Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus

Results form the DECLARE-TIMI 58 Trial

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On behalf of the DECLARE-TIMI 58 Investigators

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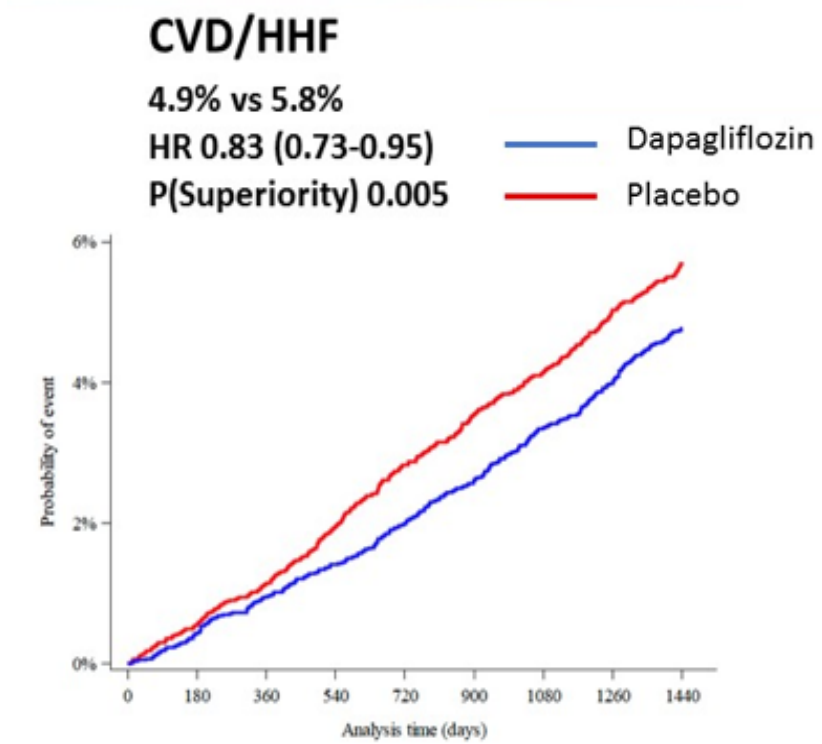
An Affiliate of Harvard Medical School

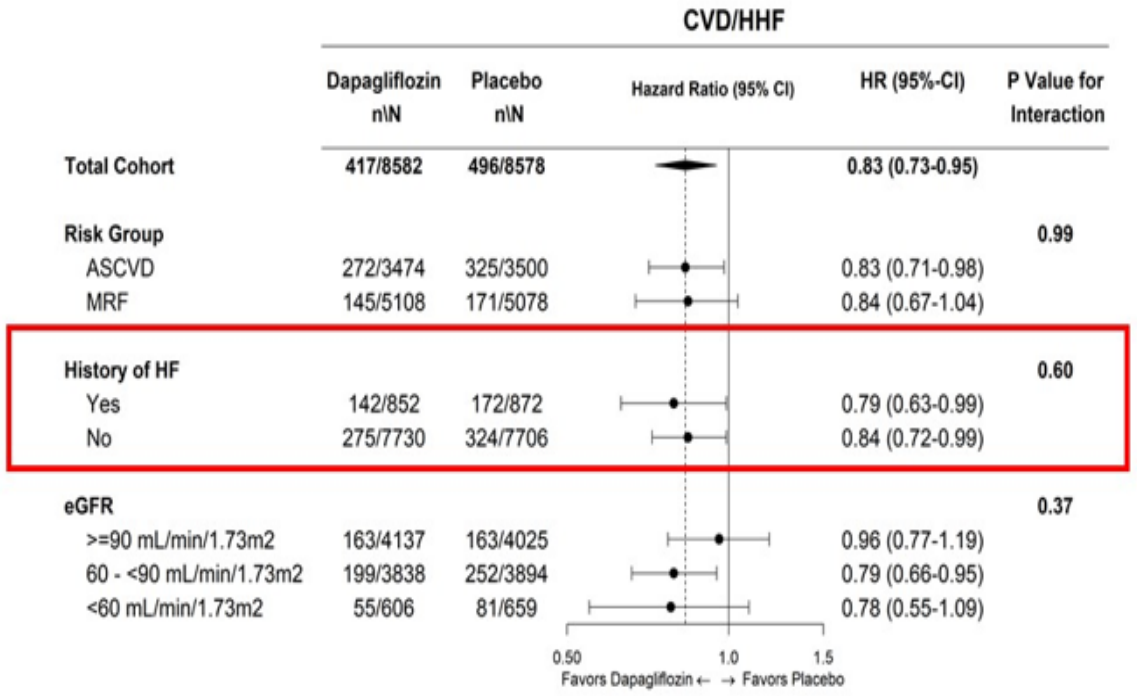
Background

- T2DM is a well-established risk factor for HF.
- SGLT2i have been shown to reduce the risk of CV death/HHF.
- The relationship between LVEF and the clinical benefit of SGLT2i is unknown.

DECLARE-TIMI 58

- 17,160 T2DM pts with established or multiple risk factors for ASCVD were randomized to dapagliflozin 10mg vs placebo.
- Sites were asked to provide data on each patient's most recent LVEF prior to randomization, if available.



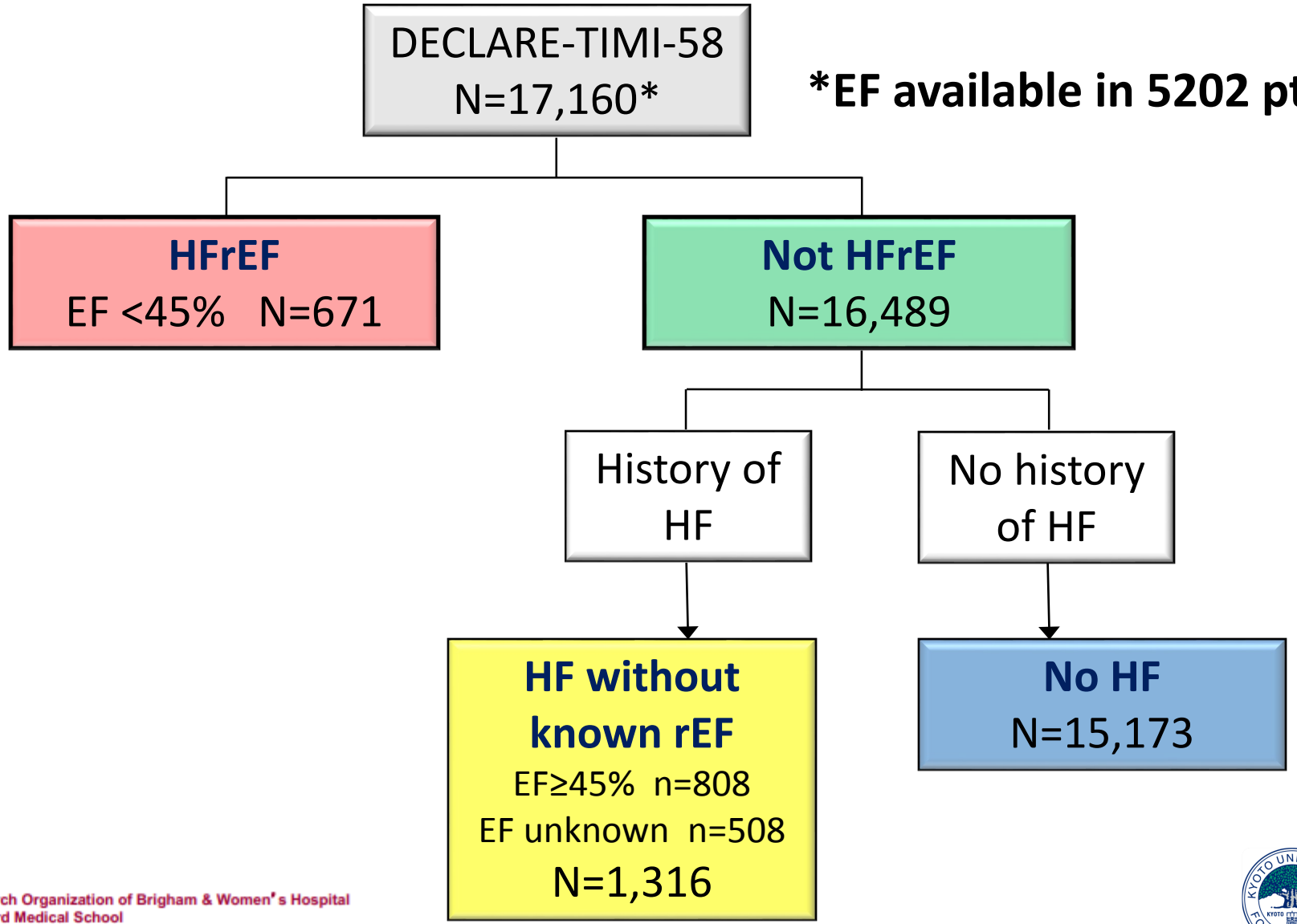


Wiviott et al. NEJM 2019;380 347-357

Aim

Prespecified analysis planned to examine the clinical benefit of dapagliflozin in patients with and without HFrEF.

Methods


DECLARE-TIMI-58
N=17,160*
*EF available in 5202 pts
HFrEF
EF <45% N=671
Not HFrEF
N=16,489
History of HF
No history of HF
HF without known rEF
EF≥45% n=808
EF unknown n=508
N=1,316
No HF
N=15,173

Outcomes of Interest

Outcomes of interest for this study were centrally adjudicated according to FDA consensus criteria:

- CV death/HHF
- CV death
- HHF
- All cause mortality

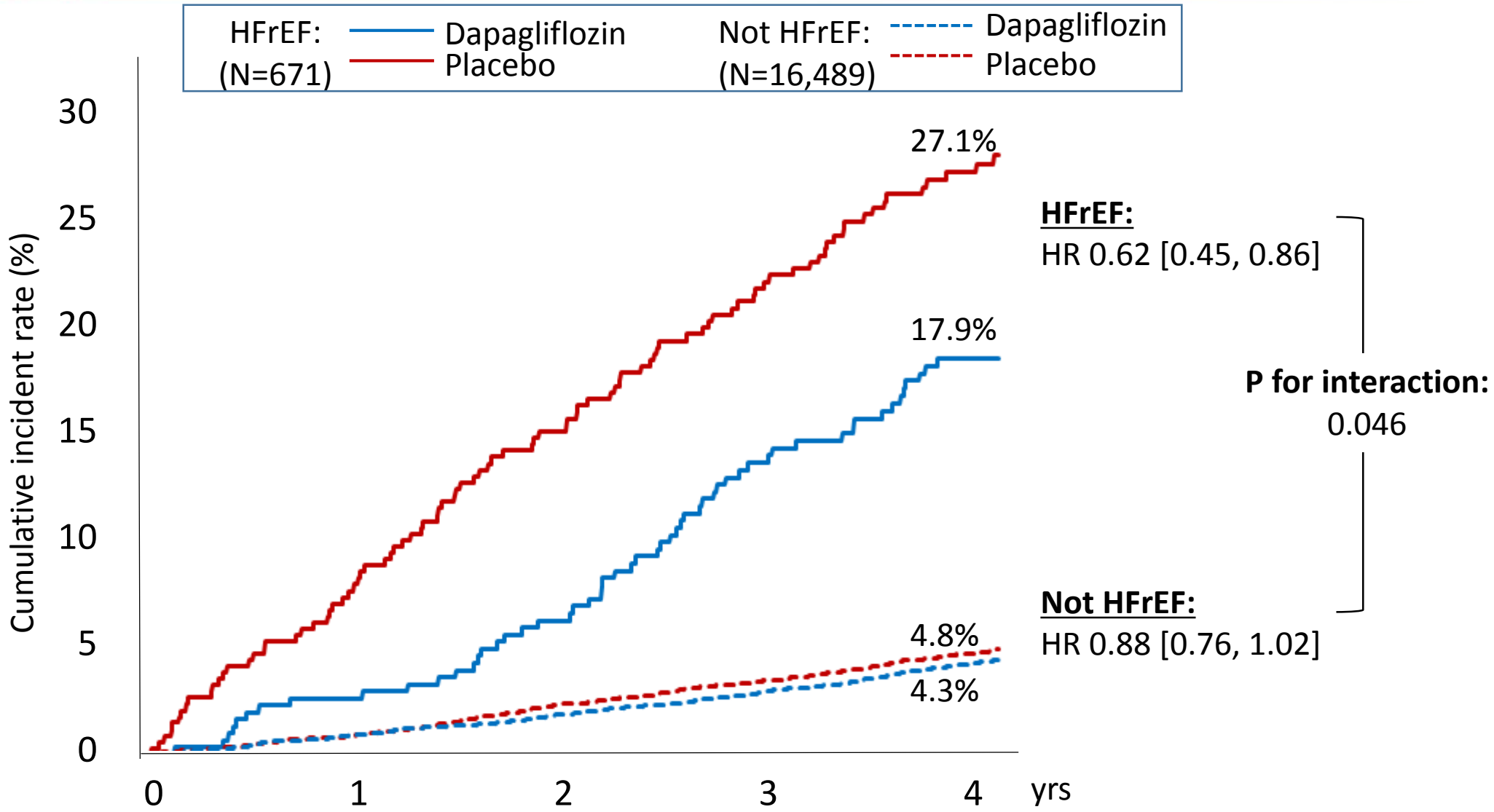
Baseline Characteristics

	HFrEF (n=671)	Not HFrEF (n=16,489)	
		HF without known rEF (n=1,316)	No hx of HF (n=15,173)
Age, yr, median (IQR)	63 (58, 68)	65 (60, 69)	64 (60, 68)
Male (%)	84	57	62
HbA1c, %, median (IQR)	8.1 (7.4, 9.2)	8.2 (7.5, 9.3)	8.0 (7.3, 9.0)
History of hypertension (%)	87	96	90
LVEF, %, median (IQR)	38 (30, 40)	55 (50, 61)	60 (55, 65)
Main etiology of HF (%)			
Ischemic	63	50	NA
Non-Ischemic	15	15	NA
Unknown	21	36	NA
Established ASCVD (%)	86	62	37
eGFR, mL/min/1.73m^2, median (IQR)	83 (66, 95)	86 (70, 96)	89 (76, 97)

Baseline Medications

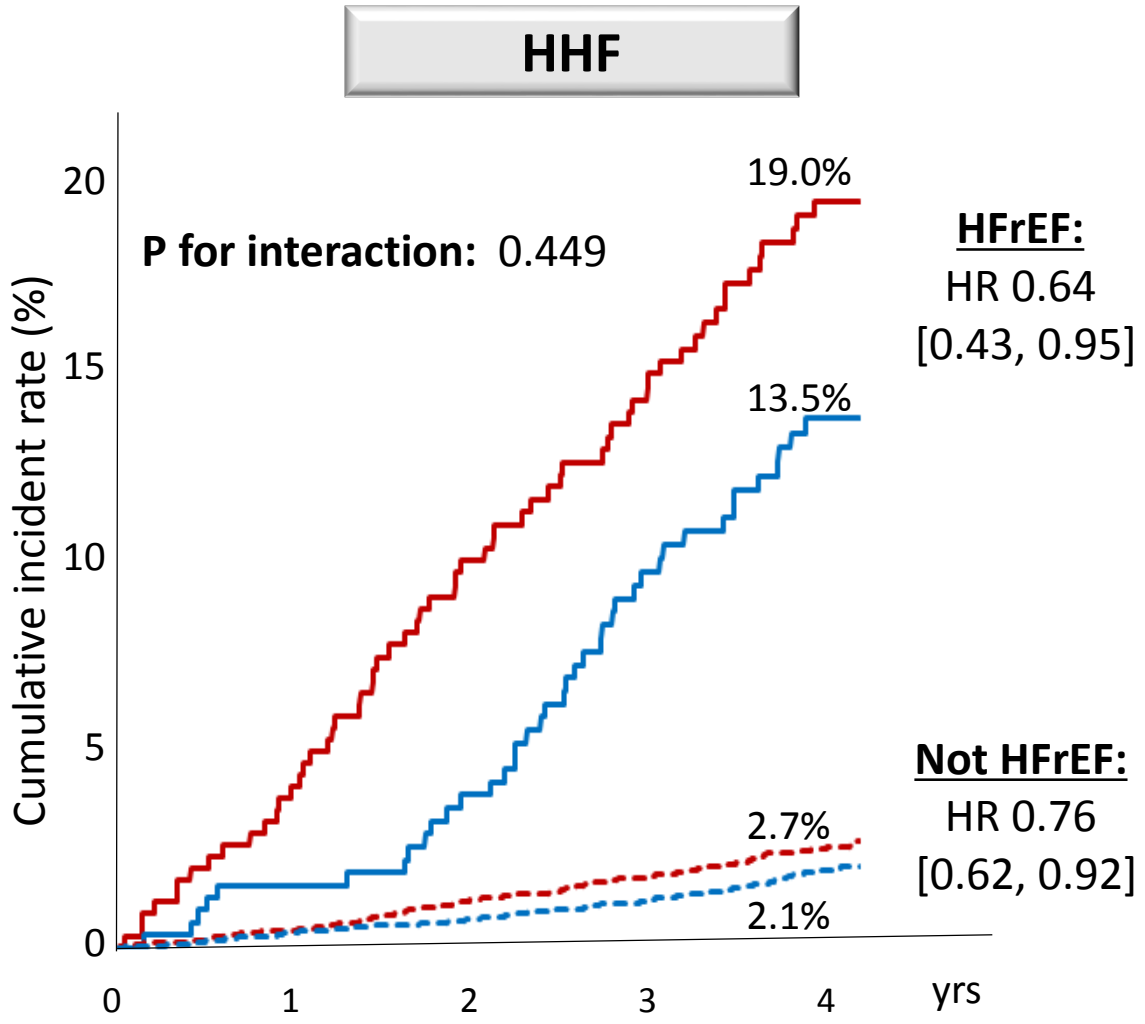
	HFrEF (n=671)	Not HFrEF (n=16,489)	
		HF without known rEF (n=1,316)	No hx of HF (n=15,173)
ACEi or ARB (%)	88	85	81
Beta-blocker (%)	88	77	49
Diuretic (%)	67	63	37
Loop	46	35	7
Thiazide	13	18	23
Mineralocorticoid receptor antagonist (%)	30	14	2

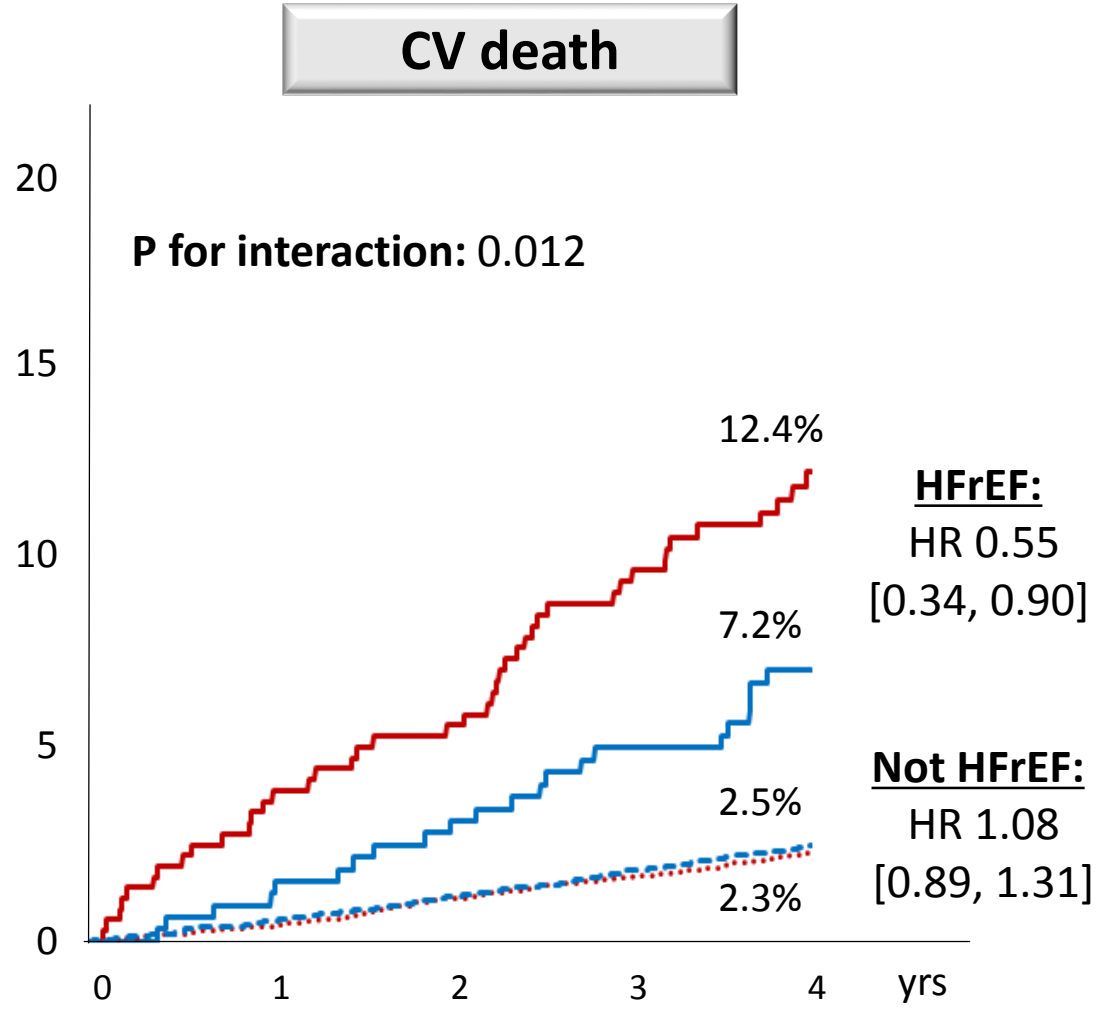
CV Death/HHF
by HFrEF vs not HFrEF subgroups



Not HFrEF defined as pts with HF without known reduced EF and pts without hx of HF

HHF and CV Death
by HFrEF vs not HFrEF subgroups



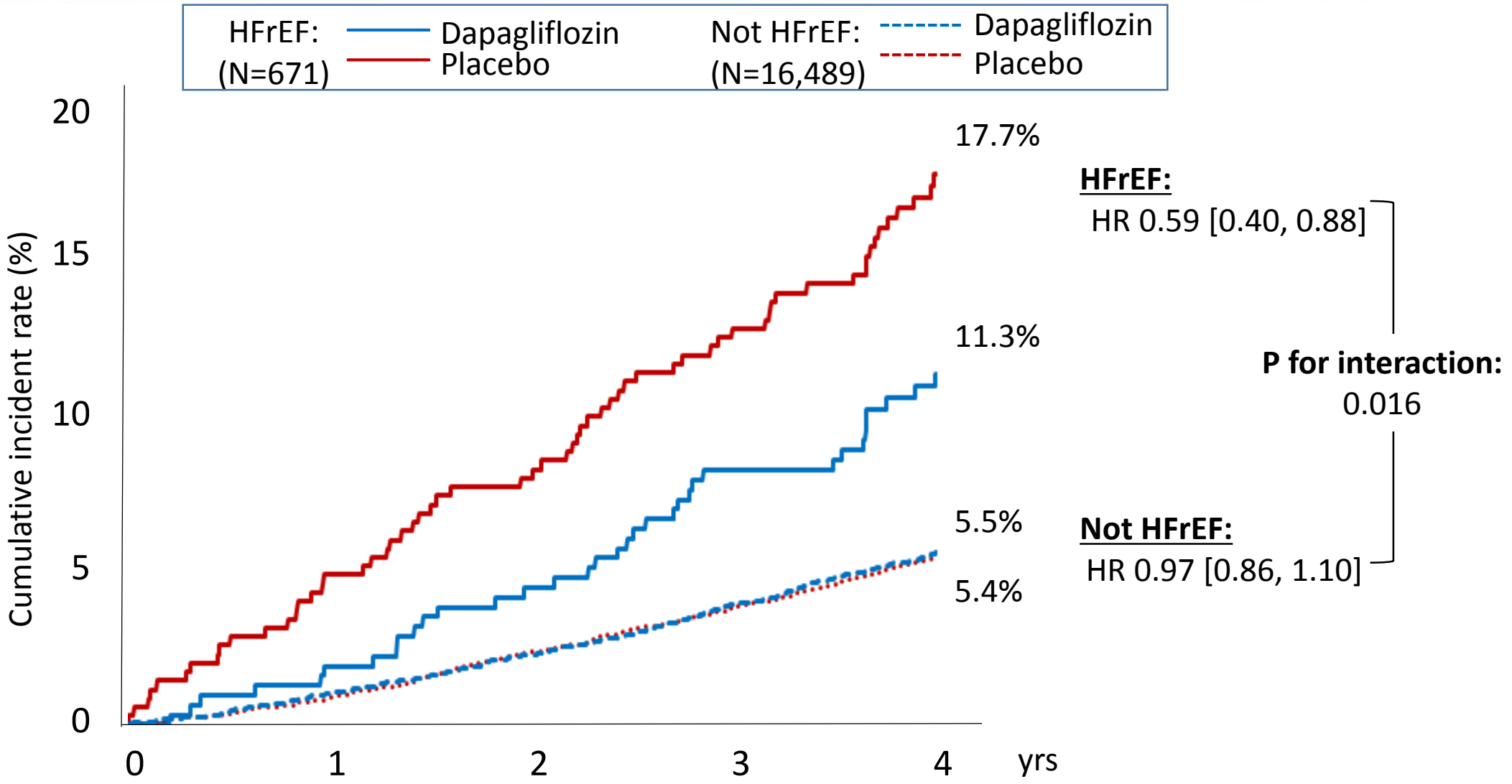


HFrEF: (N=671) — Dapagliflozin; Placebo

Not HFrEF: (N=16,489) — Dapagliflozin; Placebo

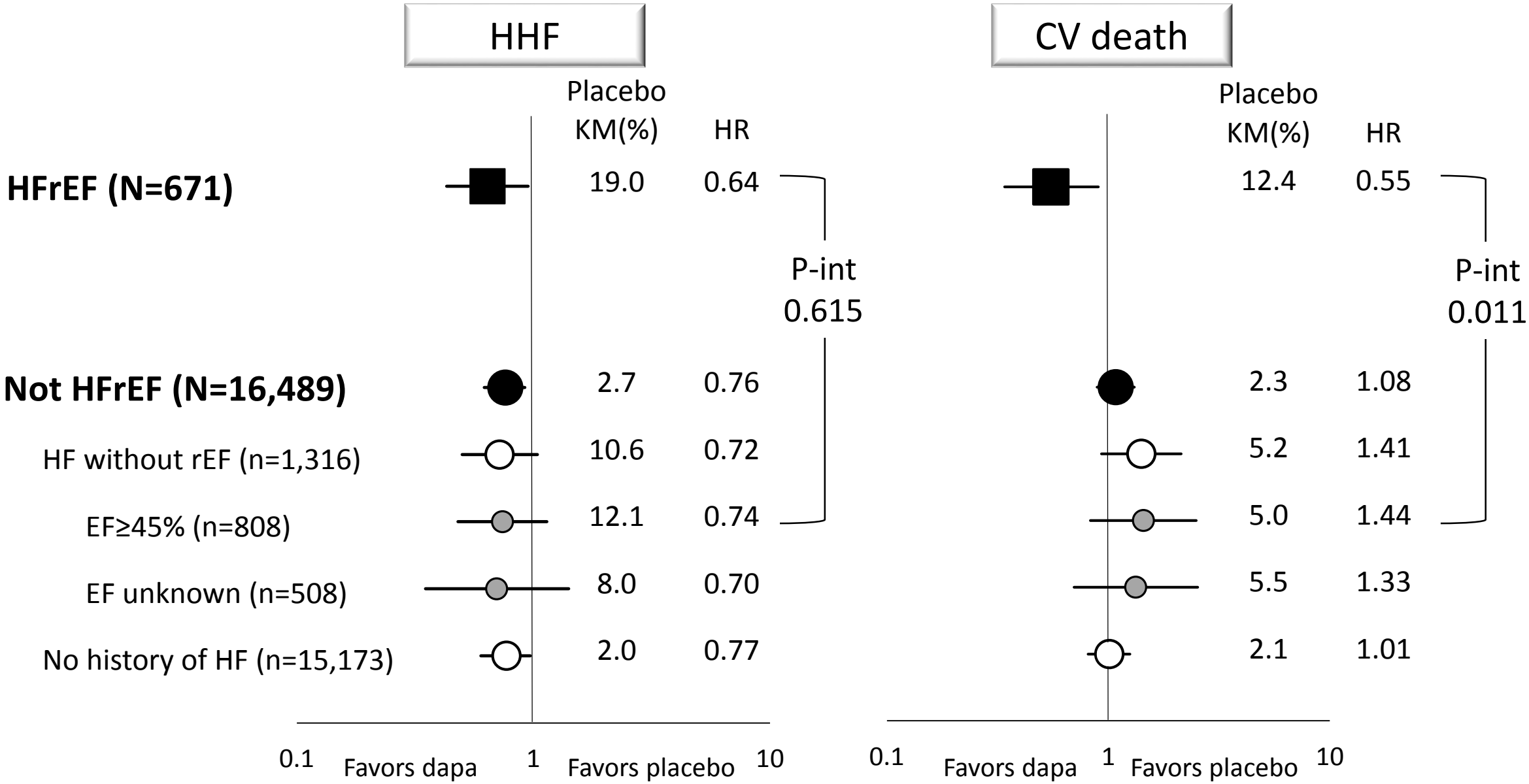
Not HFrEF defined as pts with HF without known reduced EF and pts without hx of HF

All Cause Mortality
by HFrEF vs not HFrEF subgroups

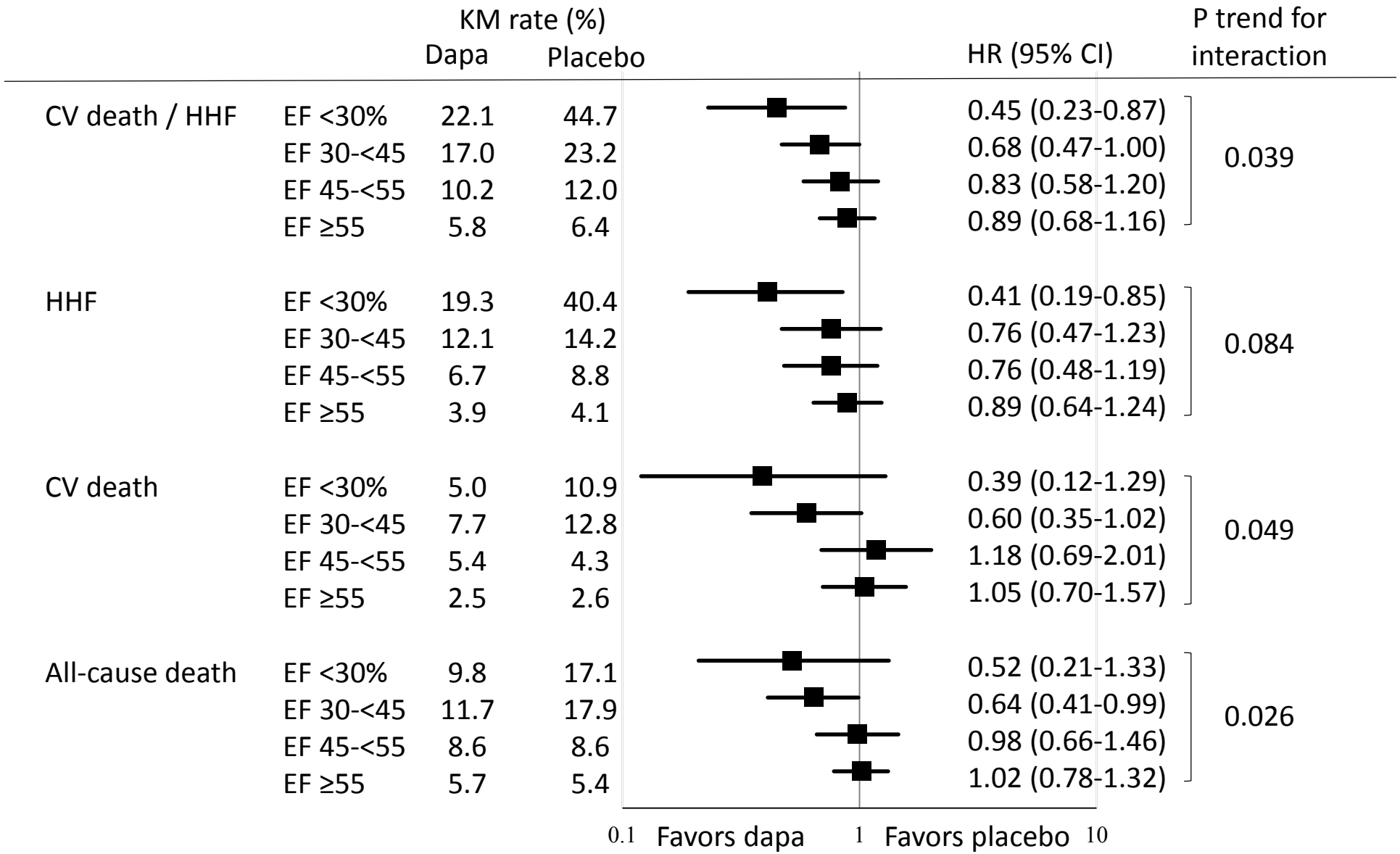


Not HFrEF defined as pts with HF without known reduced EF and pts without hx of HF

Sensitivity Analysis



Outcomes by Different EF



Safety Events

		Dapagliflozin (%)	Placebo (%)	HR (95% CI)	P-interaction
Serious adverse event	*HFrEF*	56.9	58.8	0.87 (0.71-1.07)	0.754
	Not HFrEF	35.7	38.4	0.91 (0.87-0.96)	
Symptoms of volume depletion	*HFrEF*	7.5	5.6	1.52 (0.79-2.93)	0.204
	Not HFrEF	2.5	2.6	0.96 (0.79-1.18)	
Acute renal failure	*HFrEF*	8.2	14.0	0.57 (0.34-0.96)	0.240
	Not HFrEF	3.4	4.6	0.78 (0.66-0.91)	

Limitations

- Baseline EF available in 5,202/17,160 of randomized pts
  - Consistent with a population of ~40% with established ASCVD and 12% with history of HF
  - Largest data available to date

- No universally acknowledged definition for HFpEF and predefined EF cutpoint of 45% used
  - Results consistent using various EF cutpoints

- A subgroup mortality benefit in trial with overall neutral effect on mortality should be interpreted cautiously

Ongoing Trials in Patients with Known HF

- HFrEF
  - Dapa-HF
  - EMPEROR-Reduced
- HFpEF
  - DELIVER
  - PRESERVED-HF
  - EMPEROR-Preserved

Summary

- Patients with HFrEF are at the highest risk for CV events and mortality.
- Treatment with dapagliflozin resulted in a lower rate of HHF vs placebo in a broad spectrum of patients including those with preserved EF.
- Dapagliflozin reduced CV death (NNT_{4y}=19) and all-cause mortality (NNT_{4y}=16) in patients with HFrEF, but not in those without HFrEF.
- These benefits were seen with similar safety profile for dapagliflozin regardless of HF status.

Conclusions

The use of the SGLT2 inhibitor dapagliflozin:

- Is beneficial in reducing HHF in patients with a broad range of LVEF.
- May provide an even greater benefit with lower CV death and mortality in patients with HFrEF.

Additional Information

Circulation

Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus

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