

Supplemental Material

Supplemental Table 1. Effect of empagliflozin on pre-specified measures of efficacy, by MRA use at baseline within subgroups of LVEF

Outcome events, n (%)	No MRA			MRA			Interaction P- value
	Placebo N =520	Empa. N =539	Treatment effect	Placebo N =468	Empa. N =456	Treatment effect	
LVEF 41-49%							
CV death or HF hosp.	92 (17.7) IR =8.9	68 (12.6) IR =6.1	0.69 (0.50, 0.94)	101 (21.6) IR =11.3	77 (16.9) IR =8.6	0.74 (0.55, 1.00)	0.73
Total (first and recurrent) HF hosp.	93	49	0.50 (0.31, 0.82)	116	73	0.60 (0.38, 0.96)	0.60
First HF hosp.	62 (11.9) IR =6.0	29 (5.4) IR =2.6	0.44 (0.28, 0.69)	64 (13.7) IR =7.1	48 (10.5) IR =5.3	0.72 (0.42, 1.05)	0.10
LVEF ≥50%							
	Placebo N =1346	Empa. N =1339	Treatment effect	Placebo N =657	Empa. N =663	Treatment effect	InteractionP

CV death or HF hosp.	214 (15.9) IR =8.0	165 (12.3) IR =6.1	0.75 (0.61, 0.92)	104 (15.8) IR =8.2	105 (15.8) IR =8.1	0.99 (0.75, 1.29)	0.12
Total (first and recurrent) HF hosp.	215	152	0.64 (0.48, 0.85)	117	133	1.19 (0.83, 1.71)	0.009
First HF hosp.	146 (10.8) IR =5.5	102 (7.6) IR =3.7	0.67 (0.52, 0.87)	80 (12.2) IR =6.3	80 (12.1) IR =6.2	0.98 (0.72, 1.33)	0.069

Values are n (%), hazard ratio (95% confidence interval). IR, incidence rate per 100 person-years (displayed whenever applicable).

Models included terms for age, baseline eGFR, baseline left ventricular ejection fraction, region, baseline diabetes status, sex, treatment arm, baseline use of MRA, and treatment by baseline use of MRA interaction, analyses were performed within each LVEF subgroup.

Supplemental Table 2. Effect of empagliflozin on pre-specified measures of efficacy, by MRA use at baseline within subgroups of Volume Overload

Outcome events, n (%)	No MRA			MRA			
No Volume Overload							
	Placebo N =1105	Empa. N =1121	Treatment effect	Placebo N =645	Empa. N =627	Treatment effect	Interaction P-value
CV death or HF hosp.	147 (13.3) IR =6.7	118 (10.5) IR =5.2	0.78 (0.61, 0.99)	105 (16.3) IR =8.5	99 (15.8) IR =8.0	0.95 (0.72, 1.25)	0.28
Total (first and recurrent) HF hosp.	134	88	0.62 (0.44, 0.88)	130	87	0.75 (0.50, 1.11)	0.51
First HF hosp.	94 (8.5) IR =4.3	61 (5.4) IR =2.7	0.62 (0.45, 0.86)	76 (11.8) IR =6.1	65 (10.4) IR =5.3	0.86 (0.62, 1.20)	0.17
Volume Overload							
	Placebo N =759	Empa. N =757	Treatment effect	Placebo N =480	Empa. N =491	Treatment effect	Interaction P-value
CV death or HF	157 (20.7)	115 (15.2)	0.68 (0.54,	100 (20.8)	82 (16.7)	0.77 (0.58,	0.53

hosp.	IR =10.4	IR =7.3	0.87)	IR =10.7	IR =8.6	1.03)	
Total (first and recurrent) HF hosp.	172	113	0.60 (0.43, 0.86)	103	117	1.04 (0.69, 1.56)	0.046
First HF hosp.	112 (14.8) IR =7.4	70 (9.2) IR =4.5	0.58 (0.43, 0.78)	68 (14.2) IR =7.3	62 (12.6) IR =6.5	0.84 (0.59, 1.18)	0.11

Values are n (%), hazard ratio (95% confidence interval). IR, incidence rate per 100 person-years (displayed whenever applicable). Models included terms for age, baseline eGFR, baseline left ventricular ejection fraction, region, baseline diabetes status, sex, treatment arm, baseline use of MRA, and treatment by baseline use of MRA interaction, analyses were performed within subgroup of volume overload status.

Supplemental Table 3. Effect of empagliflozin on hyperkalemia and use of potassium binders

	All patients			No MRA			MRA			Interaction P-value
	Placebo	Empa.		Placebo	Empa		Placebo	Empa.		
	n/N (%)	n/N (%)	HR (95% CI)	n/N (%)	n/N (%)	HR (95% CI)	n/N (%)	n/N (%)	HR (95% CI)	
New potassium- binder use †	51/2980 (1.7) IR=0.9	45/2986 (1.5) IR=0.8	0.82 (0.55, 1.23) P =0.35	34/1857 (1.8) IR=1.0	27/1870 (1.4) IR=0.8	0.70 (0.42, 1.16)	17/1123 (1.5) IR=0.8	18/1116 (1.6) IR=0.9	1.11 (0.57, 2.16)	0.27
Investigator- reported hyperkalemia	220/2989 (7.4) IR=4.1	186/2996 (6.2) IR=3.4	0.83 (0.68, 1.00) P =0.056	97/1865 (5.2) IR=2.9	94/1878 (5.0) IR=2.7	0.93 (0.70, 1.24)	123/1124 (10.9) IR=6.2	92/1118 (8.2) IR=4.7	0.75 (0.57, 0.98)	0.27
Serum potassium >5.5 mmol/L *	277/2872 (9.6) IR=5.9	235/2869 (8.2) IR=4.9	0.82 (0.69, 0.98) P =0.026	130/1807 (7.2) IR=4.3	130/1807 (7.2) IR=4.2	0.98 (0.77, 1.25) P =0.85	147/1065 (13.8) IR=8.6	105/1062 (9.9) IR=6.1	0.68 (0.53, 0.88)	0.044
Serum potassium >6.0	82/2937 (2.8)	47/2929 (1.6)	0.56 (0.39, 0.80)	37/1837 (2.0)	24/1842 (1.3)	0.62 (0.37, 1.04)	45/1100 (4.1)	23/1087 (2.1)	0.51 (0.31, 0.84)	0.59

mmol/L **	IR=1.6	IR=0.9	P =0.002	IR=1.2	IR=0.7		IR=2.4	IR=1.2		
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The Cox model includes terms for age, sex, baseline eGFR, baseline LVEF, region, diabetes status, randomized treatment (empagliflozin or placebo), and for the subgroup analyses additionally baseline use of MRA, and treatment by MRA interaction.

Considered potassium binding drugs were sodium polystyrene sulfonate, calcium polystyrene sulfonate, patiromer, patiromer (sorbitex) calcium, zirconium silicate and sodium zirconium cyclosilicate.

†Only patients without use of potassium binder at baseline are considered.

*Analysis performed in patients with potassium level of <5.5 mmol/L. **Analysis performed in patients with potassium level of <6.0 mmol/L.

Shown are adverse events up to 7 days and serum potassium levels up to 3 days following discontinuation of the study medication.