EMPEROR-Preserved Trial

Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction

Stefan D. Anker, MD PhD & Javed Butler, MD on behalf of the EMPEROR-Preserved Executive Committee, Trial Committees, Investigators & Coordinators

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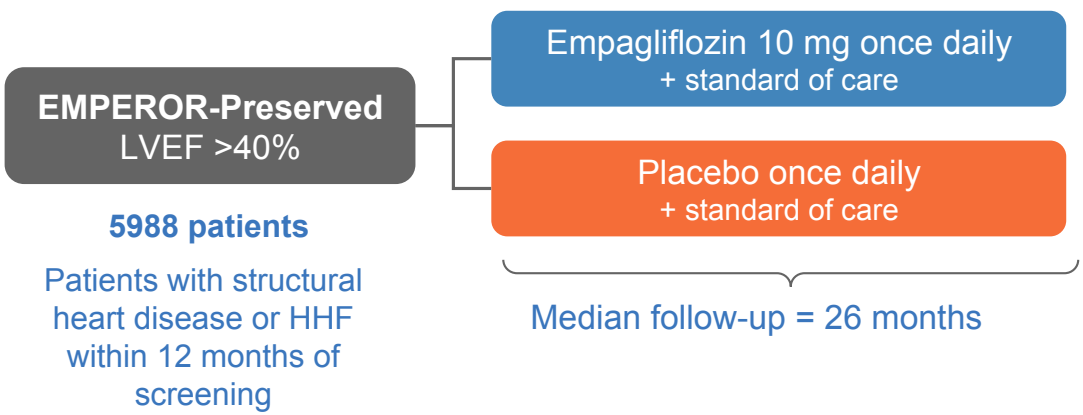
Disclosures for presenter: Fees from Abbott, Bayer, Boehringer Ingelheim, Brahms GmbH, Cardiac Dimension, Cordio, Novartis, Occlutech, Servier, and Vifor Pharma, and grant support from Abbott and Vifor Pharma

EMPEROR-Preserved – Study Design

Phase III randomised double-blind placebo-controlled trial

Aim: to evaluate efficacy and safety of empagliflozin versus placebo, on top of standard of care, in **patients with HFpEF** with or without diabetes

Population: T2DM & non-T2DM, aged ≥18 years, chronic HF (NYHA class II–IV), eGFR≥20



COMPOSITE PRIMARY ENDPOINT

Time to first event of adjudicated cardiovascular death or adjudicated HHF

SECONDARY ENDPOINTS

- **First and recurrent adjudicated HF hospitalisation events**
- **Slope of change in eGFR (CKD-EPI)**

Thank you to the trial investigators & committee members !

Executive Steering Committee

Milton Packer (chair), Stefan Anker (co-chair), Javed Butler, João Pedro Ferreira, Gerasimos Filippatos, Stuart Pocock, Faiez Zannad, Martina Brueckmann & Waheed Jamal

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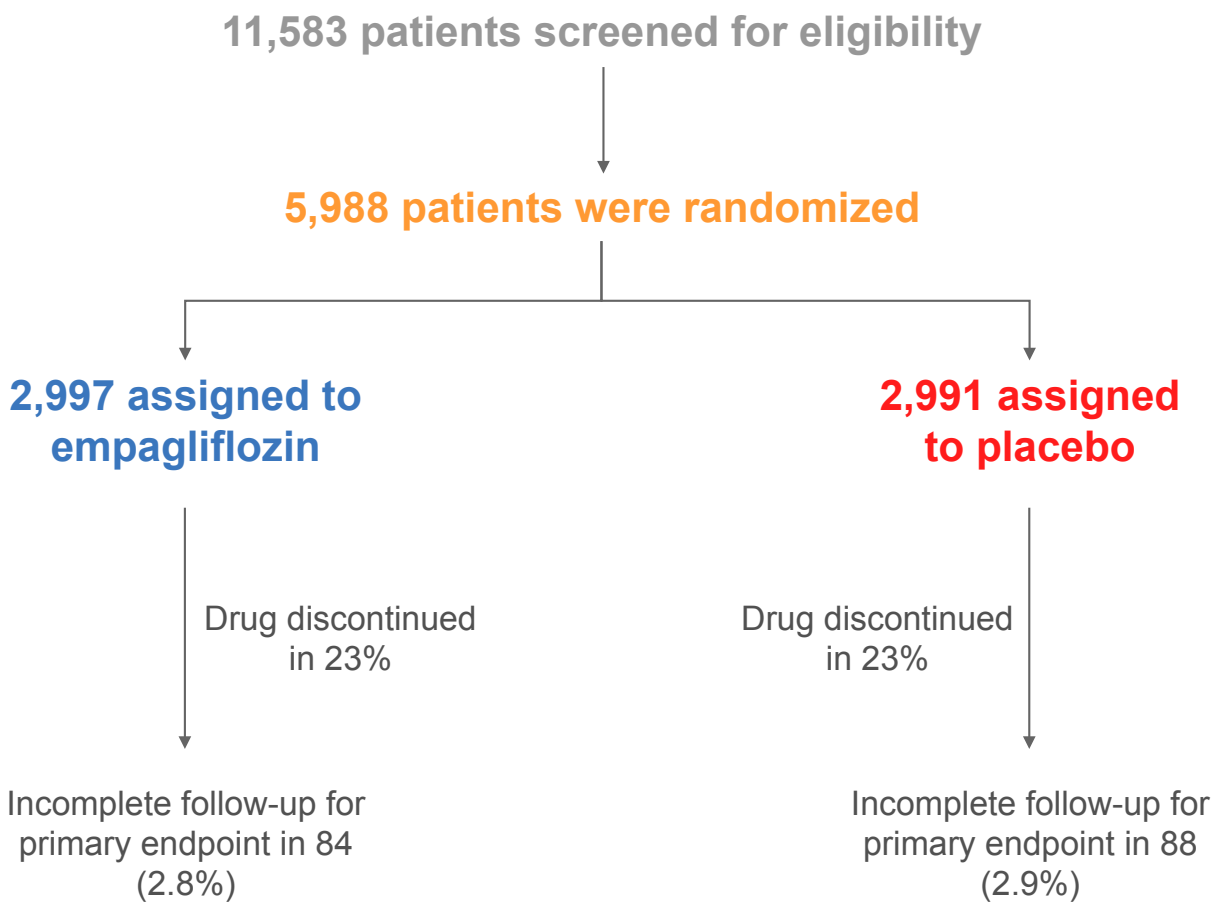
Francine K. Welty, Mike Palmer, Tim Clayton, Klaus G. Parhofer, Terje R. Pedersen, Barry Greenberg, Marvin A. Konstam & Kennedy R. Lees

Study sponsors

Boehringer Ingelheim and Eli Lilly and Company

622 sites in 23 countries

Patient Disposition



Median follow-up 26 months

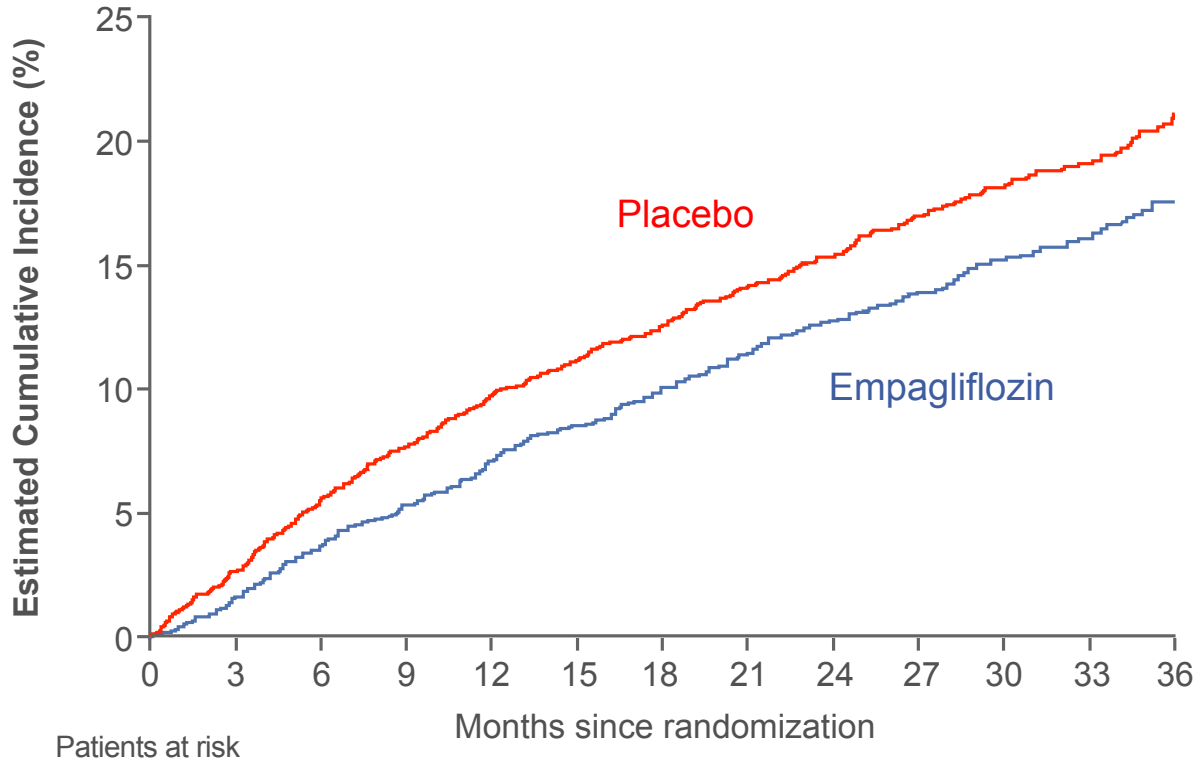
Final vital status known in 99.4%

(all but 36 patients)

Demographics and Baseline Characteristics

	Empagliflozin (n=2997)	Placebo (n=2991)
Age (yr)	71.8 ± 9.3	71.9 ± 9.6
Women (%)	1338 (45)	1338 (45)
Diabetes mellitus (%)	1466 (49)	1472 (49)
Ischaemic HF (%)	1079 (36)	1038 (35)
NYHA functional class II (%)	2432 (81)	2451 (82)
LV ejection fraction (%)	54.3 ± 8.8	54.3 ± 8.8
NT-proBNP (median, IQR), pg/mL	994 (501, 1740)	946 (498, 1725)
Atrial fibrillation	1543 (51)	1514 (51)
Glomerular filtration rate (mL/min/1.73 m^2)	60.6 ± 19.8 (50% <60)	60.6 ±19.9 (50% <60)
Co-medications of interest		
RAASi ± ARNI	2428 (81)	2404 (80)
MRA	1119 (37)	1125 (38)
Beta blocker	2598 (87)	2569 (86)
Statins	2042 (68)	2089 (70)

Primary Endpoint – Composite of Cardiovascular Death or Heart Failure Hospitalization



Patients at risk

Placebo	2991	2786	2627	2066	1534	961	400
Empagliflozin	2997	2843	2708	2134	1578	1005	402

HR 0.79
(95% CI 0.69, 0.90)
P = 0.0003

Placebo:
511 patients with event
Rate: 8.7 per 100 patient-years

Empagliflozin:
415 patients with event
Rate: 6.9 per 100 patient-years

Primary endpoint: individual components

	Empagliflozin (n=2997)		Placebo (n=2991)		Hazard ratio (95% CI)	P value
	Number of events (%)	Events/100 patient-yrs	Number of events (%)	Events/100 patient-yrs		
Primary composite outcome	415 (13.8%)	6.9	511 (17.1%)	8.7	0.79 (0.69 – 0.90)	0.0003
First hospitalization for heart failure	259 (8.6%)	4.3	352 (11.8%)	6.0	0.71 (0.60 – 0.83)	
Cardiovascular death	219 (7.3%)	3.4	244 (8.2%)	3.8	0.91 (0.76 – 1.09)	

Primary endpoint: Effects in Subgroups (1 of 2)

	Empagliflozin	Placebo	HR (95% CI)	HR (95% CI)
	n with event/N analysed			
Overall	415/2997	511/2991		0.79 (0.69–0.90)
Baseline diabetes status				
Diabetes	239/1466	291/1472		0.79 (0.67–0.94)
No diabetes	176/1531	220/1519		0.78 (0.64–0.95)
Age, years				
<70	134/1066	152/1084		0.88 (0.70–1.11)
≥70	281/1931	359/1907		0.75 (0.64–0.87)
Sex				
Male	253/1659	297/1653		0.81 (0.69–0.96)
Female	162/1338	214/1338		0.75 (0.61–0.92)
Race				
White	310/2286	370/2256		0.81 (0.69–0.94)
Black	24/133	28/125		0.73 (0.42–1.25)
Asian	54/413	77/411		0.65 (0.46–0.92)
Other	27/164	36/198		0.95 (0.58–1.57)
Baseline body-mass index				
<30 kg/m²	223/1654	292/1642		0.74 (0.62–0.88)
≥30 kg/m²	192/1343	219/1349		0.85 (0.70–1.03)
Baseline eGFR (CKD-EPI)				
≥60 mL/min/1.73 m²	152/1493	189/1505		0.81 (0.65–1.00)
<60 mL/min/1.73 m²	263/1504	321/1484		0.78 (0.66–0.91)

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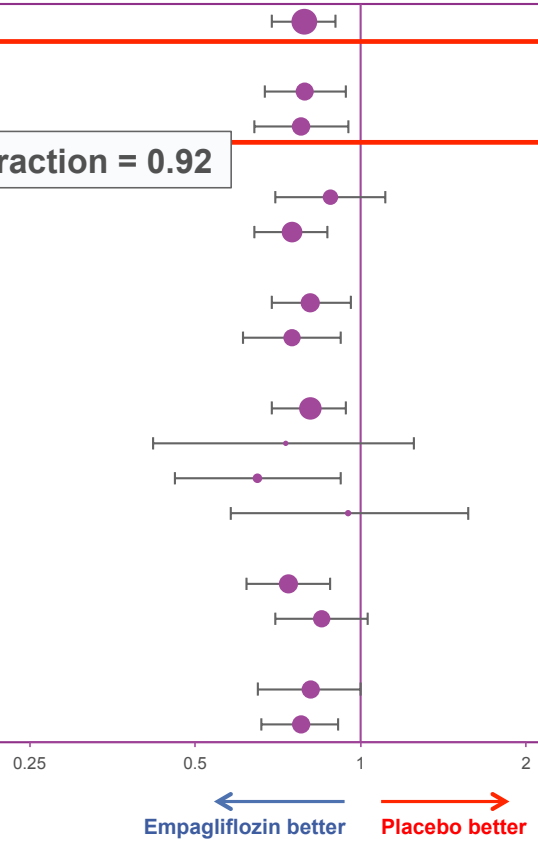

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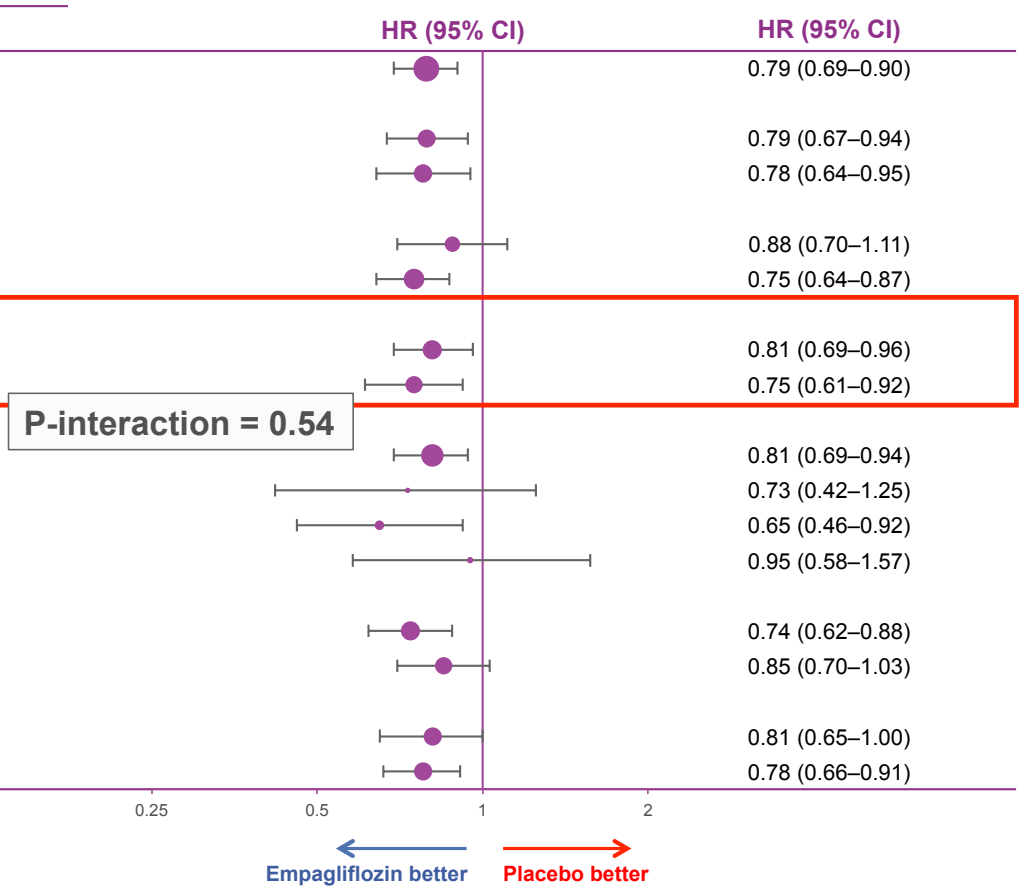

Primary Endpoint: Effects in Subgroups (2 of 2)

	Empagliflozin	Placebo	HR (95% CI)	HR (95% CI)
	n with event/N analysed			
Overall	415/2997	511/2991		0.79 (0.69–0.90)
HF hospitalization in ≤12 months				
No	258/2298	319/2321		0.81 (0.68–0.95)
Yes	157/699	192/670		0.73 (0.59–0.90)
Cause of HF				
Ischaemic	157/1079	177/1038		0.85 (0.69–1.06)
Non-ischaemic	258/1917	334/1953		0.75 (0.64–0.89)
Baseline NYHA class*				
II	275/2435	361/2452		0.75 (0.64–0.87)
III/IV	140/562	150/539		0.86 (0.68–1.09)
Baseline LVEF				
<50%	145/995	193/988		0.71 (0.57–0.88)
≥50% to <60%	138/1028	173/1030		0.80 (0.64–0.99)
≥60%	132/974	145/973		0.87 (0.69–1.10)
Baseline NT-proBNP (calculated by AF/flutter status)				
<Median	126/1477	168/1508		0.76 (0.61–0.96)
≥Median	288/1516	341/1476		0.78 (0.67–0.91)
Baseline use of MRA				
No	233/1878	306/1866		0.73 (0.62–0.87)
Yes	182/1119	205/1125		0.87 (0.71–1.06)
Baseline use of ACE-inhibitor, ARB or ARNI				
No	90/569	121/587		0.75 (0.57–0.99)
Yes	325/2428	390/2404		0.80 (0.69–0.93)

*NYHA class I are counted in class II

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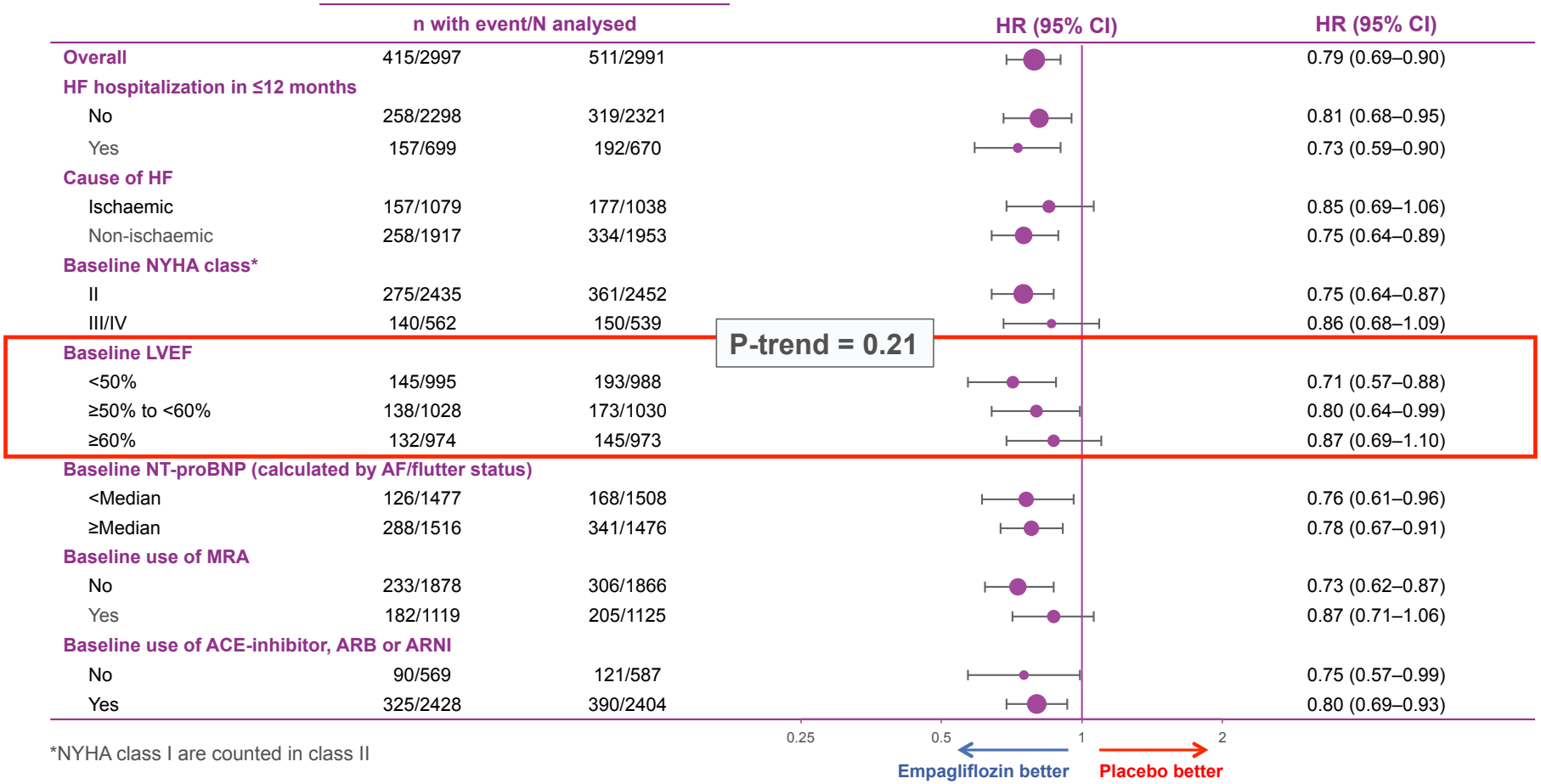

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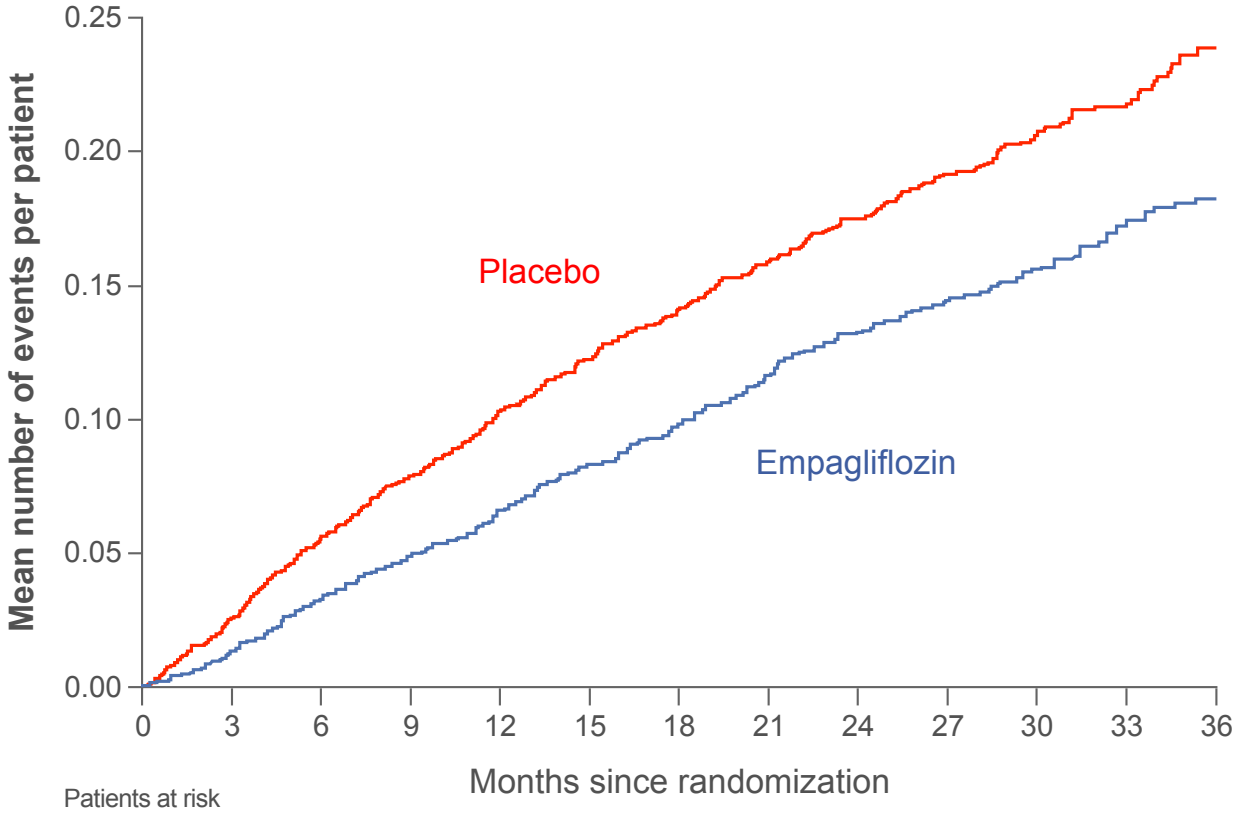
First Secondary Endpoint: Total (First and Recurrent) Heart Failure Hospitalizations



Patients at risk

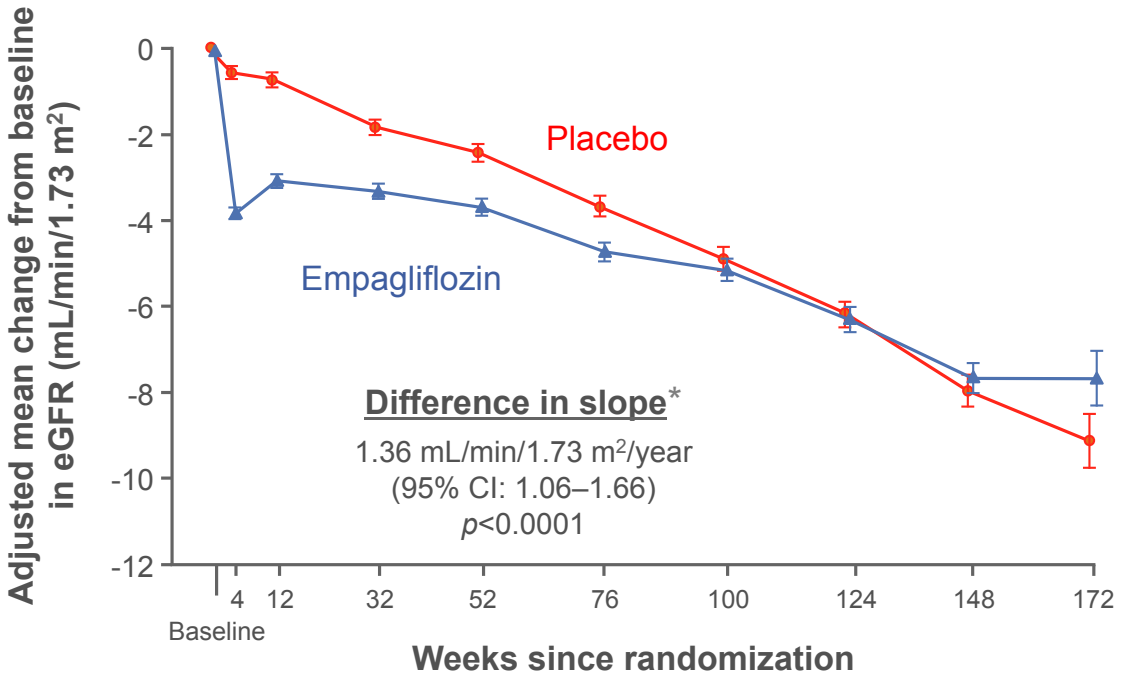
Placebo	2991	2901	2816	2258	1695	1061	448
Empagliflozin	2997	2913	2817	2247	1684	1081	446

HR 0.73
(95% CI 0.61, 0.88)
P = 0.0009

Empagliflozin:
407 heart failure hospitalisation events

Placebo:
541 heart failure hospitalisation events

Second Secondary Endpoint: Slope of Decline in Glomerular Filtration Rate Over Time



In 3176 patients, eGFR was reassessed 23-42 days after the withdrawal of double-blind therapy.** Over 28 months, eGFR deteriorated by

– 3.3 mL/min/1.73 m² on Empagliflozin

– 5.7 mL/min/1.73 m² on placebo

P < 0.0001

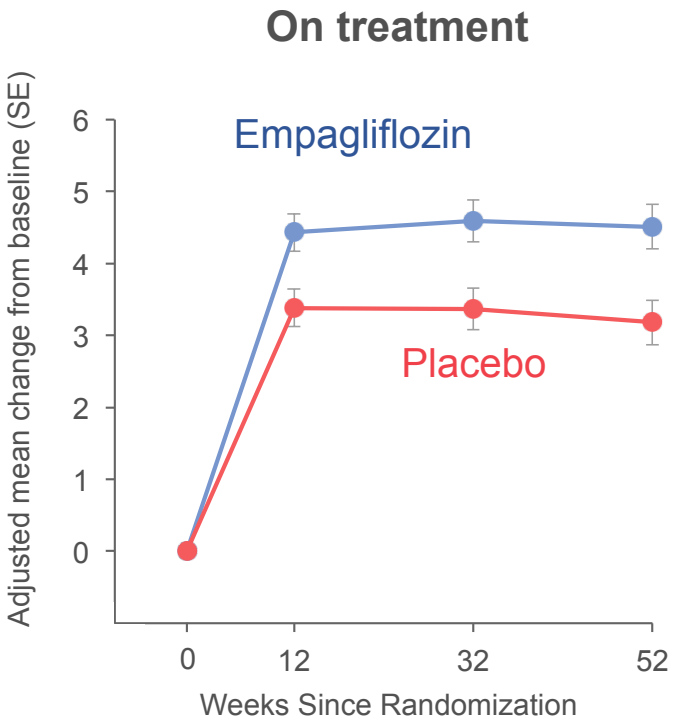
** The eGFR slope is analyzed on the basis of on-treatment data*

*** this represents the unconfounded assessment of the treatment effect*

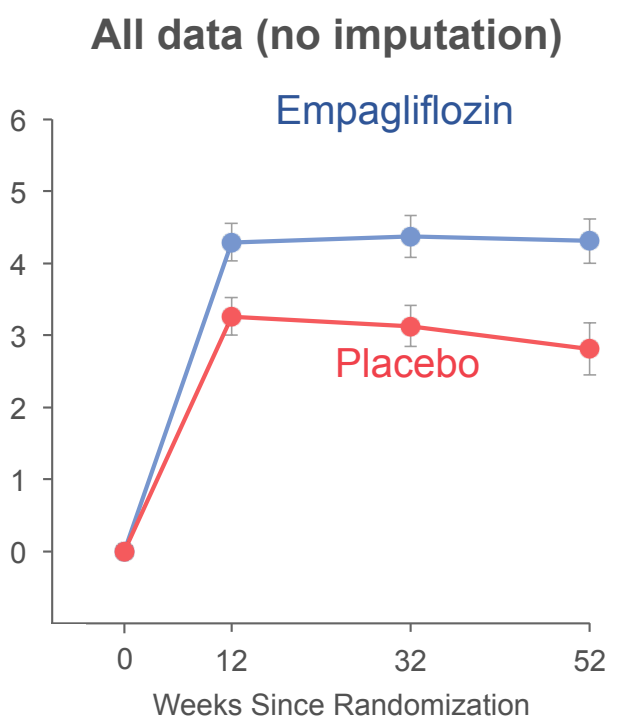
Success on all 3 prespecified hierarchical endpoints

	**Primary Endpoint** Composite of cardiovascular death or heart failure hospitalization	**21% ↓ in risk** **P = 0.0003**
	**First Secondary Endpoint** Total (first and recurrent) heart failure hospitalizations	**27% ↓ in risk** **P = 0.0009**
	**Second Secondary Endpoint** Slope of decline in glomerular filtration rate over time	**P < 0.0001** Difference: 1.36 mL/min/1.73 m^2 per year

Kansas City Cardiomyopathy Questionnaire Clinical Summary Score

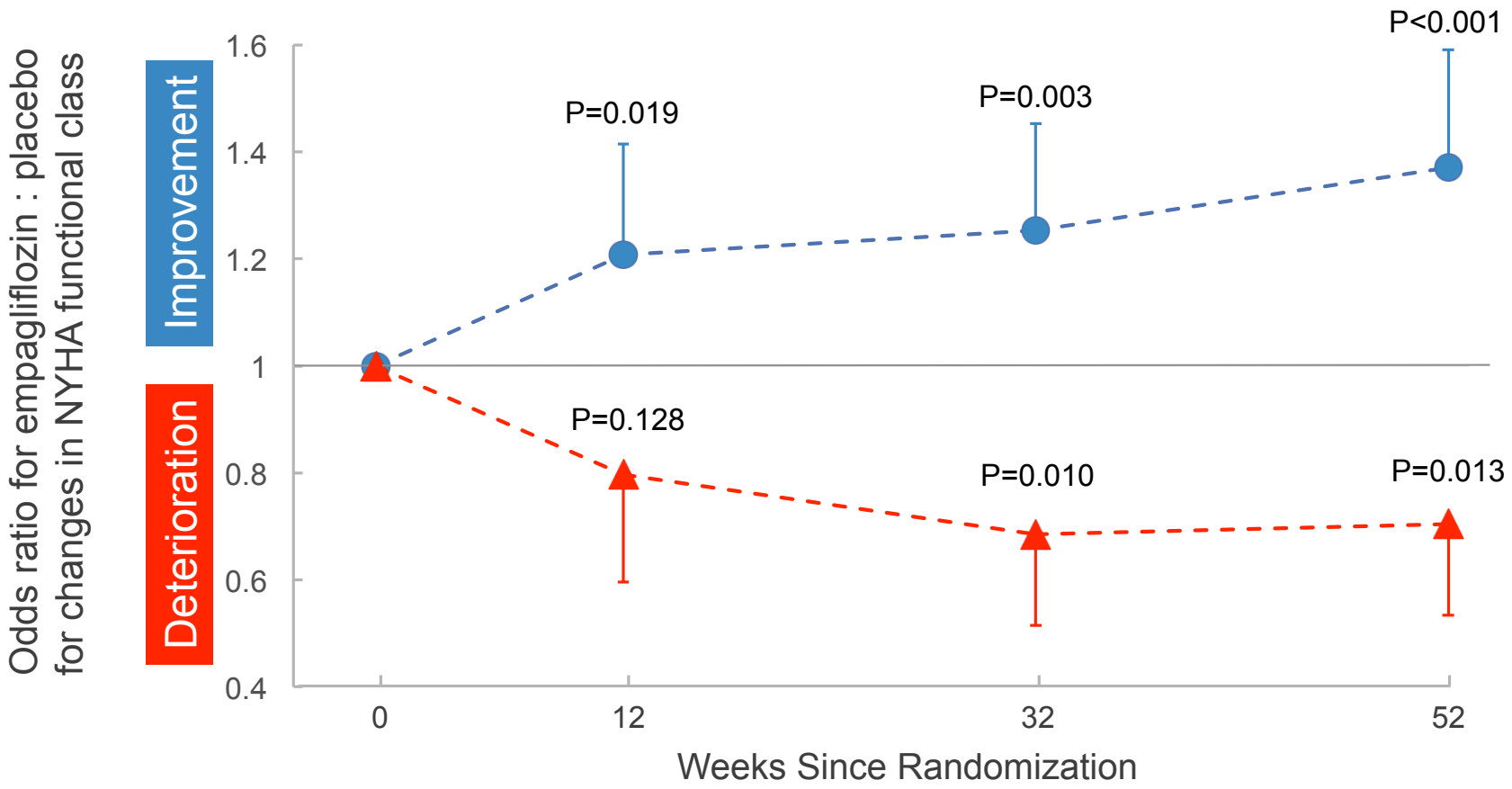


Adjusted mean difference 1.32
(95% CI: 0.45, 2.19), P=0.0028



Adjusted mean difference 1.50
(95% CI: 0.64, 2.36), P=0.0007

Effects of Empagliflozin on NYHA Class



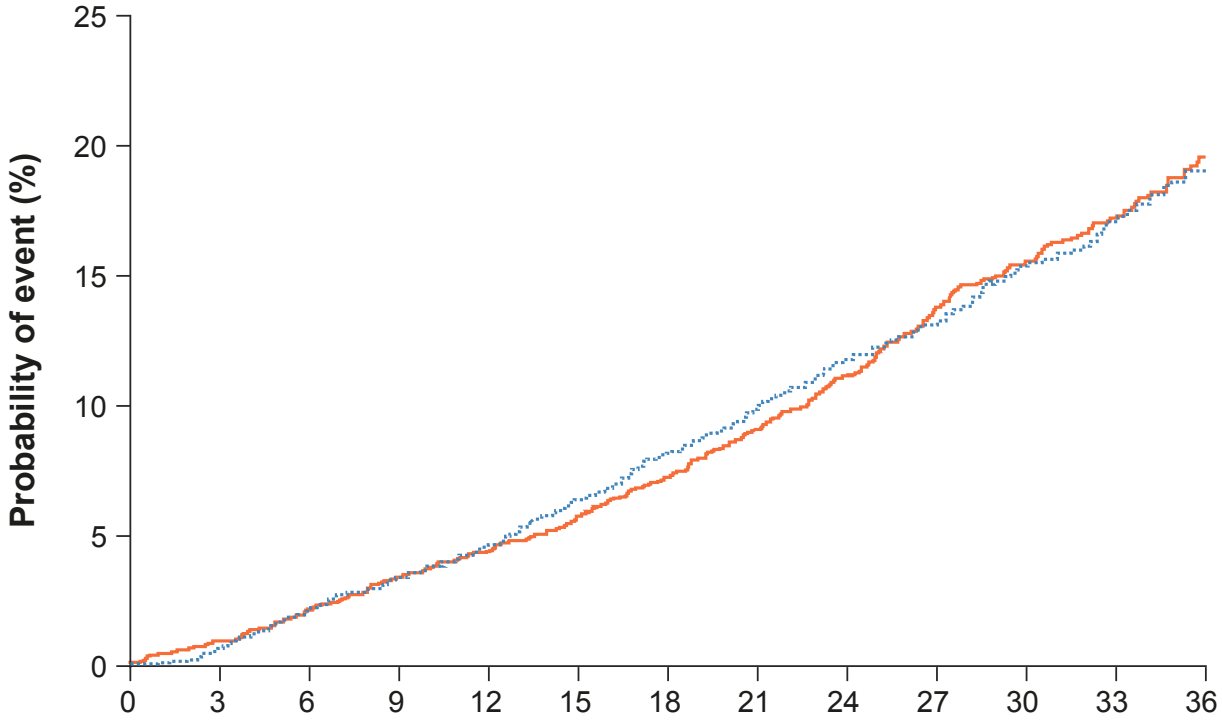
Vital Signs and Biomarkers

	Empagliflozin	Placebo	Treatment Difference	P-value
Glycated hemoglobin (%) in patients with diabetes– mean (SE)	– 0.16 ± 0.02	0.03 ± 0.02	– 0.19 (–0.25 to –0.14)	<0.0001
Hematocrit (%) – mean (SE)	1.94 ± 0.07	– 0.41 ± 0.07	2.36 (2.17 to 2.54)	<0.0001
NT-proBNP (pg/mL) – median (IQR)	– 29 (-335, 263)	– 9 (-286, 322)	0.95* (0.91 to 0.99)	0.0071
Body weight (kg) – mean (SE)	– 1.39 ± 0.09	– 0.11 ± 0.09	– 1.28 (–1.54 to –1.03)	<0.0001
Systolic blood pressure (mm Hg) – mean (SE)	– 1.8 ± 0.3	– 0.6 ± 0.3	– 1.2 (–2.1 to –0.3)	0.0071

*value given is geometric mean ratio

Change from baseline to 52 weeks

All-Cause Mortality



Patients at risk							
Placebo	2991	2923	2849	2302	1738	1107	471
Empagliflozin	2997	2930	2847	2287	1725	1118	462

HR 1.00
(95% CI 0.87, 1.15)
P = 0.99

Empagliflozin:
422 patients with event
Rate: 6.6 / 100 patient-years

Placebo:
427 patients with event
Rate: 6.7 / 100 patient-years

Safety: Selected Adverse Events

	Empagliflozin (N=2996) n (%)	Placebo (N=2989) n (%)
Serious adverse events	1436 (47.9)	1543 (51.6)
Selected adverse events of special interest		
Hypotension	311 (10.4)	257 (8.6)
Symptomatic hypotension	197 (6.6)	156 (5.2)
Hypoglycemia	73 (2.4)	78 (2.6)
Ketoacidosis	4 (0.1)	5 (0.2)
Bone fractures	134 (4.5)	126 (4.2)
Lower limb amputations	12 (0.4)	17 (0.6)
Urinary tract infections	297 (9.9)	243 (8.1)
Genital infections	67 (2.2)	22 (0.7)

EMPEROR-Preserved in the Context of Other Studies

Trial	Treatment arms	Primary endpoint	Results (HR and 95% CI)	Risk reduction	P-value
EMPEROR-Preserved (2021)	**Empagliflozin vs placebo**	**CV death + HHF**	**0.79 (0.69–0.90)**	**-21%**	**0.0003**
PARAGON-HF (2019)	Sacubitril/valsartan vs valsartan	CV death + total (first and recurrent) HHF	0.87 (0.75–1.01)	-13%	0.06
TOPCAT (2014)	Spironolactone vs placebo	CV death + HHF + aborted cardiac arrest	0.89 (0.77–1.04)	-11%	0.14
I-PRESERVE (2008)	Irbesartan vs placebo	All-cause mortality + CV Hospitalization	0.95 (0.86–1.05)	-5%	0.35
PEP-CHF (2006)	Perindopril vs placebo	All-cause mortality + HHF	0.92 (0.70–1.21)	-8%	0.55
CHARM-Preserved (2003)	Candesartan vs placebo	CV death + HHF	0.86 (0.74–1.00)	-14%	0.05

Conclusions

- In patients with heart failure and an ejection fraction >40%, empagliflozin reduced the composite of cardiovascular death and hospitalization for heart failure by 21% (P=0.0003). This is a clinically meaningful effect.
- The benefit of empagliflozin on the primary endpoint was consistent across all pre-specified subgroups, including LVEF, sex and diabetes.
- Empagliflozin reduced total (first and recurrent) hospitalizations for heart failure by 27% (P=0.0009).
- EMPEROR-Preserved is the first trial to show unequivocal clinical benefits with a drug in patients with heart failure and a preserved ejection fraction.

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ORIGINAL ARTICLE

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

S.D. Anker, J. Butler, G. Filippatos, J.P. Ferreira, E. Bocchi, M. Böhm, H.P. Brunner–La Rocca, D.-J. Choi, V. Chopra, E. Chuquiure-Valenzuela, N. Giannetti, J.E. Gomez-Mesa, S. Janssens, J.L. Januzzi, J.R. Gonzalez-Juanatey, B. Merkely, S.J. Nicholls, S.V. Perrone, I.L. Piña, P. Ponikowski, M. Senni, D. Sim, J. Spinar, I. Squire, S. Taddei, H. Tsutsui, S. Verma, D. Vinereanu, J. Zhang, P. Carson, C.S.P. Lam, N. Marx, C. Zeller, N. Sattar, W. Jamal, S. Schnaidt, J.M. Schnee, M. Brueckmann, S.J. Pocock, F. Zannad, and M. Packer, for the EMPEROR-Preserved Trial Investigators.*