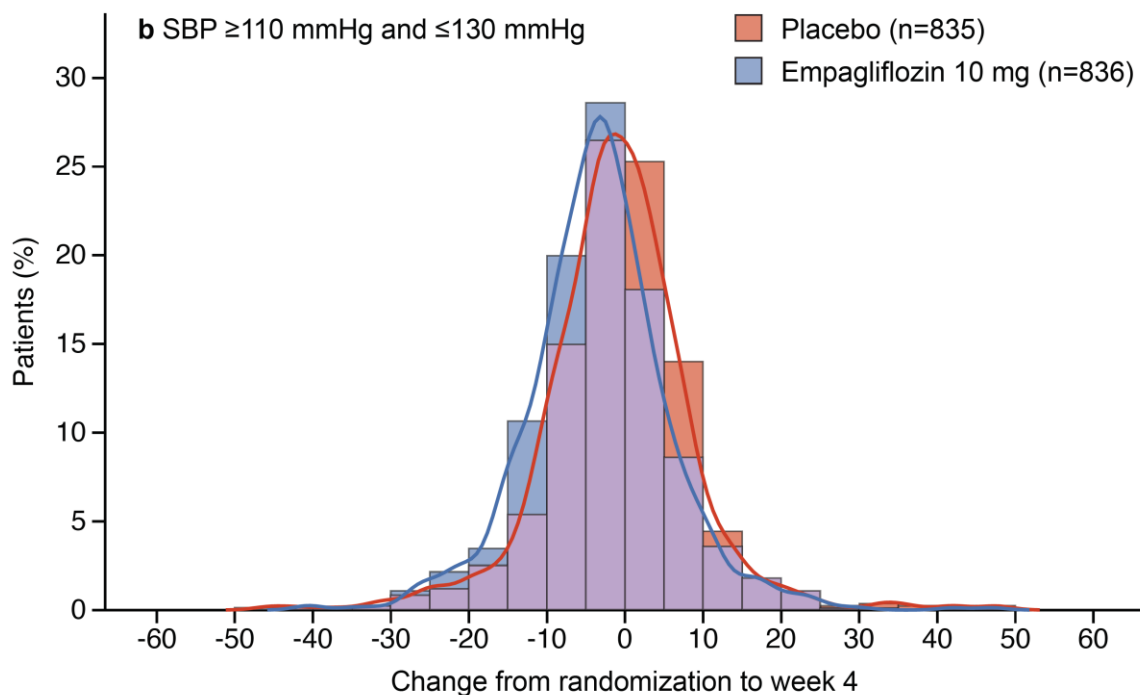
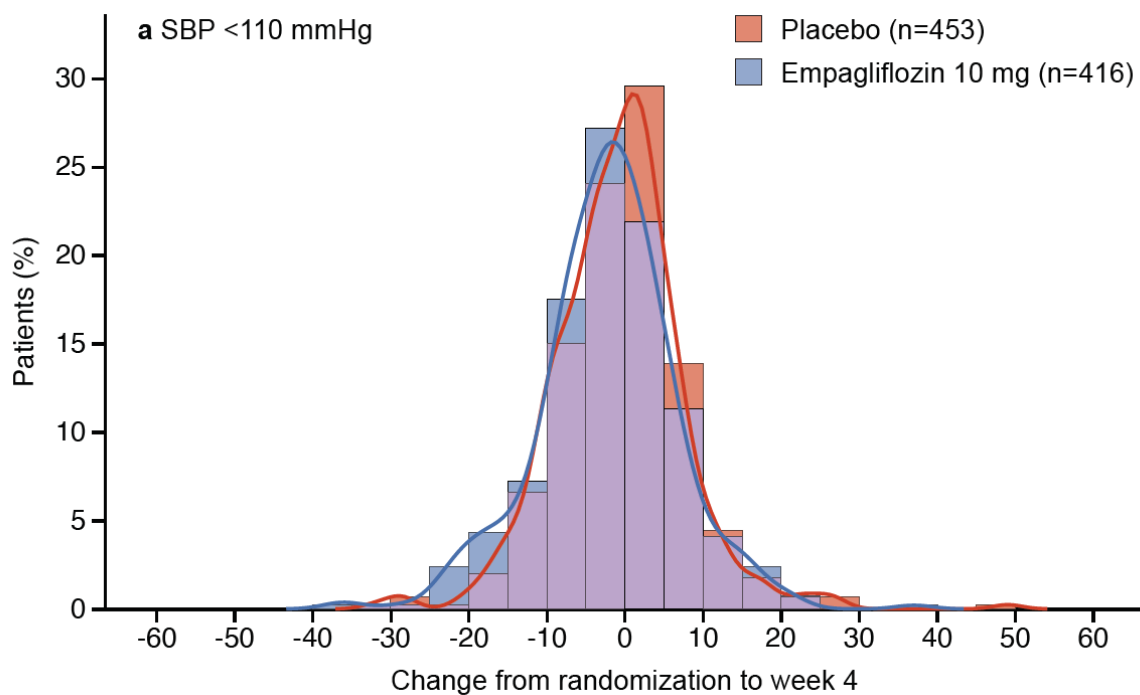
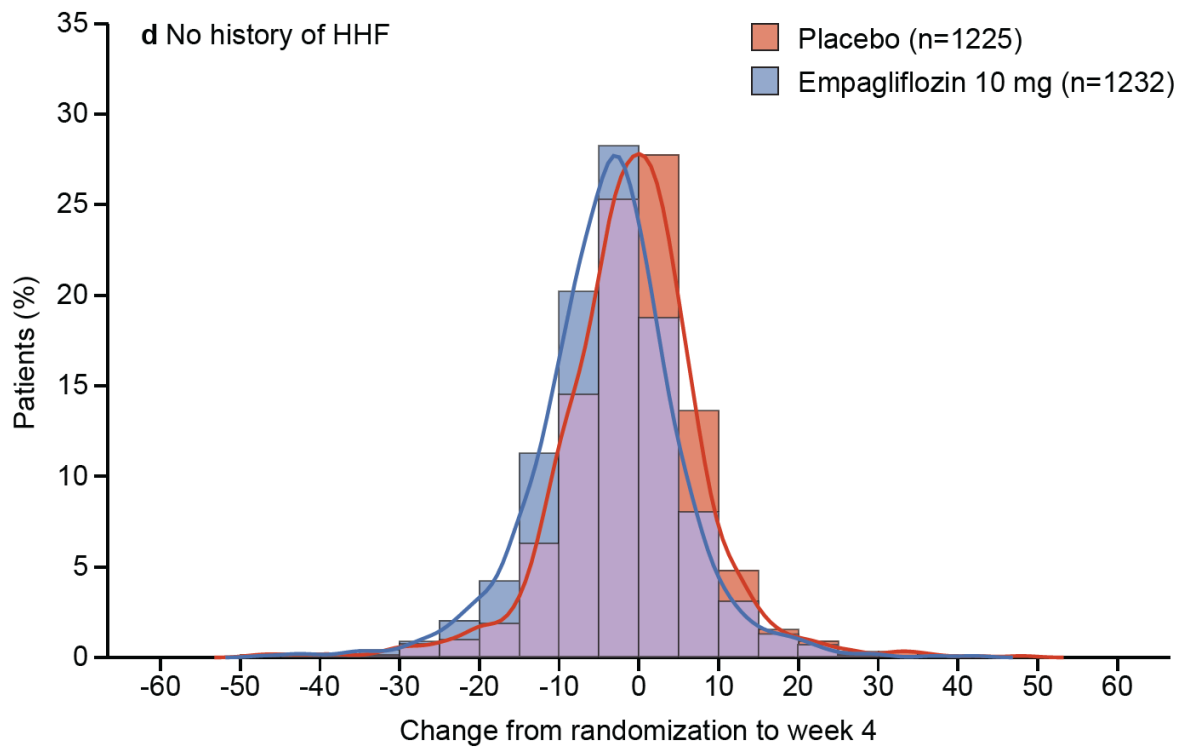
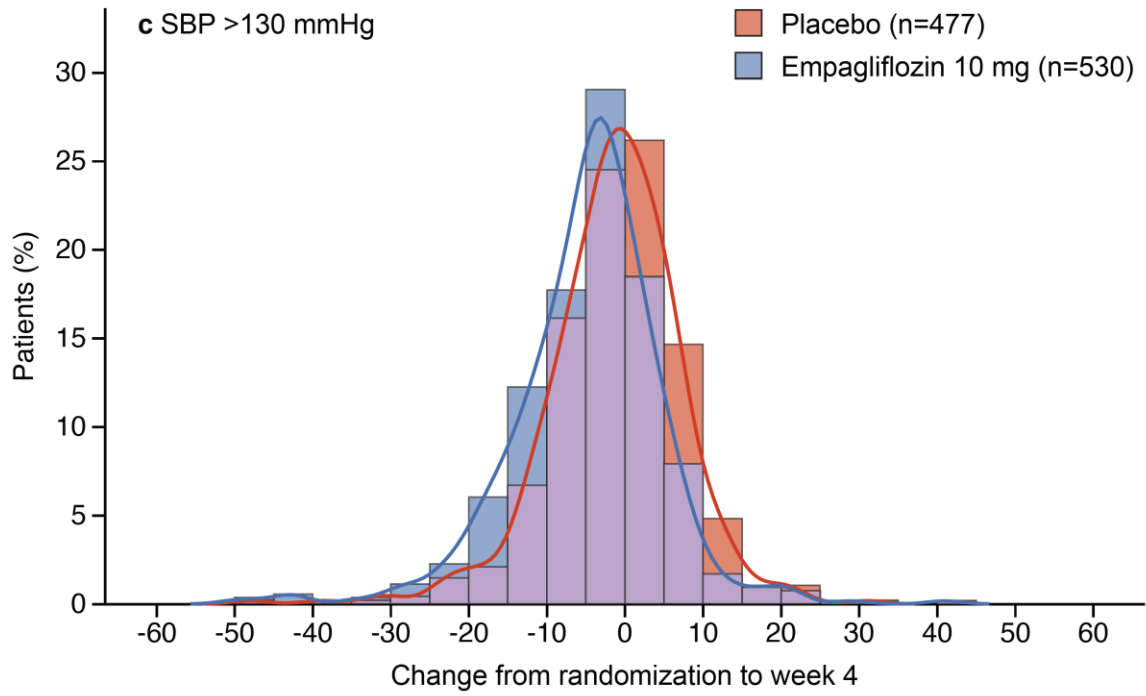
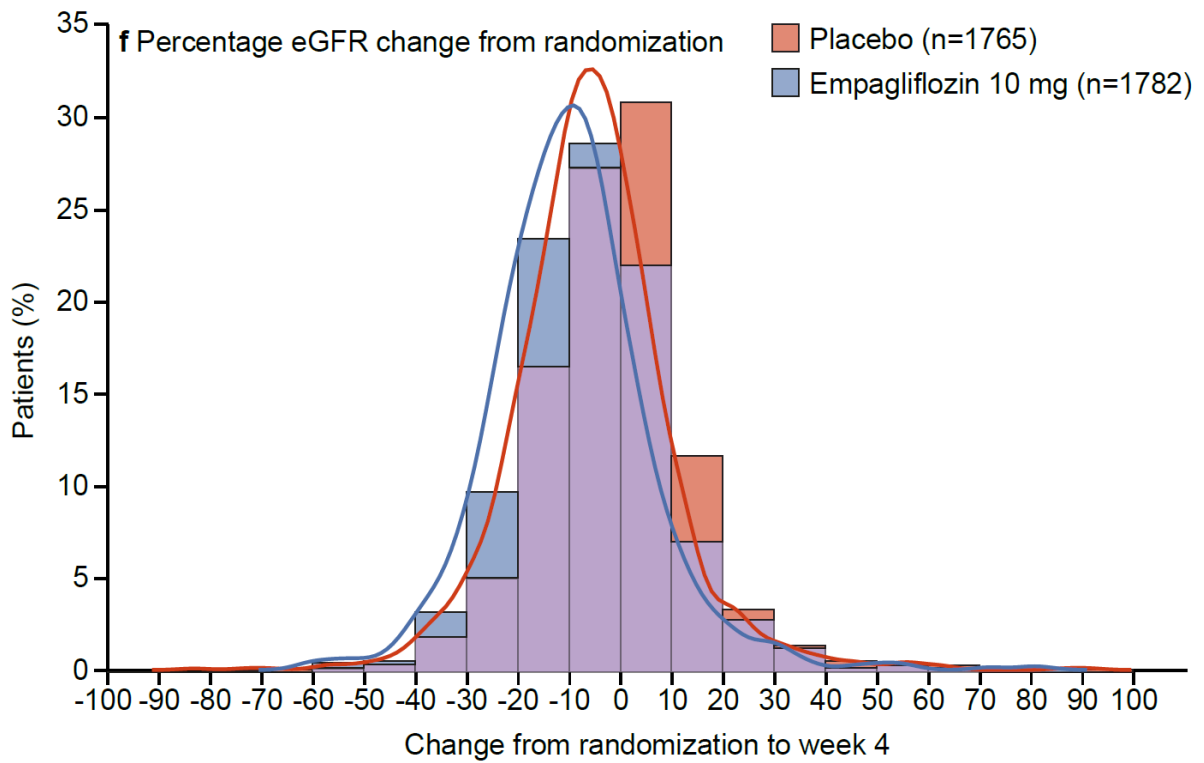
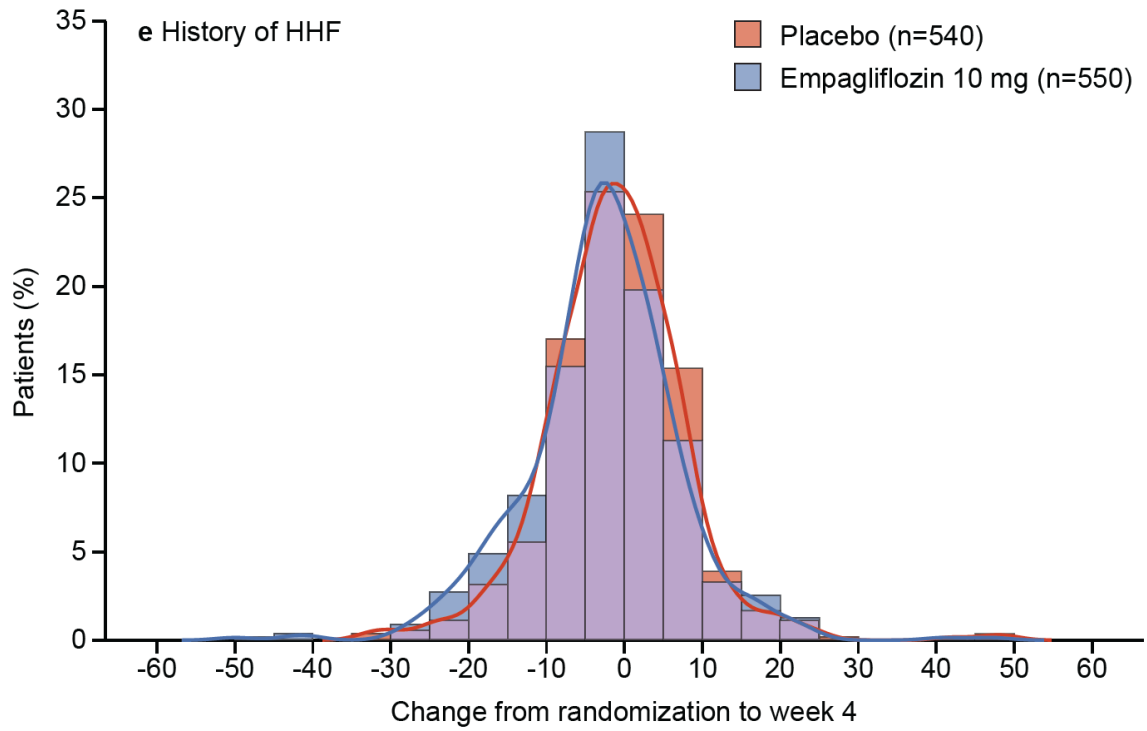


## SUPPLEMENTAL MATERIAL

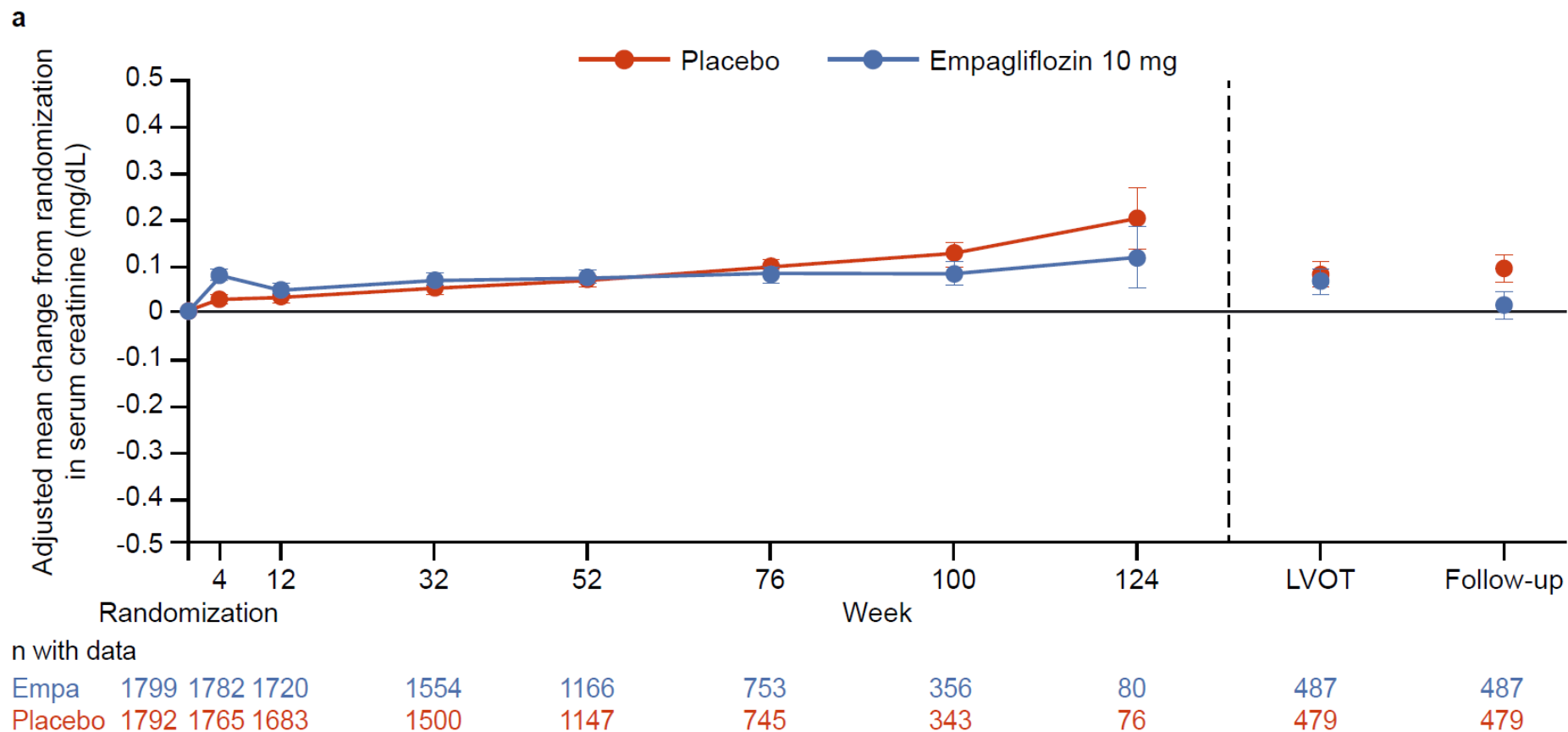
**Supplementary Figure 1** Distribution of individual eGFR change from randomization at week 4 with Empagliflozin and Placebo treatment by baseline SBP (a-c), HF hospitalization in  $\leq 12$  months (d-e), and distribution of individual percentage eGFR change from randomization (f)



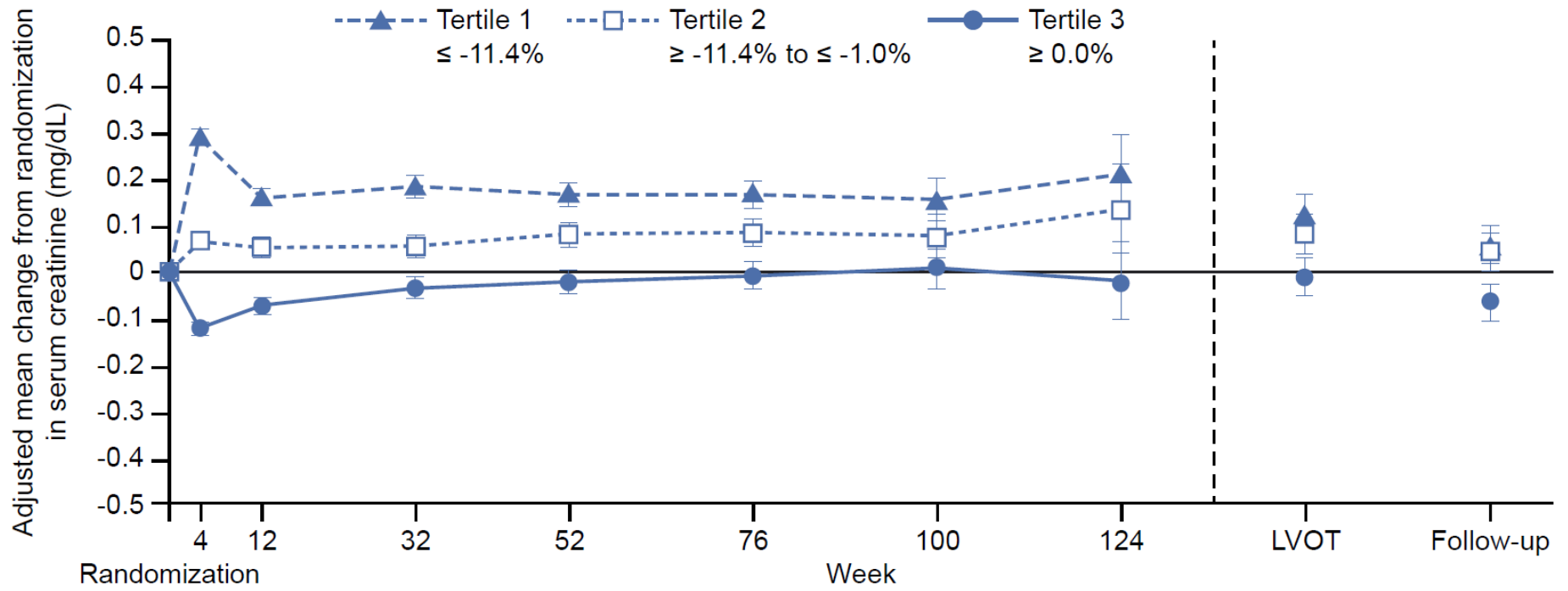




**Supplementary Figure 2.** Change in serum creatinine from randomization a) by treatment group; b) by tertiles of % eGFR change at week 4 within the empagliflozin group; c) by tertiles of % eGFR change at week 4 within the placebo group

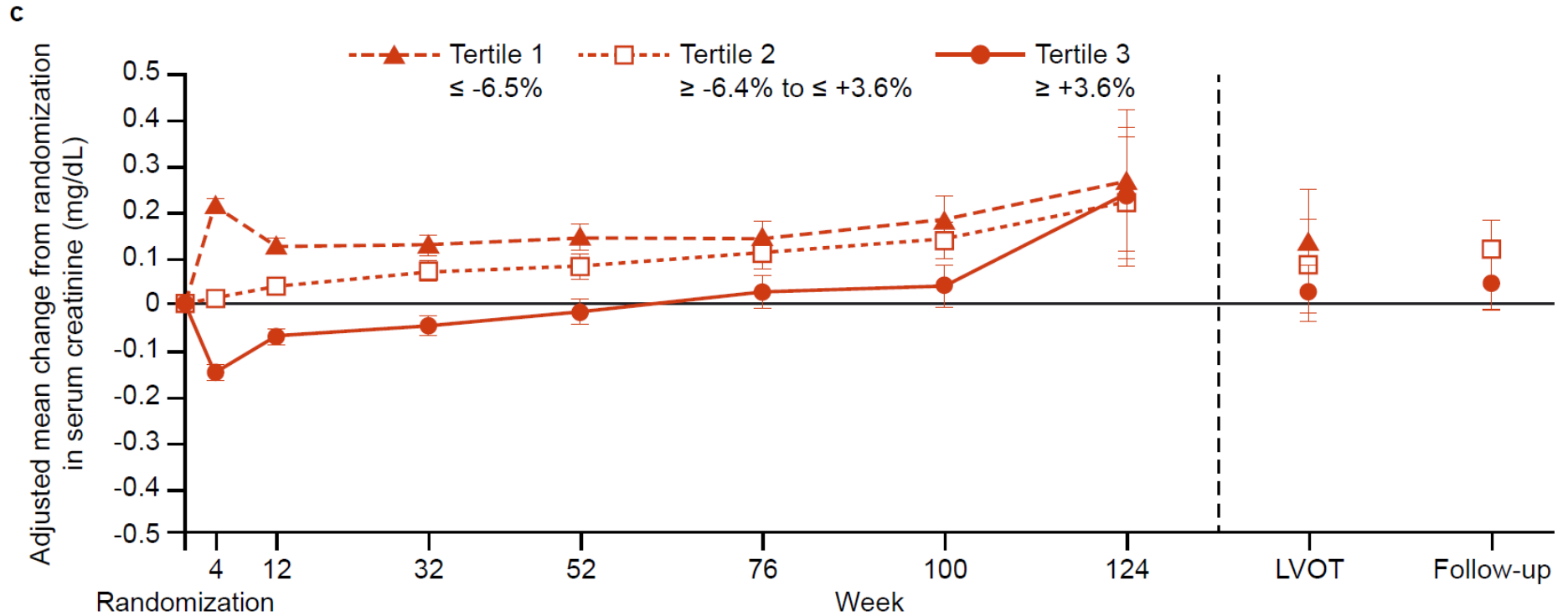


b



n with data

Tertile 1	594	594	563	515	383	245	111	28	150	150
Tertile 2	578	578	560	515	383	240	110	22	168	168
Tertile 3	610	610	580	511	383	263	135	30	167	167



n with data

Tertile 1	588	588	543	474	358	227	101	22	164	164
Tertile 2	589	589	558	500	386	248	115	26	145	145
Tertile 3	588	588	556	507	390	262	121	26	164	164

Left side: The on-treatment data were analyzed with the use of a mixed model for repeated measures based on patients who received at least one dose of a study drug and had a baseline and postbaseline measurement (A) and a week 4 measurement (B, C).

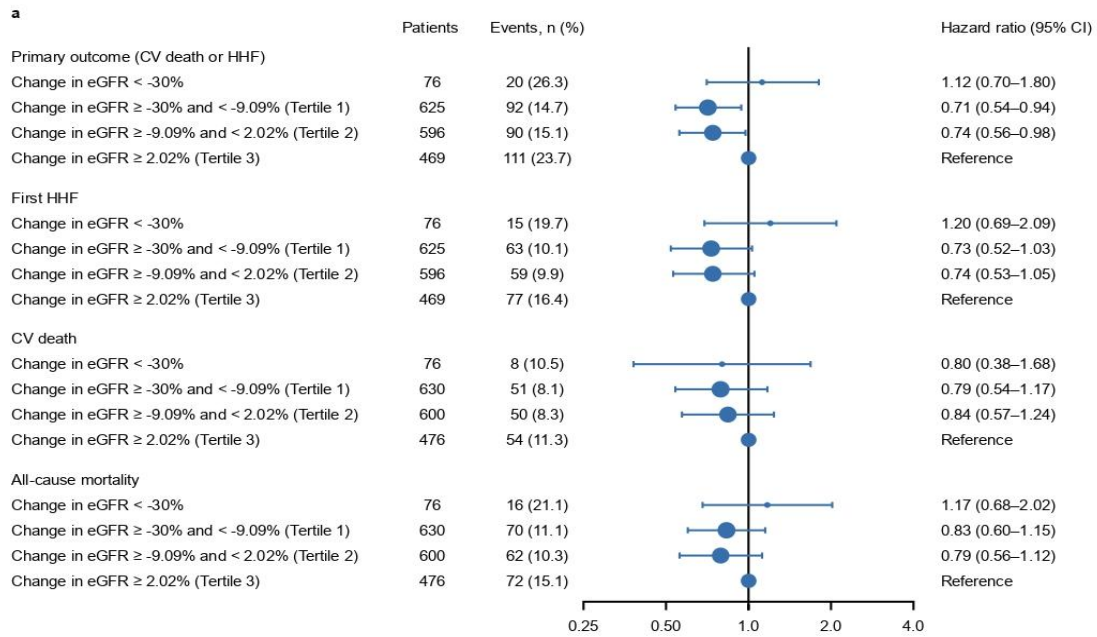
Right side: The LVOT and FUP change from randomization are based on an analysis of a covariance model in patients who underwent measurements at baseline, LVOT and FUP (A) and week 4 (B, C).

Empagliflozin: Tertile 1  $\leq -11.4\%$ ; Tertile 2  $\geq -11.4\%$  to  $\leq -1.0\%$  and Tertile 3  $\geq 0.0\%$

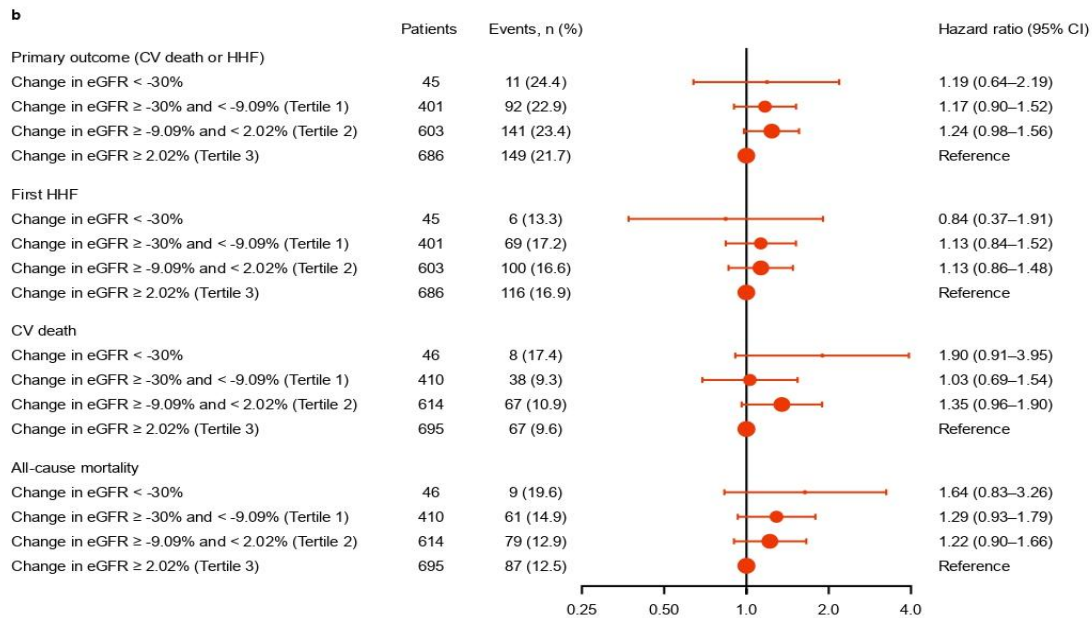
Placebo: Tertile 1  $\leq -6.5\%$ ; Tertile 2  $\geq -6.4\%$  to  $\leq +3.6\%$ ; and Tertile 3  $\geq +3.6\%$ .

### Supplementary Figure 3. Association of eGFR decrease >30% from baseline with subsequent cardiovascular outcomes

#### a) Empagliflozin group



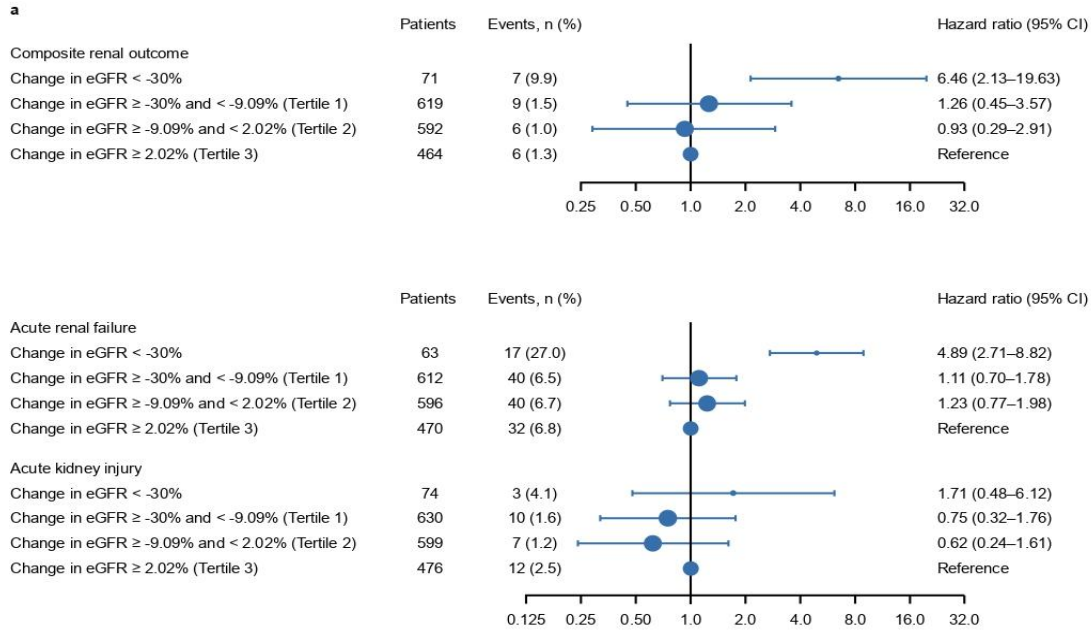
#### b) Placebo group



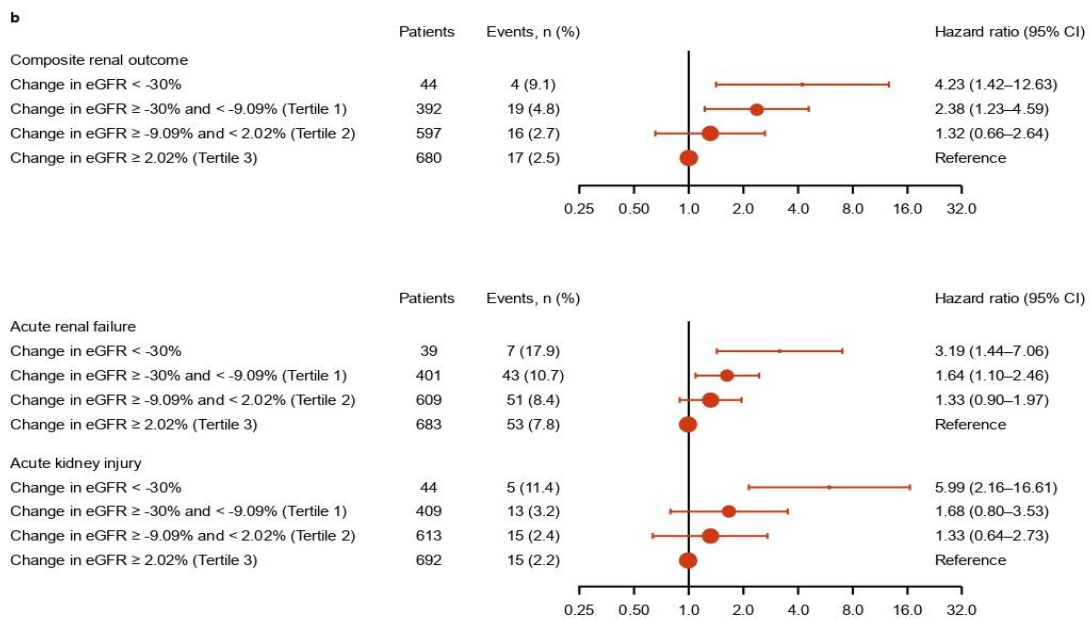


## Supplementary Figure 4. Association of eGFR decrease >30% from baseline with subsequent renal outcomes

### a) Empagliflozin group



### b) Placebo group



**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

**Empagliflozin:** Tertile 1  $\leq -11.4\%$ ; Tertile 2  $\geq -11.4\%$  to  $\leq -1.0\%$  and Tertile 3  $\geq 0.0\%$

	<b>N analyzed (total = 1782)</b>	<b>Tertile 1 (<math>\leq -11.4\%</math>) n = 594</b>	<b>Tertile 2 (<math>\geq -11.4\%</math> to <math>\leq -1.0\%</math>) n = 578</b>	<b>Tertile 3 (<math>\geq 0.0\%</math>) n = 610</b>	<b>P-value<sup>a</sup></b>
Age, years, mean (SD)		67.69 (10.51)	67.15 (10.98)	66.86 (10.93)	0.1863
Age groups, n (%)					0.3901 <sup>b</sup>
<65 years	640	202 (31.6)	212 (33.1)	226 (35.3)	
65 to <75 years	662	232 (35.0)	205 (31.0)	225 (34.0)	
$\geq 75$ years	480	160 (33.3)	161 (33.5)	159 (33.1)	
Male, n (%)	1363	422 (31.0)	453 (33.2)	488 (35.8)	0.0002
BMI, kg/m <sup>2</sup> , mean (SD)		28.47 (5.59)	27.74 (5.53)	27.75 (5.19)	0.0239
Race, n (%)					0.4872
White	1271	438 (34.5)	404 (31.8)	429 (33.8)	
Black/African-American	115	40 (34.8)	28 (24.3)	47 (40.9)	
Asian	323	91 (28.2)	121 (37.5)	111 (34.4)	
Other including mixed race	48	18 (37.5)	14 (29.2)	16 (33.3)	
Region, n (%)					0.3021
Europe	647	218 (33.7)	219 (33.8)	210 (32.5)	
North America	202	77 (38.1)	62 (30.7)	63 (31.2)	
Asia	242	63 (26.0)	94 (38.8)	85 (35.1)	
Latin America	611	213 (34.9)	173 (28.3)	225 (36.8)	
Other	80	23 (28.8)	30 (37.5)	27 (33.8)	
LVEF, %, mean (SD)		28.29 (5.87)	27.32 (6.08)	27.67 (5.85)	0.0755
LVEF, n (%)					0.0355 <sup>b</sup>
<20%	126	35 (27.8)	52 (41.3)	39 (31.0)	
20–30%	1152	361 (31.3)	376 (32.6)	415 (36.0)	
31–35%	383	153 (39.9)	119 (31.1)	111 (29.0)	
>35%	121	45 (37.2)	31 (25.6)	45 (37.2)	
NT-proBNP, pg/mL, median (IQR)		1878.50 (1115.00- 3424.00)	1710.50 (978.00- 3151.00)	1987.00 (1132.00- 3612.00)	
NT-proBNP Group, n (%) <sup>c</sup>					0.4875 <sup>b</sup>
Tertile 1	615	199 (32.4)	219 (35.6)	197 (32.0)	
Tertile 2	595	201 (33.8)	192 (32.3)	202 (33.9)	

	<b>N analyzed (total = 1782)</b>	<b>Tertile 1 (≤ -11.4%) n = 594</b>	<b>Tertile 2 (≥ -11.4% to ≤ -1.0%) n = 578</b>	<b>Tertile 3 (≥ 0.0%) n = 610</b>	<b>P-value<sup>a</sup></b>
Tertile 3	572	194 (33.9)	167 (29.2)	211 (36.9)	
Heart rate, BPM, mean (SD)		70.49 (11.54)	71.40 (11.53)	70.87 (11.91)	0.5781
Heart rate groups, n (%)					0.2141
≤70 bpm	966	345 (35.7)	289 (29.9)	332 (34.4)	
>70 bpm	816	249 (30.5)	289 (35.4)	278 (34.1)	
SBP, mmHg, mean (SD)		125.24 (16.02)	121.97 (15.21)	120.95 (16.13)	<0.0001
SBP groups, n (%)					<0.0001
<110 mmHg	416	106 (25.5)	141 (33.9)	169 (40.6)	
≥110 to ≤130 mmHg	836	275 (32.9)	280 (33.5)	281 (33.6)	
>130 mmHg	530	213 (40.2)	157 (29.6)	160 (30.2)	
DBP, mmHg, mean (SD)		74.64 (10.98)	74.05 (10.73)	73.46 (10.99)	0.0599
DBP groups, n (%)					0.2504
<90 mmHg	1621	535 (33.0)	525 (32.4)	561 (34.6)	
≥90 mmHg	161	59 (36.6)	53 (32.9)	49 (30.4)	
eGFR-CKD-EPI, mL/min/1.73m <sup>2</sup> , mean (SD)		60.65 (21.68)	65.33 (21.87)	59.30 (22.82)	0.2689
eGFR-CKD-EPI groups, n (%)					0.0570 <sup>b</sup>
<30 mL/min/1.73m <sup>2</sup>	112	37 (33.0)	16 (14.3)	59 (52.7)	
30 to <45 mL/min/1.73m <sup>2</sup>	340	121 (35.6)	96 (28.2)	123 (36.2)	
45 to <60 mL/min/1.73m <sup>2</sup>	423	141 (33.3)	137 (32.4)	145 (34.3)	
≥60 mL/min/1.73m <sup>2</sup>	907	295 (32.5)	329 (36.3)	283 (31.2)	
UACR, mg/g, median (IQR)		22.98 (8.84- 105.20)	18.56 (7.96- 60.11)	20.33 (7.96- 81.33)	0.1213 <sup>d</sup>
Hb, g/dl, mean (SD)		13.54 (1.67)	13.76 (1.56)	13.76 (1.62)	0.0231
Time since diagnosis of HF groups, n (%)					0.4941 <sup>b</sup>
≤1 year	336	104 (31.0)	108 (32.1)	124 (36.9)	
>1 to 5 years	681	229 (33.6)	230 (33.8)	222 (32.6)	
>5 to 10 years	407	141 (34.6)	122 (30.0)	144 (35.4)	
>10 years	358	120 (33.5)	118 (33.0)	120 (33.5)	
Cause of HF, n (%)					0.6275
Ischemic	934	314 (33.6)	306 (32.8)	314 (33.6)	
Non-ischemic	848	280 (33.0)	272 (32.1)	296 (34.9)	
History of AF, n (%)	638	217 (34.0)	205 (32.1)	216 (33.9)	0.7010
History of hypertension, n (%)	1297	450 (34.7)	414 (31.9)	433 (33.4)	0.0648
HHF within 12 months, n (%)	550	173 (31.5)	165 (30.0)	212 (38.5)	0.0322
<b>Concomitant medications, n (%)</b>					

	<b>N analyzed (total = 1782)</b>	<b>Tertile 1 (≤ -11.4%) n = 594</b>	<b>Tertile 2 (≥ -11.4% to ≤ -1.0%) n = 578</b>	<b>Tertile 3 (≥ 0.0%) n = 610</b>	<b>P-value<sup>a</sup></b>
ACEi/ARB	1258	410 (32.6)	407 (32.4)	441 (35.1)	0.2126
ARNI	328	118 (36.0)	108 (32.9)	102 (31.1)	0.1592
Beta-blocker	1689	568 (33.6)	550 (32.6)	571 (33.8)	0.1116
Diuretic	1682	558 (33.2)	547 (32.5)	577 (34.3)	0.6246

**Placebo:** Tertile 1 ≤ -6.5%; Tertile 2 ≥ -6.4% to ≤ +3.6%; and Tertile 3 ≥ +3.6%

	<b>N analyzed (total = 1765)</b>	<b>Tertile 1 (≤ -6.5%) n = 588</b>	<b>Tertile 2 (≥ -6.4% to ≤ +3.6%) n = 589</b>	<b>Tertile 3 (≥ +3.6%) n = 588</b>	<b>P-value<sup>a</sup></b>
Age, years, mean (SD)		67.39 (10.80)	65.66 (11.15)	66.28 (11.36)	0.0867
Age groups, n (%)					0.2426 <sup>b</sup>
<65 years	701	220 (31.4)	252 (35.9)	229 (32.7)	
65 to <75 years	602	195 (32.4)	198 (32.9)	209 (34.7)	
≥75 years	462	173 (37.4)	139 (30.1)	150 (32.5)	
Male, n (%)	1343	444 (33.1)	454 (33.8)	445 (33.1)	0.9453
BMI, kg/m <sup>2</sup> , mean (SD)		27.89 (5.23)	27.74 (5.26)	27.48 (5.47)	0.1859
Race, n (%)					0.3591
White	1230	420 (34.1)	409 (33.3)	401 (32.6)	
Black/African-American	123	41 (33.3)	38 (30.9)	44 (35.8)	
Asian	325	97 (29.8)	110 (33.8)	118 (36.3)	
Other including mixed race	58	22 (37.9)	19 (32.8)	17 (29.3)	
Region, n (%)					0.3513
Europe	643	220 (34.2)	225 (35.0)	198 (30.8)	
North America	198	63 (31.8)	76 (38.4)	59 (29.8)	
Asia	239	68 (28.5)	81 (33.9)	90 (37.7)	
Latin America	601	210 (34.9)	180 (30.0)	211 (35.1)	
Other	84	27 (32.1)	27 (32.1)	30 (35.7)	
LVEF, %, mean (SD)		27.16 (5.84)	27.17 (6.11)	27.35 (6.02)	0.6008
LVEF, n (%)					0.7381 <sup>b</sup>
<20%	168	46 (27.4)	66 (39.3)	56 (33.3)	
20–30%	1149	396 (34.5)	379 (33.0)	374 (32.6)	
31–35%	344	116 (33.7)	106 (30.8)	122 (35.5)	

	<b>N analyzed (total = 1765)</b>	<b>Tertile 1 (≤ -6.5%) n = 588</b>	<b>Tertile 2 (≥ -6.4% to ≤ +3.6%) n = 589</b>	<b>Tertile 3 (≥ +3.6%) n = 588</b>	<b>P-value<sup>a</sup></b>
>35%	104	30 (28.8)	38 (36.5)	36 (34.6)	
NT-proBNP, pg/mL, median (IQR)		1996.00 (1179.50- 3460.50)	1767.00 (1082.00- 3145.00)	1922.00 (1150.50- 3729.50)	
NT-proBNP Group <sup>c</sup>					0.8561 <sup>b</sup>
Tertile 1	568	184 (32.4)	199 (35.0)	185 (32.6)	
Tertile 2	616	203 (33.0)	217 (35.2)	196 (31.8)	
Tertile 3	581	201 (34.6)	173 (29.8)	207 (35.6)	
Heart rate, BPM, mean (SD)		71.85 (11.27)	71.03 (12.51)	71.56 (11.58)	0.6843
Heart rate groups, n (%)					1.0000
≤70 bpm	914	299 (32.7)	316 (34.6)	299 (32.7)	
>70 bpm	851	289 (34.0)	273 (32.1)	289 (34.0)	
SBP, mmHg, mean (SD)		121.79 (14.96)	121.42 (15.51)	121.29 (15.38)	0.5768
SBP groups, n (%)					0.8724 <sup>b</sup>
<110 mmHg	453	146 (32.2)	156 (34.4)	151 (33.3)	
≥110 to ≤130 mmHg	835	282 (33.8)	277 (33.2)	276 (33.1)	
>130 mmHg	477	160 (33.5)	156 (32.7)	161 (33.8)	
DBP, mmHg, mean (SD)		73.28 (9.67)	73.82 (10.61)	74.26 (11.46)	0.1117
DBP groups, n (%)					0.0076
<90 mmHg	1626	557 (34.3)	537 (33.0)	532 (32.7)	
≥90 mmHg	139	31 (22.3)	52 (37.4)	56 (40.3)	
eGFR-CKD-EPI, mL/min/1.73m <sup>2</sup> , mean (SD)		62.56 (20.89)	66.83 (23.16)	56.87 (20.21)	<0.0001
eGFR-CKD-EPI groups, n (%)					<0.0001
<30 mL/min/1.73m <sup>2</sup>	87	21 (24.1)	18 (20.7)	48 (55.2)	
30 to <45 mL/min/1.73m <sup>2</sup>	332	109 (32.8)	94 (28.3)	129 (38.9)	
45 to <60 mL/min/1.73m <sup>2</sup>	450	145 (32.2)	142 (31.6)	163 (36.2)	
≥60 mL/min/1.73m <sup>2</sup>	896	313 (34.9)	335 (37.4)	248 (27.7)	
UACR, mg/g, median (IQR)		23.87 (7.96-77.79)	21.22 (7.07-77.79)	21.22 (8.84-78.23)	0.6590 <sup>d</sup>
Hb, g/dl, mean (SD)		13.60 (1.56)	13.85 (1.63)	13.71 (1.70)	0.2449
Time since diagnosis of HF groups, n (%)					0.2324 <sup>b</sup>
≤1 year	326	99 (30.4)	104 (31.9)	123 (37.7)	
> 1 to 5 years	665	220 (33.1)	232 (34.9)	213 (32.0)	
>5 to 10 years	393	145 (36.9)	119 (30.3)	129 (32.8)	
>10 years	381	124 (32.5)	134 (35.2)	123 (32.3)	

	<b>N analyzed (total = 1765)</b>	<b>Tertile 1 (<math>\leq -6.5\%</math>) n = 588</b>	<b>Tertile 2 (<math>\geq -6.4\%</math> to <math>\leq +3.6\%</math>) n = 589</b>	<b>Tertile 3 (<math>\geq +3.6\%</math>) n = 588</b>	<b>P-value<sup>a</sup></b>
Cause of HF, n (%)					0.6407
Ischemic	907	299 (33.0)	301 (33.2)	307 (33.8)	
Non-ischemic	858	289 (33.7)	288 (33.6)	281 (32.8)	
History of AF, n (%)	665	230 (34.6)	218 (32.8)	217 (32.6)	0.4467
History of hypertension, n (%)	1271	432 (34.0)	416 (32.7)	423 (33.3)	0.5603
HHF within 12 months, n (%)	540	184 (34.1)	183 (33.9)	173 (32.0)	0.4868
<b>Concomitant medications</b>					
ACEi/ARB	1213	401 (33.1)	405 (33.4)	407 (33.6)	0.7059
ARNI	364	123 (33.8)	131 (36.0)	110 (30.2)	0.3522
Beta-blocker	1672	561 (33.6)	557 (33.3)	554 (33.1)	0.3627
Diuretic	1692	560 (33.1)	568 (33.6)	564 (33.3)	0.5514

<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: Tertile 1 represents  $<1357.00$  pg/mL; T2 represents  $\geq 1357.00$  and  $<2764.00$  pg/mL; Tertile 3 represents  $\geq 2764.00$  pg/mL. <sup>d</sup>Based on log-transformed data. ACEi, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin-receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; BPM, beats per minute; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HF, heart failure; HHF, hospitalization for heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LLN, lower limit of normal; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation; UACR, urine albumin creatinine ratio.