

Supplemental Table 1: Sensitivity analysis of primary and secondary outcome measures stratified by baseline diuretic group using $P_{\text{interaction}}$ test.

Group	Hazard Ratio (95% CI)	$P_{\text{interaction}}$
CV death or first HHF		
No diuretics	0.78 (0.47-1.29)	0.220
<40mg Equiv.	0.65 (0.46-0.92)	
=40 mg Equiv.	0.65 (0.51-0.82)	
>40 mg Equiv.	0.88 (0.71-1.10)	
Total (first and recurrent) HHF		
No diuretics	0.69 (0.35-1.36)	0.062
<40mg Equiv.	0.53 (0.34-0.84)	
=40 mg Equiv.	0.53 (0.38-0.73)	
>40 mg Equiv.	0.93 (0.68-1.28)	
First HHF		
No diuretics	0.48 (0.24-0.97)	0.202
<40mg Equiv.	0.56 (0.36-0.87)	
=40 mg Equiv.	0.63 (0.47-0.83)	
>40 mg Equiv.	0.84 (0.65-1.08)	
CV death		
No diuretics	1.32 (0.65-2.67)	0.563
<40mg Equiv.	0.88 (0.54-1.42)	
=40 mg Equiv.	0.77 (0.55-1.09)	
>40 mg Equiv.	0.96 (0.70-1.32)	
All-cause mortality		
No diuretics	1.51 (0.80-2.86)	0.376
<40mg Equiv.	0.78 (0.50-1.21)	
=40 mg Equiv.	0.86 (0.65-1.15)	
>40 mg Equiv.	0.94 (0.71-1.25)	

HHF hospitalization for heart failure; CI, confidence interval; CV, cardiovascular

Supplemental Table 2: Primary and secondary outcome measures stratified by baseline diuretics into five categories.

Group	Hazard Ratio (95% CI)	P _{trend test}	P _{interaction}
CV death or first HHF			
No diuretics	0.78 (0.47-1.29)	0.210	0.378
<40mg Equiv.	0.65 (0.45-0.92)		
=40 mg Equiv.	0.65 (0.51-0.82)		
>40 mg and ≤80 mg Equiv.	0.90 (0.68-1.20)		
>80mg Equiv.	0.84 (0.60-1.17)		
Total (first and recurrent) HHF			
No diuretics	0.69 (0.35-1.36)	0.085	0.121
<40mg Equiv.	0.53 (0.34-0.84)		
=40 mg Equiv.	0.53 (0.38-0.73)		
>40 mg and ≤80 mg Equiv.	0.96 (0.64-1.45)		
>80mg Equiv.	0.89 (0.54-1.46)		
First HHF			
No diuretics	0.48 (0.24-0.98)	0.066	0.346
<40mg Equiv.	0.56 (0.36-0.87)		
=40 mg Equiv.	0.63 (0.47-0.83)		
>40 mg and ≤80 mg Equiv.	0.87 (0.62-1.21)		
>80mg Equiv.	0.77 (0.53-1.13)		
CV death			
No diuretics	1.32 (0.65-2.67)	0.892	0.706
<40mg Equiv.	0.88 (0.54-1.42)		
=40 mg Equiv.	0.77 (0.55-1.09)		
>40 mg and ≤80 mg Equiv.	0.91 (0.60-1.38)		
>80mg Equiv.	1.03 (0.62-1.70)		
All-cause mortality			
No diuretics	1.51 (0.80-2.86)	0.779	0.486
<40mg Equiv.	0.78 (0.50-1.21)		
=40 mg Equiv.	0.86 (0.65-1.15)		
>40 mg and ≤80 mg Equiv.	0.87 (0.60-1.26)		
>80mg Equiv.	1.03 (0.66-1.61)		

HHF hospitalization for heart failure; CI, confidence interval; CV, cardiovascular

Supplemental Table 3: Body weight, SBP, NT-proBNP, Hematocrit, and Uric Acid stratified by baseline diuretic doses.

Time Point	No Diuretics	<40mg Equiv.	=40mg Equiv.	>40mg Equiv.	P-trend test across all subgroups
	Empagliflozin versus placebo	Empagliflozin versus placebo	Empagliflozin versus placebo	Empagliflozin versus placebo	
Body Weight [kg] Adjusted mean difference to placebo (95% CI)					
12 weeks	-1.38 (-2.04, -0.72)	-1.15 (-1.69, -0.62)	-0.73 (-1.12, -0.35)	-0.67 (-1.12, -0.21)	0.043
52 weeks	-1.43 (-2.43, -0.44)	-0.73 (-1.52, 0.07)	-0.87 (-1.45, -0.28)	-0.50 (-1.19, 0.20)	0.213
SBP [mmHg] Adjusted mean difference to placebo (95% CI)					
12 weeks	0.9 (-1.6, 3.5)	-1.1 (-3.1, 0.9)	-0.8 (-2.3, 0.7)	-1.8 (-3.5, -0.1)	0.134
52 weeks	1.4 (-1.7, 4.5)	-0.9 (-3.4, 1.5)	-0.6 (-2.4, 1.2)	-1.6 (-3.7, 0.6)	0.184
NT-proBNP [pg/mL] Adjusted mean ratio to placebo (95% CI)					
12 weeks	0.93 (0.82, 1.05)	0.92 (0.83, 1.01)	0.95 (0.88, 1.02)	0.95 (0.87, 1.03)	0.665
52 weeks	0.79 (0.67, 0.95)	0.88 (0.76, 1.01)	0.87 (0.78, 0.96)	0.92 (0.81, 1.04)	0.250
Hematocrit [%] Adjusted mean difference to placebo (95% CI)					
12 weeks	2.07 (1.48, 2.65)	2.31 (1.84, 2.78)	2.30 (1.96, 2.64)	2.08 (1.67, 2.48)	0.839
52 weeks	2.10 (1.33, 2.87)	2.52 (1.91, 3.13)	2.43 (1.97, 2.88)	2.11 (1.57, 2.66)	0.799
Uric Acid [mg/dL] Adjusted mean difference to placebo (95% CI)					
12 weeks	-1.17 (-1.42, -0.92)	-1.04 (-1.24, -0.84)	-0.88 (-1.02, -0.73)	-1.09 (-1.26, -0.92)	0.532
52 weeks	-1.23 (-1.55, -0.90)	-0.91 (-1.16, -0.65)	-0.96 (-1.15, -0.77)	-0.73 (-0.95, -0.50)	0.026

CI, confidence interval; NT-pro-BNP, N-terminal pro-B type natriuretic peptide; SBP, systolic blood pressure.

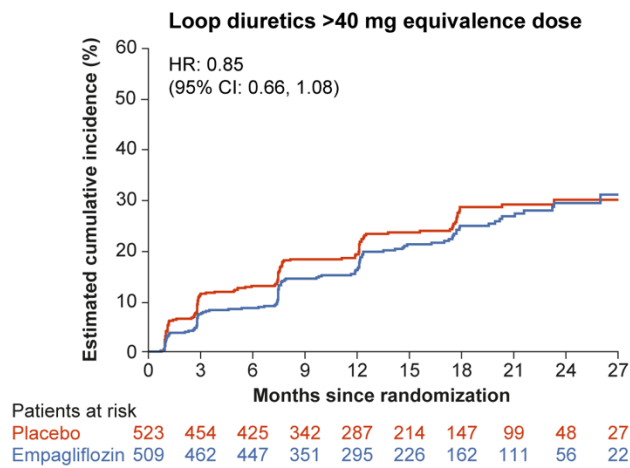
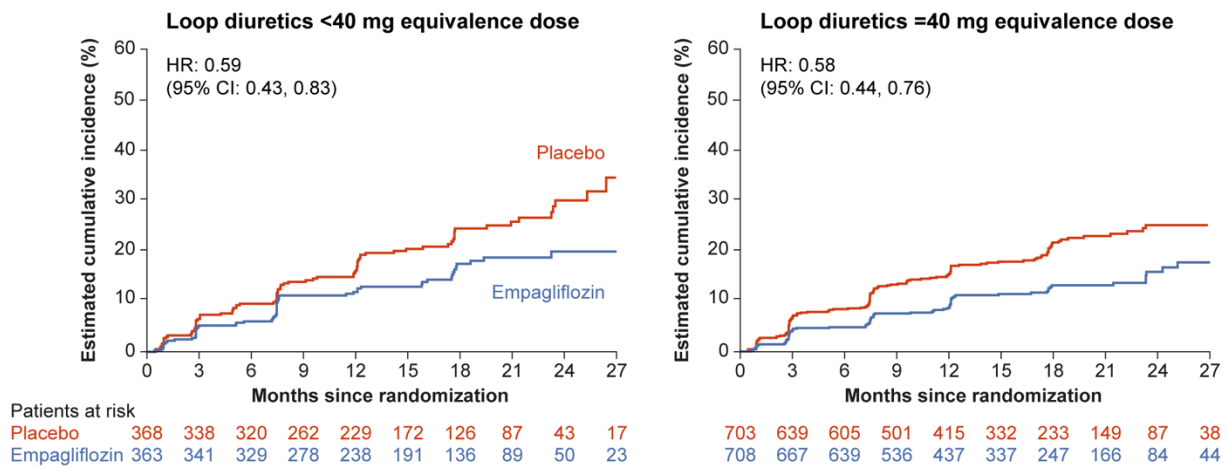
Supplemental Table 4: Safety Outcomes stratified by baseline diuretic doses.

	No Diuretics		<40mg Equiv.		=40mg Equiv.		>40mg Equiv.	
	Placebo	Empagliflozin	Placebo	Empagliflozin	Placebo	Empagliflozin	Placebo	Empagliflozin
Total with adverse events, n (%)	168 (73.7)	181 (71.5)	276 (75.2)	278 (76.6)	541 (77.0)	516 (72.9)	447 (85.8)	422 (82.9)
Total with serious adverse events, n (%)	88 (38.6)	80 (31.6)	172 (46.9)	128 (35.3)	328 (46.7)	288 (40.7)	295 (56.6)	262 (51.5)
Adverse events leading to treatment discontinuation	30 (13.2)	36 (14.2)	56 (15.3)	46 (12.7)	116 (16.5)	112 (15.8)	121 (23.2)	124 (24.4)
AKI, n (%)	6 (2.6)	4 (1.6)	6 (1.6)	4 (1.1)	21 (3.0)	11 (1.6)	22 (4.2)	15 (2.9)
Volume depletion, n (%)	19 (8.3)	21 (8.3)	41 (11.2)	37 (10.2)	64 (9.1)	65 (9.2)	58 (11.1)	71 (13.9)
Hypotension, n (%)	16 (7.0)	19 (7.5)	35 (9.5)	32 (8.8)	58 (8.3)	60 (8.5)	53 (10.2)	62 (12.2)
Hyperkalemia, n (%)	12 (5.3)	15 (5.9)	27 (7.4)	26 (7.2)	40 (5.7)	37 (5.2)	44 (8.4)	28 (5.5)
Genital infection, n (%)	2 (0.9)	7 (2.8)	2 (0.5)	3 (0.8)	4 (0.6)	9 (1.3)	4 (0.8)	12 (2.4)

Confirmed hypoglycemia, n (%)	1 (0.4)	4 (1.6)	6 (1.6)	4 (1.1)	8 (1.1)	9 (1.3)	12 (2.3)	10 (2.0)
Ketoacidosis, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Adverse events are shown up to 7 days after discontinuation of study medication. AKI, Acute kidney injury

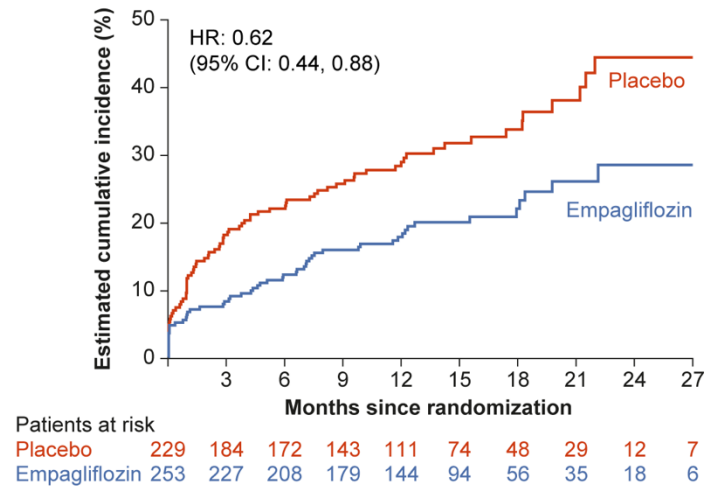
Supplemental Figure 1: Time to first diuretic dose increase stratified by baseline diuretic doses in EMPEROR-Reduced.



p-trend across diuretic dose groups: 0.054

CI, confidence interval; HR, hazard ratio

Supplemental Figure 2: Time to diuretic initiation in patients on no diuretics at baseline in EMPEROR-Reduced.



p-value for empagliflozin vs placebo: 0.008

CI, confidence interval; HR, hazard ratio