Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Characteristics of patients in the empagliflozin and placebo groups in patients with and without diuretic use at baseline

	Diuretics Not Used (n=1179)			Diuretics Used (n=4636)			**Empa (diuretics) vs Empa (no diuretics)**	**Pla (diuretics) vs Pla (no diuretics)**
	Empagliflozin (n=590)	Placebo (n=589)	p-value	Empagliflozin (n=2319)	Placebo (n=2317)	p-value		
Demographics and vitals								
Age, y; mean (SD)	70.9 (9.5)	70.9 (9.3)	0.9898	72.1 (9.2)	72.2 (9.6)	0.6394	0.0057	0.0028
Female; n (%)	231 (39.2)	221 (37.5)	0.5646	1066 (46.0)	1076 (46.4)	0.7476	0.0029	<0.001
Race; n (%)								
White	415 (70.3)	388 (65.9)	0.0628	1787 (77.1)	1791 (77.3)	0.4668	<0.001	<0.001
Asian	113 (19.2)	134 (22.8)		297 (12.8)	273 (11.8)			
Black or African American	20 (3.4)	11 (1.9)		112 (4.8)	110 (4.7)			
Other	42 (7.1)	56 (9.5)		122 (5.3)	142 (6.1)			
Region; n (%)								
Asia	99 (16.8)	119 (20.2)	0.1838	241 (10.4)	220 (9.5)	0.6972	<0.001	<0.001
Europe	215 (36.4)	187 (31.7)		1065 (45.9)	1096 (47.3)			
North America	64 (10.8)	51 (8.7)		280 (12.1)	293 (12.6)			
Latin America	182 (30.8)	201 (34.1)		575 (24.8)	551 (23.8)			
Heart rate, bpm; mean (SD)	68.7 (11.2)	69.5 (11.6)	0.2710	70.8 (12.2)	70.5 (11.8)	0.3822	0.0002	0.0572
Systolic blood pressure, mmHg; mean (SD)	132.2 (15.0)	132.5 (14.8)	0.7574	131.6 (15.8)	131.7 (15.9)	0.8513	0.3959	0.2739
Diastolic blood pressure, mmHg; mean (SD)	76.9 (10.4)	76.8 (10.6)	0.8619	75.4 (10.6)	75.5 (10.5)	0.8658	0.0027	0.0071

Weight, kg; mean (SD)	76.86 (17.73)	77.03 (17.74)	0.8756	82.93 (19.59)	82.86 (19.74)	0.9104	<0.001	<0.001
Body mass index, kg/m2; mean (SD)	27.90 (5.14)	27.98 (5.26)	0.7815	30.22 (5.87)	30.36 (6.00)	0.4199	<0.001	<0.001
Medical history, n (%)								
Atrial fibrillation	221 (37.5)	240 (40.7)	0.2472	1260 (54.3)	1218 (52.6)	0.2400	<0.001	<0.001
Hypertension	516 (87.5)	501 (85.1)	0.2317	2124 (91.6)	2125 (91.7)	0.8804	0.0020	<0.001
CKD	241 (40.8)	243 (41.3)	0.8864	1328 (57.3)	1291 (55.7)	0.3108	<0.001	<0.001
BMI >=30, Kg/m2	190 (32.2)	187 (31.7)	0.8671	1110 (47.9)	1124 (48.5)	0.6601	<0.001	<0.001
Diabetes mellitus	224 (38.0)	263 (44.7)	0.0197	1208 (52.1)	1171 (50.5)	0.2905	<0.001	0.0107
Laboratory measurements								
Estimated GFR, mL·min/1.73 m−2	66.8 (18.3)	66.3 (19.0)	0.6014	59.0 (19.8)	59.3 (19.9)	0.6245	<0.001	<0.001
Estimated GFR <60 mL·min/1.73 m−2, n (%)	217 (36.8)	221 (37.5)	0.7922	1244 (53.6)	1216 (52.5)	0.4370	<0.001	<0.001
Creatinine, µmol/L	95.3 (28.1)	96.8 (30.6)	0.3922	107.2 (36.8)	106.2 (35.6)	0.3605	<0.001	<0.001
Hematocrit, %	41.6 (4.6)	41.8 (4.8)	0.3887	40.7 (4.7)	40.7 (4.8)	0.8930	<0.001	<0.001
Heart failure history								
NYHA functional classification; n (%)								
II	531 (90.0)	530 (90.0)	0.3797[#]	1837 (79.2)	1865 (80.5)	0.7546[#]	<0.001	<0.001
III	56 (9.5)	59 (10.0)		473 (20.4)	443 (19.1)			
IV	1 (0.2)	0		8 (0.3)	8 (0.3)			
Principal cause of heart failure; n (%)								
Ischemic	259 (43.9)	247 (41.9)	0.4800	797 (34.4)	755 (32.6)	0.1983	<0.001	<0.001
Nonischemic	330 (55.9)	342 (58.1)		1522 (65.6)	1562 (67.4)			

NT-proBNP, pg/mL; mean (SD)	1090.0 (1666.8)	1107.3 (1319.9)	0.3546	1536.7 (1822.3)	1573.2 (2284.4)	0.5757	<0.001	<0.001
KCCQ clinical symptom score; mean (SD)	77.6 (18.4)	77.8 (19.4)	0.8659	68.4 (21.9)	68.7 (20.8)	0.5725	<0.001	<0.001
Left ventricular ejection fraction, %; mean (SD)	54.4 (9.2)	54.2 (9.1)	0.7851	54.3 (8.7)	54.3 (8.7)	0.8807	0.8332	0.8080
Hospitalization for heart failure	64 (10.8)	76 (12.9)	0.2753	610 (26.3)	576 (24.9)	0.2596	<0.001	<0.001
Device therapy, n (%)								
Implantable cardioverter-defibrillator§	30 (5.1)	32 (5.4)	0.7888	80 (3.4)	84 (3.6)	0.7462	0.0630	0.0454
Cardiac resynchronization**	1 (0.2)	3 (0.5)	0.3157	9 (0.4)	11 (0.5)	0.6526	0.4179	0.9138
Other heart failure therapy, n (%)								
ACE inhibitor or ARB or ARNI	465 (78.8)	462 (78.4)	0.8750	1889 (81.5)	1872 (80.8)	0.5638	0.1445	0.1991
β-Blocker	511 (86.6)	497 (84.4)	0.2770	2011 (86.7)	1999 (86.3)	0.6590	0.9449	0.2381
MRA	156 (26.4)	198 (33.6)	0.0072	924 (39.8)	889 (38.4)	0.3031	<0.001	0.0333
ARNi	14 (2.4)	18 (3.1)	0.47	48 (2.1)	49 (2.1)	0.91	0.6491	0.1741
ACE/ARB/ARNI + β-Blocker + MRA	125 (21.2)	143 (24.3)	0.2053	660 (28.5)	640 (27.6)	0.5251	0.0004	0.1024
Glucose-lowering medication, n (%)								
Biguanide	140 (62.5)	154 (58.6)	0.3751	618 (51.2)	626 (53.5)	0.2616	0.0018	0.1337
Sulfonylurea	48 (21.4)	54 (20.5)	0.8086	254 (21.0)	251 (21.4)	0.8077	0.8922	0.7466
DPP-4 inhibitor	32 (14.3)	35 (13.3)	0.7549	151 (12.5)	163 (13.9)	0.3064	0.4622	0.7950
GLP-1 receptor agonist	2 (0.9)	6 (2.3)	0.2296	27 (2.2)	23 (2.0)	0.6451	0.1902	0.7412
Insulin	47 (21.0)	66 (25.1)	0.2839	378 (31.3)	351 (30.0)	0.4860	0.0019	0.1154

including NYHA I class (2 patients in Empa group each in the group using and not using diuretics)
§ includes all the patients with an implantable cardioverter–defibrillator regardless of the presence or absence of cardiac resynchronization therapy.
** includes all the patients who were receiving cardiac resynchronization therapy regardless of the presence or absence of a defibrillator.

eTable 2. Change from baseline in estimated glomerular filtration rate slope and physiologic variables (at 52 weeks) in the placebo arm, according to baseline diuretic status and dose

	Adjusted mean change (95% CI)	Difference in means (95% CI)	p-trend (by dose)	p-value (no diuretics vs any dose)
eGFR (CKD-EPI) slope change/yr				
No diuretics	-2.67 (-3.16, -2.18)	Referent	0.5187	0.8732
<40 mg	-2.52 (-2.92, -2.13)	0.14 (-0.49, 0.76)		
40 mg	-2.54 (-2.95, -2.13)	0.12 (-0.52, 0.76)		
>40 mg	-2.92 (-3.44, -2.41)	-0.26 (-0.99, 0.46)		
Any dose	-2.62 (-2.87, -2.37)	0.05 (-0.51, 0.60)		
Glycated Hb (%) in patients with diabetes, adj. mean (95% CI)				
No diuretics	0.08 (-0.07, 0.22)	Referent	0.5556	0.6418
<40 mg	0.05 (-0.07, 0.17)	-0.02 (-0.21, 0.17)		
40 mg	0.05 (-0.07, 0.16)	-0.03 (-0.21, 0.16)		
>40 mg	0.01 (-0.12, 0.14)	-0.06 (-0.26, 0.14)		
Any dose	0.04 (-0.03, 0.11)	-0.04 (-0.20, 0.13)		
Hematocrit (%), adj. mean (95% CI)				
No diuretics	-0.47 (-0.76, -0.19)	Referent	0.6493	0.6257
<40 mg	-0.32 (-0.55, -0.08)	0.15 (-0.22, 0.52)		
40 mg	-0.38 (-0.61, -0.15)	0.09 (-0.28, 0.46)		
>40 mg	-0.55 (-0.85, -0.25)	-0.08 (-0.50, 0.34)		
Any dose	-0.39 (-0.54, -0.25)	0.08 (-0.24, 0.40)		
NT-proBNP, gMean (95% CI)				
No diuretics	0.94 (0.88, 1.00)	Referent	0.0011	0.1421
<40 mg	0.94 (0.89, 0.99)	1.01 (0.92, 1.10)		
40 mg	0.99 (0.94, 1.04)	1.06 (0.97, 1.16)		
>40 mg	1.08 (1.01, 1.16)	1.16 (1.06, 1.28)		
Any dose	0.99 (0.96, 1.02)	1.06 (0.98, 1.14)		
Body weight (kg), adj. mean (95% CI)				
No diuretics	0.13 (-0.28, 0.53)	Referent	0.0188	0.2160
<40 mg	-0.04 (-0.37, 0.30)	-0.17 (-0.69, 0.35)		
40 mg	0.03 (-0.30, 0.36)	-0.10 (-0.63, 0.42)		

>40 mg	-0.69 (-1.12, -0.27)	-0.83 (-1.42, -0.23)		
Any dose	-0.16 (-0.37, 0.04)	-0.29 (-0.74, 0.17)		
Systolic blood pressure (mmHg), adj. mean (95% CI)				
No diuretics	-0.1 (-1.5, 1.3)	Referent	0.1583	0.4751
<40 mg	-0.1 (-1.2, 1.1)	0.0 (-1.9, 1.8)		
40 mg	-0.9 (-2.1, 0.2)	-0.9 (-2.7, 0.9)		
>40 mg	-1.2 (-2.7, 0.3)	-1.2 (-3.3, 0.9)		
Any dose	-0.7 (-1.4, 0.0)	-0.6 (-2.2, 1.0)		
Uric acid (mg/dL), adj. Mean (95% CI)				
No diuretics	-0.19 (-0.32, -0.06)	Referent	0.3844	0.1358
<40 mg	-0.07 (-0.17, 0.03)	0.12 (-0.04, 0.28)		
40 mg	-0.09 (-0.19, 0.02)	0.10 (-0.06, 0.27)		
>40 mg	-0.09 (-0.22, 0.05)	0.10 (-0.09, 0.29)		
Any dose	-0.08 (-0.14, -0.02)	0.11 (-0.03, 0.25)		

eTable 3. Effect of empagliflozin versus placebo on eGFR slope and physiologic outcomes (at 52 weeks), according to baseline diuretic therapy

	Placebo	Empagliflozin			P-value
	Adjusted mean change (95% CI)	Adjusted mean change (95% CI)	Difference in means (95% CI)	P-value (by dose)	(no diuretics vs any dose)
eGFR (CKD-EPI) slope change/yr					
All patients	-2.62 (-2.83, -2.41)	-1.25 (-1.47, -1.04)	1.36 (1.06, 1.66)	0.8749	0.6168
No diuretics	-2.95 (-3.42, -2.48)	-1.73 (-2.20, -1.26)	1.22 (0.55, 1.89)		
<40 mg	-2.61 (-2.99, -2.23)	-1.11 (-1.50, -0.72)	1.50 (0.96, 2,05)		
40 mg	-2.48 (-2.88, -2.08)	-1.15 (-1.54, -0.76)	1.33 (0.77, 1,89)		
>40 mg	-2.58 (-3.08, -2.08)	-1.20 (-1.70, -0.69)	1.38 (0.67, 2.10)		
Any dose	-2.55 (-2.79, -2.31)	-1.14 (-1.38, -0.90)	1.41 (1.07, 1.75)		
Glycated Hb (%) in patients with diabetes, adj. mean (95% CI)					
All patients	0.03 (-0.01, 0.08)	-0.16 (-0.20, -0.12)	-0.19 (-0.25, -0.14)	0.0399	0.3414
No diuretics	0.11 (-0.02, 0.25)	-0.17 (-0.32, -0.02)	-0.28 (-0.48, -0.08)		
<40 mg	0.08 (-0.02, 0.19)	-0.17 (-0.28, -0.07)	-0.25 (-0.40, -0.10)		
40 mg	-0.00 (-0.11, 0.10)	-0.22 (-0.32, -0.12)	-0.22 (-0.36, -0.07)		
>40 mg	-0.06 (-0.18, 0.06)	-0.09 (-0.21, 0.03)	-0.03 (-0.20, 0.14)		
Any dose	0.01 (-0.05, 0.07)	-0.17 (-0.23, -0.10)	-0.18 (-0.27, -0.09)		
Hematocrit (%), adj. mean (95% CI)					
All patients	-0.41 (-0.54, -0.28)	1.94 (1.81, 2.08)	2.36 (2.17, 2.54)	0.0605	0.4132
No diuretics	-0.61 (-0.90, -0.31)	1.90 (1.60, 2.20)	2.51 (2.09, 2.92)		

<40 mg	-0.34 (-0.58, -0.09)	2.24 (1.99, 2.48)	2.57 (2.23, 2.92)		
40 mg	-0.32 (-0.56, -0.07)	1.89 (1.65, 2.14)	2.21 (1.86, 2.56)		
>40 mg	-0.38 (-0.69, -0.07)	1.68 (1.38, 1.98)	2.06 (1.63, 2.50)		
Any dose	-0.34 (-0.49, -0.19)	1.97 (1.82, 2.12)	2.31 (2.10, 2.52)		
NT-proBNP (pg/mL), gMean ratio (95% CI)					
All patients	0.98 (0.95, 1.01)	0.93 (0.90, 0.95)	0.95 (0.91, 0.99)	0.7628	0.4041
No diuretics	0.96 (0.90, 1.02)	0.87 (0.82, 0.93)	0.91 (0.83, 1.00)		
<40 mg	0.94 (0.90, 0.99)	0.92 (0.87, 0.97)	0.98 (0.91, 1.05)		
40 mg	0.97 (0.92, 1.02)	0.94 (0.89, 0.99)	0.96 (0.90, 1.04)		
>40 mg	1.06 (0.99, 1.13)	0.95 (0.89, 1.01)	0.90 (0.82, 0.98)		
Any dose	0.98 (0.95, 1.01)	0.93 (0.90, 0.96)	0.95 (0.91, 1.00)		
Body weight (kg), adj. mean (95% CI)					
All patients	-0.11 (-0.29, 0.08)	-1.39 (-1.57, -1.21)	-1.28 (-1.54, -1.03)	0.0014	0.1040
No diuretics	0.25 (-0.15, 0.66)	-1.47 (-1.88, -1.06)	-1.72 (-2.30, -1.15)		
<40 mg	-0.01 (-0.35, 0.32)	-1.52 (-1.85, -1.18)	-1.50 (-1.98, -1.03)		
40 mg	0.01 (-0.32, 0.35)	-1.45 (-1.79, -1.12)	-1.46 (-1.94, -0.99)		
>40 mg	-0.77 (-1.19, -0.34)	-1.03 (-1.45, -0.61)	-0.26 (-0.85, 0.34)		
Any dose	-0.18 (-0.39, 0.02)	-1.37 (-1.58, -1.16)	-1.19 (-1.48, -0.90)		
Systolic blood pressure (mmHg), adj. mean (95% CI)					
All patients	-0.6 (-1.2, 0.0)	-1.8 (-2.4, -1.2)	-1.2 (-2.1, -0.3)	0.2872	0.5805
No diuretics	-0.3 (-1.7, 1.1)	-1.9 (-3.3, -0.6)	-1.7 (-3.6, 0.3)		

<40 mg	-0.4 (-1.6, 0.7)	-2.1 (-3.2, -0.9)	-1.6 (-3.3, 0.0)		
40 mg	-0.9 (-2.0, 0.3)	-1.8 (-2.9, -0.6)	-0.9 (-2.5, 0.7)		
>40 mg	-0.6 (-2.1, 0.8)	-1.0 (-2.4, 0.4)	-0.4 (-2.4, 1.6)		
Any dose	-0.6 (-1.3, 0.1)	-1.7 (-2.4, -1.0)	-1.1 (-2.1, -0.1)		
Uric acid (mg/dL), adj. mean (95% CI)					
All patients	-0.10 (-0.15, -0.04)	-0.90 (-0.95, -0.84)	-0.80 (-0.88, -0.72)	0.1401	0.8597
No diuretics	0.13 (0.01, 0.26)	-0.65 (-0.78, -0.53)	-0.79 (-0.96, -0.62)		
<40 mg	0.05 (-0.05, 0.15)	-0.88 (-0.98, -0.78)	-0.93 (-1.07, -0.79)		
40 mg	-0.18 (-0.28, -0.07)	-0.95 (-1.05, -0.85)	-0.77 (-0.92, -0.63)		
>40 mg	-0.46 (-0.59, -0.33)	-1.12 (-1.25, -1.00)	-0.66 (-0.84, -0.48)		
Any dose	-0.16 (-0.22, -0.10)	-0.97 (-1.03, -0.91)	-0.81 (-0.89, -0.72)		

eTable 4. Adverse effects in the empagliflozin versus placebo arm according to baseline diuretic use (shown up to 7 days after discontinuation of study medication)

	Placebo		Empagliflozin				
	n/N	Events/100 patient-yr	n/N	Events/100 patient-yr	Adjusted HR (95% CI)	p-trend test (by dose)	p-value (no diuretics vs any dose)
Adverse events leading to treatment discontinuation (incl. fatal events)							
No diuretics	87/589	7.9	96/590	8.7	1.10 (0.82, 1.47)	0.91	0.62
<40 mg	134/864	8.0	129/860	7.8	0.98 (0.77, 1.24)		
40 mg	189/889	11.8	185/883	11.2	0.97 (0.79, 1.19)		
>40 mg	130/562	12.6	148/575	14.3	1.11 (0.87, 1.40)		
Any dose	453/2315	10.5	462/2318	10.6	1.02 (0.89, 1.16)		
Volume depletion events							
No diuretics	43/589	4.1	46/590	4.3	1.06 (0.70, 1.61)	0.75	0.32
<40 mg	76/864	4.7	102/860	6.6	1.42 (1.05, 1.91)		
40 mg	80/889	5.2	104/883	6.7	1.31 (0.98, 1.75)		
>40 mg	75/562	7.7	95/575	10.1	1.27 (0.94, 1.73)		
Any dose	231/2315	5.6	301/2318	7.5	1.34 (1.13, 1.59)		
Acute renal failure							
No diuretics	52/589	4.9	40/590	3.7	0.79 (0.53, 1.20)	0.48	0.38

<40 mg	82/864	5.1	82/860	5.2	0.99 (0.73, 1.34)		
40 mg	127/889	8.4	113/883	7.3	0.92 (0.71, 1.18)		
>40 mg	112/562	12.0	120/575	13.2	1.00 (0.77, 1.29)		
Any dose	321/2315	7.9	315/2318	7.8	0.97 (0.83, 1.13)		
Hyperkalemia							
No diuretics	43/589	4.1	39/590	3.7	0.96 (0.62, 1.48)	0.84	0.49
<40 mg	49/864	3.0	40/860	2.5	0.78 (0.51, 1.19)		
40 mg	78/889	5.2	61/883	3.8	0.78 (0.56, 1.09)		
>40 mg	43/562	4.4	43/575	4.3	0.90 (0.59, 1.38)		
Any dose	170/2315	4.1	144/2318	3.4	0.81 (0.65, 1.01)		

Adverse events are shown up to 7 days after discontinuation of study medication.

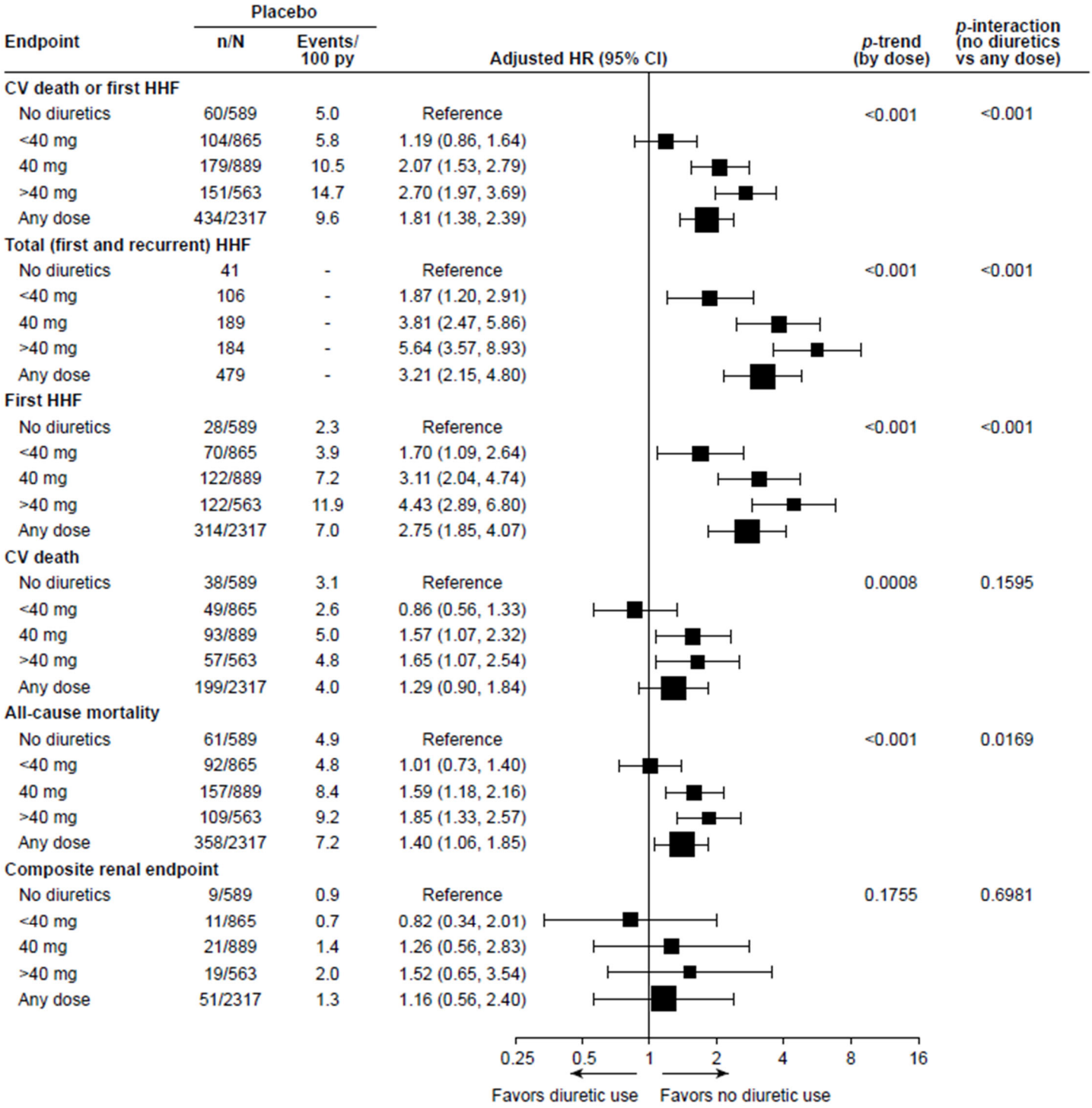
eTable 5. Frequency of each preferred term grouped under 'volume depletion' (shown up to 7 days after discontinuation of study medication)

	Placebo		Empagliflozin	
	n/N	Events/100 patient-yr	n/N	Events/100 patient-yr
Hypotension				
No diuretics	27/589	2.50	27/590	2.51
<40 mg	49/864	3.00	62/2318	3.92
40 mg	57/889	3.67	69/883	4.33
>40 mg	47/562	4.73	66/575	6.81
Any dose	153/2315	3.66	197/2318	4.75
Orthostatic hypotension				
No diuretics	3/589	0.27	1/590	0.09
<40 mg	2/864	0.12	6/860	0.36
40 mg	7/889	0.44	6/883	0.36
>40 mg	5/562	0.48	5/575	0.48
Any dose	14/2315	0.32	17/2318	0.39
Hypovolemic shock				
No diuretics	1/589	0.09	0/590	0
<40 mg	1/864	0.06	0/860	0
40 mg	2/889	0.12	1/883	0.06
>40 mg	2/562	0.19	1/575	0.10
Any dose	5/2315	0.12	2/2318	0.05
Circulatory collapse				
No diuretics	0/589	0	1/590	0.09
<40 mg	0/864	0	0/860	0
40 mg	0/864	0	1/883	0.06
>40 mg	4/562	0.39	1/575	0.10
Any dose	4/2315	0.09	2/2318	0.05
Syncope				
No diuretics	8/589	0.73	12/590	1.09
<40 mg	18/864	1.08	22/860	1.34

40 mg	12/889	0.75	16/883	0.96
>40 mg	11/562	1.07	13/575	1.27
Any dose	41/2315	0.95	51/2318	1.18
Presyncope				
No diuretics	0/589	0	2/590	0.18
<40 mg	3/864	0.18	3/860	0.18
40 mg	2/889	0.12	4/883	0.24
>40 mg	2/562	0.19	4/575	0.39
Any dose	7/2315	0.16	11/2318	0.25
Dehydration				
No diuretics	8/589	0.73	8/590	0.73
<40 mg	14/864	0.83	12/860	0.73
40 mg	0/889	0	0/883	0
>40 mg	16/562	1.57	19/575	1.85
Any dose	39/2315	0.91	52/2318	1.20
Hypovolemia				
No diuretics	0/589	0	1/590	0.09
<40 mg	0/864	0	3/860	0.18
40 mg	0/889	0	0/883	0
>40 mg	3/562	0.29	0/575	0
Any dose	4/2315	0.09	4/2318	0.09

Adverse events are shown up to 7 days after discontinuation of study medication.

eFigure 1. Event rates for primary and secondary outcomes in placebo arm according to baseline diuretic status



eFigure 2. Change in Kansas City Cardiomyopathy Questionnaire subdomain scores KCCQ-CSS (**A**), KCCQ-TSS (**B**) and KCCQ-OSS (**C**) in the placebo arm according to baseline diuretic status and dose