

## Supplementary material

**Supplementary Table 1. Baseline characteristics by tertiles of % eGFR change at week 4 within the empagliflozin group and by tertiles of % eGFR change at week 4 within the placebo group in EMPEROR-Preserved**

**Empagliflozin:** Tertile 1  $\leq -11.8\%$ ; Tertile 2  $\geq -11.8\%$  to  $-1.1\%$  and Tertile 3  $\geq -1.1\%$

	<b>N analyzed (total = 2893)</b>	<b>Tertile 1 (<math>\leq -11.8\%</math>) n = 966</b>	<b>Tertile 2 (<math>\geq -11.8\%</math> to <math>-1.1\%</math>) n = 962</b>	<b>Tertile 3 (<math>\geq -1.1\%</math>) n = 965</b>	<b>P-value<sup>a</sup></b>
Age, years, mean (SD)	2893	72.25 (9.02)	72.27 (9.20)	70.95 (9.58)	0.0021
Age groups, n (%)					0.0060 <sup>b</sup>
<65 years	574	183 (31.9)	170 (29.6)	221 (38.5)	
65 to <75 years	1088	349 (32.1)	376 (34.6)	363 (33.4)	
$\geq 75$ years	1231	434 (35.3)	416 (33.8)	381 (31.0)	
Male, n (%)	1609	511 (31.8)	550 (34.2)	548 (34.1)	0.0850
BMI, kg/m <sup>2</sup> , mean (SD)	2893	30.21 (5.94)	29.36 (5.68)	29.79 (5.78)	0.1117
Race, n (%)					0.3944
White	2207	734 (33.3)	748 (33.9)	725 (32.9)	
Black/African-American	126	53 (42.1)	32 (25.4)	41 (32.5)	
Asian	402	127 (31.6)	135 (33.6)	140 (34.8)	
Other including mixed race	157	52 (33.1)	46 (29.3)	59 (37.6)	
Region, n (%)					0.9631
Europe	1301	427 (32.8)	461 (35.4)	413 (31.7)	
North America	342	112 (32.7)	111 (32.5)	119 (34.8)	
Asia	336	109 (32.4)	113 (33.6)	114 (33.9)	
Latin America	731	259 (35.4)	210 (28.7)	262 (35.8)	
Other	183	59 (32.2)	67 (36.6)	57 (31.1)	
LVEF, %, mean (SD)	2893	55.20 (8.81)	53.64 (8.65)	54.22 (8.83)	0.0138
LVEF, n (%)					0.0219 <sup>b</sup>
<50%	962	285 (29.6)	362 (37.6)	315 (32.7)	
50–60%	991	332 (33.5)	306 (30.9)	353 (35.6)	
$\geq 60\%$	940	349 (37.1)	294 (31.3)	297 (31.6)	
NT-proBNP, pg/ml, median (IQR)	2893	1049.00 (534.00, 1828.00)	977.50 (520.00, 1697.00)	962.00 (457.00, 1721.00)	0.0244
NT-proBNP group, n (%) <sup>c</sup>					0.0081 <sup>b</sup>
Tertile 1	957	280 (29.3)	333 (34.8)	344 (35.9)	
Tertile 2	953	334 (35.0)	322 (33.8)	297 (31.2)	
Tertile 3	979	352 (36.0)	306 (31.3)	321 (32.8)	

	<b>N analyzed (total = 2893)</b>	<b>Tertile 1 (≤ -11.8%) n = 966</b>	<b>Tertile 2 (≥ -11.8% to -1.1%) n = 962</b>	<b>Tertile 3 (≥ -1.1%) n = 965</b>	<b>P-value<sup>a</sup></b>
Heart rate, BPM, mean (SD)	2893	70.32 (11.92)	70.07 (11.74)	70.70 (12.15)	0.4891
Heart rate group, n (%)					0.4795
≤70 bpm	1590	532 (33.5)	542 (34.1)	516 (32.5)	
>70 bpm	1303	434 (33.3)	420 (32.2)	449 (34.5)	
SBP, mmHg, mean (SD)	2893	132.73 (15.68)	132.23 (15.30)	130.33 (15.76)	0.0007
SBP groups, n (%)					0.0017
<110 mmHg	219	61 (27.9)	65 (29.7)	93 (42.5)	
≥110 to ≤130 mmHg	1174	381 (32.5)	380 (32.4)	413 (35.2)	
>130 mmHg	1500	524 (34.9)	517 (34.5)	459 (30.6)	
DBP, mmHg, mean (SD)	2893	75.83 (10.63)	75.95 (10.18)	75.48 (11.01)	0.4584
DBP groups, n (%)					0.5384
<90 mmHg	2614	865 (33.1)	877 (33.6)	872 (33.4)	
≥90 mmHg	279	101 (36.2)	85 (30.5)	93 (33.3)	
eGFR-CKD-EPI, mL/min/1.73m <sup>2</sup> , mean (SD)	2893	59.31 (18.57)	63.87 (20.52)	58.30 (21.10)	0.2773
eGFR-CKD-EPI groups, n (%)					0.0105 <sup>b</sup>
<30 mL/min/1.73m <sup>2</sup>	168	44 (26.2)	37 (22.0)	87 (51.8)	
30 to <45 mL/min/1.73m <sup>2</sup>	539	204 (37.8)	146 (27.1)	189 (35.1)	
45 to <60 mL/min/1.73m <sup>2</sup>	739	247 (33.4)	241 (32.6)	251 (34.0)	
≥60 mL/min/1.73m <sup>2</sup>	1447	471 (32.6)	538 (37.2)	438 (30.3)	
UACR, mg/g, median (IQR)	2881	25.64 (8.84, 92.38)	17.34 (6.19, 62.76)	18.56 (7.07, 61.88)	<0.01
Hb, g/dl, mean (SD)	2893	131.38 (15.85)	134.38 (15.03)	134.21 (15.70)	<0.0001
Time since diagnosis of HF groups, n (%)					0.4204 <sup>b</sup>
≤1 year	711	234 (32.9)	237 (33.3)	240 (33.8)	
>1 to 5 years	1322	435 (32.9)	444 (33.6)	443 (33.5)	
>5 to 10 years	523	176 (33.7)	174 (33.3)	173 (33.1)	
>10 years	337	121 (35.9)	107 (31.8)	109 (32.3)	
Cause of HF, n (%)					0.7406
Ischemic	1044	345 (33.0)	361 (34.6)	338 (32.4)	
Non-ischemic	1848	620 (33.5)	601 (32.5)	627 (33.9)	
History of AF, n (%)	1522	492 (32.3)	525 (34.5)	505 (33.2)	0.4899
History of hypertension, n (%)	2630	904 (34.4)	863 (32.8)	863 (32.8)	0.0018
HHF within 12 months, n (%)	671	228 (34.0)	201 (30.0)	242 (36.1)	0.4390
Concomitant medications, n (%)					
ACEi/ARB	2285	785 (34.4)	761 (33.3)	739 (32.3)	0.0115

	<b>N analyzed (total = 2893)</b>	<b>Tertile 1 (<math>\leq -11.8\%</math>) n = 966</b>	<b>Tertile 2 (<math>\geq -11.8\%</math> to <math>-1.1\%</math>) n = 962</b>	<b>Tertile 3 (<math>\geq -1.1\%</math>) n = 965</b>	<b>P-value<sup>a</sup></b>
Beta-blocker	2510	838 (33.4)	848 (33.8)	824 (32.8)	0.3726
Diuretic	2472	854 (34.5)	809 (32.7)	809 (32.7)	0.0048

**Placebo:** Tertile 1  $\leq -5.1\%$ ; Tertile 2  $\geq -5.1\%$  to  $+4.0\%$ ; and Tertile 3  $\geq +4.0\%$

	<b>N analyzed (total = 2887)</b>	<b>Tertile 1 (<math>\leq -5.1\%</math>) n = 962</b>	<b>Tertile 2 (<math>\geq -5.1\%</math> to <math>+4.0\%</math>) n = 964</b>	<b>Tertile 3 (<math>\geq +4.0\%</math>) n = 961</b>	<b>P-value<sup>a</sup></b>
Age, years, mean (SD)	2887	72.05 (9.46)	71.69 (9.75)	72.05 (9.33)	1.0000
Age groups, n (%)					0.8516 <sup>b</sup>
<65 years	579	202 (34.9)	195 (33.7)	182 (31.4)	
65 to <75 years	1067	331 (31.0)	372 (34.9)	364 (34.1)	
$\geq 75$ years	1241	429 (34.6)	397 (32.0)	415 (33.4)	
Male, n (%)	1592	526 (33.0)	543 (34.1)	523 (32.9)	0.9107
BMI, kg/m <sup>2</sup> , mean (SD)	2887	30.11 (6.22)	29.89 (5.84)	29.83 (5.73)	0.2950
Race, n (%)					0.0627
White	2179	738 (33.9)	730 (33.5)	711 (32.6)	
Black/African-American	119	49 (41.2)	31 (26.1)	39 (32.8)	
Asian	400	123 (30.8)	143 (35.8)	134 (33.5)	
Other including mixed race	189	52 (27.5)	60 (31.7)	77 (40.7)	
Region, n (%)					0.6142
Europe	1298	436 (33.6)	430 (33.1)	432 (33.3)	
North America	344	111 (32.3)	131 (38.1)	102 (29.7)	
Asia	336	105 (31.3)	119 (35.4)	112 (33.3)	
Latin America	729	243 (33.3)	225 (30.9)	261 (35.8)	
Other	180	67 (37.2)	59 (32.8)	54 (30.0)	
LVEF, %, mean (SD)	2887	54.32 (8.69)	54.81 (8.81)	54.05 (8.86)	0.4911
LVEF, n (%)					0.3668 <sup>b</sup>
<50%	943	319 (33.8)	283 (30.0)	341 (36.2)	
50–60%	992	331 (33.4)	343 (34.6)	318 (32.1)	
$\geq 60\%$	952	312 (32.8)	338 (35.5)	302 (31.7)	
NT-proBNP, pg/ml, median (IQR)	2886	1009.50 (542.00, 1830.00)	848.00 (448.00, 1559.00)	964.00 (499.00, 1785.00)	0.2299
NT-proBNP Group <sup>c</sup>					0.1148 <sup>b</sup>
Tertile 1	975	283 (29.0)	366 (37.5)	326 (33.4)	
Tertile 2	974	337 (34.6)	332 (34.1)	305 (31.3)	

	<b>N analyzed (total = 2887)</b>	<b>Tertile 1 (<math>\leq -5.1\%</math>) n = 962</b>	<b>Tertile 2 (<math>\geq -5.1\%</math> to <math>+4.0\%</math>) n = 964</b>	<b>Tertile 3 (<math>\geq +4.0\%</math>) n = 961</b>	<b>P-value<sup>a</sup></b>
Tertile 3	933	341 (36.5)	264 (28.3)	328 (35.2)	
Heart rate, BPM, mean (SD)	2887	70.55 (11.72)	69.95 (11.59)	70.26 (11.97)	0.5886
Heart rate groups, n (%)					0.8344
$\leq 70$ bpm	1597	525 (32.9)	543 (34.0)	529 (33.1)	
$> 70$ bpm	1290	437 (33.9)	421 (32.6)	432 (33.5)	
SBP, mmHg, mean (SD)	2887	133.41 (15.81)	132.22 (14.84)	129.96 (15.91)	$< 0.0001$
SBP groups, n (%)					0.0021
$< 110$ mmHg	219	66 (30.1)	60 (27.4)	93 (42.5)	
$\geq 110$ to $\leq 130$ mmHg	1164	373 (32.0)	376 (32.3)	415 (35.7)	
$> 130$ mmHg	1504	523 (34.8)	528 (35.1)	453 (30.1)	
DBP, mmHg, mean (SD)	2887	76.18 (10.75)	75.85 (10.42)	75.19 (10.30)	0.0388
DBP groups, n (%)					0.0269
$< 90$ mmHg	2598	848 (32.6)	874 (33.6)	876 (33.7)	
$\geq 90$ mmHg	289	114 (39.4)	90 (31.1)	85 (29.4)	
eGFR-CKD-EPI, mL/min/1.73m <sup>2</sup> , mean (SD)	2887	61.39 (19.80)	65.74 (21.70)	54.33 (17.45)	$< 0.0001$
eGFR-CKD-EPI groups, n (%)					$< 0.0001^b$
$< 30$ mL/min/1.73m <sup>2</sup>	157	43 (27.4)	39 (24.8)	75 (47.8)	
30 to $< 45$ mL/min/1.73m <sup>2</sup>	534	172 (32.2)	136 (25.5)	226 (42.3)	
45 to $< 60$ mL/min/1.73m <sup>2</sup>	769	242 (31.5)	235 (30.6)	292 (38.0)	
$\geq 60$ mL/min/1.73m <sup>2</sup>	1427	505 (35.4)	554 (38.8)	368 (25.8)	
UACR, mg/g, median (IQR)	2876	22.98 (8.84, 92.82)	19.00 (7.07, 61.44)	19.00 (7.07, 60.00)	
Hb, g/dl, mean (SD)	2887	132.06 (15.72)	134.49 (15.09)	133.61 (16.31)	0.0298
Time since diagnosis of HF groups, n (%)					0.4957 <sup>b</sup>
$\leq 1$ year	749	239 (31.9)	280 (37.4)	230 (30.7)	
$> 1$ to 5 years	1285	420 (32.7)	415 (32.3)	450 (35.0)	
$> 5$ to 10 years	534	188 (35.2)	165 (30.9)	181 (33.9)	
$> 10$ years	319	115 (36.1)	104 (32.6)	100 (31.3)	
Cause of HF, n (%)					0.2578
Ischemic	1006	346 (34.4)	338 (33.6)	322 (32.0)	
Non-ischemic	1881	616 (32.7)	626 (33.3)	639 (34.0)	
History of AF, n (%)	1511	504 (33.4)	500 (33.1)	507 (33.6)	0.8533
History of hypertension, n (%)	2612	875 (33.5)	875 (33.5)	862 (33.0)	0.3458
HHF within 12 months, n (%)	638	237 (37.1)	187 (29.3)	214 (33.5)	0.2053
Concomitant medications					

	<b>N analyzed (total = 2887)</b>	<b>Tertile 1 (≤ -5.1%) n = 962</b>	<b>Tertile 2 (≥ -5.1% to +4.0%) n = 964</b>	<b>Tertile 3 (≥ +4.0%) n = 961</b>	<b>P-value<sup>a</sup></b>
ACEi/ARB	2265	777 (34.3)	748 (33.0)	740 (32.7)	0.0453
Beta-blocker	2481	826 (33.3)	828 (33.4)	827 (33.3)	0.9030
Diuretic	2511	874 (34.8)	792 (31.5)	845 (33.7)	0.0662

<sup>a</sup>P-values from ordinal regression likelihood ratio test. <sup>b</sup>Parameter in rows modelled ordinally.

<sup>c</sup>NT-proBNP tertiles for patients with history of atrial fibrillation or atrial flutter T1: 1006 pg/ml, T2: 1778 pg/ml. NT-proBNP tertiles for patients without history of atrial fibrillation or atrial flutter T1: 442 pg/ml, T2: 889 pg/ml.

ACEi, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin-receptor blockers; BMI, body mass index; BPM, beats per minute; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HF, heart failure; HHF, hospitalization for heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure; SD, standard deviation; UACR, urine albumin creatinine ratio.

**Supplementary Table 2: Absolute mean (SE) eGFR changes [mL/min/1.73m<sup>2</sup>] the values per treatment group**

eGFR at baseline	Absolute mean eGFR changes	Absolute mean eGFR changes
	Empagliflozin	Placebo
Overall	-3.7 (0.2)	-0.5 (0.2)
eGFR ≥60	-5.4 (0.2)	-1.9 (0.2)
eGFR 45 to <60	-2.7 (0.3)	0.6 (0.3)
eGFR 30 to <45	-1.7 (0.4)	1.4 (0.4)
eGFR <30	1.8 (0.6)	1.6 (0.7)

**Supplementary Table 3: Absolute eGFR change at week 4 after randomization according to diuretic use**

Subgroup at baseline	N analysed	Change from randomization in placebo at week 4 [adjusted mean (95% CI)]	N analysed	Change from randomization in empagliflozin at week 4 [adjusted mean (95% CI)]	Comparison vs placebo[adjusted mean difference (95% CI)], p-value	p-value for interaction
Use of any diuretic at baseline						0.8764
No	376	0.1 (-0.8, 0.9)	421	-3.1 (-3.8, -2.3)	-3.1 (-4.3,-2.0), <0.0001	
Yes	2511	-0.5 (-0.8, -0.2)	2472	-3.7 (-4.0, -3.4)	-3.2 (-3.7,-2.8), <0.0001	
Use of diuretic other than MRA						0.2955
No	568	0.0(-0.7, 0.7)	570	-3.6 (-4.3, -2.9)	-3.6 (-4.6,-2.7), <0.0001	
Yes	2319	-0.5 (-0.9, -0.2)	2323	-3.6 (-3.9, -3.3)	-3.1 (-3.5,-2.6), <0.0001	
Use of thiazide or low ceiling diuretic						0.5261
No	2283	-0.3 (-0.6, 0.0)	2293	-3.4 (-3.8, -3.1)	-3.1 (-3.6,-2.6), <0.0001	
Yes	604	-0.8 (-1.5, -0.1)	600	-4.3 (-4.9, -3.6)	-3.4 (-4.4,-2.5), <0.0001	
Use of loop or high-ceiling diuretic						0.1456
No	934	-0.4 (-0.9, 0.1)	934	-4.0 (-4.6, -3.5)	-3.6 (-4.4,-2.9), <0.0001	
Yes	1953	-0.4 (-0.8, -0.1)	1959	-3.4 (-3.8,-3.0)	-3.0 (-3.5,-2.5), <0.0001	
Loop or High-ceiling						0.2810

diuretic dose					
Low dose	1485	-0.6 (1.0, -0.2)	1470	-3.4(-3.8, -3.0)	-2.8 (-3.4,-2.2), <0.0001
Medium dose	277	-0.2 (-1.2, 0.8)	273	-3.5 (-4.5, -2.5)	-3.3 (-4.7,-1.9), <0.0001
High dose	142	0.3 (-1.1, 1.6)	171	-2.6 (-3.8, -1.3)	-2.8 (-4.6,-1.0), 0.0024

The low, medium, high dose were defined as follows.

a) Low:  $\leq 40$  mg/day of furosemide equivalents,  $\leq 20$  mg/day of torasemide,  $\leq 1$  mg/day of bumetanide

b) Medium:  $>40$ - $\leq 80$  mg/day of furosemide equivalents,  $>20$  to  $\leq 40$  mg/day of torasemide,  $>1$  to  $\leq 2$  mg/day of bumetanide.

c) High:  $>80$  mg/day of furosemide equivalents,  $>40$  mg/day of torasemide,  $>2$  mg/day of bumetanide.

**Supplementary Table 4: Association of eGFR at randomization with Renal endpoints.**

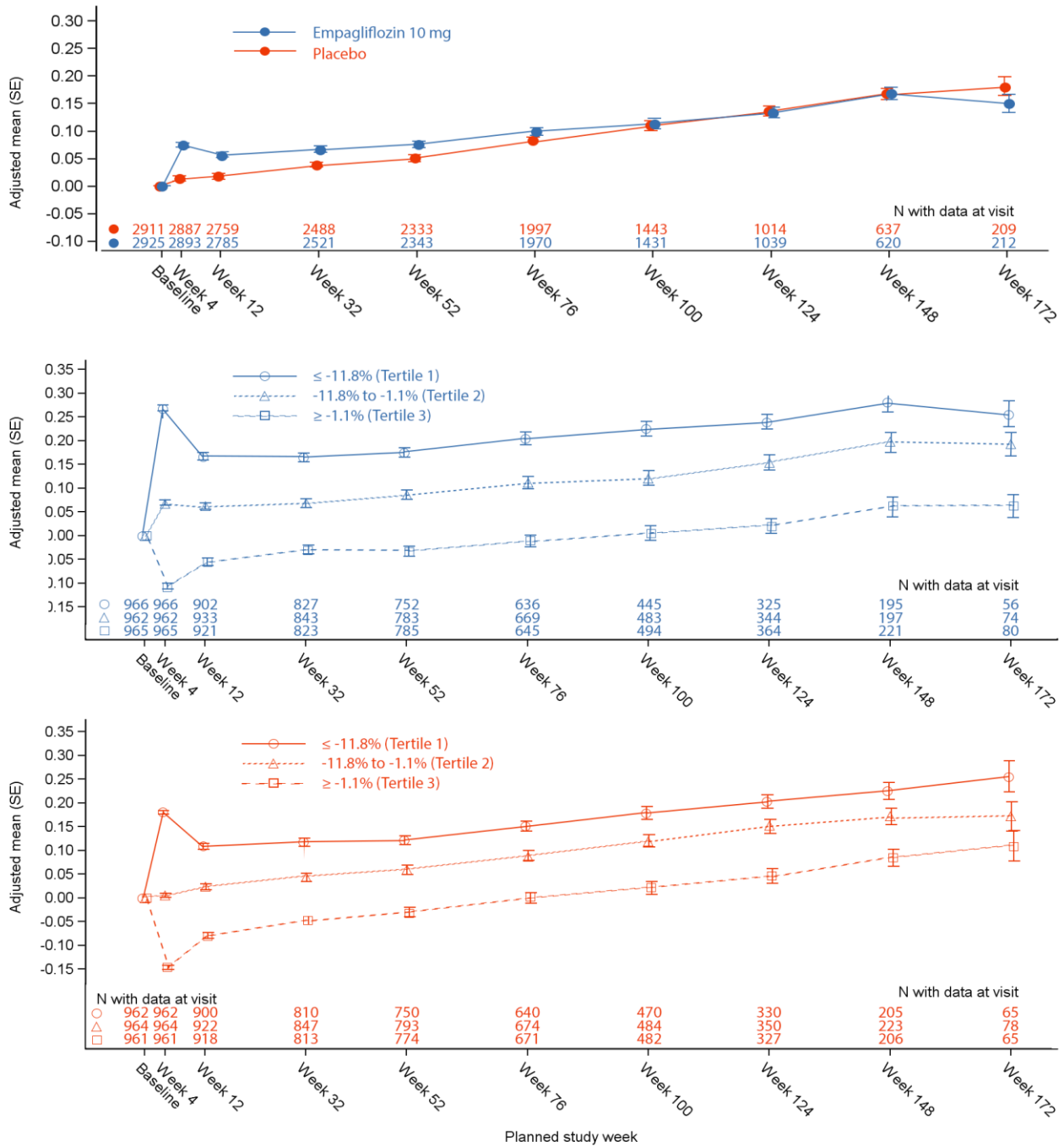
Treatment group	Renal endpoint	Hazard Ratio (95% confidence interval) for a 1-unit increase in eGFR at randomisation (mL/min/1.73 m <sup>2</sup> )
Placebo	Composite renal endpoint	0.979 (0.968, 0.989)
Empagliflozin	Composite renal endpoint	0.977 (0.967, 0.988)
Placebo	Acute kidney injury	0.971 (0.960, 0.982)
Empagliflozin	Acute kidney injury	0.961 (0.947, 0.975)
Placebo	Acute renal failure	0.970 (0.964, 0.977).
Empagliflozin	Acute renal failure	0.969 (0.963, 0.976)

Hazard ratios and Confidence Intervals based on Cox regression models with adjustment for age, sex, baseline LVEF, region, diabetes at baseline and tertiles of initial % eGFR changes within each treatment group



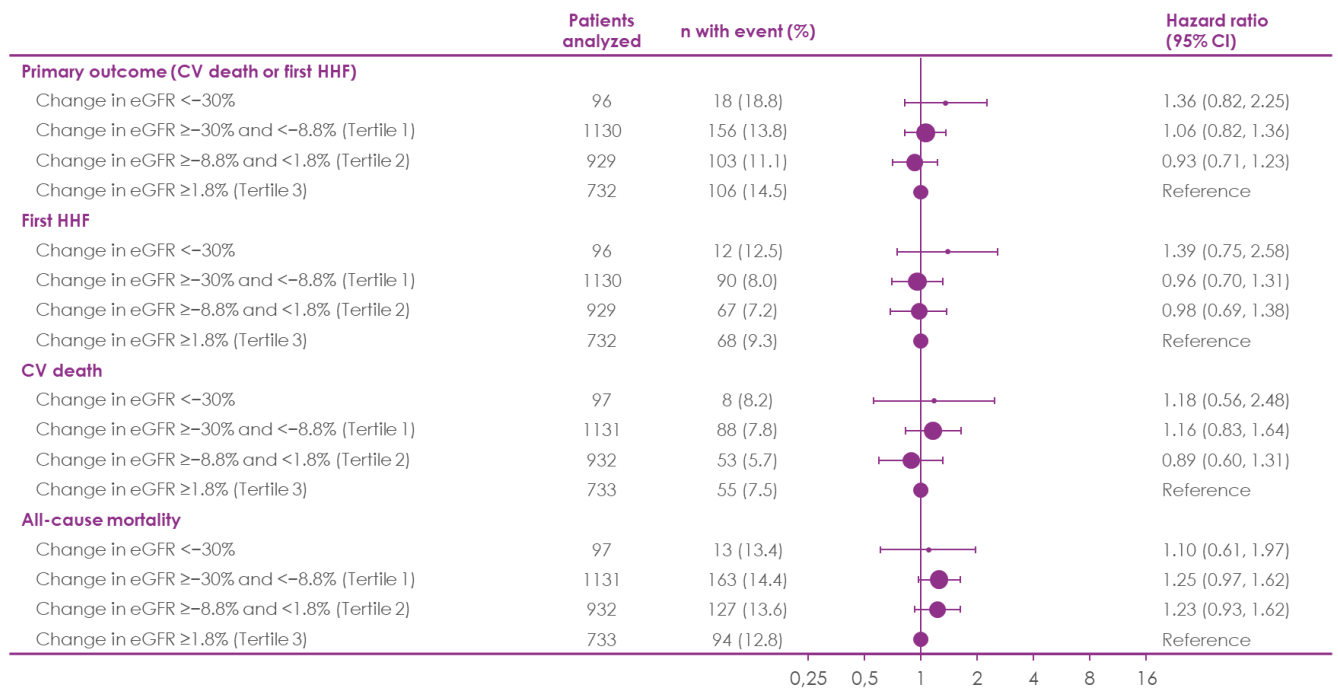


**Supplemental Figure 1. EMPEROR-Preserved Creatinine change over time a) overall; b) by Tertiles in Empagliflozin; c) by Tertiles in Placebo**

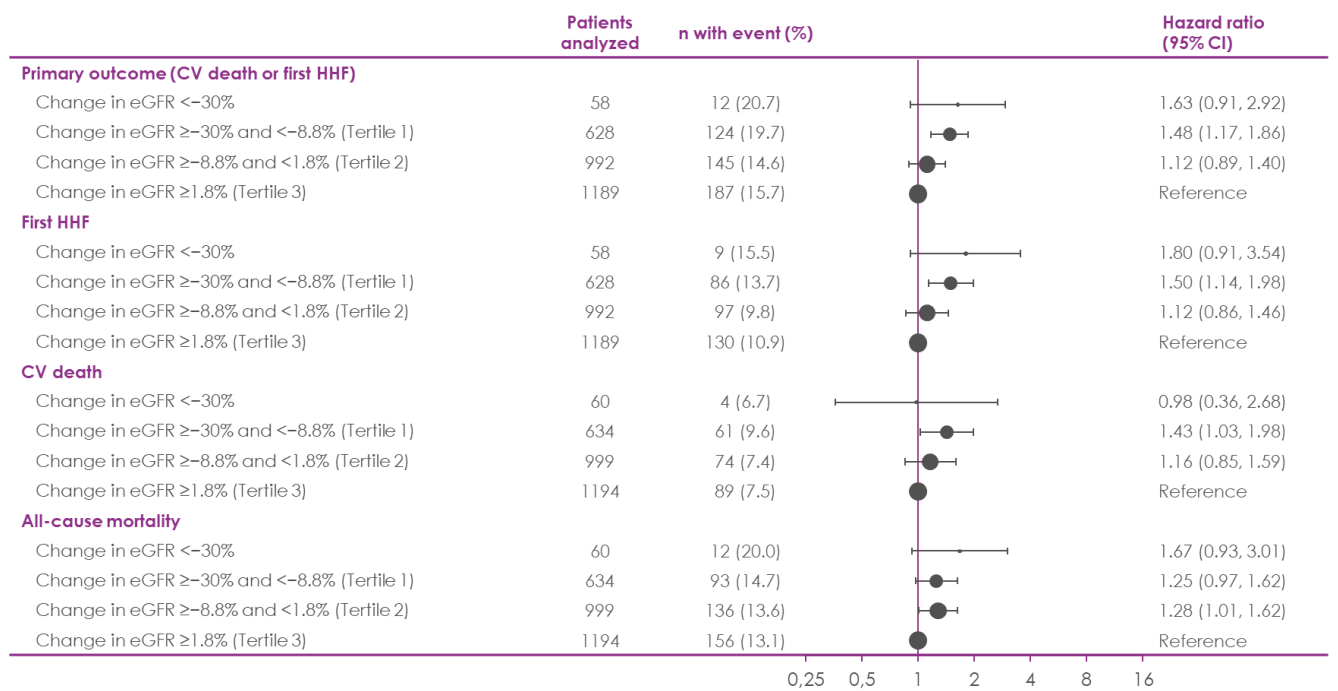


## Supplemental Figure 2: Efficacy outcomes following week 4 by Overall Tertiles and >30% eGFR decrease in EMPEROR-Preserved (a empagliflozin; b placebo)

**a**

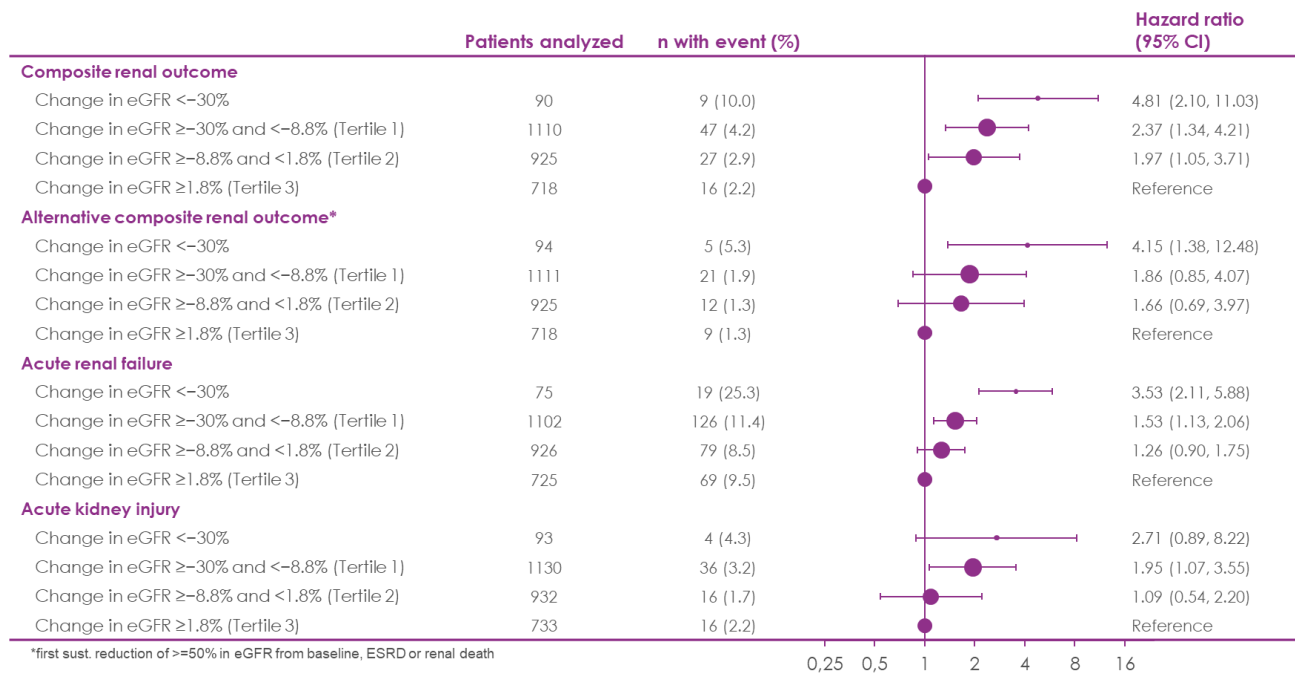


**b**

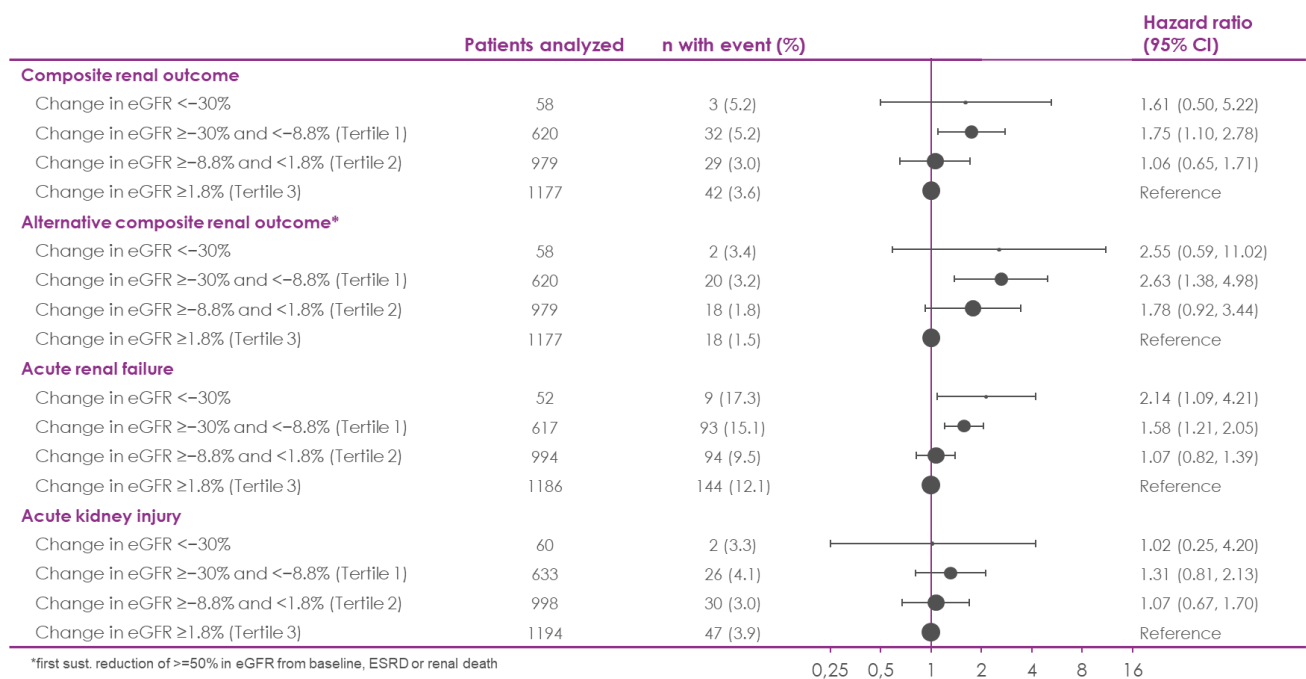


**Supplemental Figure 3: Composite renal and renal safety outcomes following week 4 by tertiles of %eGFR change + 30% dip by treatment group in EMPEROR-Preserved (a empagliflozin; b placebo)**

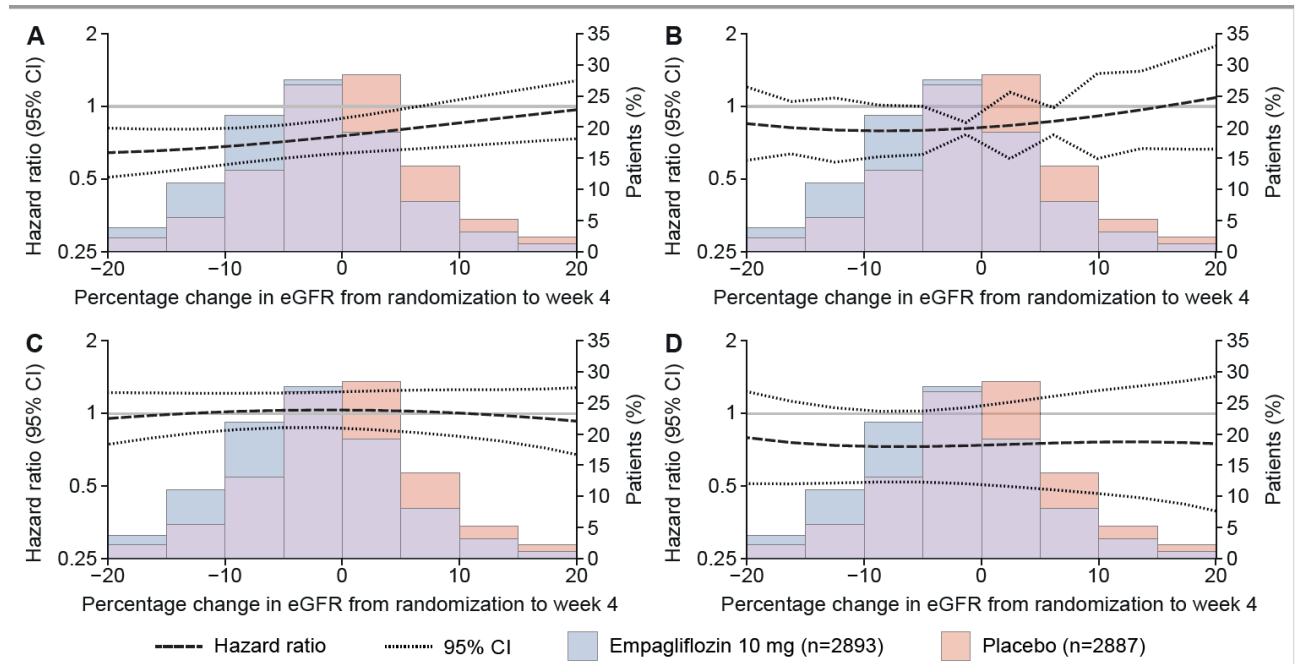
**a**



**b**



**Supplementary Figure 4. Effect of empagliflozin versus placebo following week 4 across the spectrum of % eGFR change at Week 4 in EMPEROR-Preserved**



Legend: Effect of empagliflozin versus placebo following week 4 across the spectrum of percent estimated glomerular filtration rate (eGFR) change at week 4. (A) Primary composite outcome of cardiovascular death or heart failure hospitalization; (B) cardiovascular mortality; (C) all-cause mortality; (D) composite renal endpoint. Percent eGFR change-by-treatment interaction p-values for the endpoints: (A) primary outcome, interaction p = 0.1018; (B) cardiovascular mortality, interaction p = 0.4074; (C) all-cause mortality, interaction p = 0.7866; (D) renal composite, interaction p < 0.0001.