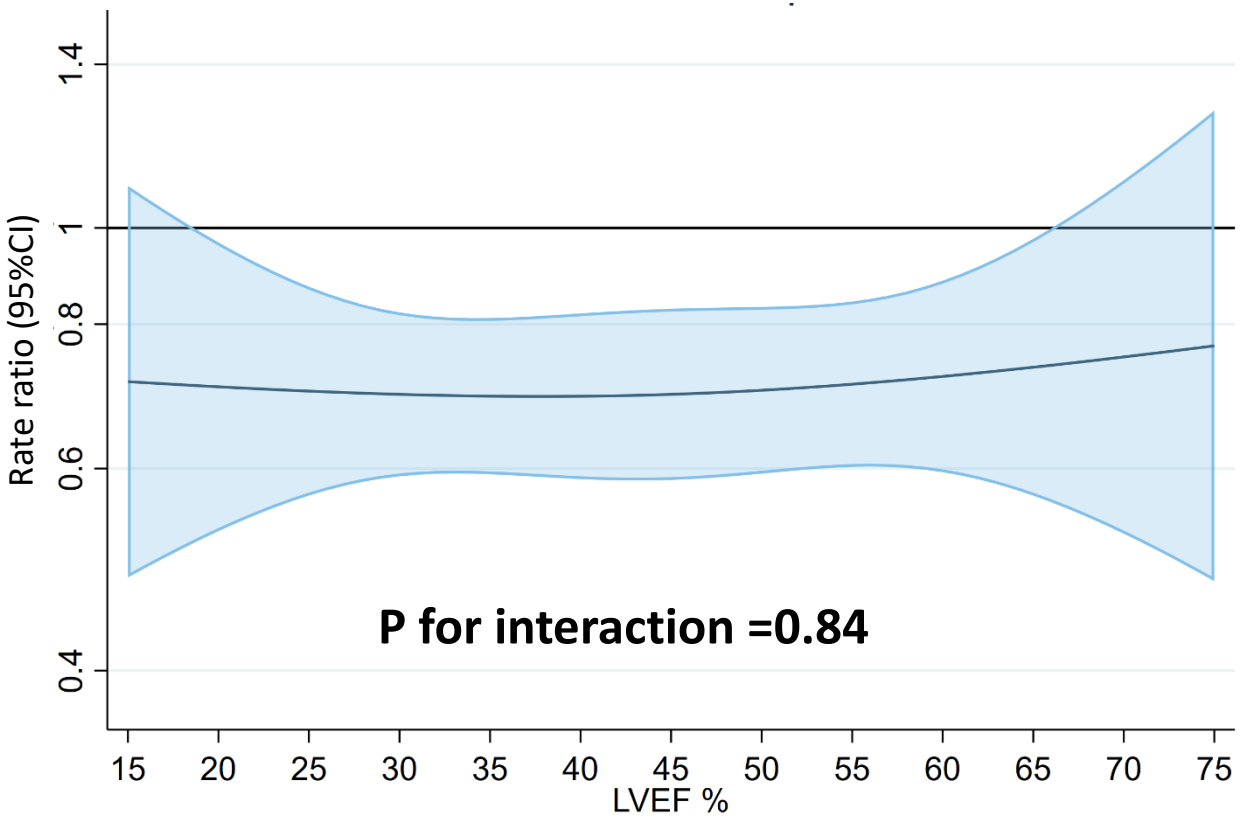
DAPA-HF & DELIVER pooled: All-cause death



DAPA-HF & DELIVER pooled: HF hospitalisations

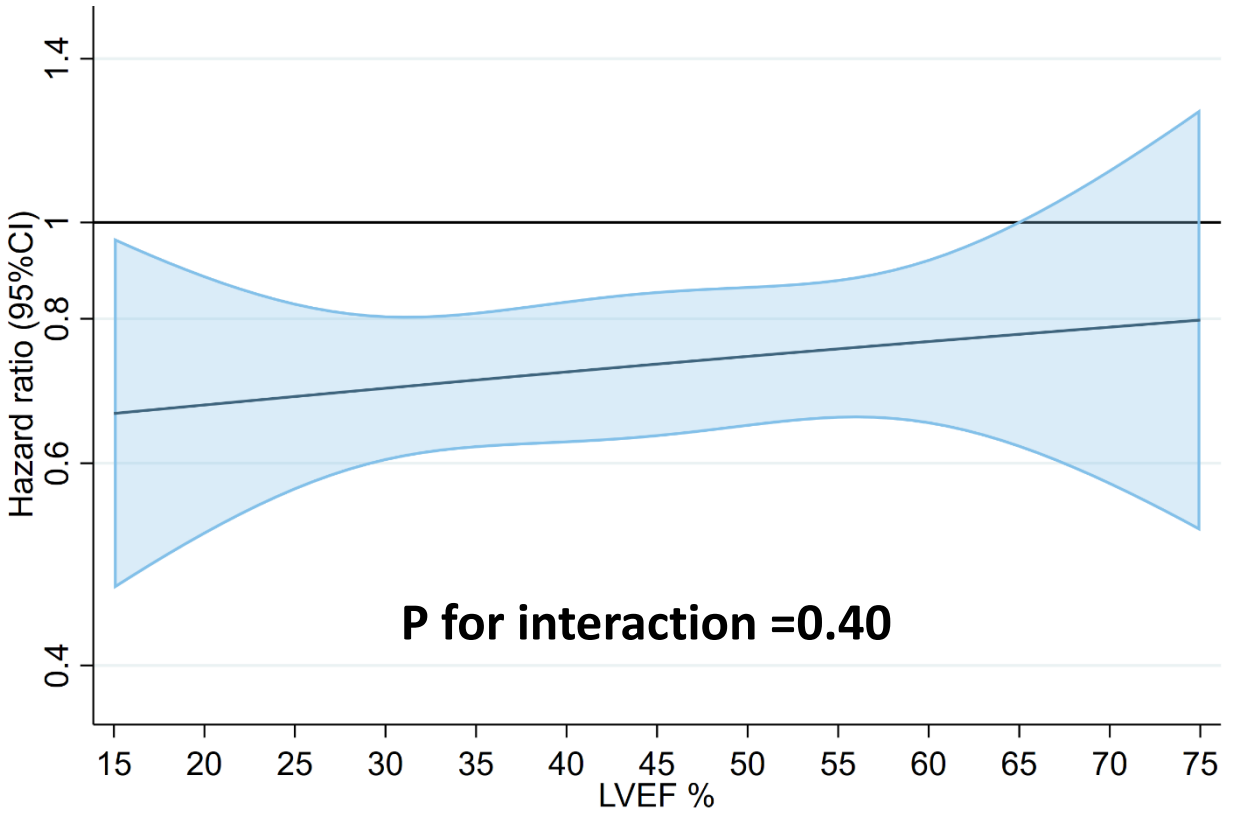
Total HF hospitalisations

RR 0.71 (95% CI 0.65-0.78) p<0.001

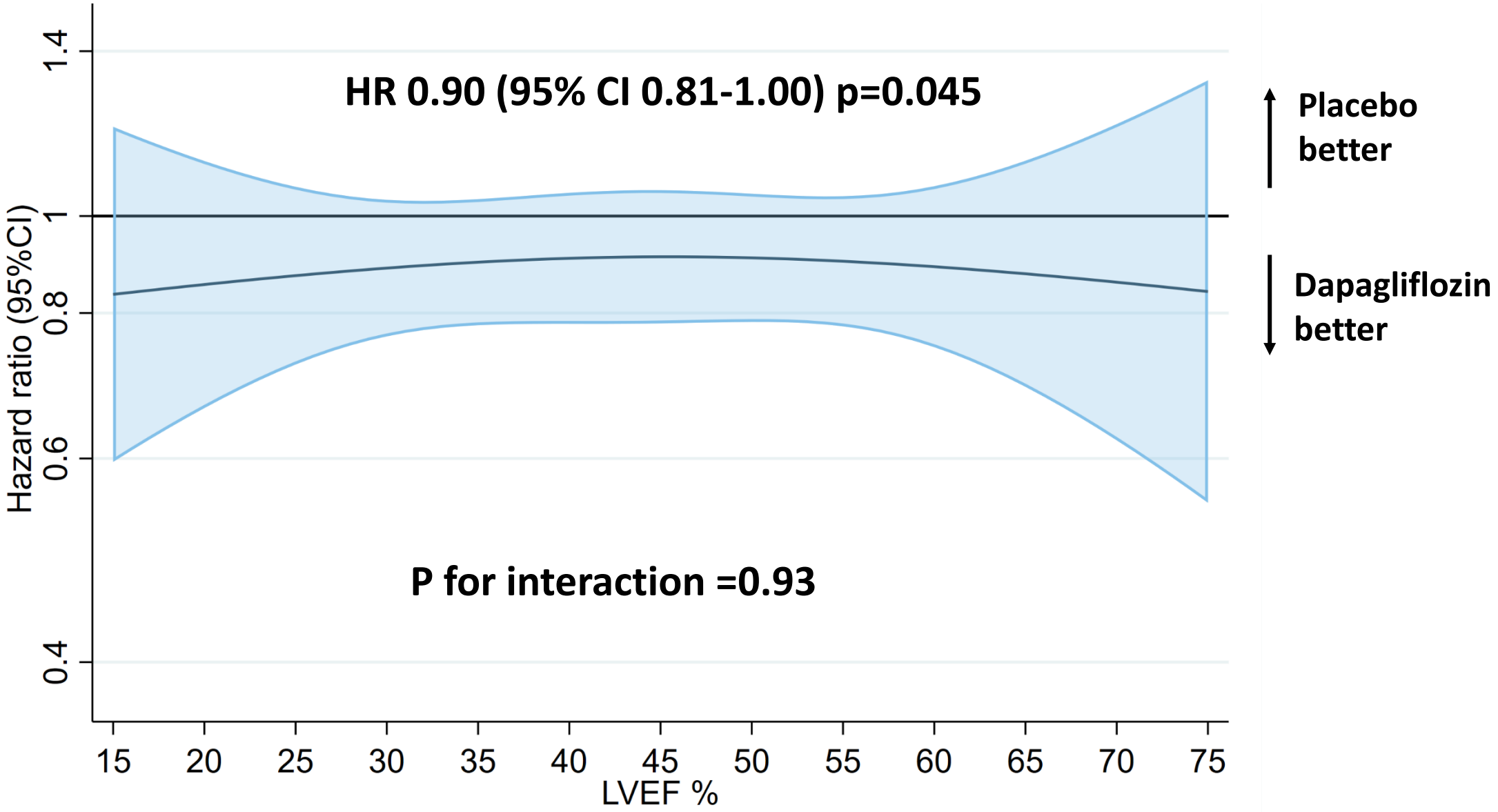


First HF hospitalisation

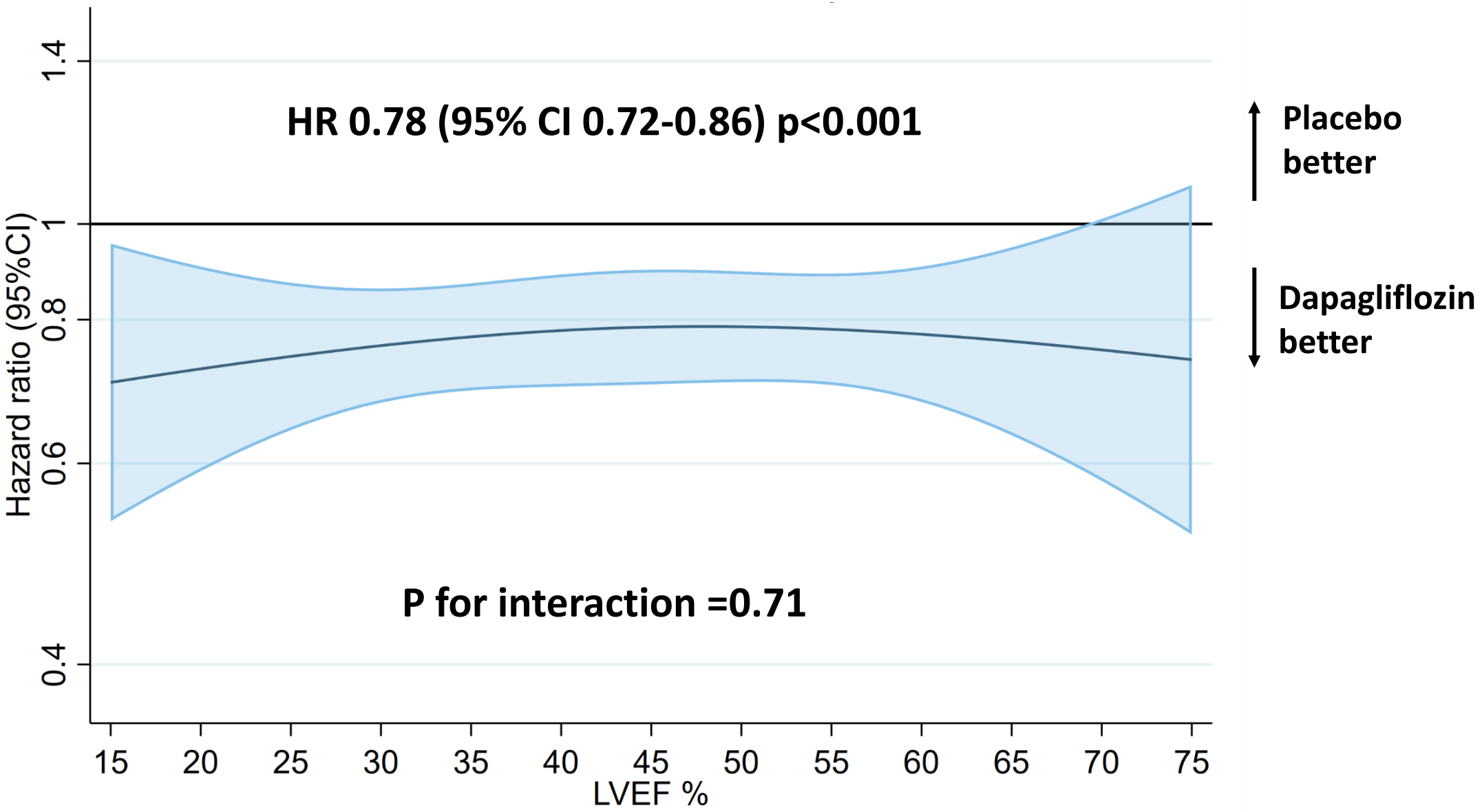
HR 0.74 (95% CI 0.66-0.82) p<0.001



DAPA-HF & DELIVER pooled: CV death/MI/stroke



DAPA-HF & DELIVER: CV death/HF hospitalisation



DAPA-HF & DELIVER pooled: Summary and conclusions

- In a large population with heart failure, dapagliflozin reduced the risk of cardiovascular and all-cause death, heart failure hospitalisations and MACE
- The benefits of dapagliflozin were observed in all patients regardless of ejection fraction
- Most patients with heart failure, regardless of ejection fraction, are likely to benefit from treatment with a SGLT2 inhibitor
- SGLT2 inhibitors could be initiated in patients with a clinical diagnosis of HF and no contraindications while awaiting a measurement of ejection fraction

nature medicine

ANALYSIS

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Dapagliflozin across the range of ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER

Pardeep S. Jhund[1], Toru Kondo[1], Jawad H. Butt[1], Kieran F. Docherty[1], Brian L. Claggett[2], Akshay S. Desai[2], Muthiah Vaduganathan[2], Samvel B. Gasparyan[3], Olof Bengtsson[3], Daniel Lindholm[3], Magnus Petersson[3], Anna Maria Langkilde[3], Rudolf A. de Boer[4], David DeMets[5], Adrian F. Hernandez[6], Silvio E. Inzucchi[7], Mikhail N. Kosiborod[8], Lars Køber[9], Carolyn S. P. Lam[10], Felipe A. Martinez[11], Marc S. Sabatine[12], Sanjiv J. Shah[13], Scott D. Solomon[2] and John J. V. McMurray[1]✉

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