Efficacy of empagliflozin in patients with heart failure according to baseline KDIGO risk categories

Findings from the EMPEROR-Pooled

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on behalf of the EMPEROR Trial Committees & Investigators

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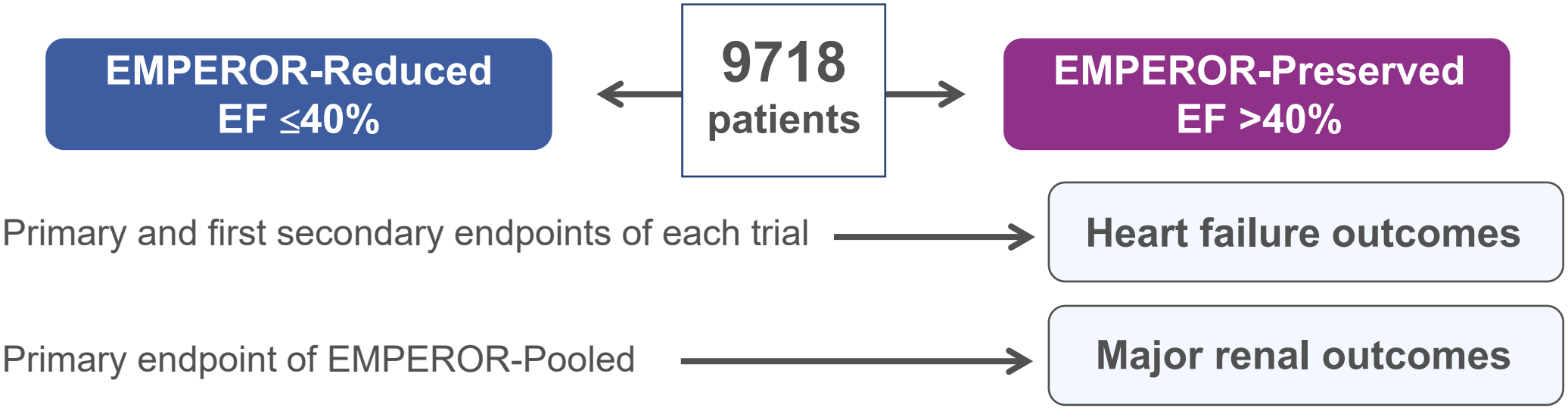
EMPEROR-Pooled: Background and design

- EMPEROR-Reduced and EMPEROR-Preserved were sister trials, with very similar protocols, case report forms, investigators, endpoints, statistical plans and administrative structures, which were carried out in a similar time period — separated by an ejection fraction of 40%

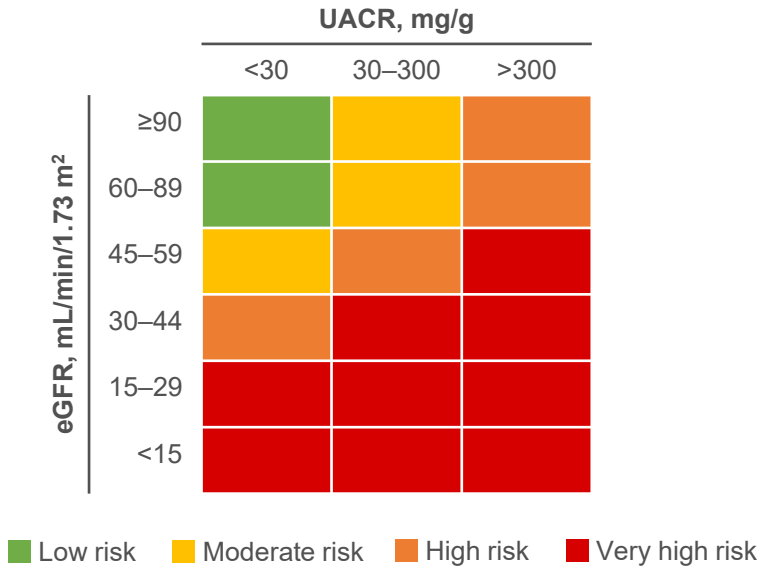
- EMPEROR-Pooled was a prospectively designed, individual patient-level pooled analysis of the data from the two trials, which had its own statistical plan that was finalized before the first patient was enrolled in either trial

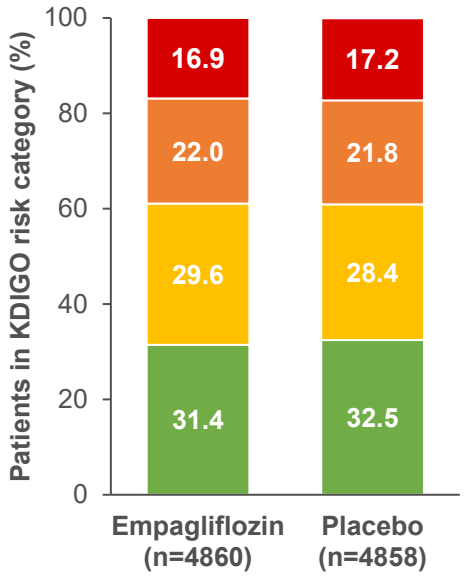


EF, ejection fraction
Packer M *et al. Eur J Heart Fail* 2020;22:2393

Objectives of this analysis

- Explore the effect of empagliflozin on CV and kidney endpoints in patients across KDIGO (Kidney Disease Improving Global Outcomes) risk categories in EMPEROR-Pooled
- Distribution of patients across KDIGO risk categories:





- 3730 patients with LVEF ≤40% (EMPEROR-Reduced)
- 5988 patients with LVEF >40% (EMPEROR-Preserved)

CV, cardiovascular; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; UACR, urine albumin-to-creatinine ratio

Baseline characteristics by KDIGO subgroups 1/2

	Low risk (n=3105)	Moderate risk (n=2822)	High risk (n=2131)	Very high risk (n=1656)	*P* value for trend
Age, y	66.7 (10.7)	70.1 (10.0)	72.3 (9.6)	72.9 (9.6)	<0.001
Female, n (%)	1052 (33.9)	1052 (37.3)	833 (39.1)	632 (38.2)	<0.001
Race, n (%)					0.490
Asian	492 (15.8)	457 (16.2)	308 (14.5)	239 (14.4)	
Black or African-American	171 (5.5)	150 (5.3)	96 (4.5)	97 (5.9)	
White	2261 (72.8)	2067 (73.2)	1621 (76.1)	1219 (73.6)	
Other including mixed race	164 (5.3)	130 (4.6)	91 (4.3)	91 (5.5)	
Missing	17 (0.5)	18 (0.6)	15 (0.7)	10 (0.6)	
KCCQ-CSS	74.0 (20.2)	71.2 (21.1)	68.1 (21.8)	66.1 (22.7)	<0.001
HHF within 1 year, n (%)	733 (23.6)	696 (24.7)	608 (28.5)	483 (29.2)	<0.001
Body weight, kg	80.5 (18.9)	80.4 (19.4)	80.7 (18.6)	81.3 (19.9)	0.213
EF at screening, %	43.5 (14.9)	44.3 (15.3)	43.8 (15.4)	44.8 (15.5)	0.027
NYHA Class II, n (%)	2616 (84.3)	2256 (79.9)	1620 (76.0)	1188 (71.7)	<0.001
SBP, mmHg	126.8 (15.5)	127.7 (16.3)	128.2 (16.4)	130.8 (17.7)	<0.001
Heart rate, bpm	70.1 (11.4)	71.0 (11.9)	71.1 (12.1)	70.8 (12.0)	0.008

Data are mean (SD) or number (%). Race was self-reported. bpm, beats per minute; HHF, hospitalization for heart failure; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score; NYHA, New York Heart Association; SBP, systolic blood pressure

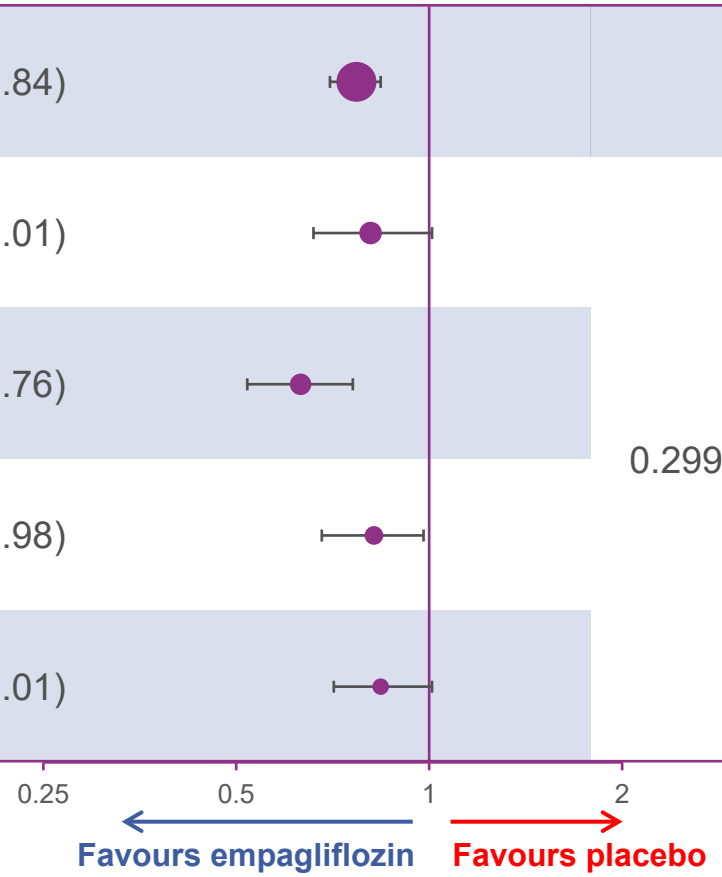
Baseline characteristics by KDIGO subgroups 2/2

	Low risk (n=3105)	Moderate risk (n=2822)	High risk (n=2131)	Very high risk (n=1656)	*P* value for trend
Hypertension, n (%)	2416 (77.8)	2359 (83.6)	1844 (86.5)	1500 (90.6)	<0.001
Diabetes mellitus, n (%)	1269 (40.9)	1343 (47.6)	1132 (53.1)	1046 (63.2)	<0.001
Atrial fibrillation, n (%)	1172 (37.7)	1343 (47.6)	1114 (52.3)	797 (48.1)	<0.001
Ischaemic aetiology, n (%)	1307 (42.1)	1111 (39.4)	888 (41.7)	738 (44.6)	0.193
ACEi, ARB, ARNI, n (%)	2665 (85.8)	2395 (84.9)	1775 (83.3)	1287 (77.7)	<0.001
Diuretic, n (%)	2677 (86.2)	2525 (89.5)	1959 (91.9)	1543 (93.2)	<0.001
Beta-blocker, n (%)	2781 (89.6)	2528 (89.6)	1910 (89.6)	1478 (89.3)	0.823
MRA, n (%)	1629 (52.5)	1464 (51.9)	1104 (51.8)	706 (42.6)	<0.001
Statin, n (%)	2083 (67.1)	1918 (68.0)	1490 (69.9)	1191 (71.9)	<0.001
Uric acid, mg/dL	6.2 (1.7)	6.6 (1.9)	7.2 (2.1)	7.7 (2.2)	<0.001
Haematocrit, %	42.3 (4.3)	41.7 (4.8)	41.0 (5.1)	39.6 (5.3)	<0.001
Haemoglobin, g/dL	13.8 (1.4)	13.6 (1.6)	13.3 (1.7)	12.8 (1.7)	<0.001
eGFR, ml/min/1.73 m²	77.9 (12.9)	65.3 (15.9)	51.0 (15.8)	35.8 (9.2)	<0.001
NT-proBNP, pg/mL	927 (513–1613)	1253 (642–2113)	1577 (824–2814)	1992 (1043–3926)	<0.001

Data are mean (SD) or number (%) except NT-proBNP, which is median (IQR). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal prohormone of brain natriuretic peptide

Effect of empagliflozin vs placebo: CV death or HHF (primary outcome) by KDIGO subgroups

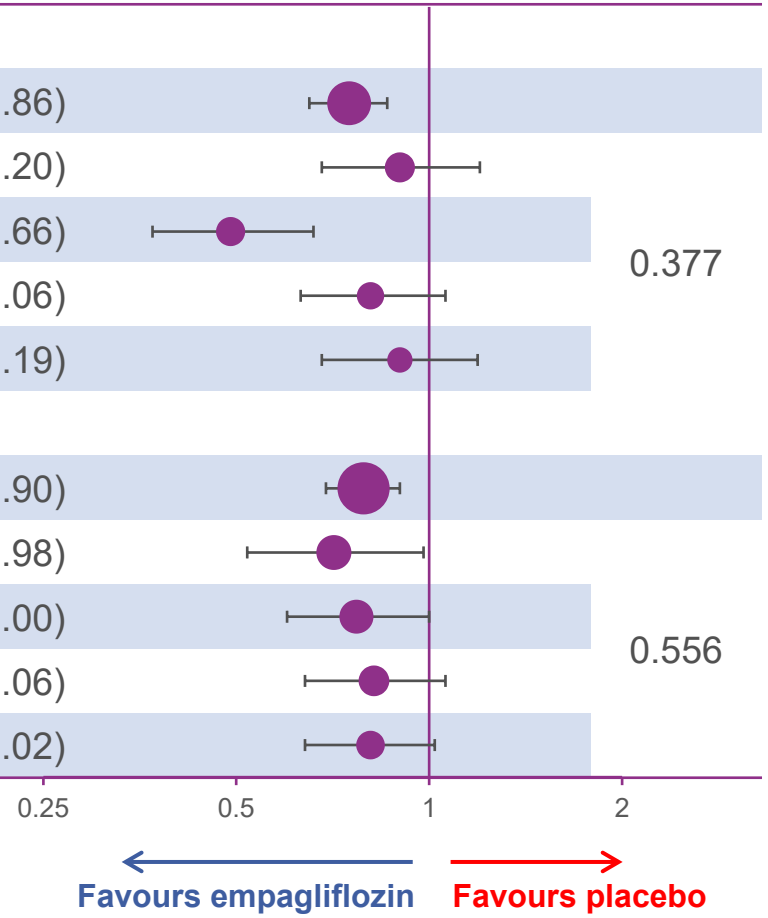
Subgroup	Empagliflozin n/N	Empagliflozin Events/ 100 py	Placebo n/N	Placebo Events/ 100 py	HR (95% CI)	*P* trend
All patients	776/4860	9.31	973/4858	12.03	0.77 (0.70, 0.84)	
Low risk	151/1528	5.52	190/1577	6.78	0.81 (0.66, 1.01)	
Moderate risk	184/1440	7.27	265/1382	11.30	0.63 (0.52, 0.76)	0.299
High risk	212/1071	11.88	253/1060	15.15	0.82 (0.68, 0.98)	
Very high risk	229/820	17.86	263/836	20.70	0.84 (0.71, 1.01)	



CI, confidence interval; HR, hazard ratio; py, patient-year

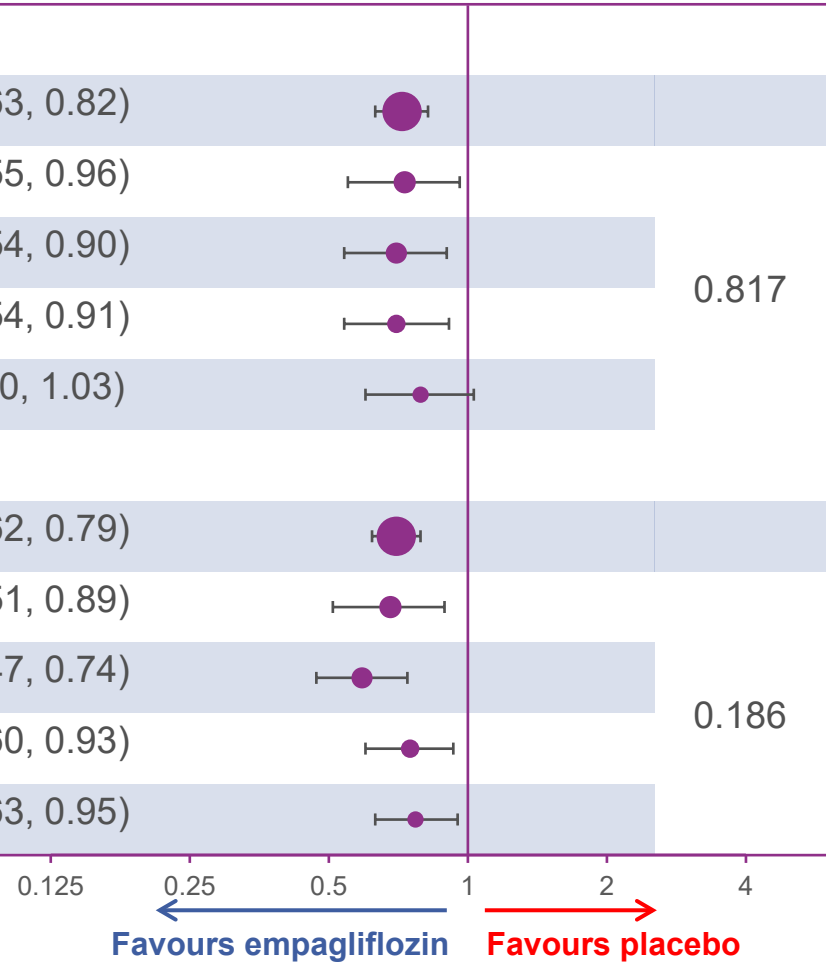
Effect of empagliflozin vs placebo in patients with LVEF ≤40% or >40%: CV death or HHF (primary outcome) by KDIGO subgroups

Subgroup	Empagliflozin n/N	Empagliflozin Events/ 100 py	Placebo n/N	Placebo Events/ 100 py	HR (95% CI)	*P* trend
EMPEROR-Reduced (LVEF ≤40%)						
All patients	361/1863	15.77	462/1867	21.00	0.75 (0.65, 0.86)	
Low risk	88/584	12.10	98/590	13.41	0.90 (0.68, 1.20)	
Moderate risk	74/538	10.60	133/521	21.79	0.49 (0.37, 0.66)	0.377
High risk	100/415	20.72	126/438	25.28	0.81 (0.63, 1.06)	
Very high risk	99/325	26.09	104/317	28.94	0.90 (0.68, 1.19)	
EMPEROR-Preserved (LVEF >40%)						
All patients	415/2997	6.86	511/2991	8.67	0.79 (0.69, 0.90)	
Low risk	63/944	3.14	92/987	4.44	0.71 (0.52, 0.98)	
Moderate risk	110/902	6.00	132/861	7.61	0.77 (0.60, 1.00)	0.556
High risk	112/656	8.60	127/622	10.84	0.82 (0.64, 1.06)	
Very high risk	130/495	14.41	159/519	17.45	0.81 (0.64, 1.02)	



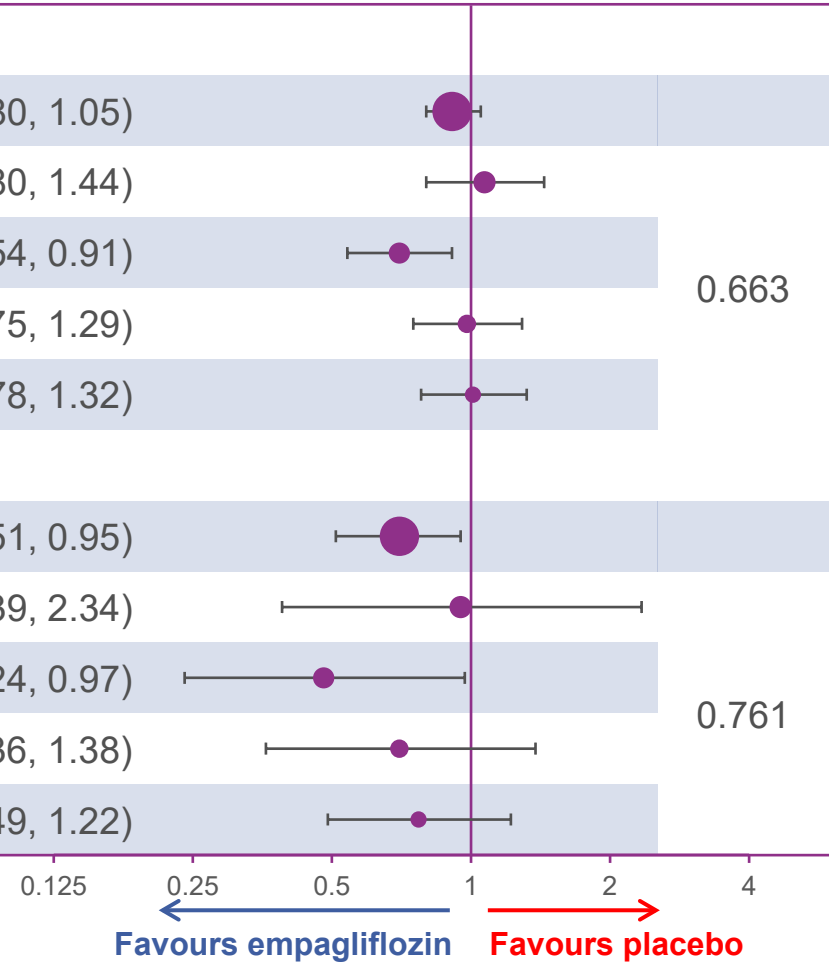
Effect of empagliflozin vs placebo: Total HHF and first HHF (secondary outcomes) by KDIGO subgroups

Subgroup	Empagliflozin n/N	Empagliflozin Events/ 100 py	Placebo n/N	Placebo Events/ 100 py	HR (95% CI)	*P* trend
Total (first and recurrent) heart failure hospitalizations						
All patients	795		1094		0.72 (0.63, 0.82)	
Low risk	132		195		0.73 (0.55, 0.96)	
Moderate risk	197		265		0.70 (0.54, 0.90)	
High risk	207		309		0.70 (0.54, 0.91)	0.817
Very high risk	259		325		0.79 (0.60, 1.03)	
First heart failure hospitalization						
All patients	505/4860	6.06	694/4858	8.58	0.70 (0.62, 0.79)	
Low risk	83/1528	3.03	125/1577	4.46	0.68 (0.51, 0.89)	
Moderate risk	116/1440	4.58	180/1382	7.68	0.59 (0.47, 0.74)	
High risk	142/1071	7.96	186/1060	11.14	0.75 (0.60, 0.93)	0.186
Very high risk	164/820	12.79	203/836	15.98	0.77 (0.63, 0.95)	



Effect of empagliflozin vs placebo: CV death and composite renal endpoint (secondary outcomes) by KDIGO subgroups

Subgroup	Empagliflozin n/N	Empagliflozin Events/ 100 py	Placebo n/N	Placebo Events/ 100 py	HR (95% CI)	*P* trend
Cardiovascular death						
All patients	406/4860	4.58	446/4858	5.02	0.91 (0.80, 1.05)	
Low risk	91/1528	3.20	88/1577	2.98	1.07 (0.80, 1.44)	
Moderate risk	101/1440	3.79	135/1382	5.31	0.70 (0.54, 0.91)	0.663
High risk	104/1071	5.40	108/1060	5.69	0.98 (0.75, 1.29)	
Very high risk	110/820	7.67	113/836	7.60	1.01 (0.78, 1.32)	
Composite renal endpoint						
All patients	68/4860	0.96	95/4858	1.36	0.70 (0.51, 0.95)	
Low risk	9/1528	0.39	10/1577	0.42	0.95 (0.39, 2.34)	
Moderate risk	12/1440	0.56	23/1382	1.16	0.48 (0.24, 0.97)	0.761
High risk	14/1071	0.93	21/1060	1.41	0.70 (0.36, 1.38)	
Very high risk	33/820	2.97	41/836	3.63	0.77 (0.49, 1.22)	



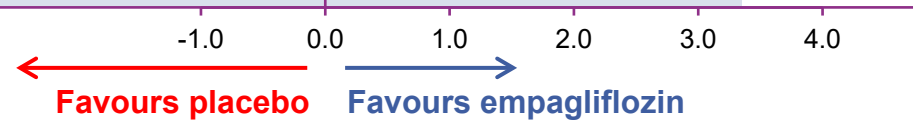
Effect of empagliflozin vs placebo: eGFR slope change per year (secondary outcome) by KDIGO subgroups

Subgroup	Empagliflozin	Placebo	Difference (95% CI)	*P* trend
	Mean change (SE)	Mean change (SE)		
All patients	−1.10 (0.10)	−2.56 (0.10)	1.46 (1.18, 1.73)	
Low risk	−1.51 (0.17)	−3.13 (0.17)	1.62 (1.15, 2.09)	
Moderate risk	−1.14 (0.18)	−2.81 (0.18)	1.67 (1.17, 2.17)	0.069
High risk	−0.86 (0.22)	−2.17 (0.22)	1.31 (0.72, 1.91)	
Very high risk	−0.76 (0.26)	−1.61 (0.25)	0.86 (0.16, 1.56)	

SE, standard error

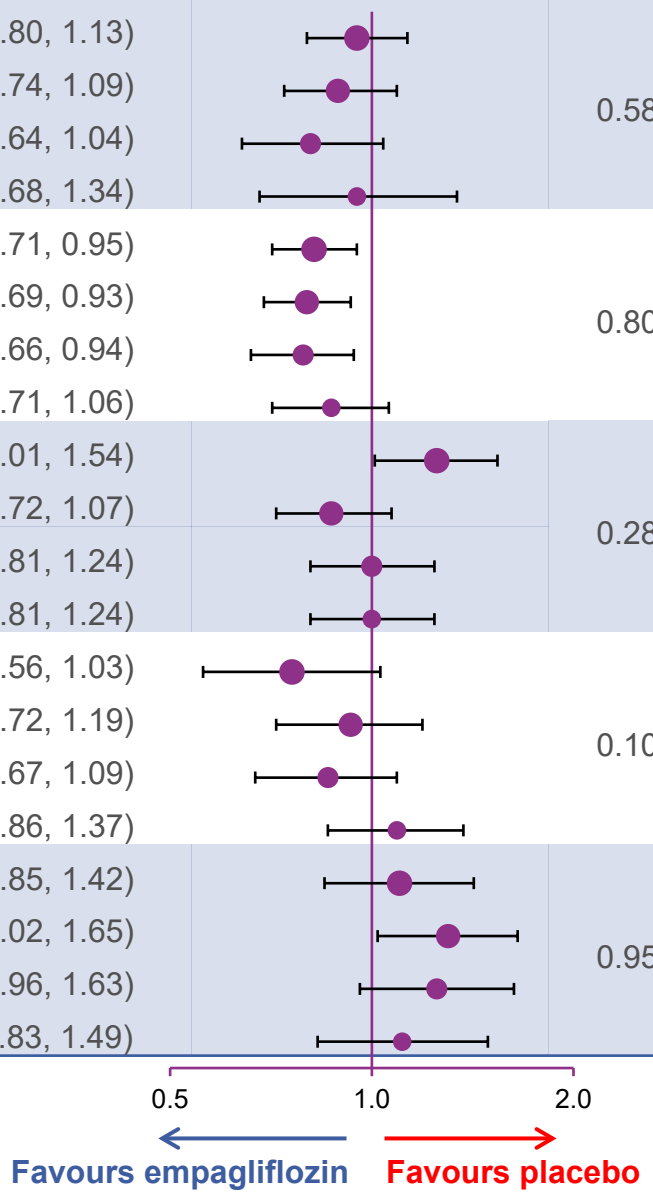
Effect of empagliflozin vs placebo: KCCQ-CSS change from baseline at Week 52 (secondary outcome) by KDIGO subgroups

Subgroup	Empagliflozin	Placebo	Difference (95% CI)	*P* trend
	Mean change (SE)	Mean change (SE)		
All patients	4.74 (0.25)	3.17 (0.25)	1.56 (0.86, 2.27)	
Low risk	4.94 (0.45)	3.31 (0.44)	1.63 (0.41, 2.85)	
Moderate risk	4.74 (0.46)	3.20 (0.48)	1.54 (0.23, 2.85)	0.949
High risk	5.07 (0.55)	3.88 (0.55)	1.19 (−0.33, 2.71)	
Very high risk	4.69 (0.63)	2.74 (0.63)	1.95 (0.19, 3.70)	



Safety of empagliflozin vs placebo by KDIGO subgroups

		Placebo, n/N (%)	Empagliflozin, n/N (%)	OR (95% CI)	*P* trend
Any adverse events	Low risk	1231/1575 (78.2)	1183/1528 (77.4)	0.95 (0.80, 1.13)	0.584
	Moderate risk	1141/1380 (82.7)	1170/1440 (81.3)	0.89 (0.74, 1.09)	
	High risk	915/1060 (86.3)	898/1070 (83.9)	0.81 (0.64, 1.04)	
	Very high risk	759/834 (91.0)	743/820 (90.6)	0.95 (0.68, 1.34)	
Serious adverse events	Low risk	642/1575 (40.8)	553/1528 (36.2)	0.82 (0.71, 0.95)	0.808
	Moderate risk	665/1380 (48.2)	617/1440 (42.8)	0.80 (0.69, 0.93)	
	High risk	603/1060 (56.9)	545/1070 (50.9)	0.79 (0.66, 0.94)	
	Very high risk	528/834 (63.3)	493/820 (60.1)	0.87 (0.71, 1.06)	
Any adverse event leading to discontinuation of trial drug	Low risk	182/1575 (11.6)	214/1528 (14.0)	1.25 (1.01, 1.54)	0.287
	Moderate risk	244/1380 (17.7)	230/1440 (16.0)	0.87 (0.72, 1.07)	
	High risk	214/1060 (20.2)	215/1070 (20.1)	1.00 (0.81, 1.24)	
	Very high risk	238/834 (28.5)	234/820 (28.5)	1.00 (0.81, 1.24)	
Acute renal failure	Low risk	105/1575 (6.7)	78/1528 (5.1)	0.76 (0.56, 1.03)	0.103
	Moderate risk	138/1380 (10.0)	135/1440 (9.4)	0.93 (0.72, 1.19)	
	High risk	157/1060 (14.8)	139/1070 (13.0)	0.86 (0.67, 1.09)	
	Very high risk	176/834 (21.1)	186/820 (22.7)	1.09 (0.86, 1.37)	
Volume depletion	Low risk	127/1575 (8.1)	135/1528 (8.8)	1.10 (0.85, 1.42)	0.957
	Moderate risk	131/1380 (9.5)	174/1440 (12.1)	1.30 (1.02, 1.65)	
	High risk	113/1060 (10.7)	138/1070 (12.9)	1.25 (0.96, 1.63)	
	Very high risk	99/834 (11.9)	106/820 (12.9)	1.11 (0.83, 1.49)	



Conclusions

- Empagliflozin reduced the risk for CV death or HF hospitalization and slowed the rate of eGFR decline similarly in all KDIGO CKD risk categories
- Empagliflozin also improved health status and was associated with acceptable safety outcomes across the KDIGO risk categories
- The safety of empagliflozin was comparable across all KDIGO risk categories
- These data outline the important benefits of empagliflozin across a broad range of kidney functions as assessed by KDIGO CKD risk categories in patients with HF, including those with severe kidney function impairment down to an eGFR of 20 mL/min/1.73 m^2 and irrespective of albuminuria