EMPEROR-Reduced Trial

Effect of Empagliflozin on Cardiovascular and Renal Events in Heart Failure With a Reduced Ejection Fraction

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Disclosures for presenter: Abbvie, Actavis, Akcea, Amgen, Amarin, AstraZeneca, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Eli LillyJohnson & Johnson, NovoNordisk, Pfizer, Relypsa, Sanofi, Synthetic Biologics and Theravance

Background and Study Design

- In DAPA-HF, dapagliflozin improved outcomes in patients with heart failure and a reduced ejection fraction (with or without diabetes), largely those mild-to-moderate LV systolic dysfunction and increases in natriuretic peptides.

- In the EMPEROR-Reduced trial, we evaluated the effects of empagliflozin in a broad population of patients with chronic heart failure and a reduced ejection fraction (with and without diabetes) that was enriched for patients with more severe left ventricular systolic dysfunction and marked increases in natriuretic peptides.

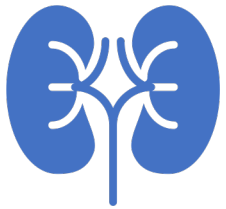
- Our goal was to enroll a patient population that was particularly enriched for those with an ejection fraction ≤ 30%. If the ejection fraction was > 30%, eligible patients were required to show very high levels of NTproBNP or a hospitalization for heart failure within 12 months.

- Eligible patients were randomized double-blind (1:1 ratio) to empagliflozin 10 mg once daily or placebo, in addition to their usual therapy.

EMPEROR-Reduced Trial Specified Only Three Endpoints to be Tested in Hierarchical Manner

Primary Endpoint
Composite of cardiovascular death or heart failure hospitalization

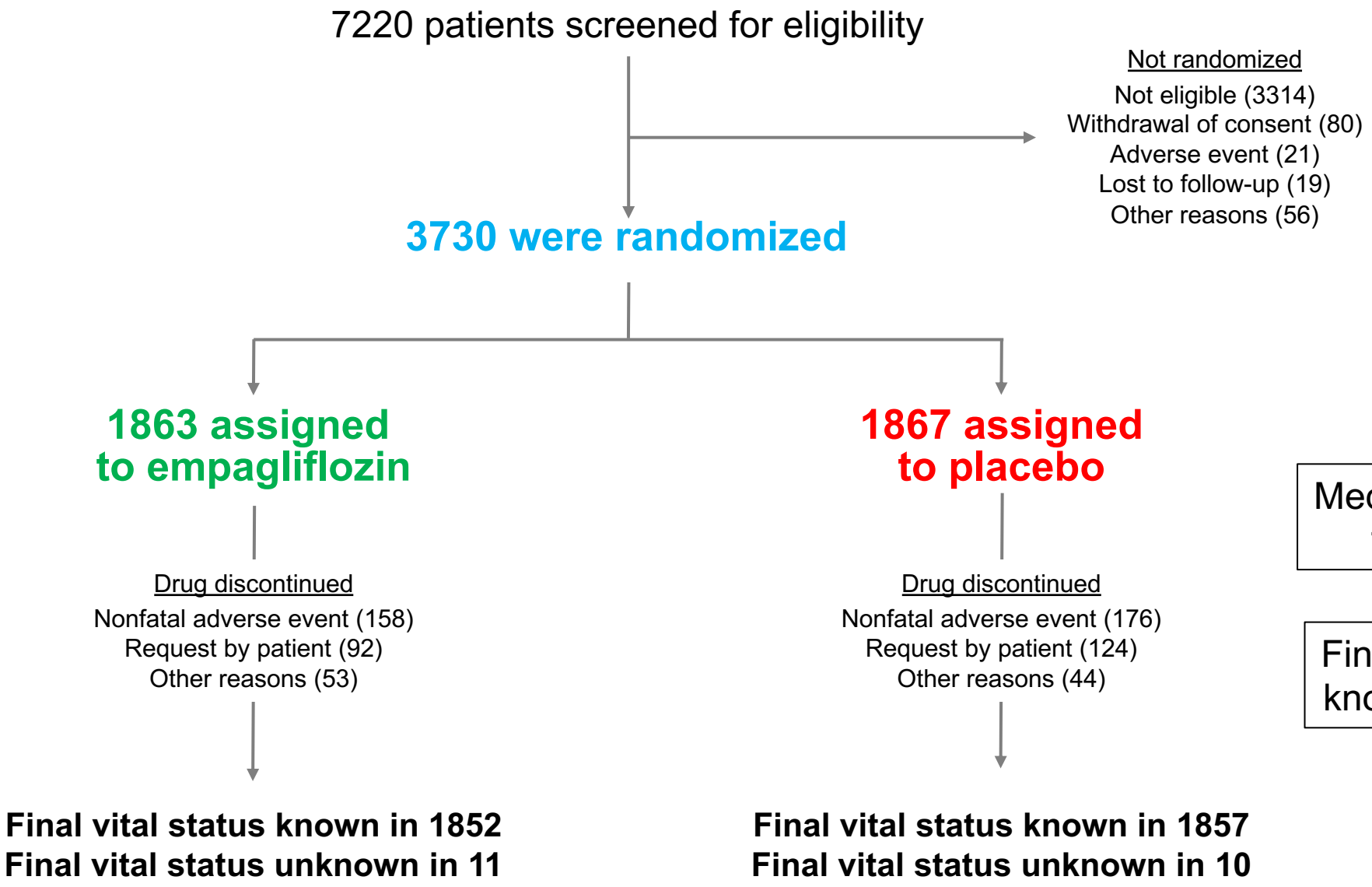
First Secondary Endpoint
Total (first and recurrent heart failure hospitalizations)



Second Secondary Endpoint
Slope of decline in glomerular filtration rate over time

Other prespecified endpoints: Composite renal endpoint, KCCQ clinical summary score, total number of hospitalizations for any reason, all-cause mortality, new onset diabetes

EMPEROR-Reduced: Patient Disposition



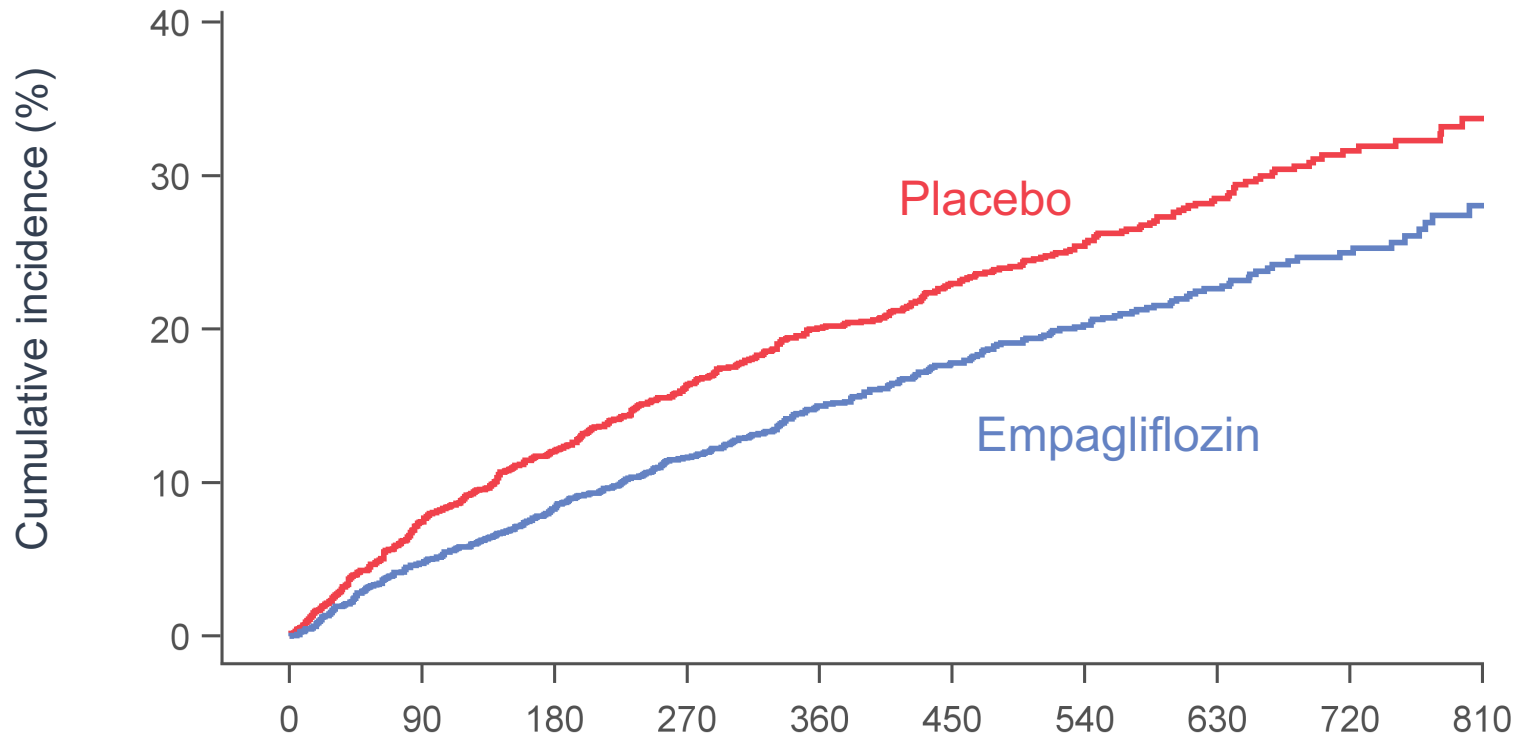
Median follow-up 16 months

Final vital status known in 99.4%

Baseline Characteristics

	EMPEROR-Reduced		DAPA-HF
	Empagliflozin (n=1863)	**Placebo (n=1867)**	**Dapagliflozin (n=2373)**
Age (yr)	67.2 ± 10.8	66.5 ± 11.2	66.2 ± 11.0
Women (%)	437 (23.5)	456 (24.4)	564 (23.8)
Diabetes mellitus (%)	927 (49.8)	929 (49.8)	993 (41.8)
Ischemic cardiomyopathy (%)	983 (52.8)	946 (50.7)	1316 (55.5%)
NYHA functional class II (%)	1399 (75.1)	1401 (75.0)	1606 (67.7%)
LV ejection fraction (%)	**27.7 ± 6.0 (72% ≤30%)**	**27.2 ± 6.1 (75% ≤30%)**	**31.2±6.7**
NT-proBNP (median, IQR), pg/mL	**1887 (1077, 3429) (79% ≥1000)**	**1926 (1153, 3525) (80% ≥1000)**	**1428 (857-2655)**
Hospitalization for heart failure within 12 months	577 (31.0)	574 (30.7)	1124 (47.4)
Atrial fibrillation	664 (35.6)	705 (37.8)	916 (38.6)
Glomerular filtration rate (ml/min/1.73 m^2)	**61.8 ± 21.7**	**62.2 ± 21.5**	**66.0 ± 19.6**
Treatment for heart failure			
RAS inhibitor without neprilysin inhibitor	1314 (70.5)	1286 (68.9)	2007 (84.6)
RAS inhibitor with neprilysin inhibitor	**340 (18.3)**	**387 (20.7)**	**250 (10.5)**
Mineralocorticoid receptor antagonist	1306 (70.1)	1355 (72.6)	1696 (71.5)
Beta blocker	1765 (94.7)	1768 (94.7)	2278 (96.0)
Implantable cardioverter-defibrillator	578 (31.0)	593 (31.8)	622 (26.2%)
Cardiac resynchronization therapy	220 (11.8)	222 (11.9)	190 (8.0%)

EMPEROR-Reduced: Time to Cardiovascular Death or Hospitalization for Heart Failure (Primary Endpoint)



462 patients with event
Rate: 21.0/100 patient-years

361 patients with event
Rate: 15.8/100 patient-years

HR 0.75
(95% CI 0.65, 0.86)
P < 0.0001

Patients at risk

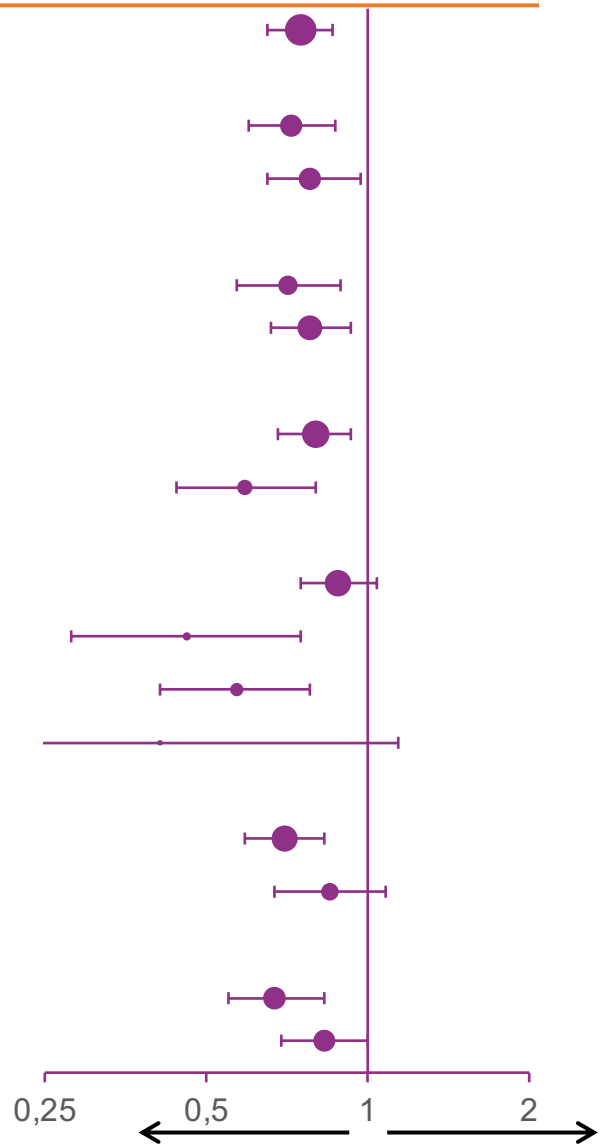
Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

EMPEROR-Reduced: Effect on Individual Components of the Primary Endpoint

	Empagliflozin (n=1863)		Placebo (n=1867)		Hazard ratio (95% CI)	P value
	Number of events (%)	Events/100 patient-yr	Number of events (%)	Events/100 patient-yr		
Primary composite outcome	361 (19.4%)	15.8	462 (24.7%)	21.0	0.75 (0.65 – 0.86)	<0.0001
First hospitalization for heart failure	246 (13.2%)	10.7	342 (18.3%)	15.5	0.69 (0.59 – 0.81)	
Cardiovascular death	187 (10.0%)	7.6	202 (10.8%)	8.1	0.92 (0.75 – 1.12)	

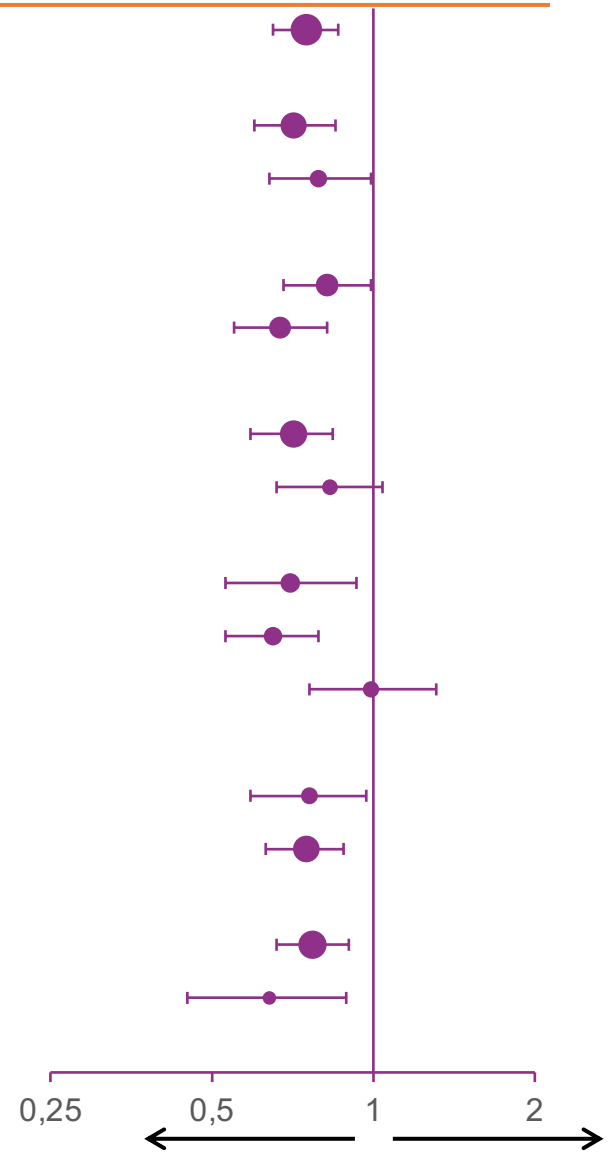
EMPEROR-Reduced: Primary Endpoint Subgroups

	Empagliflozin	Placebo	
	n with event/N analysed		Hazard ratio (95% CI)
Overall	361/1863	462/1867	0.75 (0.65, 0.86)
Baseline diabetes status			
Diabetic	200/927	265/929	0.72 (0.60, 0.87)
Non-diabetic	161/936	197/938	0.78 (0.64, 0.97)
Age, years			
<65	128/675	193/740	0.71 (0.57, 0.89)
≥65	233/1188	269/1127	0.78 (0.66, 0.93)
Sex			
Male	294/1426	353/1411	0.80 (0.68, 0.93)
Female	67/437	109/456	0.59 (0.44, 0.80)
Race			
White	264/1325	289/1304	0.88 (0.75, 1.04)
Black/African-American	24/123	48/134	0.46 (0.28, 0.75)
Asian	62/337	99/335	0.57 (0.41, 0.78)
Other	5/51	14/63	0.41 (0.15, 1.14)
Body mass index (kg/m^2)			
<30	226/1263	322/1300	0.70 (0.59, 0.83)
≥30	135/600	140/567	0.85 (0.67, 1.08
Baseline eGFR (CKD-EPI), ml/min/1.73 m^2			
<60	159/969	224/960	0.67 (0.55, 0.83)
≥60	202/893	237/906	0.83 (0.69, 1.00)

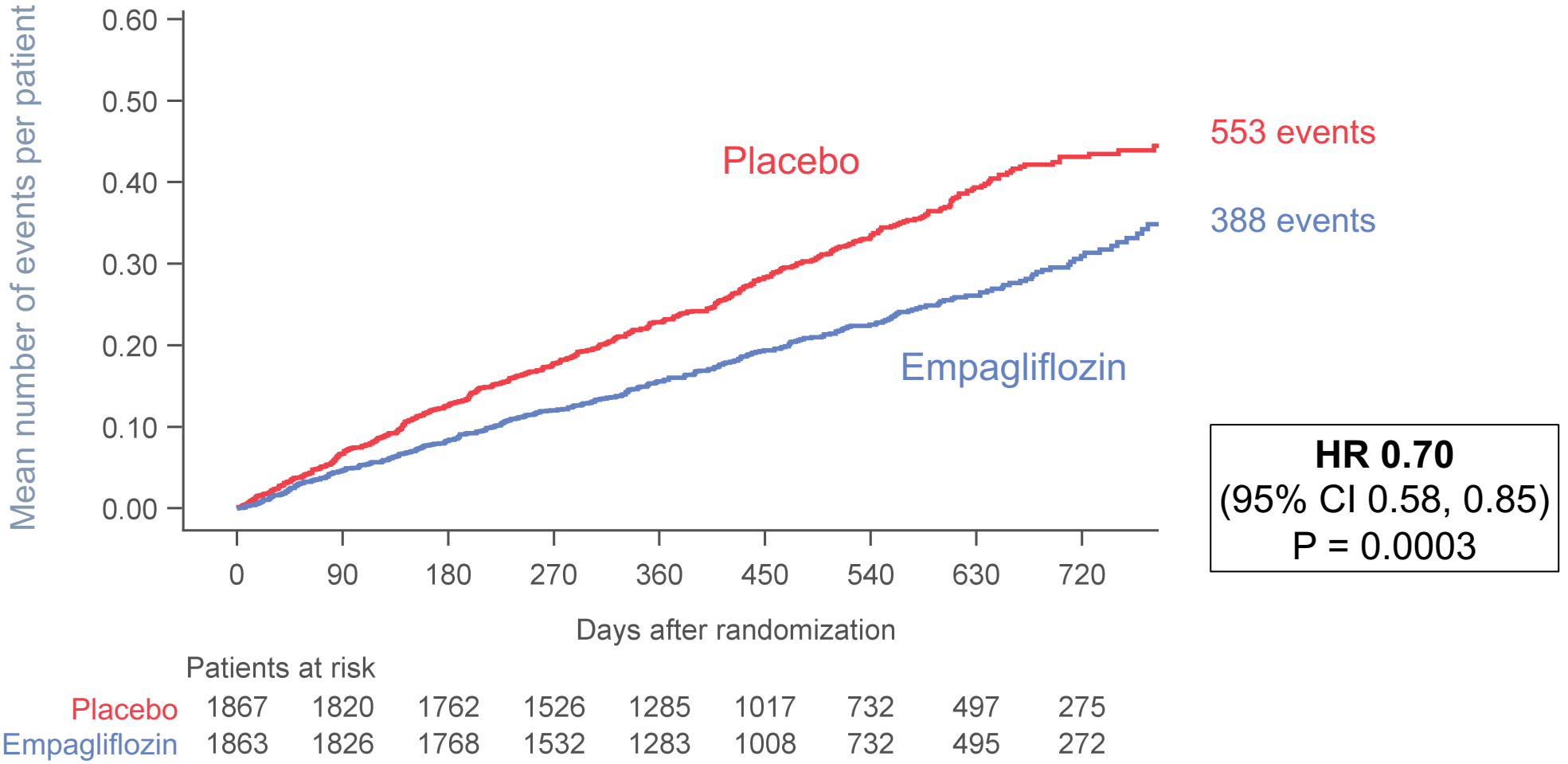


EMPEROR-Reduced: Primary Endpoint Subgroups

	Empagliflozin	Placebo	
	n with event/N analysed		HR (95% CI)
Overall	361/1863	462/1867	0.75 (0.65, 0.86)
Heart failure hospitalization within 12 months			
No	208/1286	285/1293	0.71 (0.60, 0.85)
Yes	153/577	177/574	0.79 (0.64, 0.99)
Etiology of heart failure			
Ischaemic	207/983	236/946	0.82 (0.68, 0.99)
Non-ischaemic	154/880	226/921	0.67 (0.55, 0.82)
Baseline NYHA functional class			
II	220/1399	299/1401	0.71 (0.59, 0.84)
III/IV	141/464	163/466	0.83 (0.66, 1.04)
Heart failure physiology			
LVEF ≤30% and NTproBNP <median	80/699	115/724	0.70 (0.53, 0.93)
LVEF ≤30% and NTproBNP ≥median	169/631	249/661	0.65 (0.53, 0.79)
LVEF >30%	108/526	97/475	0.99 (0.76, 1.31)
Use of mineralocorticoid receptor antagonist			
No	118/557	132/512	0.76 (0.59, 0.97)
Yes	243/1306	330/1355	0.75 (0.63, 0.88)
Use of angiotensin receptor neprilysin inhibitor			
No	310/1523	369/1480	0.77 (0.66, 0.90)
Yes	51/340	93/387	0.64 (0.45, 0.89)

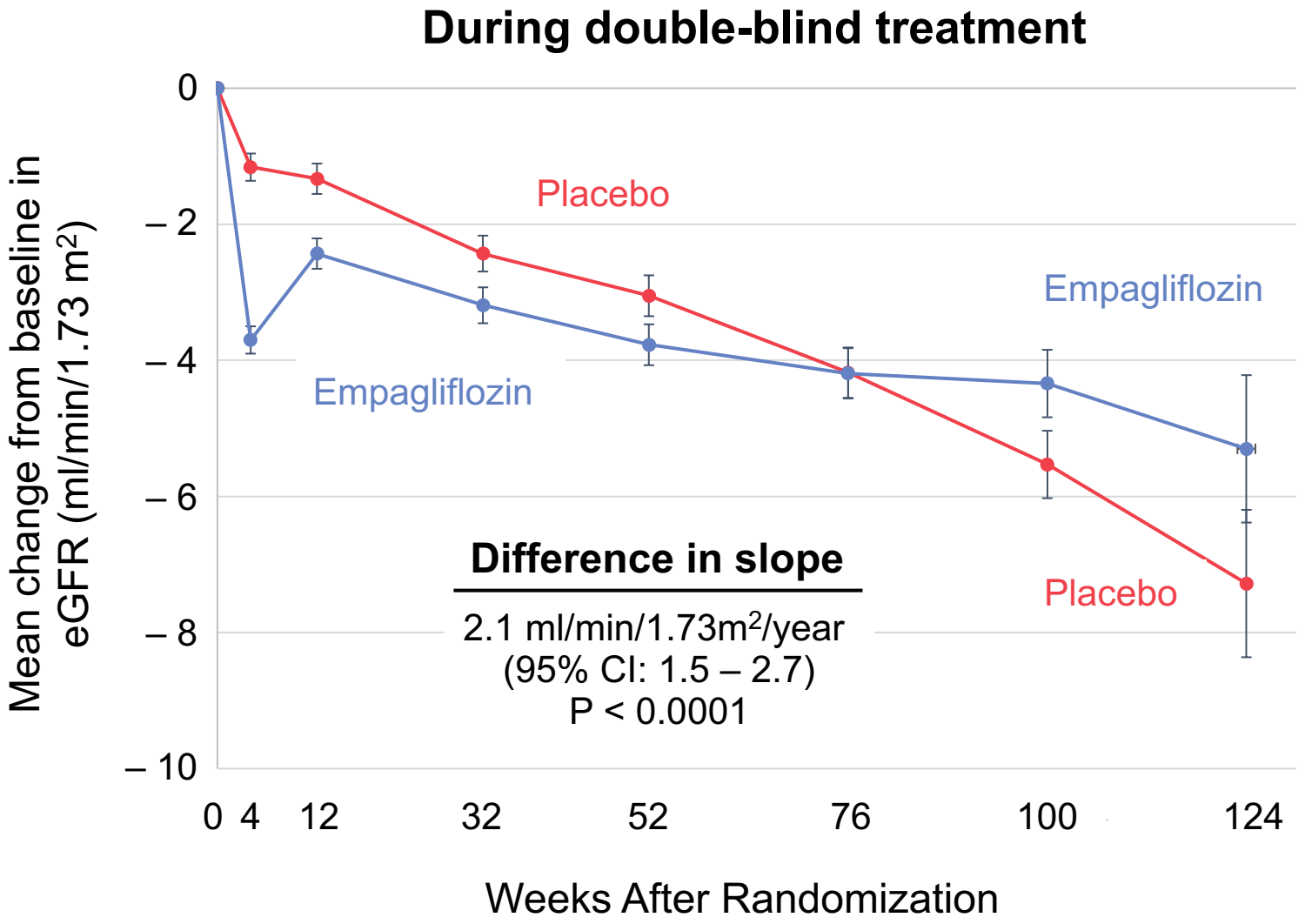


EMPEROR-Reduced: Total Hospitalizations for Heart Failure (First and Recurrent) — Hierarchical Endpoint #2



HR 0.70
(95% CI 0.58, 0.85)
P = 0.0003

EMPEROR-Reduced: Slope of Decline in Glomerular Filtration Rate — Hierarchical Endpoint #3



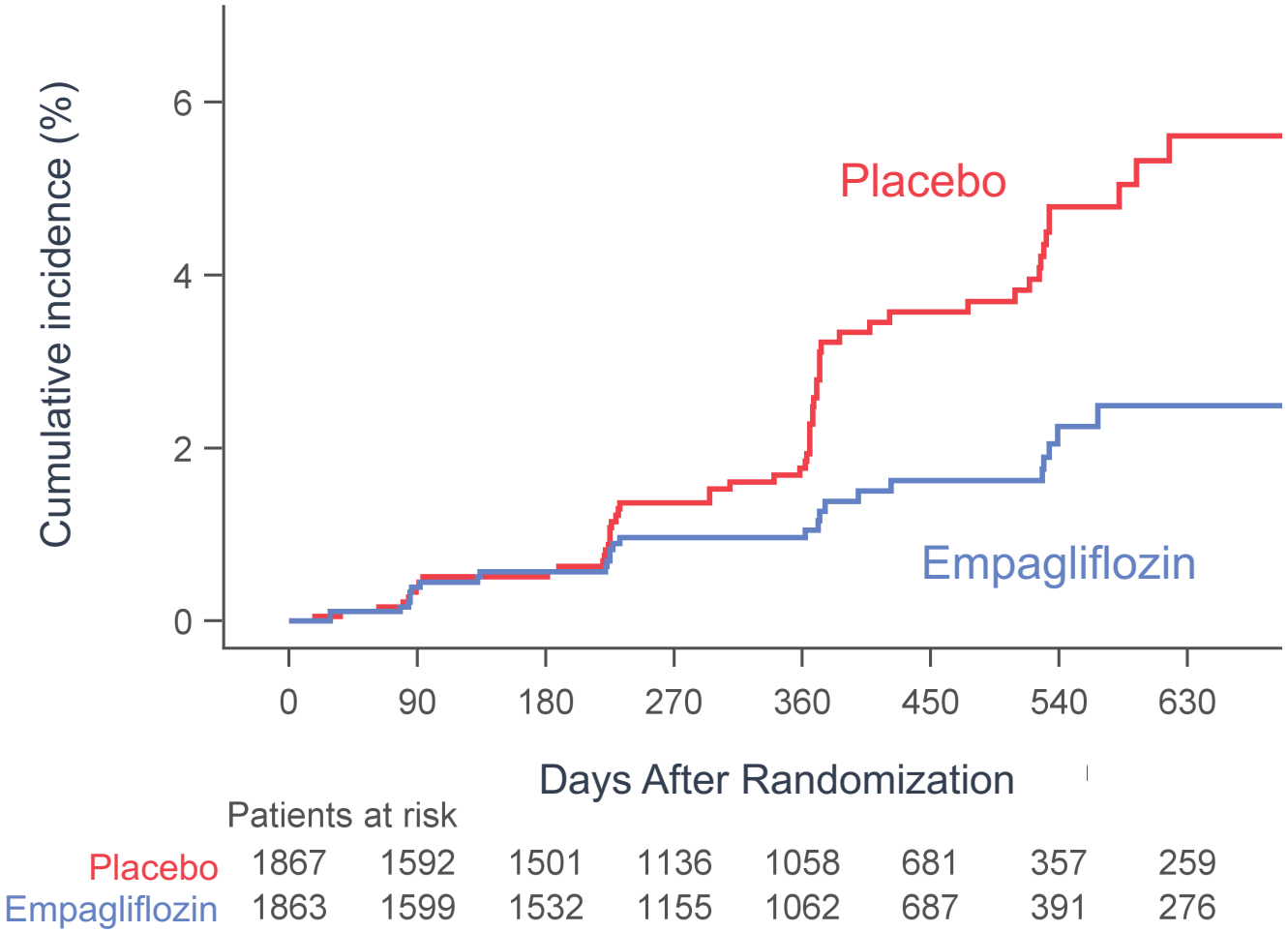
In 966 patients, eGFR was reassessed at the end of the trial 23-42 days after the withdrawal of double-blind therapy, thus allowing unconfounded assessment of the effects of treatment. Over 16 months, eGFR deteriorated by

– 4.2 ml/min/1.73 m² on placebo

– 0.9 m/min/1.73 m² on empagliflozin

P < 0.0001

EMPEROR-Reduced: Composite Renal Endpoint

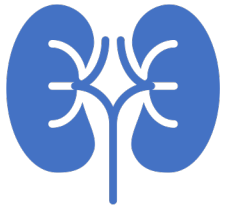


58 patients with event
Rate: 3.1/100 patient-years

30 patients with event
Rate: 1.6/100 patient-years

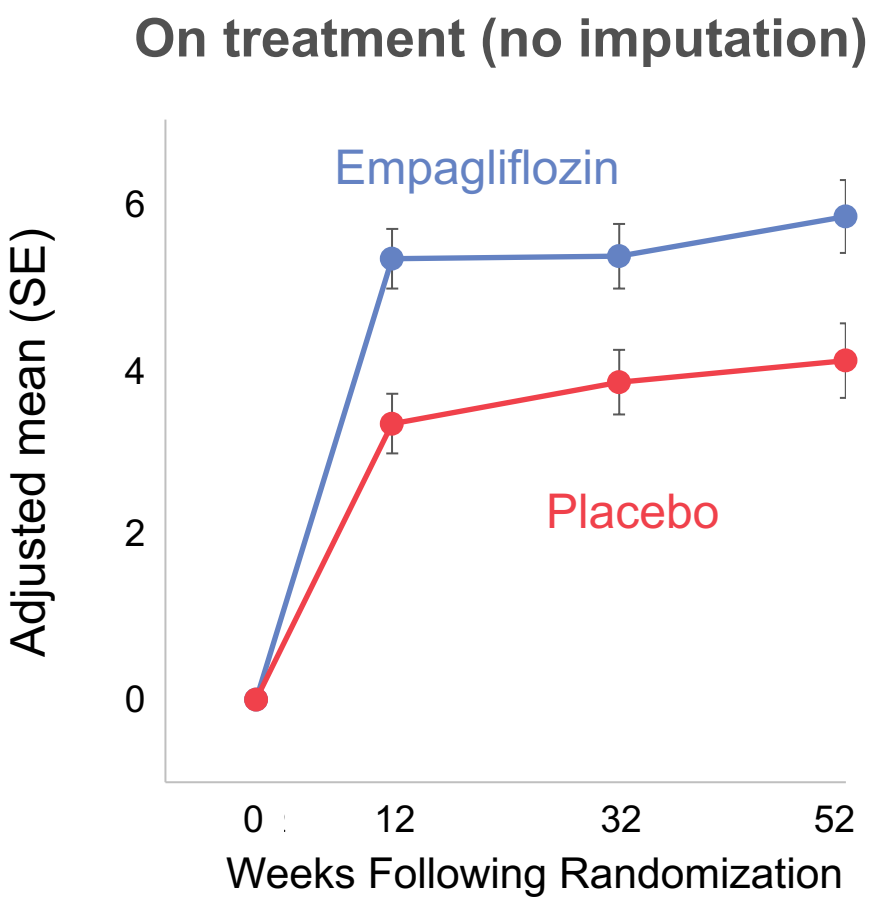
HR 0.50
(95% CI 0.32, 0.77)

EMPEROR-Reduced Achieved All Three Hierarchically Specified Endpoints at P < 0.001

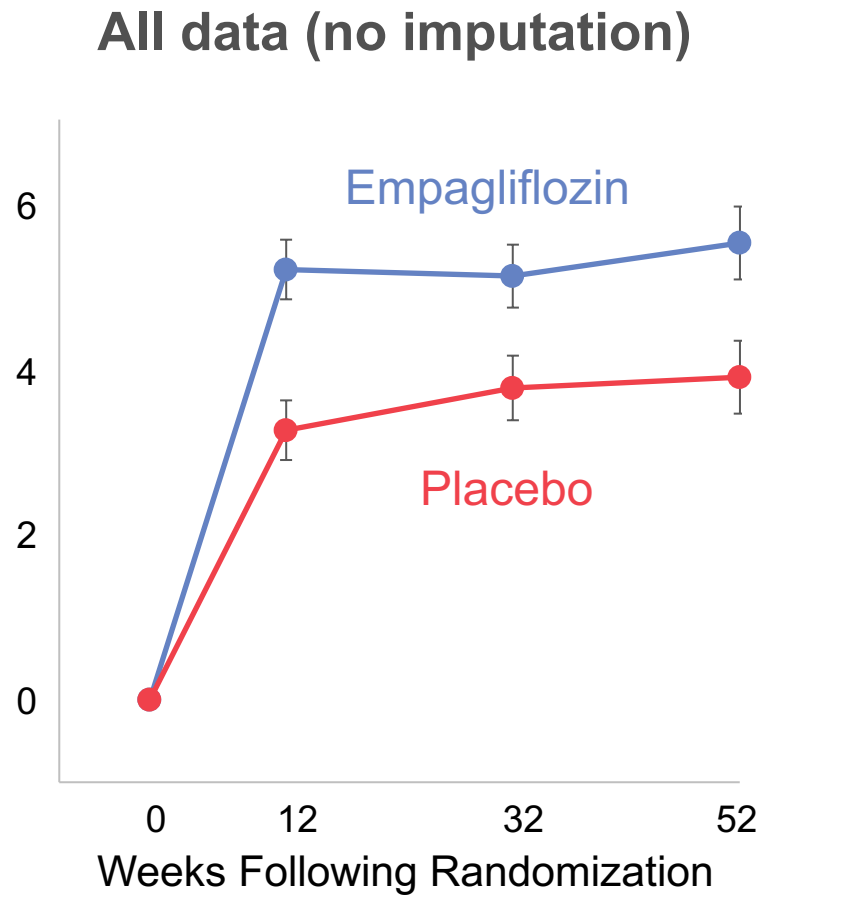
	**Primary Endpoint** Composite of cardiovascular death or heart failure hospitalization	**Achieved** **P < 0.001**
	**First Secondary Endpoint** Total (first and recurrent heart failure hospitalizations)	**Achieved** **P < 0.001**
	**Second Secondary Endpoint** Slope of decline in glomerular filtration rate over time	**Achieved** **P < 0.001**

Also achieved success on composite renal endpoint, KCCQ clinical summary score, and total number of hospitalizations for any reason (all nominal P < 0.01)

EMPEROR-Reduced: KCCQ Clinical Summary Score At 52 Weeks (No Imputation for Death)

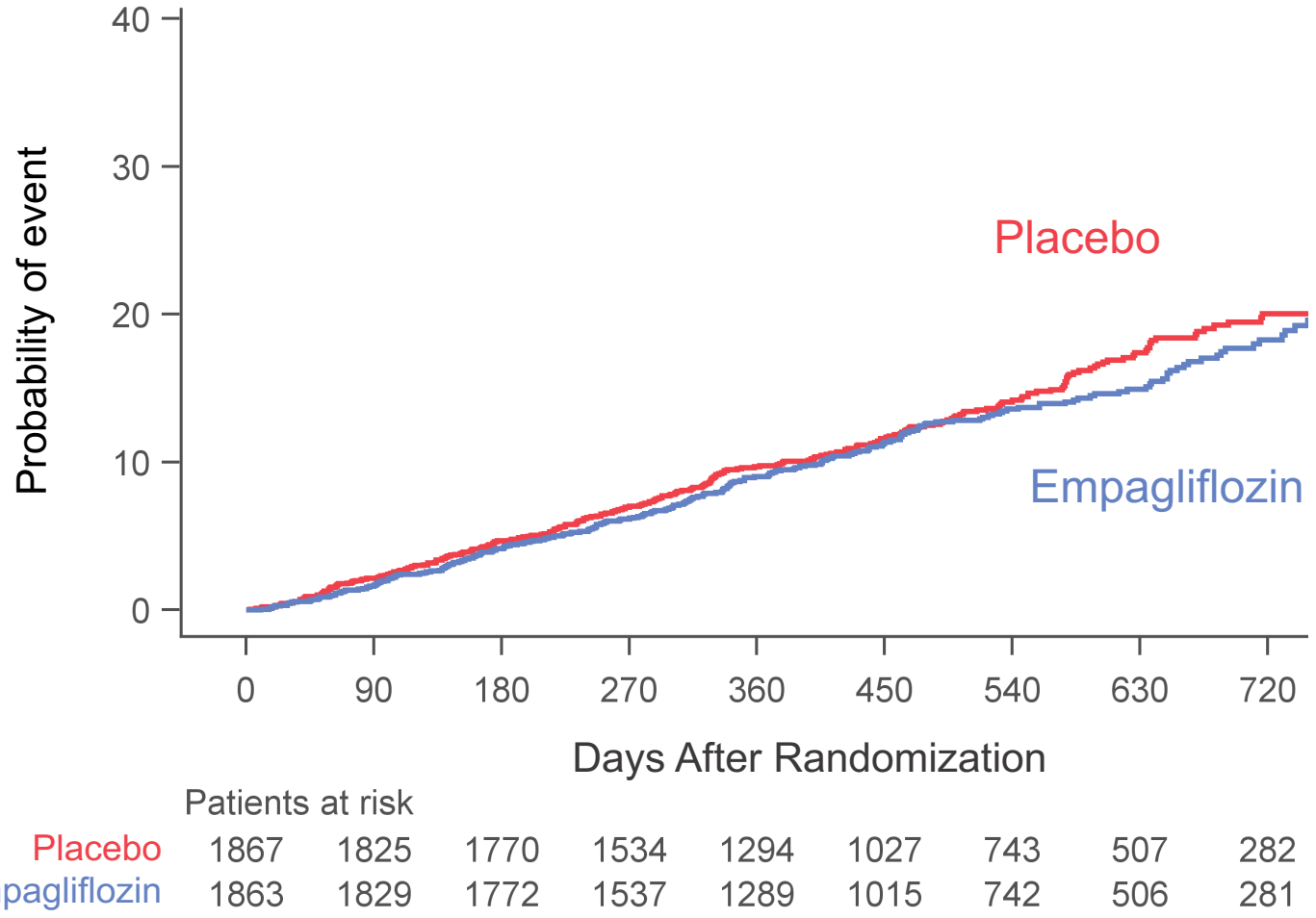


Adjusted mean difference 1.75
(95% CI: 0.51, 2.99)



Adjusted mean difference 1.61
(95% CI: 0.39, 2.84)

EMPEROR-Reduced: All-Cause Mortality



266 patients with event
Rate: 10.7/100 patient-years

249 patients with event
Rate: 10.1/100 patient-years

HR 0.92
(95% CI 0.77, 1.10)

EMPEROR-Reduced: Vital Signs and Biomarkers

	Empagliflozin	Placebo	Treatment Difference
Glycated hemoglobin (%) in patients with diabetes– mean (SE)	– 0.28 ± 0.03	– 0.12 ± 0.03	– 0.16 (–0.25 to – 0.08)
Hematocrit (%) – mean (SE)	1.98 ± 0.10	– 0.38 ± 0.10	2.36 (2.08 to 2.63)
NT-proBNP (pg/ml) – median (IQR)	–244 (-890, 260)	–141 (-787, 585)	0.87 (0.82 to 0.93)
Body weight (kg) – mean (SE)	– 0.73 ± 0.13	0.08 ± 0.13	– 0.82 (–1.18 to –0.45)
Systolic blood pressure (mm Hg) – mean (SE)	– 2.4 ± 0.4	– 1.7 ± 0.4	– 0.7 (–1.8 to 0.4)

EMPEROR-Reduced: Adverse Events

	Empagliflozin (n=1863)	Placebo (n=1863)
Serious adverse events	772 (41.4)	896 (48.1)
Related to cardiac disorder	**500 (26.8)**	**634 (34.0)**
Related to worsening renal function	**59 (3.2)**	**95 (5.1)**
Selected adverse events of special interest		
Volume depletion	197 (10.6)	184 (9.9)
Hypotension	176 (9.4)	163 (8.7)
Symptomatic hypotension	106 (5.7)	103 (5.5)
Hypoglycemia	27 (1.4)	28 (1.5)
Ketoacidosis	0 (0.0)	0 (0.0)
Urinary tract infections	91 (4.9)	83 (4.5)
Genital tract infections	31 (1.7)	12 (0.6)
Bone fractures	45 (2.4)	42 (2.3)
Lower limb amputations	13 (0.7)	10 (0.5)

Trials in Heart Failure and a Reduced Ejection Fraction (With or Without Diabetes)		
	DAPA-HF (dapagliflozin)	**EMPEROR-Reduced (empagliflozin)**
Cardiovascular death or hospitalization for heart failure	**0.75 (0.65 – 0.85) [877 events]**	**0.75 (0.65 – 0.86) [823 events]**
First hospitalization for heart failure	**0.70 (0.59 – 0.83) [549 events]**	**0.69 (0.59 – 0.81) [588 events]**
Renal composite endpoint	0.71 (0.44 – 1.16) [67 events]	0.50 (0.32 – 0.77) [88 events]
Cardiovascular death	0.82 (0.69 – 0.98) [500 events]	0.92 (0.75 – 1.12) [389 events]

Trials in Heart Failure and a Reduced Ejection Fraction (With or Without Diabetes)		
	DAPA-HF (dapagliflozin)	**EMPEROR-Reduced (empagliflozin)**
Cardiovascular death or hospitalization for heart failure	0.75 (0.65 – 0.85) [877 events]	0.75 (0.65 – 0.86) [823 events]
First hospitalization for heart failure	0.70 (0.59 – 0.83) [549 events]	0.69 (0.59 – 0.81) [588 events]
Renal composite endpoint	0.71 (0.44 – 1.16) [67 events]	0.50 (0.32 – 0.77) [88 events]
Cardiovascular death	0.82 (0.69 – 0.98) [500 events]	0.92 (0.75 – 1.12) [389 events]
Trials in Type 2 Diabetes (With or Without Heart Failure)		
	DECLARE-TIMI58 (dapagliflozin)	**EMPA-REG OUTCOME (empagliflozin)**
Cardiovascular death or hospitalization for heart failure	0.83 (0.73 – 0.95) [913 events]	0.66 (0.55 – 0.79) [463 events]
First hospitalization for heart failure	0.73 (0.61 – 0.88) [498 events]	0·65 (0·50 – 0·85) [221 events]
Renal composite endpoint	**0.53 (0·43 – 0·66)** [365 events]	**0·54 (0·40 – 0·75)** [152 events]
Cardiovascular death in patients with prior myocardial infarction	**0.92 (0.61 – 1.23)** [183 events]	**0.59 (0.44 – 0.79)** [183 events]

Conclusions

- In patients with chronic heart failure and a reduced ejection fraction, EMPEROR-Reduced achieved all three endpoints prespecified as key outcomes by hierarchical testing, each with a $P < 0.001$.
- The 25% decrease in the risk of the composite of cardiovascular death and heart failure hospitalization observed in EMPEROR-Reduced was identical to that seen in DAPA-HF. Empagliflozin reduced the total number of hospitalizations for heart failure and slowed the rate of progression of renal disease.
- Although the effect on cardiovascular death in EMPEROR-Reduced was smaller than that seen in DAPA-HF, the reverse was true when the effects of dapagliflozin and empagliflozin on cardiovascular death were assessed in comparable patients in trials of type 2 diabetes. Accordingly, the effects of these drugs on survival is characterized by significant heterogeneity.
- Taken together, we believe that the concordant results of DAPA-HF and EMPEROR-Reduced should be sufficient to establish SGLT2 inhibitors as a new standard of care for patients with heart failure and a reduced ejection fraction.