SUPPLEMENTAL MATERIAL

Effect of Empagliflozin on the Clinical Stability of Patients with Heart Failure and a Reduced Ejection Fraction: the EMPEROR-Reduced Trial

Figure I
Time to first event analysis of all-cause mortality or all-cause hospitalization in the placebo and empagliflozin groups

Figure II
Effect of empagliflozin on total (first and recurrent) adjudicated hospitalizations for heart failure in 12 prespecified subgroups

Figure III
Time to first event analysis of all-cause mortality, heart failure hospitalization or emergent/urgent care visit for worsening heart failure in the placebo and empagliflozin groups during first 40 days following randomization

Figure IV
Total study visits reporting interval intensification of diuretics for worsening heart failure in the placebo and empagliflozin groups

Figure V
Changes in hematocrit during double-blind treatment in the placebo and empagliflozin groups

Figure VI
Changes in uric acid during double-blind treatment in the placebo and empagliflozin groups

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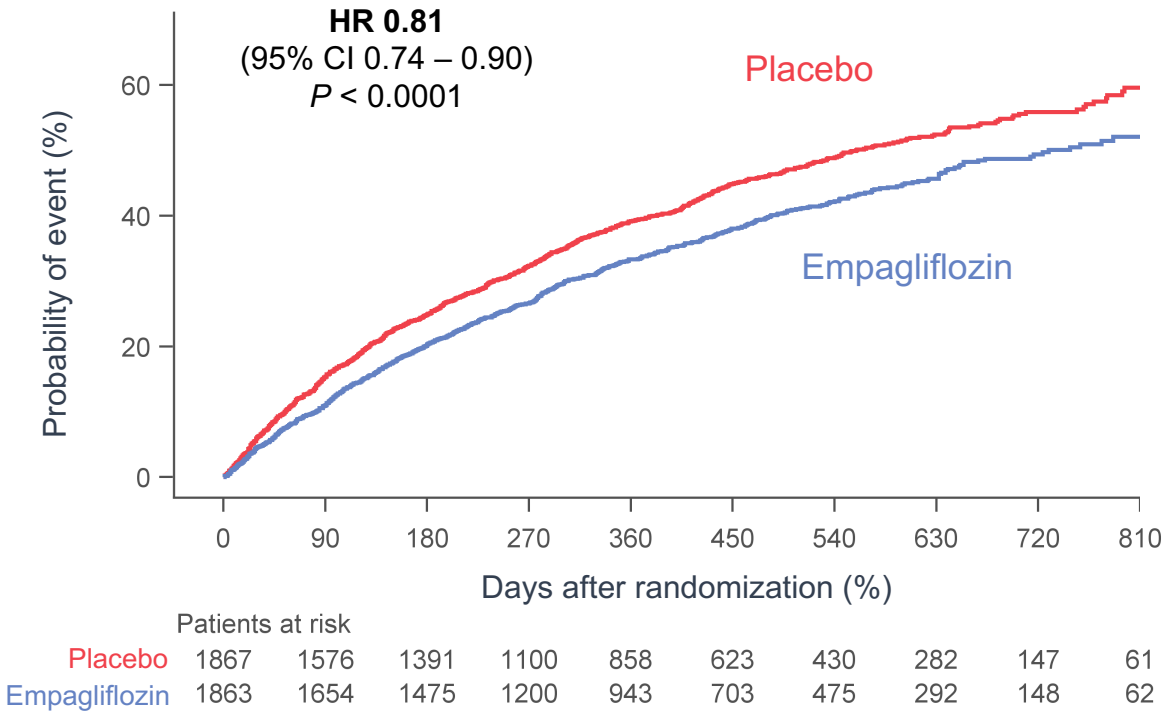
Figure VIII
Changes in N-terminal proBNP during double-blind treatment in the placebo and empagliflozin groups

Figure IX
Changes in systolic blood pressure during double-blind treatment in the placebo and empagliflozin groups

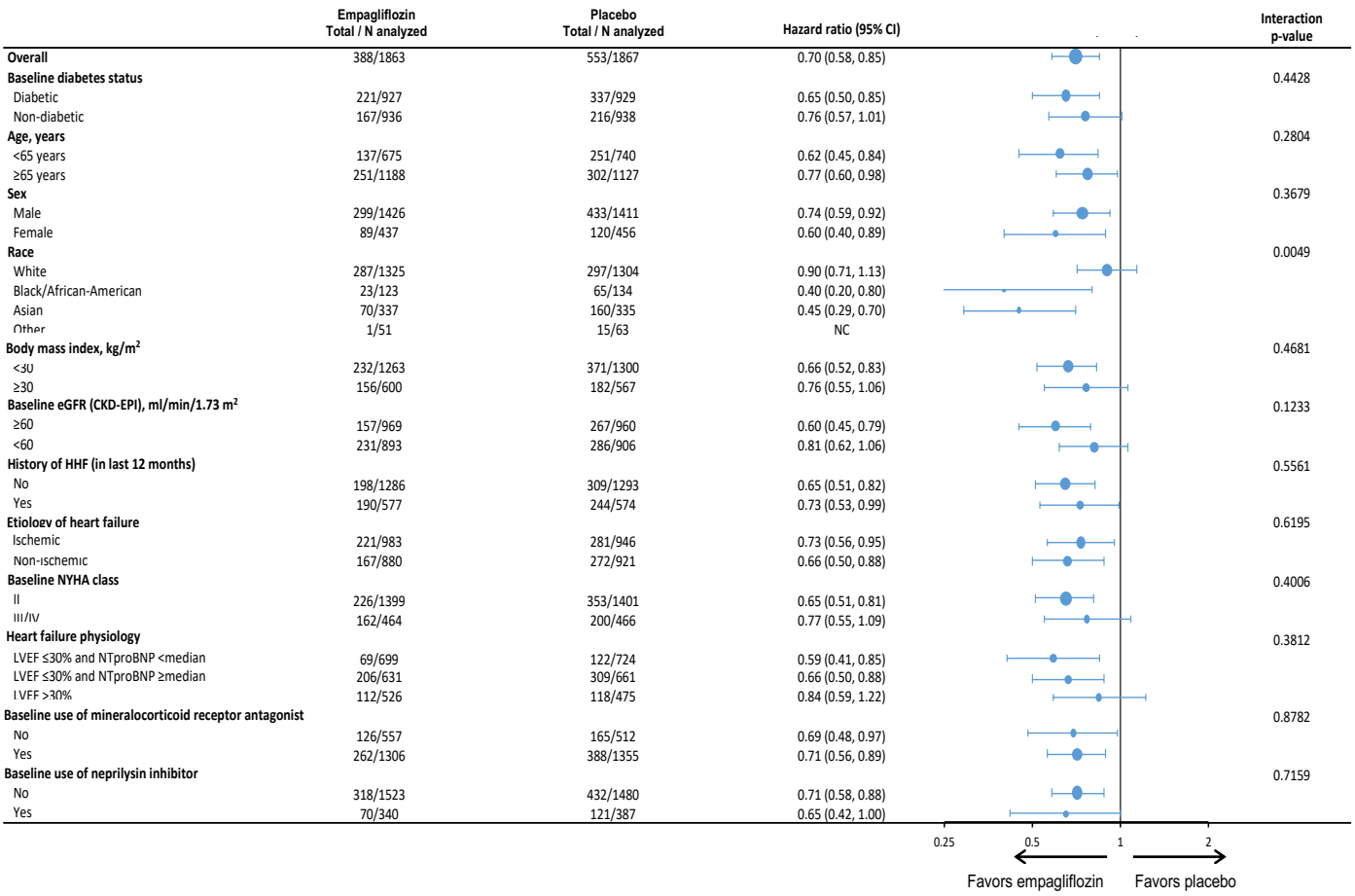
Table I
Frequencies of major outcomes and worsening heart failure events

Figure I
Time to first event of all-cause mortality or all-cause hospitalization



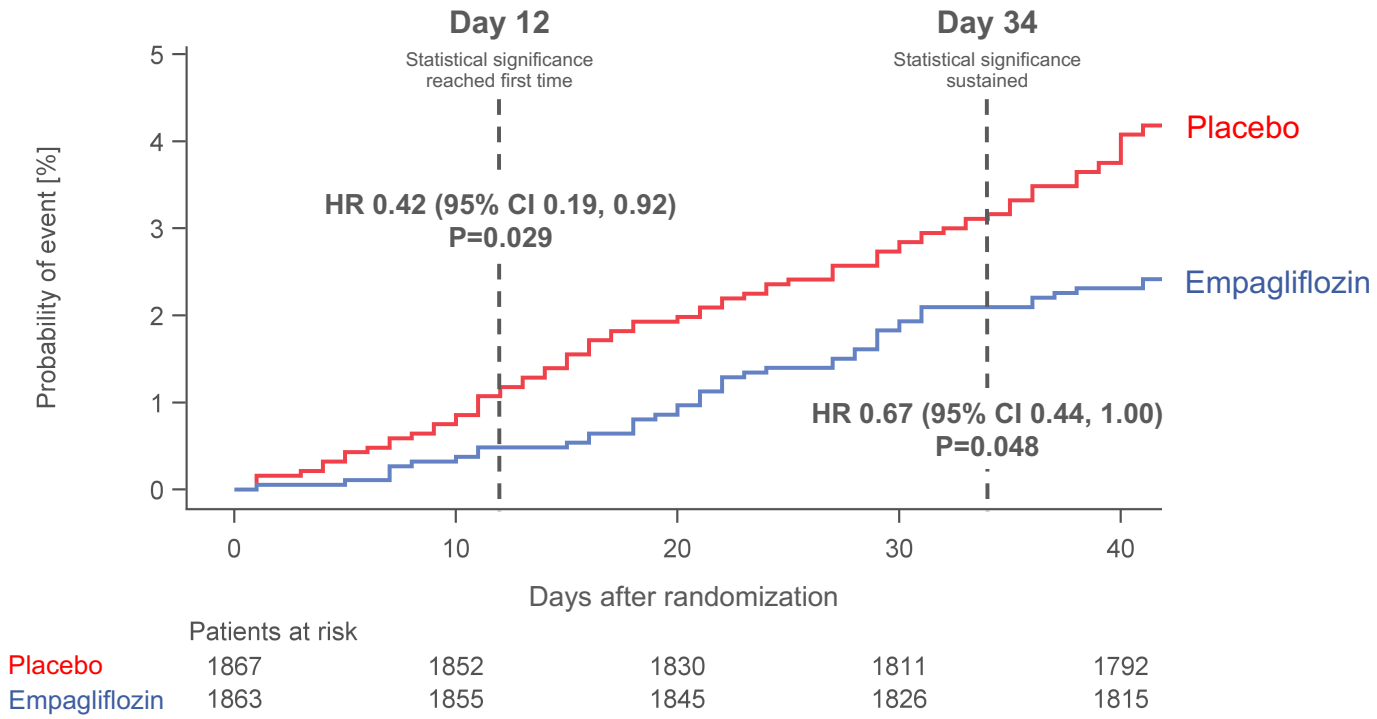
Abbreviations: HR=hazard ratio; CI = confidence interval

Figure II
Effect of empagliflozin on total (first and recurrent) adjudicated hospitalizations for heart failure in 12 prespecified subgroups



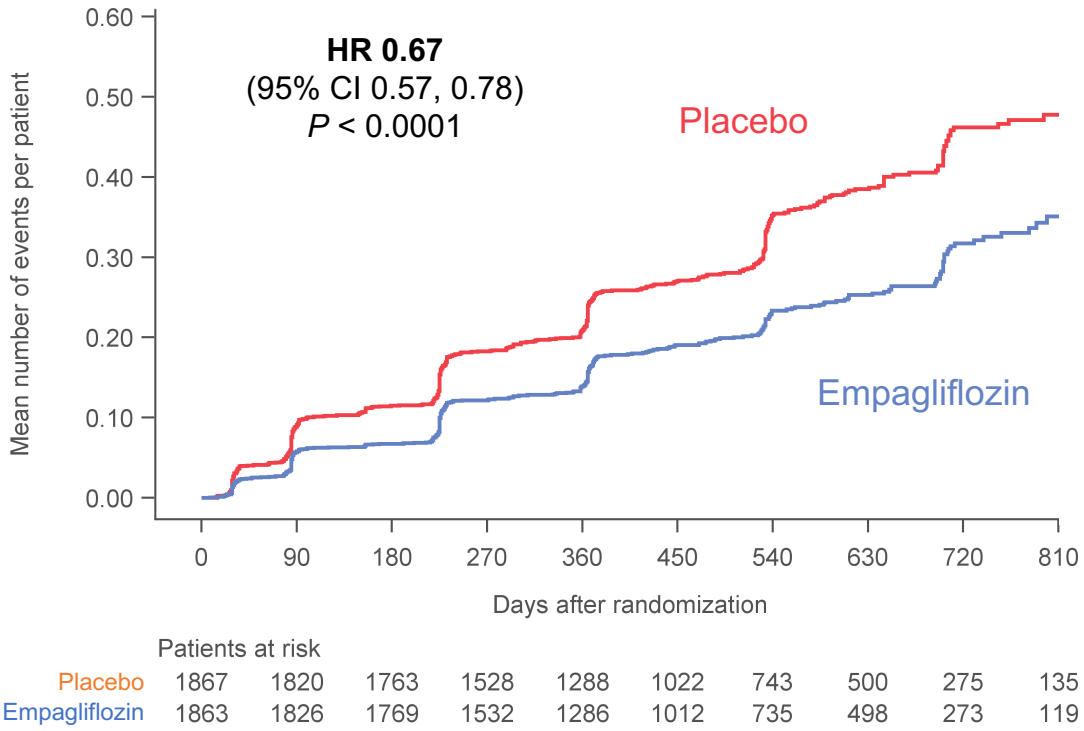
Abbreviations: HHF= heart failure hospitalization; LVEF = left ventricular ejection fraction; NYHA= New York Heart Association

Figure III
Time to first event analysis of all-cause mortality, heart failure hospitalization or emergent/urgent care visit for worsening heart failure in the placebo and empagliflozin groups during first 40 days following randomization



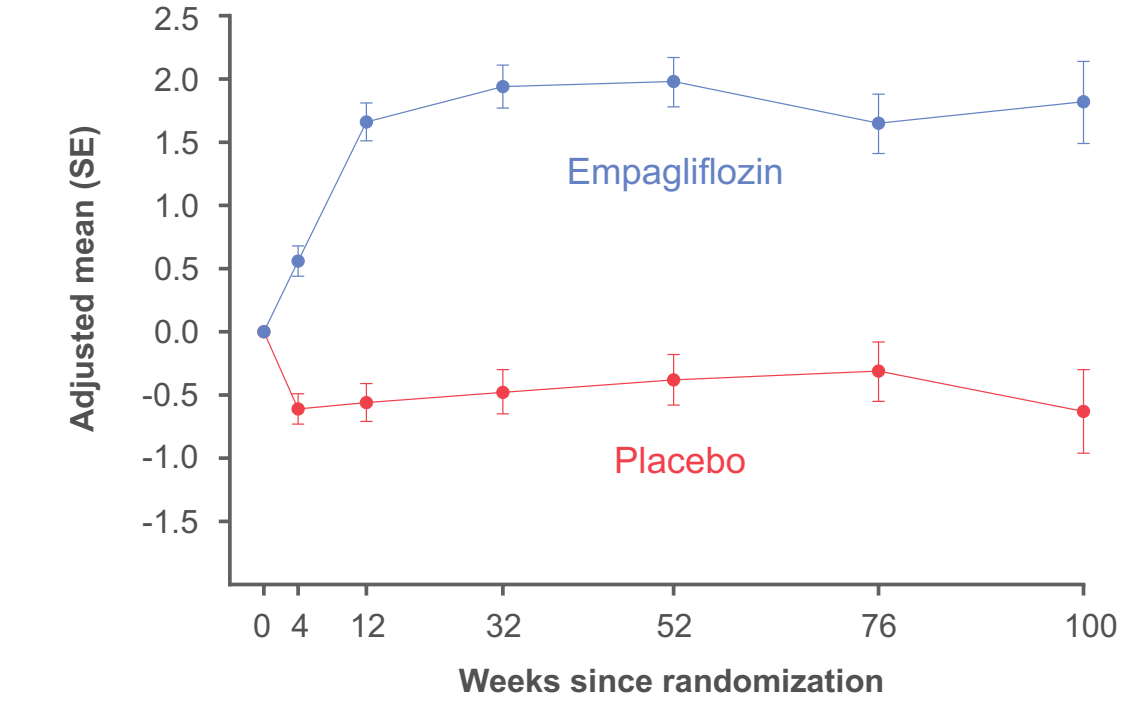
Abbreviations: HR=hazard ratio; CI = confidence interval

Figure IV
Total study visits reporting interval intensification of diuretics for worsening heart failure



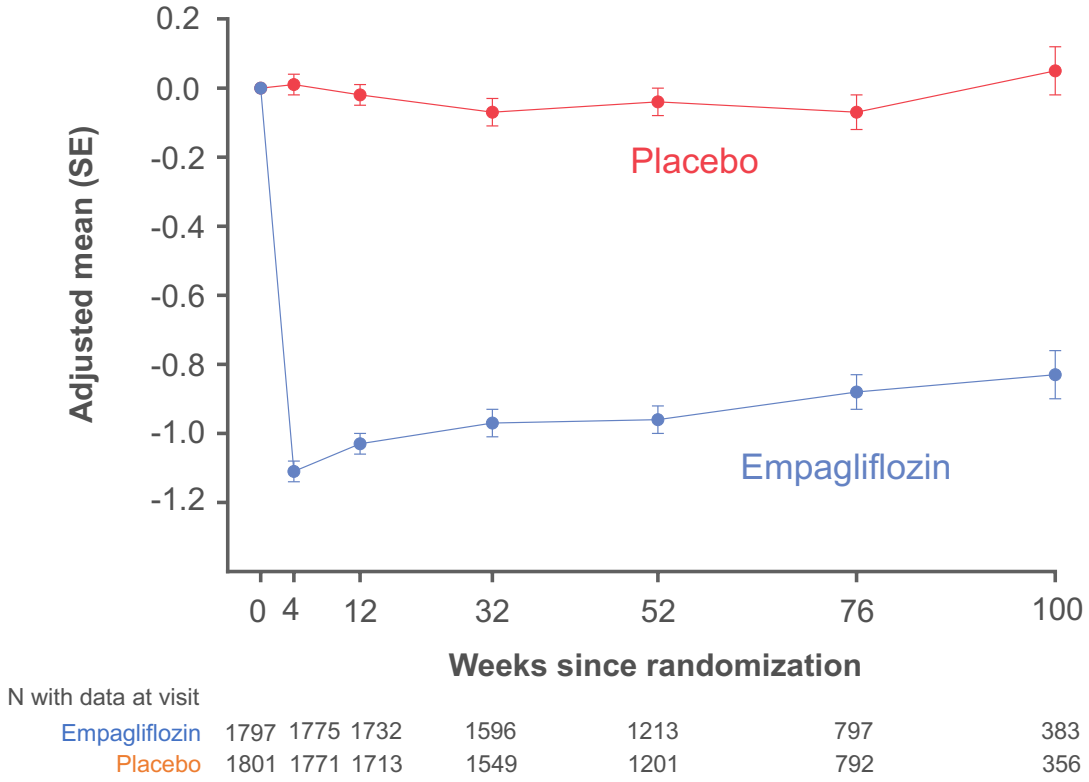
Abbreviations: HR=hazard ratio; CI = confidence interval

Figure V
Changes in hematocrit in the placebo and empagliflozin groups



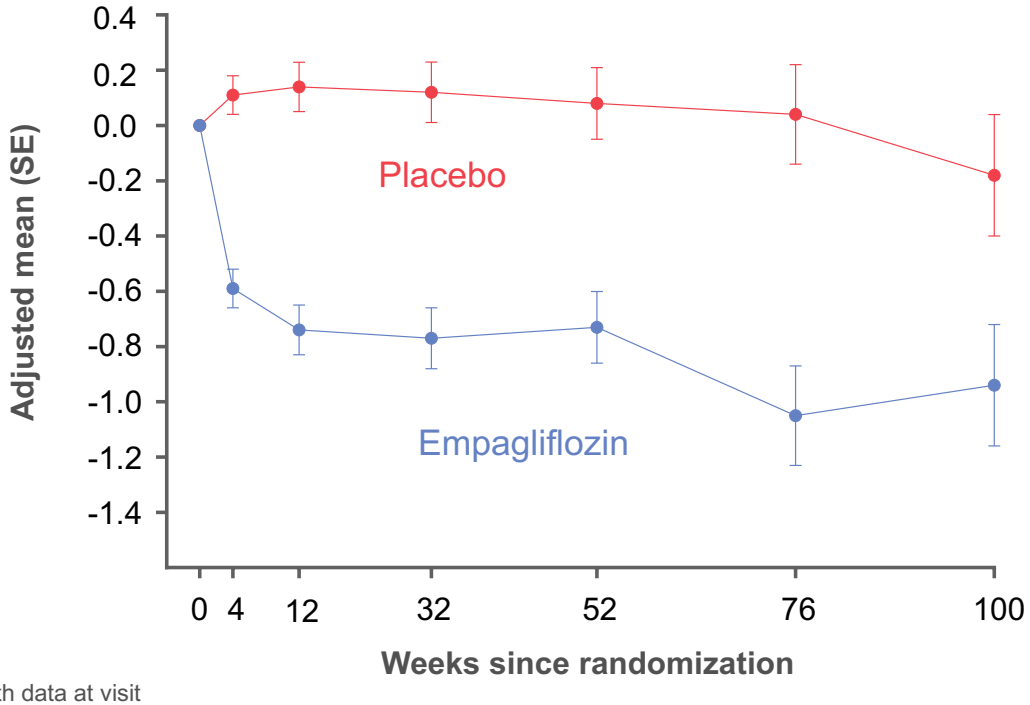
N with data at visit							
Empagliflozin	1822	1780	1742	1605	1211	798	381
Placebo	1820	1775	1712	1557	1195	793	356

Figure VI
Changes in uric acid in the placebo and empagliflozin group



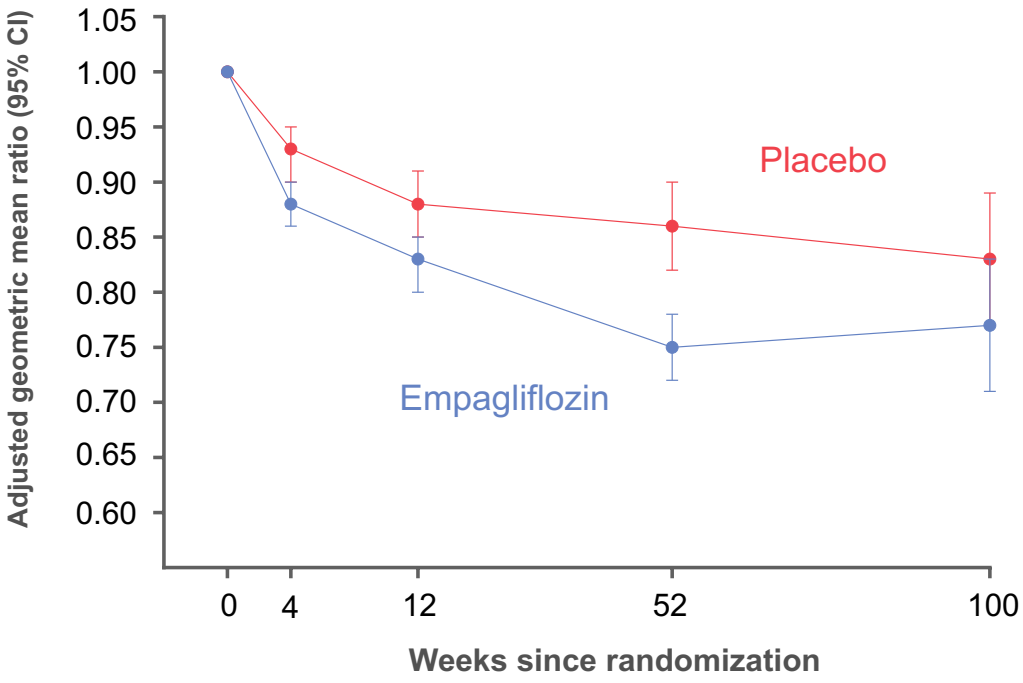
N with data at visit							
Empagliflozin	1797	1775	1732	1596	1213	797	383
Placebo	1801	1771	1713	1549	1201	792	356

Figure VII
Changes in body weight in the placebo and empagliflozin groups



N with data at visit							
Empagliflozin	1828	1808	1768	1629	1240	818	395
Placebo	1823	1803	1745	1586	1229	813	373

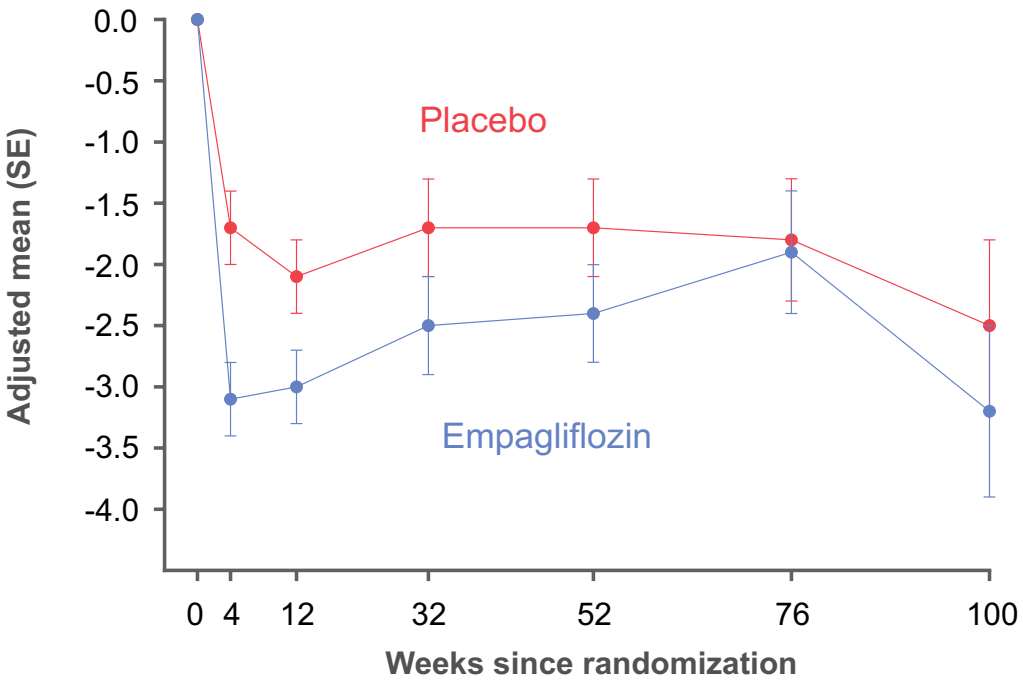
Figure VIII
Changes in N-terminal proBNP in the placebo and empagliflozin groups



N with data at visit					
Empagliflozin	1824	1792	1748	1323	451
Placebo	1819	1779	1731	1311	429

Abbreviations: NT-proBNP = N-terminal prohormone B-type natriuretic peptide

Figure IX
Changes in systolic blood pressure in the placebo and empagliflozin groups



N with data at visit							
Empagliflozin	1829	1813	1769	1630	1241	811	395
Placebo	1823	1803	1744	1579	1226	809	367

Table I. Frequencies of Major Outcomes and Worsening Heart Failure Events

	Placebo	Empagliflozin
Adjudicated hospitalizations for heart failure		
Patients hospitalized once	231	160
Patients hospitalized twice	61	50
Patients hospitalized ≥ 3 times	50	36
Total (first and recurrent) adjudicated hospitalizations for heart failure		
Number of hospitalizations requiring only oral diuretics	27	15
Number of hospitalizations requiring only intravenous diuretics	266	204
Number of hospitalizations requiring IV vasodilators	54	36
Number of hospitalizations requiring IV vasopressors or positive inotropic drugs	152	92
Number of hospitalizations with mechanical or surgical intervention	34	24
Total (first and recurrent) emergent or urgent care visits for heart failure requiring intravenous therapy		
Patients who required emergent or urgent care once	141	87
Patients who required emergent or urgent care twice	22	27
Patients who required emergent or urgent care ≥ 3 times	22	12
Changes in diuretic dose since prior study visit		
Number of patients who had diuretics were intensified since prior study visit	414 (22.2%)	297 (15.9%)
Total number of study visits that reported that the dose of diuretics had been intensified since prior study visit	564	380
Number of patients who had reduction in the dose of diuretics since prior study visit	246 (13.2)	281 (15.1%)
Total number of study visits that reported that the dose of diuretics had been reduced since prior study visit	293	334
Adjudicated cardiovascular events other than heart failure		
Adjudicated myocardial infarction	20 (1.1%)	19 (1.0%)
Adjudicated stroke	35 (1.9%)	40 (2.1%)
Adjudicated transient ischemic attack	7 (0.4%)	7 (0.4%)

Categories are ordered according to severity of intervention, with each category including less intensive but excluding more intensive interventions, i.e., use of intravenous vasopressors or positive inotropic drugs includes the use of diuretics or intravenous vasodilators, but exclude mechanical or surgical intervention). A total of 20 patients in the placebo group and 16 in empagliflozin group did not have complete information on the utilization or drug or non-drug interventions during hospitalization.