

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: Treatment effects and number needed to treat with SGLT-2 inhibitors in the EMPEROR-Reduced and EMPEROR-Preserved trials using negative binomial analysis.

Endpoint	Rate (95% CI) (per 100 patient years)		Measure* (95% CI)	Rate difference (95% CI)		Number needed to treat (NNT) (95% CI)	
	Placebo	Empagliflozin		1-year outcome	3-year outcome	1-year outcome	3-year outcome
EMPEROR-Reduced and EMPEROR-Preserved, all LVEFs							
Total HF hospitalization	14.78 (13.39, 16.32)	10.53 (9.47, 11.71)	0.72 (0.63, 0.83)	-5.34 (-7.46, -3.22)	-4.27 (-6.10, -2.44)	19 (14, 32)	8 (6, 14)
CV death and total HF hospitalization	23.86 (21.81, 26.10)	18.24 (16.61, 20.04)	0.77 (0.69, 0.87)	-6.49 (-9.46, -3.52)	-5.62 (-8.34, -2.90)	16 (11, 29)	6 (4, 12)
Worsening HF events †	26.20 (23.97, 28.63)	19.77 (18.02, 21.69)	0.76 (0.68, 0.86)	-7.67 (-10.90, -4.43)	-6.42 (-9.35, -3.48)	14 (10, 23)	6 (4, 10)
EMPEROR-Preserved trial, LVEF >40%							
Total HF hospitalization	9.73 (8.49, 11.16)	7.21 (6.23, 8.33)	0.73 (0.60, 0.89)	-3.98 (-6.10, -1.86)	-2.56 (-4.24, -0.87)	26 (17, 54)	14 (8, 39)
CV death and total HF hospitalization	15.90 (14.10, 17.93)	12.54 (11.06, 14.21)	0.78 (0.66, 0.93)	-4.46 (-7.26, -1.66)	-3.37 (-5.83, -0.91)	23 (14, 61)	10 (6, 37)
Worsening HF events or CV death**	17.55 (15.60, 19.74)	13.69 (12.11, 15.48)	0.77 (0.65, 0.91)	-4.98 (-8.03, -1.94)	-3.83 (-6.47, -1.19)	21 (13, 52)	9 (6, 28)

** Negative binomial event rate ratio or hazard ratio depending on endpoint based on a model with standard study covariates.*

† Worsening HF events include HF hospitalizations and urgent visits for HF requiring intravenous therapy.

HF: heart failure; CV: cardiovascular; EMPEROR-Reduced: Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction; EMPEROR-Preserved: Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; LVEF: left ventricular ejection fraction.

eTable 2: Characteristics of NHANES participants with heart failure without potential clinical intolerance based on blood pressure or kidney function

Baseline Characteristics	All			Females			Males		
	Estimate	Lower 95% CI	Upper 95% CI	Estimate	Lower 95% CI	Upper 95% CI	Estimate	Lower 95% CI	Upper 95% CI
Mean Age (years)	66.4	64.8	68.0	68.6	66.1	71.0	64.7	62.5	67.0
Population ≥65	60.2%	51.6%	68.7%	68.8%	57.5%	80.0%	53.6%	43.9%	63.3%
Race/Ethnicity									
Mexican American	4.1%	2.0%	6.1%	3.5%	0.6%	6.4%	4.5%	2.2%	6.7%
Other Hispanic	6.4%	3.4%	9.4%	6.1%	2.6%	9.6%	6.7%	1.6%	11.7%
Non-Hispanic White	67.3%	60.0%	74.7%	63.8%	55.3%	72.3%	70.0%	60.7%	79.4%
Non-Hispanic Black	16.1%	10.5%	21.7%	20.2%	12.3%	28.1%	13.0%	6.6%	19.4%
Non-Hispanic Asian	2.3%	1.0%	3.7%	1.5%	0.0%	2.9%	3.0%	0.8%	5.1%
Other	3.8%	1.3%	6.3%	4.9%	0.7%	9.2%	2.9%	0.7%	5.1%
Estimated Glomerular Filtration Rate									
Mean (<20 mL/min/1.73 m ²)	70.8	67.1	74.5	67.9	62.7	73.2	73.0	68.4	77.5
≥60	64.6%	57.3%	71.8%	58.5%	47.6%	69.4%	69.2%	59.9%	78.5%
45-59	20.7%	14.0%	27.3%	20.9%	12.0%	29.8%	20.5%	13.2%	14.8%
30-44	12.4%	7.0%	17.8%	16.6%	7.9%	25.3%	9.2%	3.6%	27.9%
<30	2.3%	0.9%	3.7%	4.0%	0.5%	7.5%	1.1%	-0.2%	2.3%
Mean Urine Albumin to Creatinine Ratio	73.7	53.9	93.6	50.0	30.3	69.7	91.3	55.2	127.4
Mean Systolic Blood Pressure (mmHg)	132.3	129.3	135.3	132.5	128.9	136.1	132.1	128.3	136.0
Mean Diastolic Blood Pressure (mmHg)	69.1	67.1	71.1	65.6	62.5	68.7	71.7	69.3	74.0
Mean Body Mass Index (kg/m²)	33.3	32.2	34.4	34.5	32.0	37.0	32.4	31.5	33.2
History of Diabetes	45.7%	38.2%	53.1%	38.1%	27.9%	48.4%	51.4%	40.2%	62.7%
History of Myocardial Infarction	45.5%	38.2%	52.7%	35.0%	24.4%	45.6%	53.5%	41.8%	65.1%
History of Stroke	20.0%	14.8%	25.2%	21.5%	12.2%	30.8%	18.9%	10.5%	27.2%
Chronic Obstructive Pulmonary Disease	29.2%	22.0%	36.4%	26.9%	15.9%	37.9%	31.0%	22.9%	39.0%

eTable 3: Adverse event rates and numbers needed to harm with SGLT-2 inhibitors in the EMPEROR-Reduced and EMPEROR-Preserved trials.

Endpoint	Rate (95% CI) (per 100 patient years)		Measure* (95% CI)	Rate difference (95% CI)		Number needed to Harm (NNH) (95% CI)	
	Placebo	SGLT-2 inhibitor		1-year outcome	3-year outcome	1-year outcome	3-year outcome
EMPEROR-Reduced and EMPEROR-Preserved, all LVEFs							
Symptomatic hypotension	3.39 (2.99, 3.82)	3.98 (3.54, 4.44)	1.16 (0.99, 1.37)	1.47 (0.52, 2.42)	0.54 (-0.07, 1.15)	72 (45, 181)	70 (38, 440)
Genital infections	0.43 (0.30, 0.59)	1.25 (1.02, 1.51)	2.90 (1.96, 4.28)	1.29 (0.84, 1.73)	0.83 (0.54, 1.12)	79 (60, 117)	42 (33, 56)
EMPEROR-Preserved trial, LVEF >40%							
Symptomatic hypotension	2.86 (2.43, 3.32)	3.63 (3.14, 4.16)	1.28 (1.04, 1.58)	1.97 (0.84, 3.09)	0.71 (0.03, 1.40)	54 (35, 117)	52 (30, 212)
Genital infections	0.39 (0.25, 0.57)	1.20 (0.93, 1.51)	3.06 (1.89, 4.96)	1.40 (0.86, 1.94)	0.82 (0.48, 1.16)	73 (53, 115)	42 (32, 62)