Efficacy and Safety of Empagliflozin According to Background Diuretic Use in Patients with Heart Failure and a Reduced Ejection Fraction

Post Hoc Analysis of the EMPEROR-REDUCED Trial

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Disclosures

No COIs to disclose for presenting author

Background

- In EMPEROR-Reduced[1] and DAPA-HF[2], SGLT2 inhibitors reduced the rates of CV death or HHF by approximately 25% among patients with HFrEF

- Patients with HFrEF are often prescribed diuretics for sign/symptom control

- Whether the efficacy and safety of SGLT2 inhibitors vary by baseline use and intensity of diuretics is an important and unanswered question

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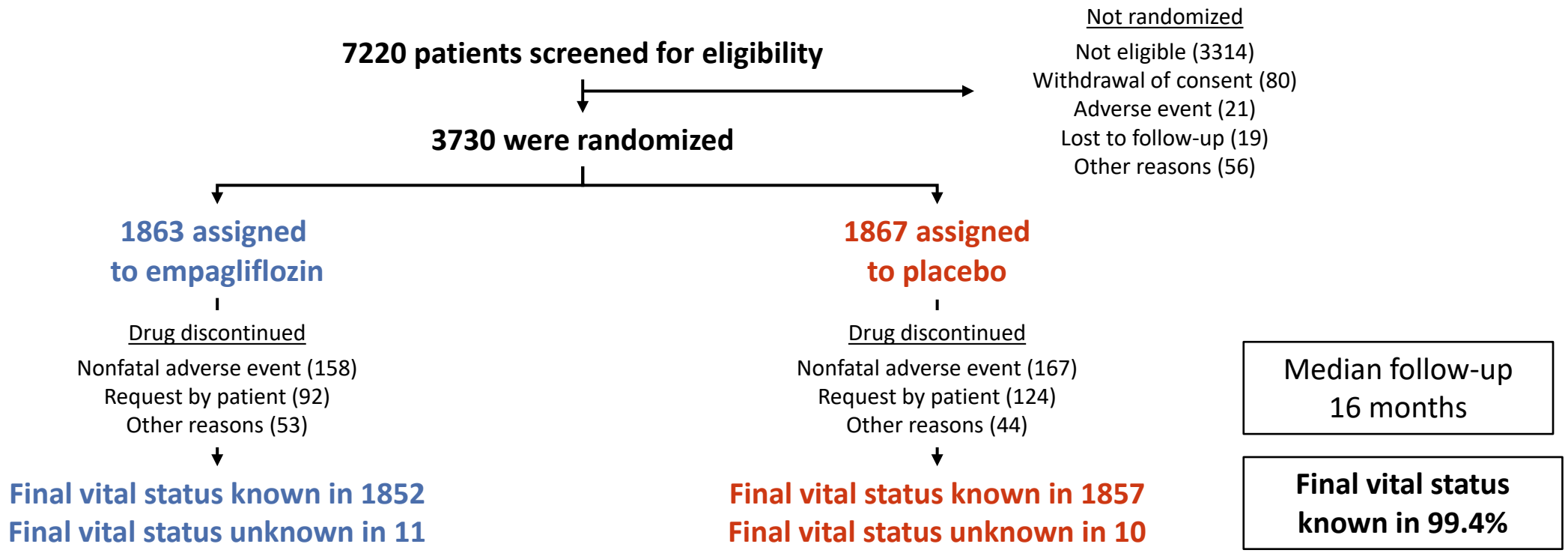
- Patients with HFrEF are often prescribed diuretics for sign/symptom control

- Whether the efficacy and safety of SGLT2 inhibitors vary by baseline use and intensity of diuretics is an important and unanswered question

This post hoc analysis of EMPEROR-Reduced was conducted to investigate whether background diuretic therapy alters the efficacy and safety of empagliflozin in HFrEF

EMPEROR-Reduced[1]: Study design

- EMPEROR-Reduced randomized patients with an LVEF ≤ 40%, NYHA II-IV symptoms and elevated natriuretic peptide levels to empagliflozin 10mg or matching placebo



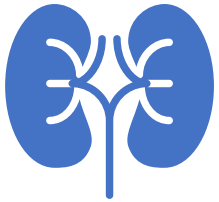
EMPEROR-Reduced[1]: Central Findings

Primary Endpoint
Composite of cardiovascular death or heart failure hospitalization

25% ↓ in risk
P < 0.001

First Secondary Endpoint
Total (first and recurrent heart failure hospitalizations)

30% ↓ in risk
P < 0.001



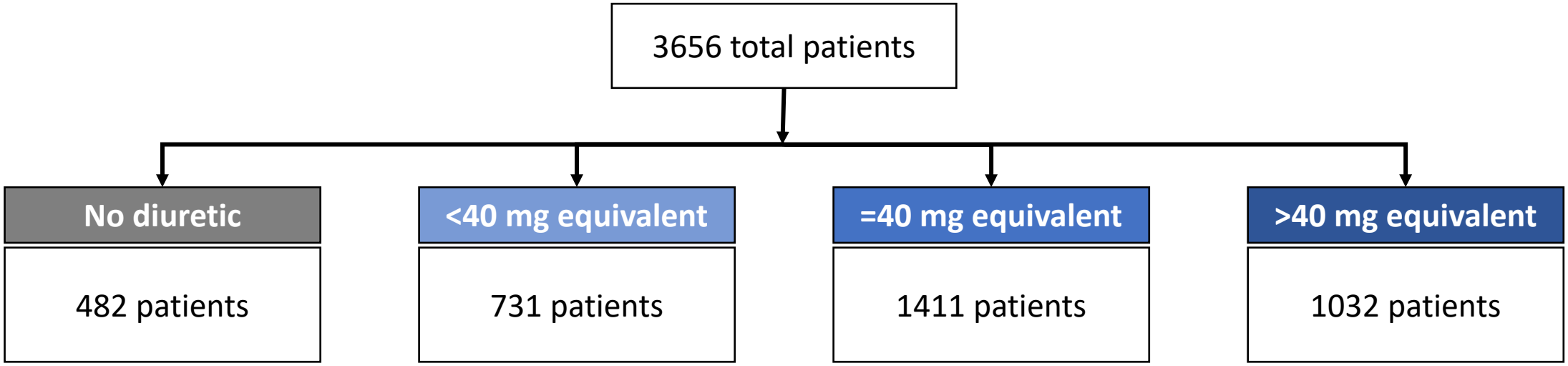
Second Secondary Endpoint
Slope of decline in glomerular filtration rate over time

P < 0.001
(50% ↓ in renal events)

Also achieved success on composite renal endpoint, KCCQ clinical summary score at 52 weeks, and total number of hospitalizations for any reason (all nominal P<0.01)

Methods of current analysis

Patients were divided into 4 groups based on their baseline diuretic use



Diuretic dose equivalents were defined as follows: Furosemide doses, 40 mg IV or 80 mg PO; dose equivalents, bumetanide 1 mg, torsemide 20 mg, azosemide 60 mg or etacrynic acid 100 mg. Patients receiving neither a loop diuretic nor a non-loop diuretics were assigned to the 'no diuretic' group. Patients receiving a non-loop diuretic but no loop diuretic were assigned to the '<40 mg equivalent' group. MRA was not classified as a diuretic.

IV, intravenous; MRA, mineralocorticoid receptor antagonist; PO, per orem (orally).

Baseline characteristics (1/2)

	No diuretic (n=482)	<40 mg equivalent (n=731)	=40 mg equivalent (n=1411)	>40 mg equivalent (n=1032)	*p*-trend
Demographics					
Female	133 (27.6)	170 (23.3)	351 (24.9)	220 (21.3)	0.027
Age, years	68.0 (60.0–74.0)	69.0 (62.0–77.0)	68.0 (60.0–75.0)	68.0 (59.0–75.0)	0.405
HF characteristics					
LVEF, %	28.1± 5.6	28.3 ± 5.8	27.3 ± 6.1	26.8 ± 6.2	<0.001
Cause of HF					0.002
Ischaemic	241 (50.0)	362 (49.5)	700 (49.6)	585 (56.7)	
Non-ischaemic	241 (50.0)	369 (50.5)	711 (50.4)	447 (43.3)	
NYHA					<0.001
Class II	398 (82.6)	591 (80.8)	1088 (77.1)	673 (65.2)	
Class III	83 (17.2)	136 (18.6)	315 (22.3)	352 (34.1)	
Class IV	1 (0.2)	4 (0.5)	8 (0.6)	7 (0.7)	
NT-proBNP, pg/mL	1555.00 (940.00–2636.00)	1714.00 (1072.00–3106.00)	1926.00 (1101.00–3450.00)	2175.00 (1335.00–4385.50)	<0.001
KCCQ-CSS	82.3 (63.0–92.7)	81.0 (66.4–91.7)	72.9 (53.6–89.3)	67.7 (49.0–83.6)	<0.001
HHF in last 12 months	97 (20.1)	211 (28.9)	406 (28.8)	410 (39.7)	<0.001

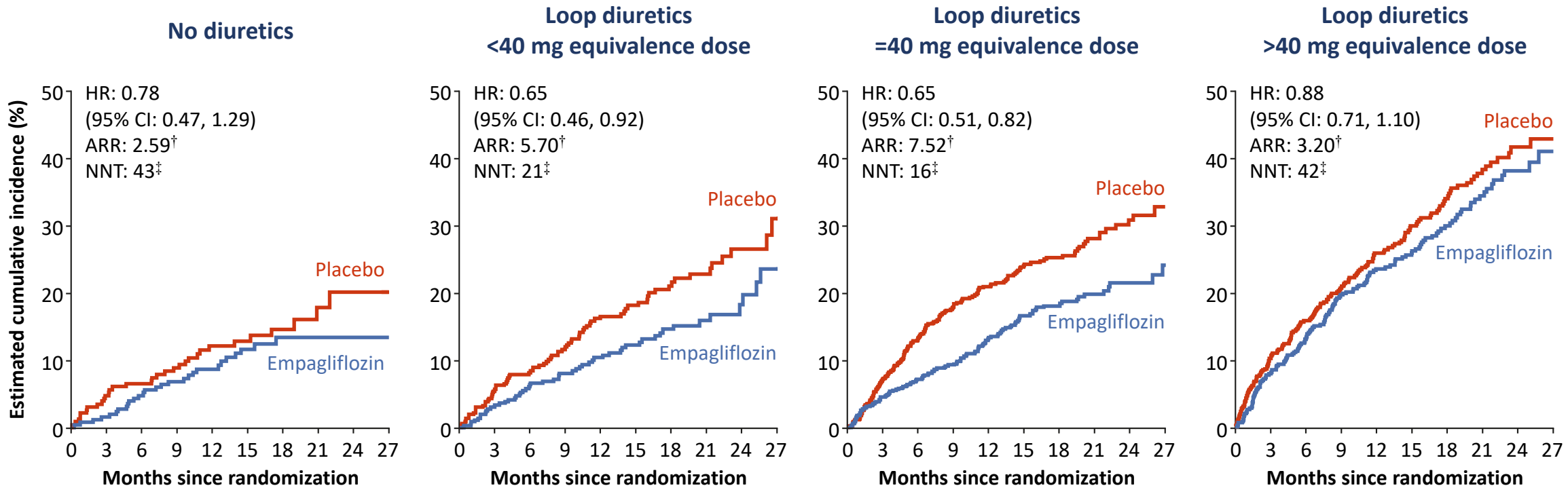
Data are n (%), mean ± standard deviation, or median (Q1–Q3).
HF, heart failure; HHF, hospitalization for heart failure; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire- Clinical Summary Score; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro-B type natriuretic peptide; NYHA, New York Heart Association

Baseline characteristics (2/2)

	No diuretic (n=482)	<40 mg equivalent (n=731)	=40 mg equivalent (n=1411)	>40 mg equivalent (n=1032)	*p*-trend
Comorbidities					
Diabetes	196 (40.7)	318 (43.5)	693 (49.1)	618 (59.9)	<0.001
CKD*	188 (39.0)	361 (49.4)	730 (51.7)	658 (63.8)	<0.001
eGFR, mL/min/1.73 m^2	68.2 ± 19.9	63.9 ± 20.9	62.7 ± 21.8	57.0 ± 21.8	<0.001
Diuretics use					
Receiving loop diuretics only	0 (0)	593 (81.1)	1286 (91.1)	898 (87.0)	<0.001
Furosemide equivalent dose, mg†	0	20.0	40.0	80.0	<0.001
HFrEF medical therapy					
ACEi/ARB/ARNi	434 (90.0)	644 (88.1)	1254 (88.9)	897 (86.9)	0.126
BB	452 (93.8)	684 (93.6)	1356 (96.1)	972 (94.2)	0.449
MRA	297 (61.6)	509 (69.6)	1041 (73.8)	760 (73.6)	<0.001
ACEi/ARB/ARNi +BB/Ivabradine	417 (86.5)	615 (84.1)	1222 (86.6)	855 (82.8)	0.132
ACEi/ARB/ARNi + BB/Ivabradine + MRA	260 (53.9)	442 (60.5)	905 (64.1)	651 (63.1)	0.002
Device therapy					
ICD	122 (25.3)	137 (18.7)	266 (18.9)	303 (29.4)	<0.001
CRT-D	28 (5.8)	51 (7.0)	122 (8.6)	168 (16.3)	<0.001
CRT-P	4 (0.8)	12 (1.6)	25 (1.8)	23 (2.2)	0.075

*eGFR <60 mL/min/1.73 m^2 or UACR >300 mg/g; †median. Data are n (%) or mean ± standard deviation unless otherwise stated. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; CKD, chronic kidney disease; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillators; MRA, mineralocorticoid receptor antagonist.

Treatment efficacy: Primary endpoint*



Patients at risk

Placebo	229	218	212	184	145	106	68	44	20	10
Empagliflozin	253	244	232	208	172	118	71	47	28	8

Placebo	368	344	333	275	237	183	132	92	52	24
Empagliflozin	363	351	338	300	257	208	148	98	54	22

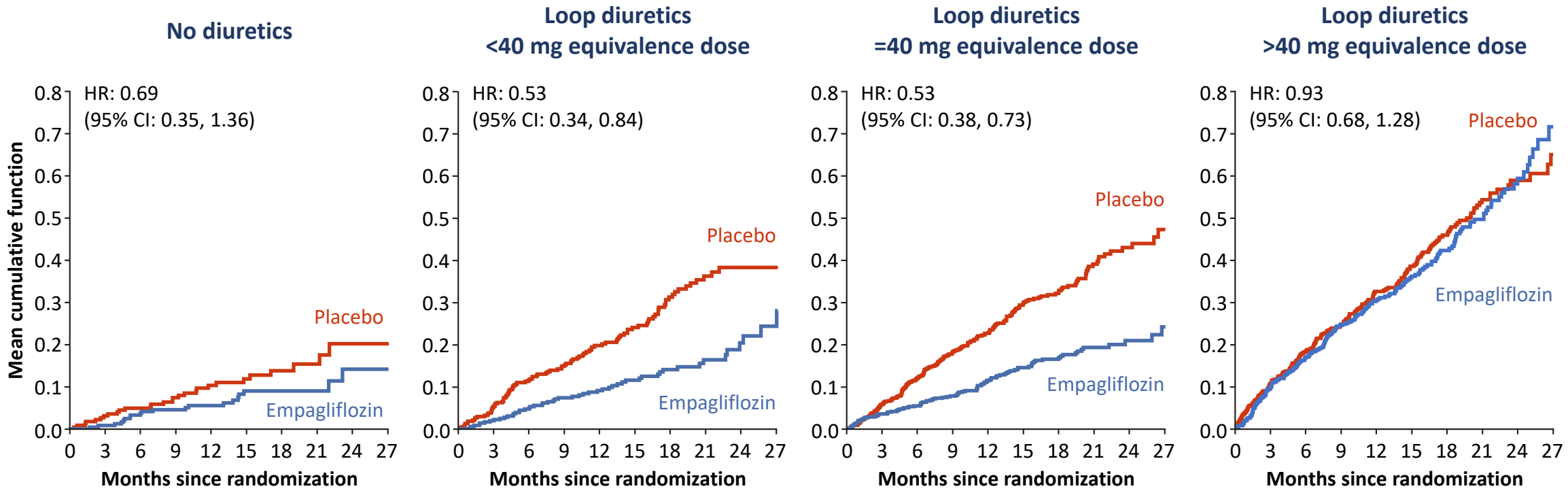
Placebo	703	647	600	501	412	327	239	155	91	40
Empagliflozin	708	671	641	547	439	340	250	159	90	47

Placebo	523	467	428	353	286	219	164	113	58	32
Empagliflozin	509	467	437	346	288	231	171	116	57	22

***p*-trend across diuretic dose groups: 0.192**

*CV death or first HHF. †Per 100 patient-years at risk. ‡Per 1 year at risk.
ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; NNT, number needed to treat.

Treatment efficacy: Total HHF



Patients at risk

Placebo	229	225	221	194	157	115	74	49	22	10
Empagliflozin	253	247	238	215	179	123	76	51	31	10

Placebo	368	361	354	303	268	211	158	111	62	29
Empagliflozin	363	358	348	312	269	219	162	111	60	27

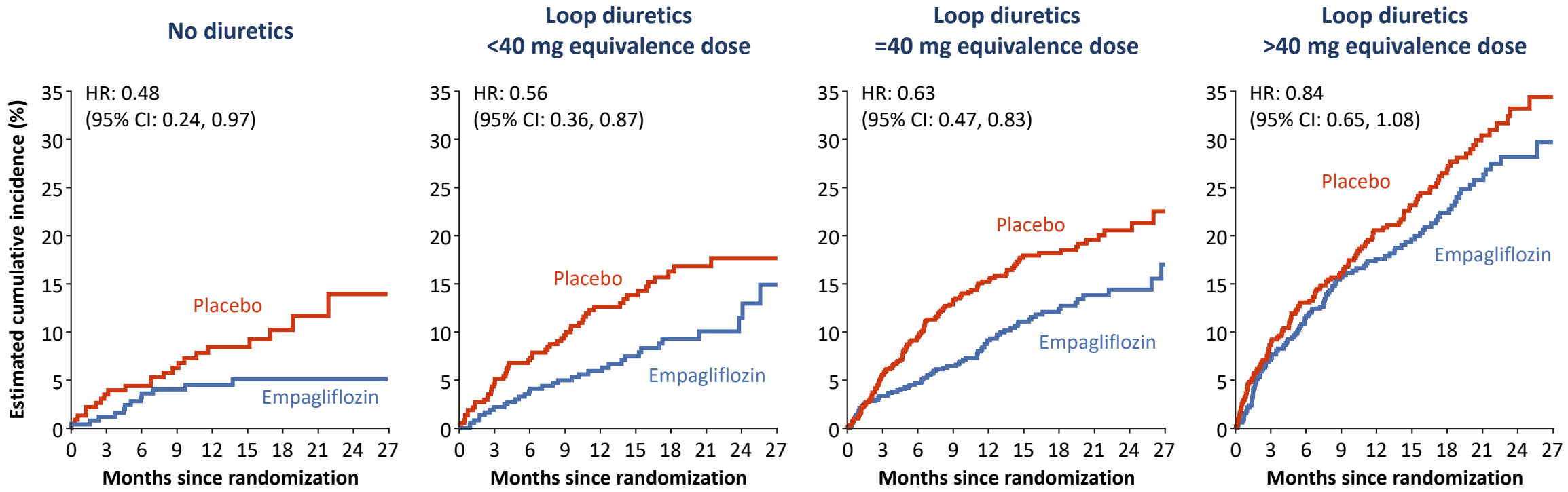
Placebo	703	684	661	577	479	390	282	183	109	50
Empagliflozin	708	693	667	578	476	375	278	184	102	51

Placebo	523	508	484	417	350	278	209	147	78	42
Empagliflozin	509	498	485	403	341	276	208	145	77	28

***p*-trend across diuretic dose groups: 0.082**

CI, confidence interval; HHF, hospitalization for heart failure; HR, hazard ratio.

Treatment efficacy: Time to first HHF



Patients at risk

Placebo	229	218	212	184	145	106	68	44	20	10
Empagliflozin	253	244	232	208	172	118	71	47	28	8

Placebo	368	344	333	275	237	183	132	92	52	24
Empagliflozin	363	351	338	300	257	208	148	98	54	22

Placebo	703	647	600	501	412	327	239	155	91	40
Empagliflozin	708	671	641	547	439	340	250	159	90	47

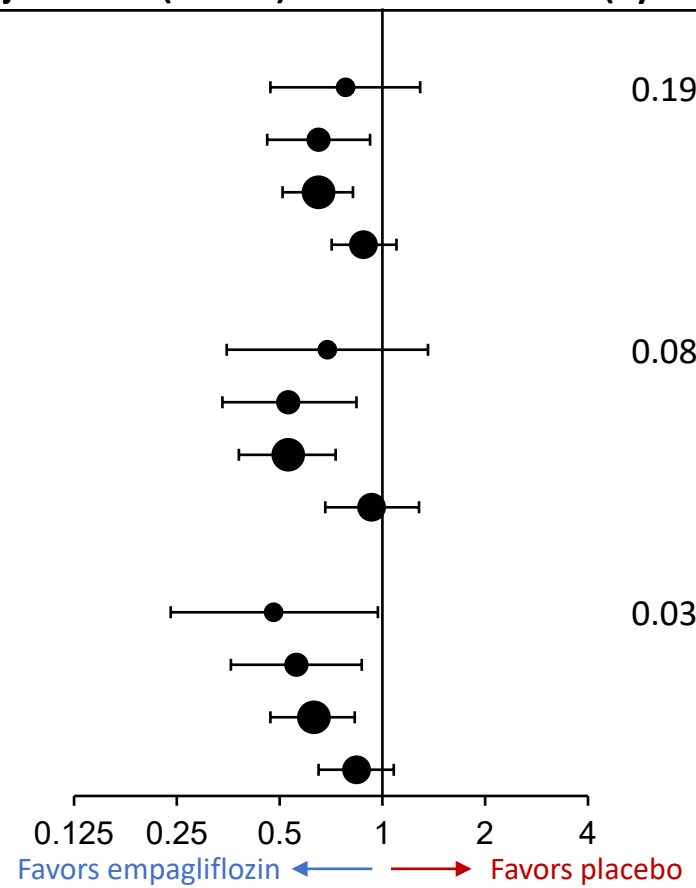
Placebo	523	467	428	353	286	219	164	113	58	32
Empagliflozin	509	467	437	346	288	231	171	116	57	22

***p*-trend across diuretic dose groups: 0.036**

CI, confidence interval; HHF, hospitalization for heart failure; HR, hazard ratio.

CV outcomes (1/2)

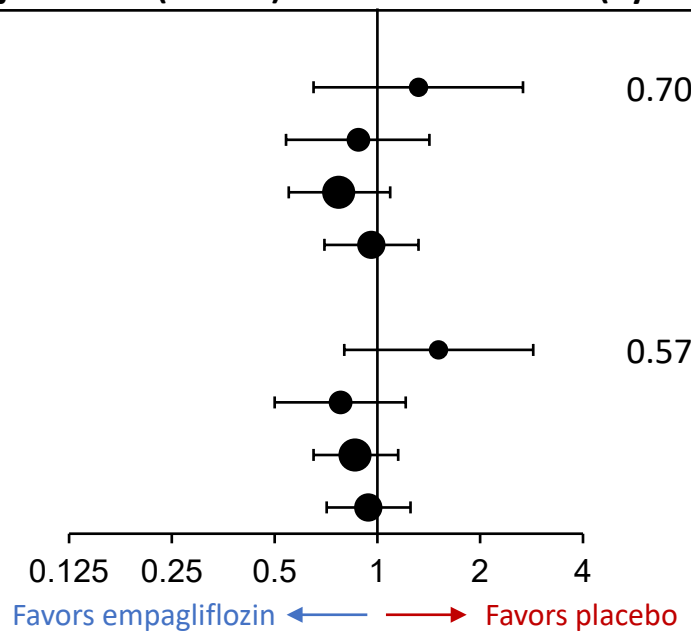
Endpoint	Placebo n/N	Placebo Events/100 py	Empagliflozin n/N	Empagliflozin Events/100 py	Adjusted HR (95% CI)	*p*-trend (by dose)
CV death or first HHF						
No diuretics	32/229	11.7	28/253	9.1	0.78 (0.47, 1.29)	0.192
<40 mg	76/368	16.6	53/363	10.9	0.65 (0.46, 0.92)	
40 mg	177/703	21.3	120/708	13.8	0.65 (0.51, 0.82)	
>40 mg	171/523	29.1	153/509	25.9	0.88 (0.71, 1.10)	
Total (first and recurrent) HHF						
No diuretics	29	–	21	–	0.69 (0.35, 1.36)	0.082
<40 mg	99	–	51	–	0.53 (0.34, 0.84)	
40 mg	208	–	104	–	0.53 (0.38, 0.73)	
>40 mg	211	–	204	–	0.93 (0.68, 1.28)	
First HHF						
No diuretics	22/229	8.0	12/253	3.9	0.48 (0.24, 0.97)	0.036
<40 mg	54/368	11.8	33/363	6.8	0.56 (0.36, 0.87)	
40 mg	125/703	15.0	81/708	9.3	0.63 (0.47, 0.83)	
>40 mg	135/523	23.0	115/509	19.5	0.84 (0.65, 1.08)	



CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; py, patient-years.

CV outcomes (2/2)

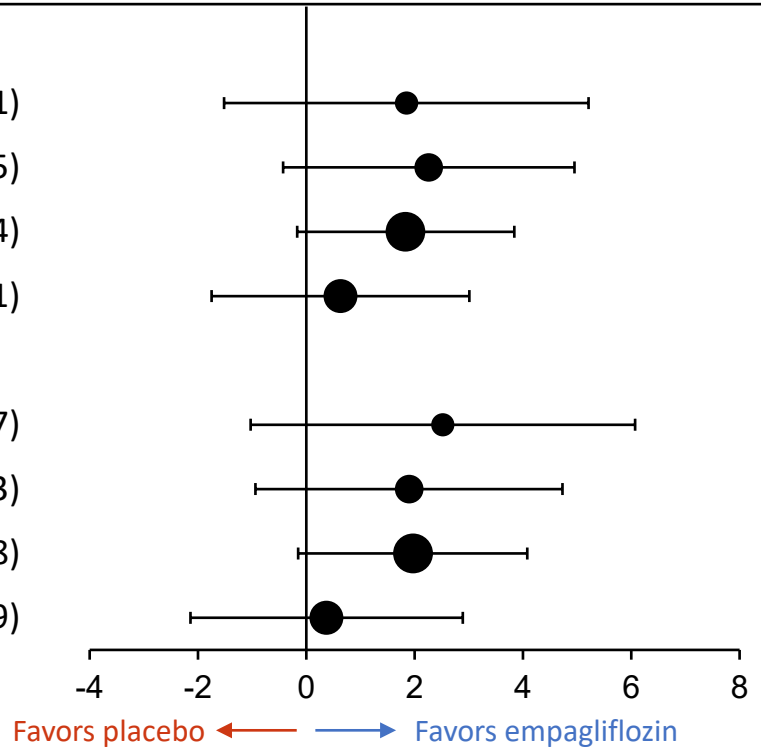
Endpoint	Placebo n/N	Placebo Events/100 py	Empagliflozin n/N	Empagliflozin Events/100 py	Adjusted HR (95% CI)	*p*-trend (by dose)
CV death						
No diuretics	13/229	4.5	19/253	5.8	1.32 (0.65, 2.67)	0.700
<40 mg	35/368	6.9	31/363	6.1	0.88 (0.54, 1.42)	
40 mg	76/703	8.1	60/708	6.5	0.77 (0.55, 1.09)	
>40 mg	78/523	11.3	73/509	10.9	0.96 (0.70, 1.32)	
All-cause mortality						
No diuretics	15/229	5.2	26/253	8.0	1.51 (0.80, 2.86)	0.575
<40 mg	46/368	9.1	36/363	7.1	0.78 (0.50, 1.21)	
40 mg	100/703	10.7	88/708	9.5	0.86 (0.65, 1.15)	
>40 mg	101/523	14.6	95/509	14.1	0.94 (0.71, 1.25)	



CI, confidence interval; CV, cardiovascular; HR, hazard ratio; py, patient-years.

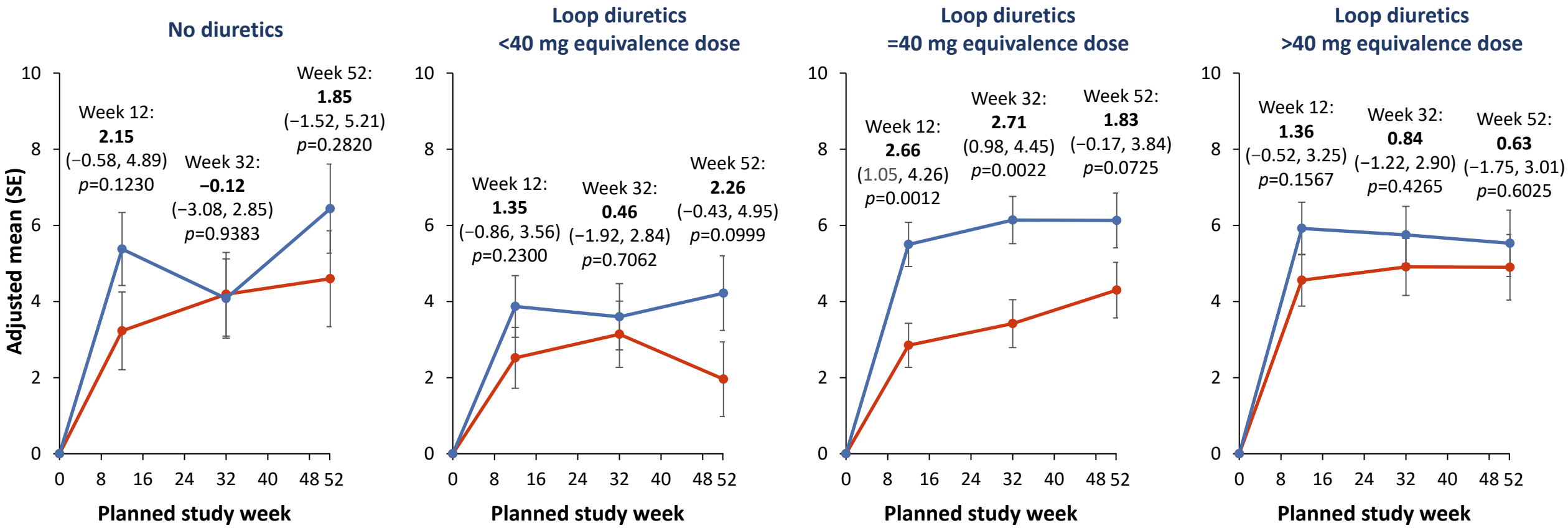
KCCQ summary at 12 months

Endpoint	Adjusted mean difference to placebo (95% CI)	*p*-trend (by dose)
KCCQ-CSS		
No diuretics	1.85 (−1.52, 5.21)	0.431
<40 mg	2.26 (−0.43, 4.95)	
40 mg	1.83 (−0.17, 3.84)	
>40 mg	0.63 (−1.75, 3.01)	
KCCQ-TSS		
No diuretics	2.52 (−1.03, 6.07)	0.315
<40 mg	1.90 (−0.94, 4.73)	
40 mg	1.97 (−0.15, 4.08)	
>40 mg	0.37 (−2.14, 2.89)	



CI, confidence interval; KCCQ, Kansas City Cardiomyopathy Questionnaire; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score.

KCCQ-CSS change from baseline

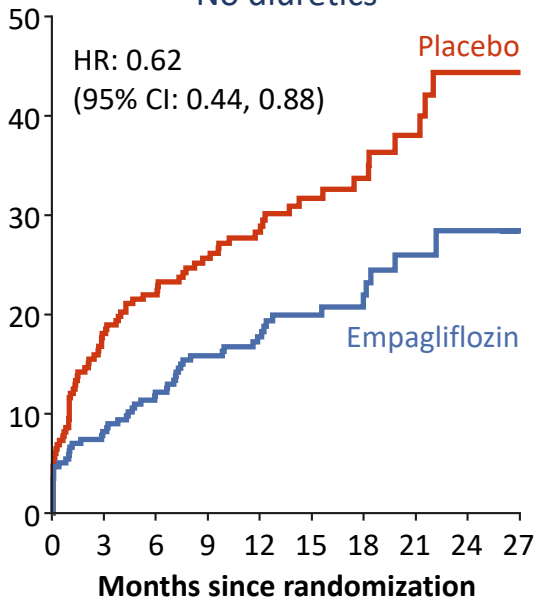


***p*-trend across diuretic dose groups (week 52): 0.431**

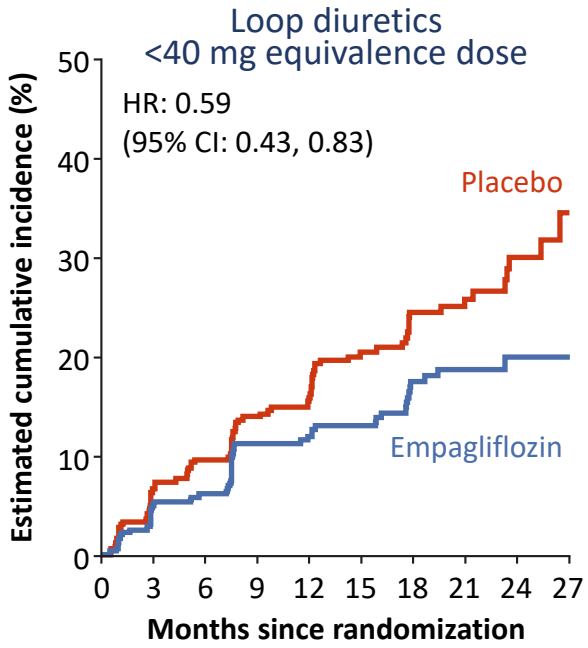
Labels show adjusted mean difference (95% CI) p-value.
CI, confidence interval; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; SE, standard error.

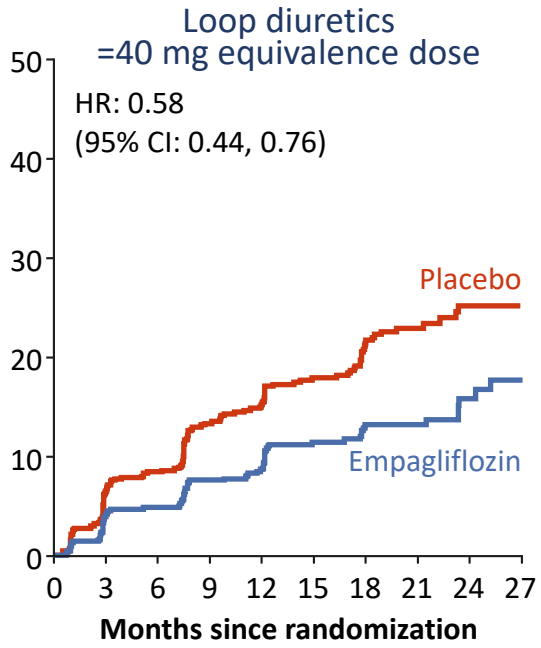
Changes in diuretic dosing (1/2)

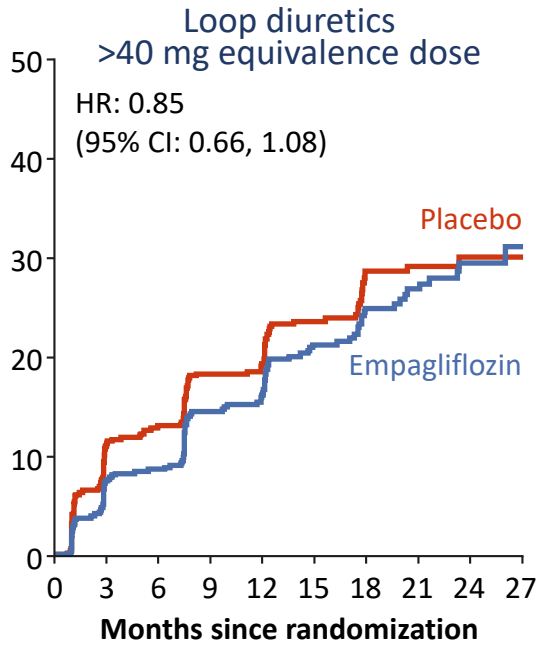
Time to diuretic initiation



Time to first diuretic dose increase







Patients at risk

Placebo	368	338	320	262	229	172	126	87	43	17	703	639	605	501	415	332	233	149	87	38	523	454	425	342	287	214	147	99	48	27
Empagliflozin	363	341	329	278	238	191	136	89	50	23	708	667	639	536	437	337	247	166	84	44	509	462	447	351	295	226	162	111	56	22

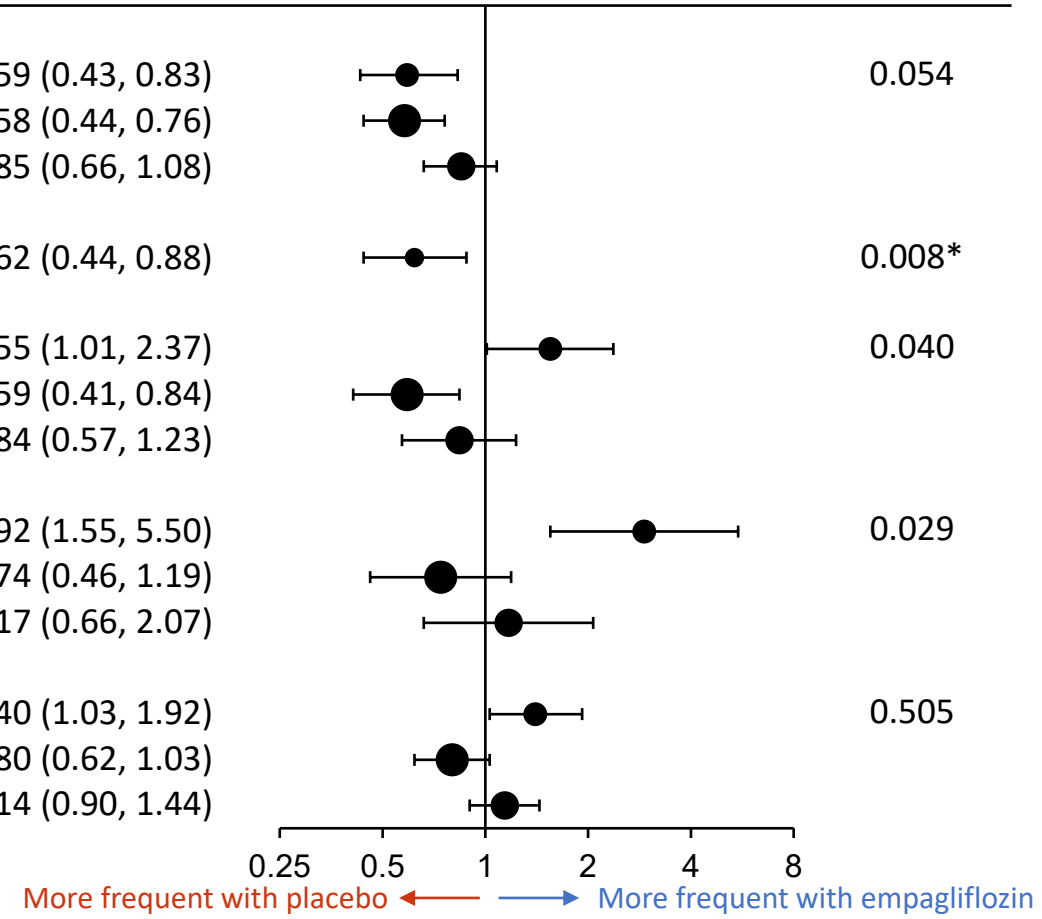
***p*-value for empagliflozin vs placebo: 0.008**

***p*-trend across diuretic dose groups: 0.054**

CI, confidence interval; HR, hazard ratio.

Changes in diuretic dosing (2/2)

Endpoint	Placebo n/N	Placebo Events/100 py	Empagliflozin n/N	Empagliflozin Events/100 py	Adjusted HR (95% CI)	*p*-trend (by dose)
Time to first diuretic dose increase						
<40 mg	86/368	19.7	58/363	12.6	0.59 (0.43, 0.83)	0.054
40 mg	141/703	17.0	85/708	9.8	0.58 (0.44, 0.76)	
>40 mg	133/523	23.4	118/509	20.0	0.85 (0.66, 1.08)	
Time to diuretic initiation						
No diuretics	77	–	54	–	0.62 (0.44, 0.88)	0.008*
Time to first discontinuation of diuretics use (any)						
<40 mg	35/368	7.5	53/363	11.7	1.55 (1.01, 2.37)	0.040
40 mg	80/703	9.4	48/708	5.4	0.59 (0.41, 0.84)	
>40 mg	57/523	8.9	47/509	7.4	0.84 (0.57, 1.23)	
Time to permanent discontinuation of diuretics use						
<40 mg	13/368	2.6	37/363	7.8	2.92 (1.55, 5.50)	0.029
40 mg	41/703	4.6	30/708	3.3	0.74 (0.46, 1.19)	
>40 mg	23/523	3.4	25/509	3.8	1.17 (0.66, 2.07)	
Time to de-escalation of diuretics (discontinuation or dose decrease)						
<40 mg	69/368	15.6	93/363	22.4	1.40 (1.03, 1.92)	0.505
40 mg	135/703	16.6	109/708	13.0	0.80 (0.62, 1.03)	
>40 mg	130/523	22.7	143/509	26.3	1.14 (0.90, 1.44)	



*p-value for empagliflozin vs placebo.
CI, confidence interval; HR, hazard ratio; py, patient-years.

Adverse events of interest

	No diuretics		<40 mg equiv.		=40 mg equiv.		>40 mg equiv.	
	Placebo	Empagliflozin	Placebo	Empagliflozin	Placebo	Empagliflozin	Placebo	Empagliflozin
Total with AEs	168 (73.7)	181 (71.5)	276 (75.2)	278 (76.6)	541 (77.0)	516 (72.9)	447 (85.8)	422 (82.9)
AKI	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	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	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	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	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	1 (0.4)	4 (1.6)	6 (1.6)	4 (1.1)	8 (1.1)	9 (1.3)	12 (2.3)	10 (2.0)
DKA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Values are n (%). Adverse events are shown up to 7 days after discontinuation of study medication.
AE, adverse event; AKI, acute kidney injury; DKA, diabetic ketoacidosis.

Discussion

- Central findings of this analysis of EMPEROR-Reduced:
  - Consistent benefit of empagliflozin on the primary endpoint of time to HHF or CV death regardless of background diuretic therapy
  - For outcomes of total HHF and time to first HHF, suggestion of potential attenuation of effect of empagliflozin among those on the highest doses of diuretics
  - Empagliflozin demonstrated a diuretic-sparing effect in EMPEROR-Reduced

Discussion

- Present findings mirror those of previous analyses of DAPA-HF[3]
  - Time to first HHF and total HHF was not evaluated in this analysis

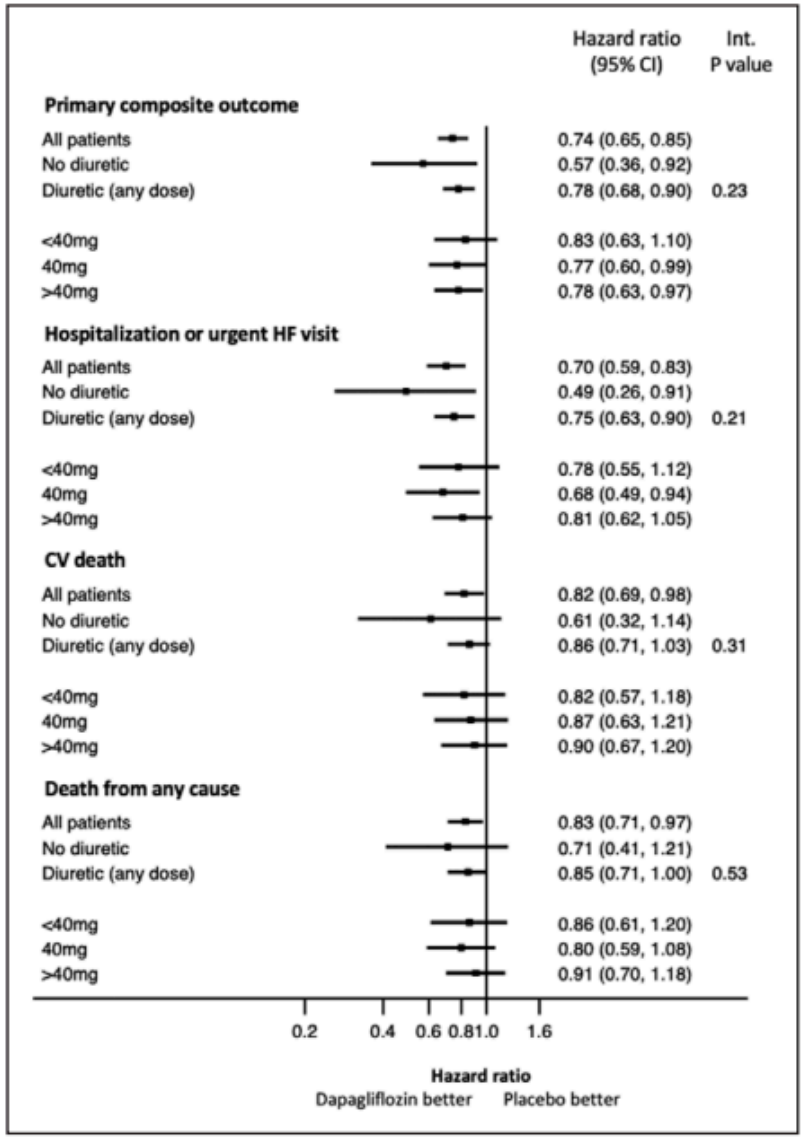


Figure 2. Forest plot of efficacy outcomes according to diuretic therapy at baseline.

Discussion

Baseline Differences

- Attenuation of effect on HF hospitalizations could reflect baseline differences between groups, with more severe stages of HF being harder to modify
- However, empagliflozin has been shown to have consistent efficacy across important subgroups in previous analyses[4-9], with no suggestion of decreased efficacy amongst patients with more advanced HF syndromes

Mechanistic Overlap

- Attenuation of effect on HF hospitalizations could reflect mechanistic overlap, with high diuretic doses dampening empagliflozin's osmotic diuretic effects
- However, previous findings have shown that combination with loop diuretics potentiates SGLT2i-associated natriuresis rather than dampens it[10]
- In addition, SGLT2 inhibitors' mechanisms of effect likely include a variety of pleiotropic effects beyond diuresis including alteration of circulating proteomics, enhancement of nutrient deprivation signaling and others[11-13]

Statistical Chance

- Analyses were post hoc and not corrected for multiplicity
- A similar attenuation not seen in DAPA-HF

Discussion

Baseline Differences

- Attenuation of effect on HF hospitalizations could reflect baseline differences between groups, with more severe stages of HF being harder to modify
- However, empagliflozin has been shown to have consistent efficacy across important subgroups in previous analyses[4-9], with no suggestion of decreased efficacy amongst patients with more advanced HF syndromes

Mechanistic Overlap

- Attenuation of effect on HF hospitalizations could reflect mechanistic overlap, with high diuretic doses dampening empagliflozin's osmotic diuretic effects
- However, previous findings have shown that combination with loop diuretics potentiates SGLT2i-associated natriuresis rather than dampens it[10]
- In addition, SGLT2 inhibitors' mechanisms of effect likely include a variety of pleiotropic effects beyond diuresis including alteration of circulating proteomics, enhancement of nutrient deprivation signaling and others[11-13]

Statistical Chance

- Analyses were post hoc and not corrected for multiplicity
- A similar attenuation not seen in DAPA-HF

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Conclusions

- In EMPEROR-Reduced, empagliflozin demonstrated a consistent effect on the primary composite outcome of hospitalization for HF or CV death, along with a comparable safety profile, regardless of baseline diuretic doses.

- We observed a trend of an attenuated effect of empagliflozin on heart failure hospitalizations amongst patients treated with the highest doses of loop diuretics – a hypothesis generating observation which requires additional evaluation.

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Supplementary Slides

Statistical Analysis

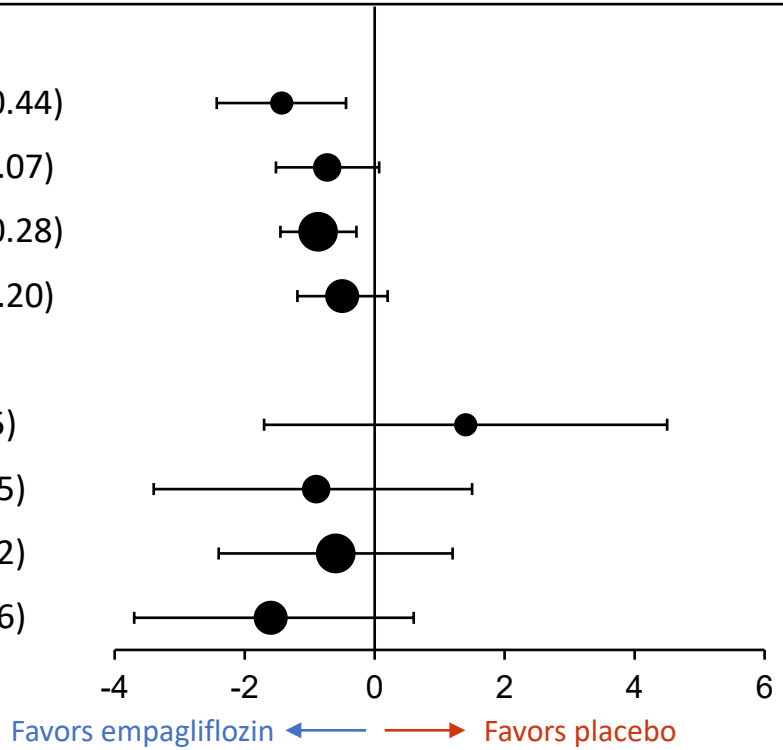
- Baseline characteristics were presented descriptively using post-hoc analyses with an ordinal regression likelihood ratio test to evaluate whether there is a linear trend across group
- Time-to-event analyses were performed using a multivariable Cox proportional hazards model to derive hazard ratio (HR) and 95% confidence interval (95% CI)
- Total (first and recurrent) hospitalisations endpoint was analysed with a joint frailty model together with cardiovascular death to obtain HR and 95% CI
- Both multivariable models included the following baseline characteristics as covariates: LVEF, age, sex, eGFR, diabetes status, and region
- Endpoints related to change in diuretics therapy were analysed as time-to-first occurrence of the event of interest
- For changes in KCCQ scores and physiologic outcomes analyses, mixed model with repeated measures (MMRM) was used. This MMRM model included age, baseline eGFR, and baseline LVEF as linear covariates and sex, region, diabetes status at baseline, visit by treatment by baseline diuretics interaction, and baseline value by visit interaction as fixed effects

Statistical Analysis

- The treatment effect of empagliflozin (compared to placebo) by diuretics therapy was assessed of each outcome, therefore the subgroup of diuretics use or dose and all necessary interactions were added to the model, where applicable.
- HRs, mean differences and estimates for slope analysis were compared across subgroups by adding p-value for trend across all subgroups.
- P-values <0.05 are described as significant, p-values and 95% confidence intervals presented here were not adjusted for multiplicity

Additional outcomes at 12 months (1/2)

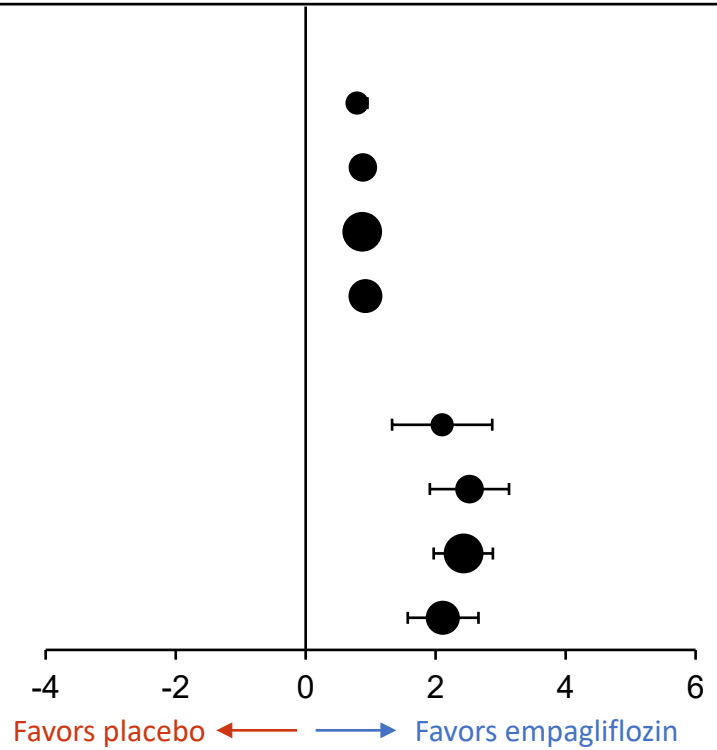
Endpoint	Adjusted mean difference to placebo (95% CI)	*p*-trend (by dose)
Body weight, kg		
No diuretics	−1.43 (−2.43, −0.44)	0.213
<40 mg	−0.73 (−1.52, 0.07)	
40 mg	−0.87 (−1.45, −0.28)	
>40 mg	−0.50 (−1.19, 0.20)	
SBP, mmHg		
No diuretics	1.4 (−1.7, 4.5)	0.184
<40 mg	−0.9 (−3.4, 1.5)	
40 mg	−0.6 (−2.4, 1.2)	
>40 mg	−1.6 (−3.7, 0.6)	



CI, confidence interval; SBP, systolic blood pressure.

Additional outcomes at 12 months (2/2)

Endpoint	Adjusted mean difference to placebo (95% CI)*	*p*-trend (by dose)
NT-proBNP, pg/mL *(adjusted mean ratio shown)*		
No diuretics	0.79 (0.67, 0.95)	0.250
<40 mg	0.88 (0.76, 1.01)	
40 mg	0.87 (0.78, 0.96)	
>40 mg	0.92 (0.81, 1.04)	
Hematocrit, %		
No diuretics	2.10 (1.33, 2.87)	0.799
<40 mg	2.52 (1.91, 3.13)	
40 mg	2.43 (1.97, 2.88)	
>40 mg	2.11 (1.57, 2.66)	



*Adjusted mean ratio to placebo (95% CI) reported for NT-proBNP; point markers may obscure error bars.
CI, confidence interval; NT-proBNP, NT-pro-BNP, N-terminal pro-B type natriuretic peptide.