Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus
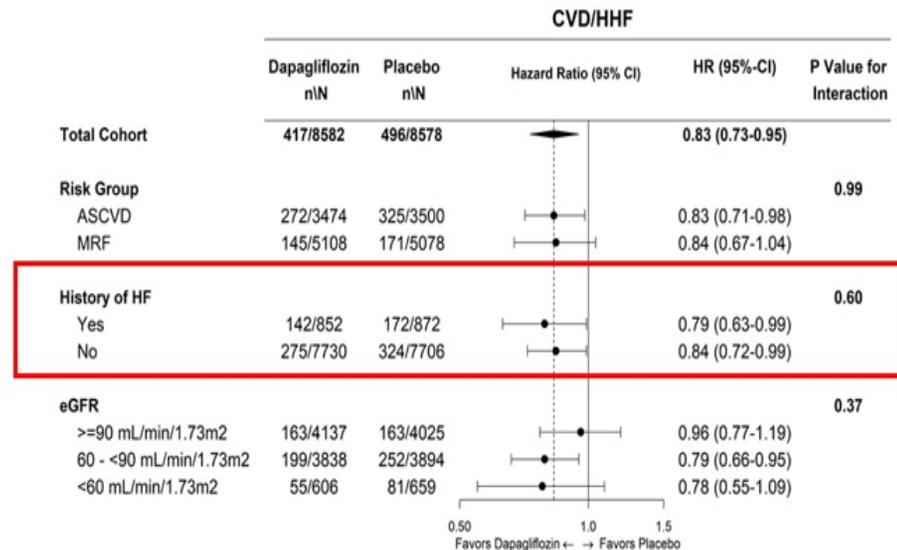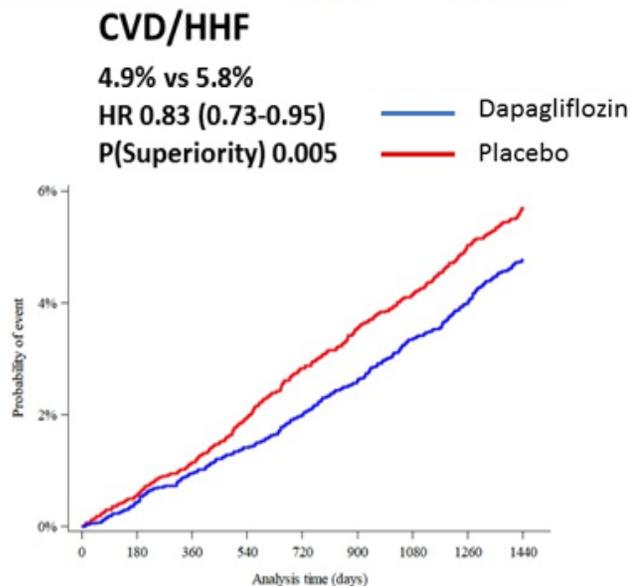
Results form the DECLARE-TIMI 58 Trial

Eri T. Kato, Michael G. Silverman, Ofri Mosenzon, Thomas A. Zelniker, Avivit Cahn, Remo H.M. Furtado, Julia Kuder, Sabina A. Murphy, Deepak L. Bhatt, Lawrence A. Leiter, Darren K. McGuire, John P.H. Wilding, Marc P. Bonaca, Christian T. Ruff, Akshay S. Desai, Shinya Goto, Peter A. Johansson, Ingrid Gause-Nilsson, Per Johanson, Anna Maria Langkilde, Itamar Raz, Marc S. Sabatine and Stephen D. Wiviott

On behalf of the DECLARE-TIMI 58 Investigators

An Academic Research Organization of Brigham & Women's Hospital
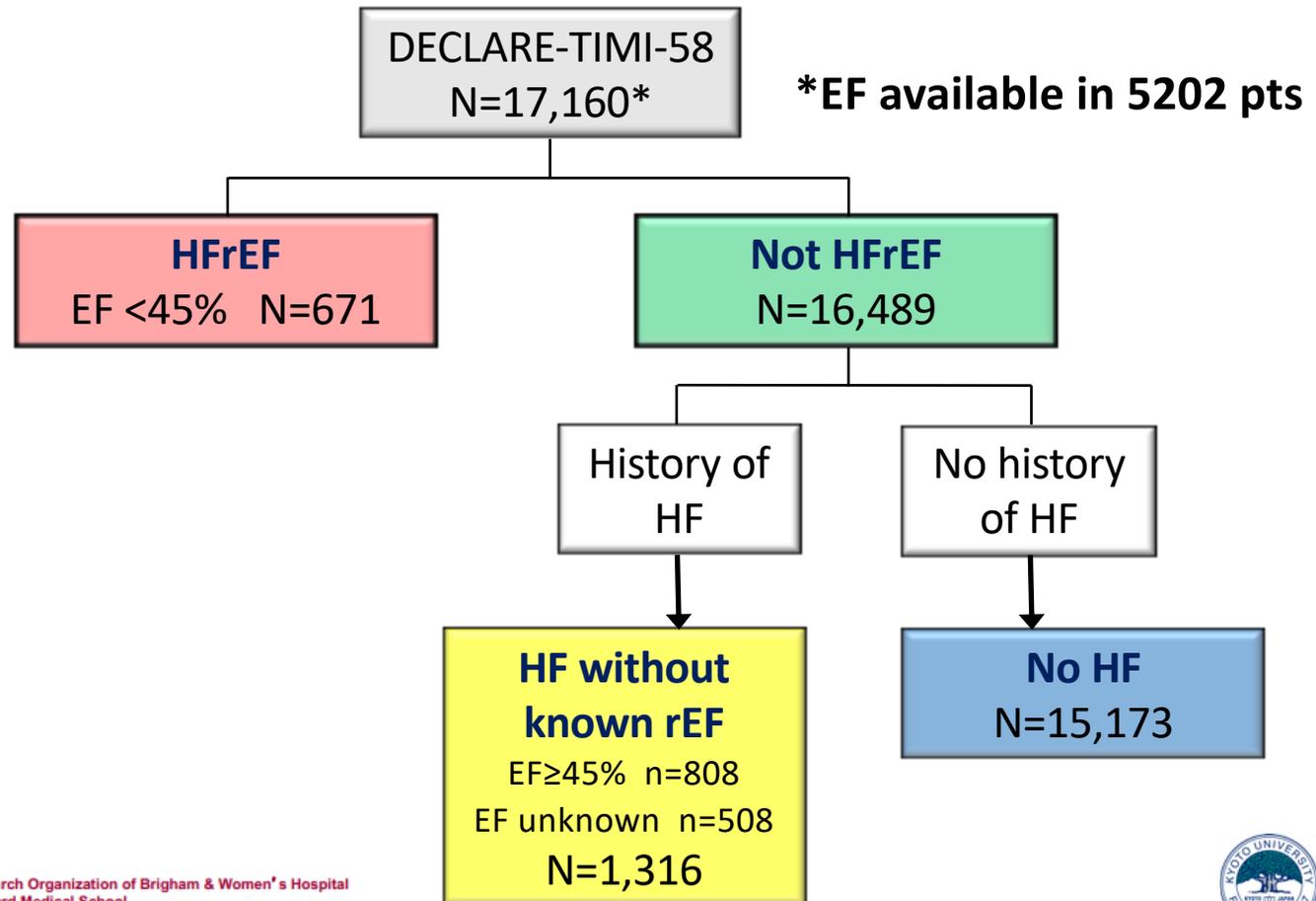An Affiliate of Harvard Medical School

➢ 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.

➤ 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.

CVD/HHF

4.9% vs 5.8%
HR 0.83 (0.73-0.95)
P(Superiority) 0.005

— Dapagliflozin
— Placebo

	Dapagliflozin n\N	Placebo n\N	Hazard Ratio (95% CI)	HR (95%-CI)	P Value for Interaction
Total Cohort	417/8582	496/8578		0.83 (0.73-0.95)	
Risk Group					0.99
ASCVD	272/3474	325/3500		0.83 (0.71-0.98)	
MRF	145/5108	171/5078		0.84 (0.67-1.04)	
History of HF					0.60
Yes	142/852	172/872		0.79 (0.63-0.99)	
No	275/7730	324/7706		0.84 (0.72-0.99)	
eGFR					0.37
>=90 mL/min/1.73m2	163/4137	163/4025		0.96 (0.77-1.19)	
60 - <90 mL/min/1.73m2	199/3838	252/3894		0.79 (0.66-0.95)	
<60 mL/min/1.73m2	55/606	81/659		0.78 (0.55-1.09)	

CVD/HHF

0.50   1.0   1.5
Favors Dapagliflozin ← → Favors Placebo

Wiviott et al. NEJM 2019;380 347-357

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

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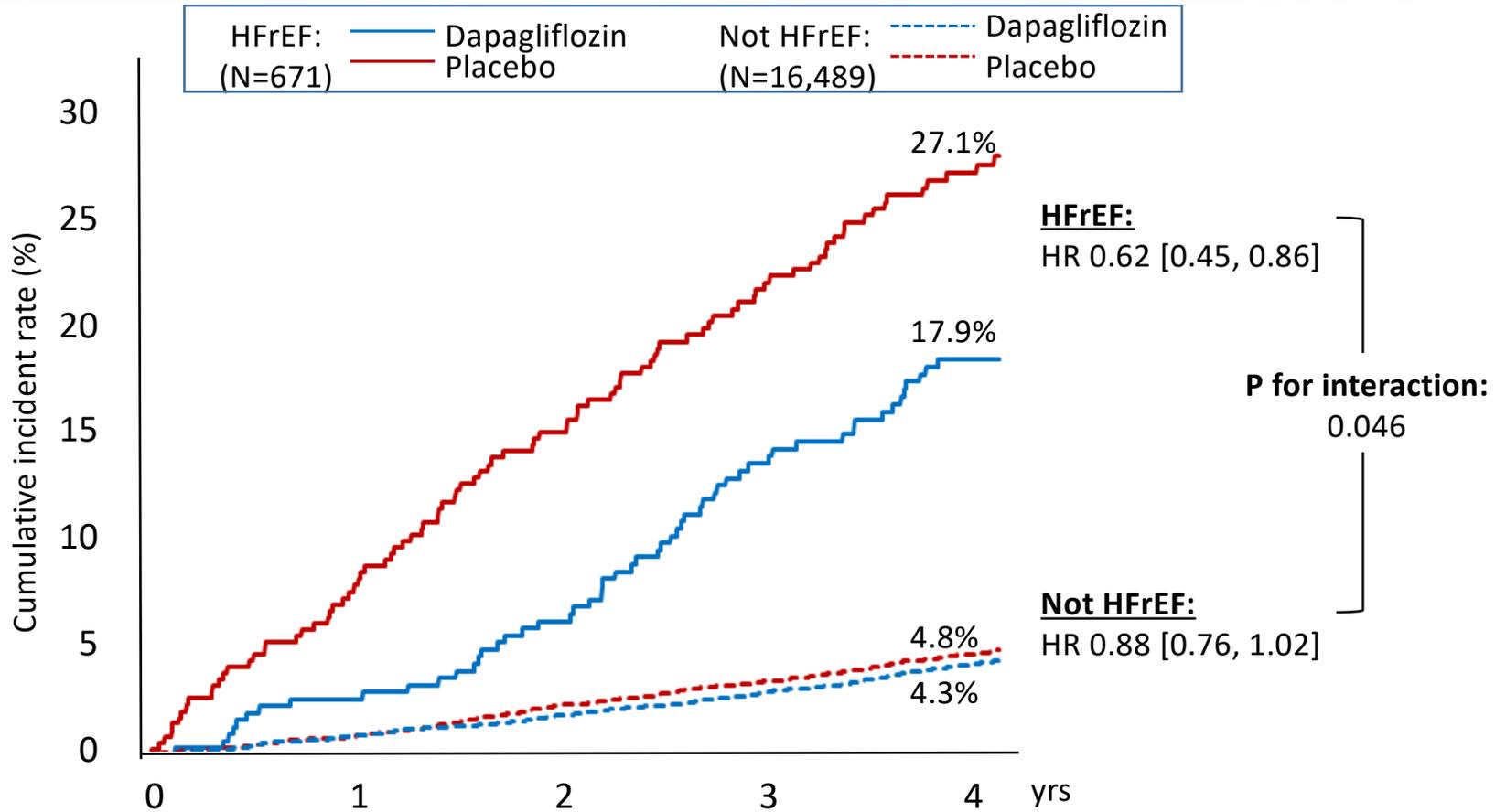- HHF
- All cause mortality

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

HFrEF: ——— Dapagliflozin
(N=671)   Placebo

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

Cumulative incident rate (%)

30
27.1%

25

HFrEF:
HR 0.62 [0.45, 0.86]

20
17.9%

P for interaction:
0.046

15

10

Not HFrEF:
HR 0.88 [0.76, 1.02]

5
4.8%
4.3%

0

0   1   2   3   4   yrs

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

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HHF and CV Death
by HFrEF vs not HFrEF subgroups

HHF

Cumulative incident rate (%)

P for interaction: 0.449

19.0%

13.5%

2.7%

2.1%

HFrEF:
HR 0.64
[0.43, 0.95]

Not HFrEF:
HR 0.76
[0.62, 0.92]

0 1 2 3 4   yrs

CV death

P for interaction: 0.012

12.4%

7.2%

2.5%

2.3%

HFrEF:
HR 0.55
[0.34, 0.90]

Not HFrEF:
HR 1.08
[0.89, 1.31]

0 1 2 3 4   yrs
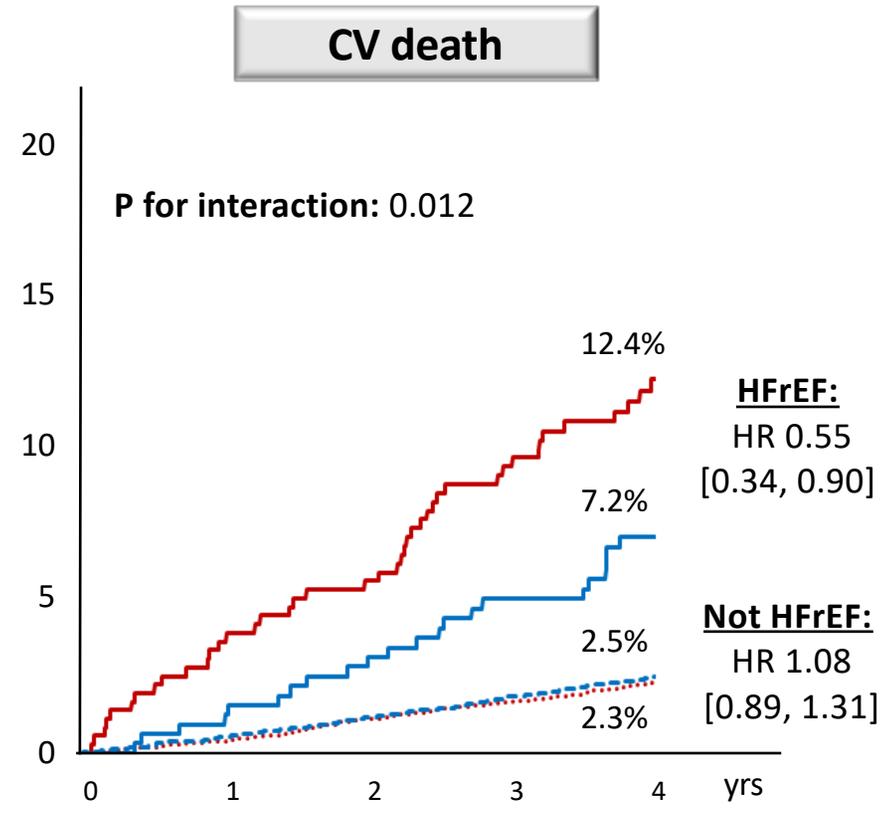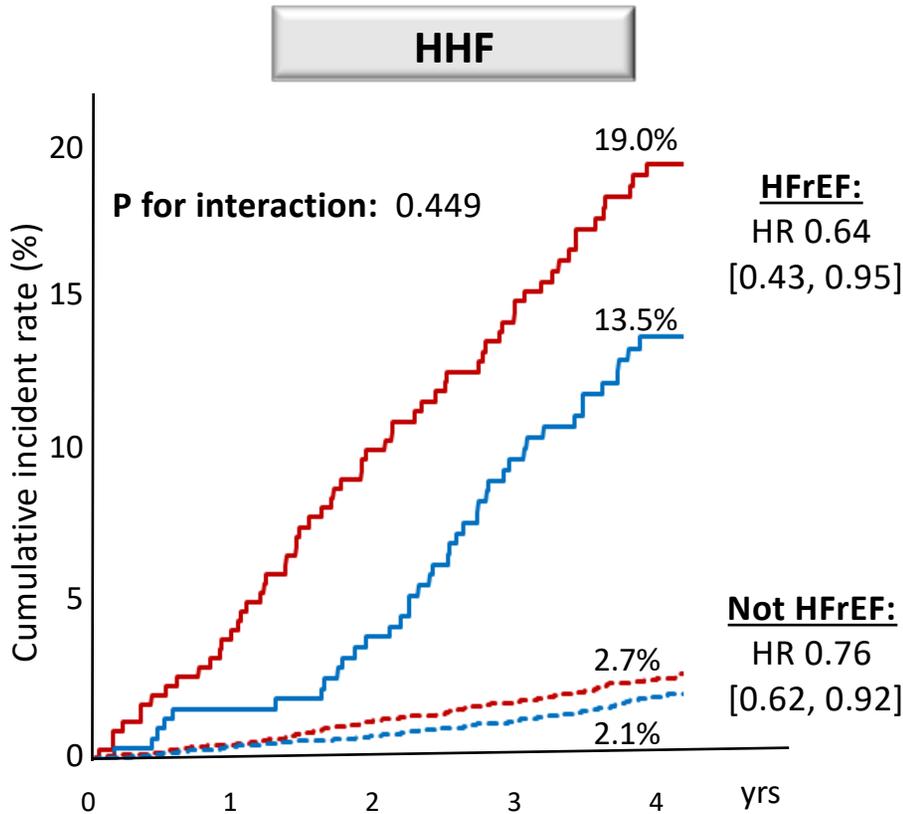
HFrEF: ——— Dapagliflozin   Not HFrEF: ------ Dapagliflozin
(N=671)   ——— Placebo   (N=16,489)   ------ Placebo

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

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All Cause Mortality
by HFrEF vs not HFrEF subgroups

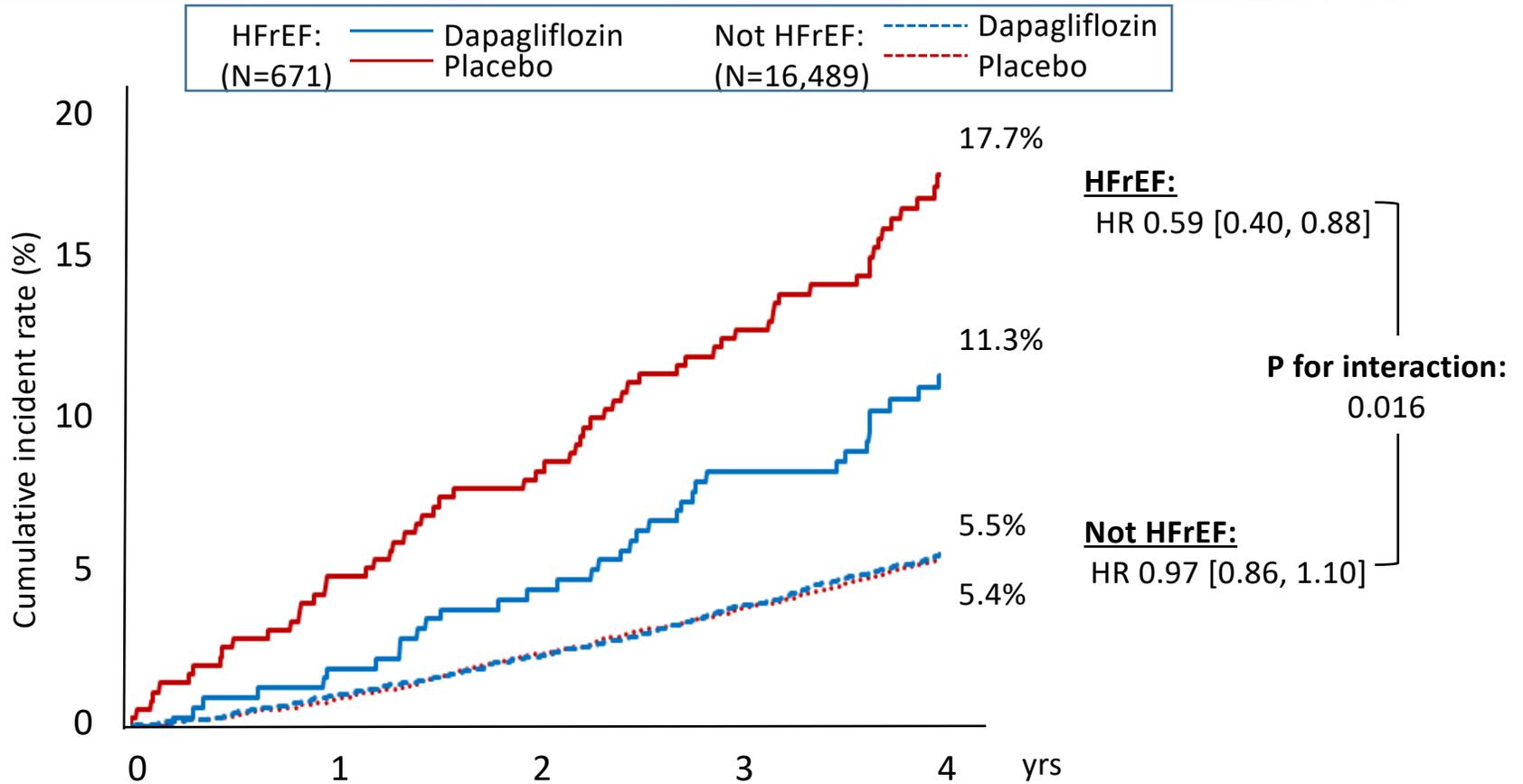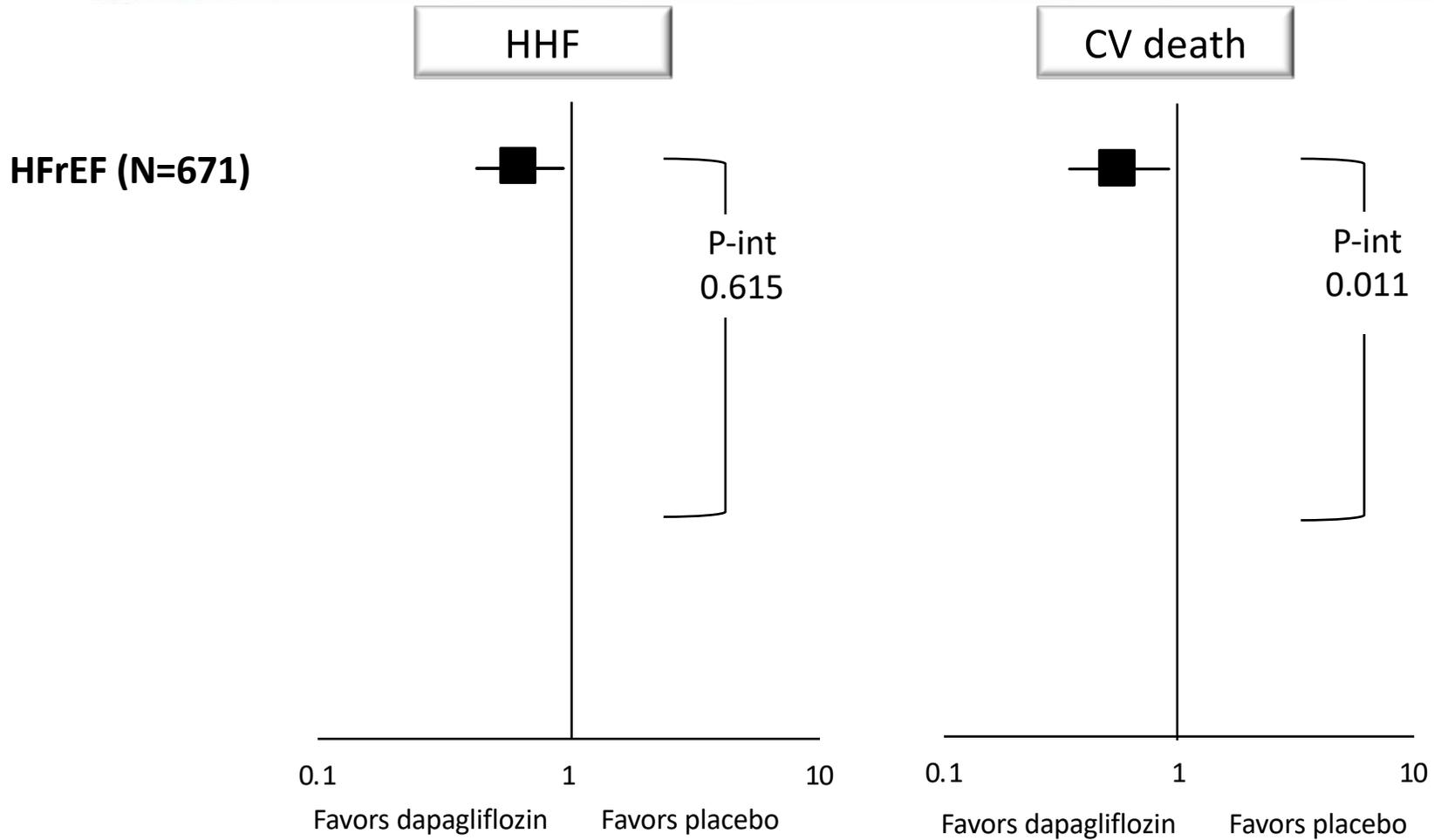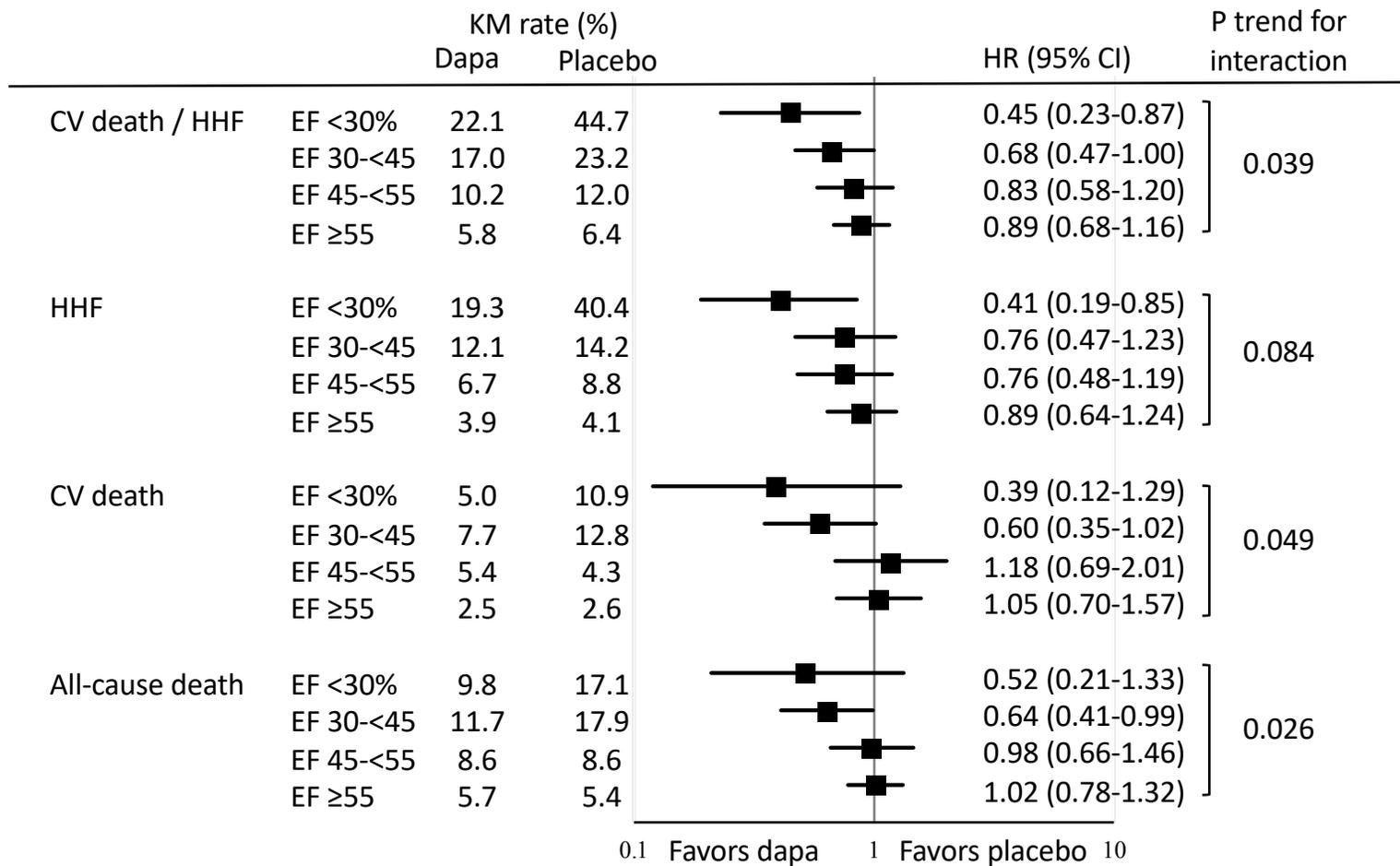*Not HFrEF defined as pts with HF without known reduced EF and pts without hx of HF*

Sensitivity Analysis

HHF

CV death

HFrEF (N=671)

P-int
0.615

P-int
0.011

0.1   1   10

0.1   1   10

Favors dapagliflozin   Favors placebo

Favors dapagliflozin   Favors placebo

Outcomes by Different EF

		KM rate (%)			HR (95% CI)	P trend for interaction
		Dapa	Placebo			
CV death / HHF	EF <30%	22.1	44.7		0.45 (0.23-0.87)	
	EF 30-<45	17.0	23.2		0.68 (0.47-1.00)	0.039
	EF 45-<55	10.2	12.0		0.83 (0.58-1.20)	
	EF ≥55	5.8	6.4		0.89 (0.68-1.16)	
HHF	EF <30%	19.3	40.4		0.41 (0.19-0.85)	
	EF 30-<45	12.1	14.2		0.76 (0.47-1.23)	0.084
	EF 45-<55	6.7	8.8		0.76 (0.48-1.19)	
	EF ≥55	3.9	4.1		0.89 (0.64-1.24)	
CV death	EF <30%	5.0	10.9		0.39 (0.12-1.29)	
	EF 30-<45	7.7	12.8		0.60 (0.35-1.02)	0.049
	EF 45-<55	5.4	4.3		1.18 (0.69-2.01)	
	EF ≥55	2.5	2.6		1.05 (0.70-1.57)	
All-cause death	EF <30%	9.8	17.1		0.52 (0.21-1.33)	
	EF 30-<45	11.7	17.9		0.64 (0.41-0.99)	0.026
	EF 45-<55	8.6	8.6		0.98 (0.66-1.46)	
	EF ≥55	5.7	5.4		1.02 (0.78-1.32)	

0.1   Favors dapa   1   Favors placebo   10

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

➤ 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.

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.

Circulation

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Diabetes Mellitus

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