Efficacy of Empagliflozin in Heart Failure Patients with a History of Peripheral Arterial Disease: Analysis from EMPEROR-Pooled

EMPEROR Heart failure studies

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BACKGROUND

- While it is well established that peripheral arterial disease (PAD) is associated with worsening major adverse cardiovascular events (CV) and major adverse limb events[1], the relationship between PAD and heart failure (HF) is less well defined.[2]
- The sodium-glucose co-transporter-2 (SGLT2) inhibitor empagliflozin has been shown to reduce HF outcomes in HF with a reduced or preserved ejection fraction (HFrEF or HFpEF).[3,4] However, its efficacy and safety in patients with HF and PAD have not been investigated.

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OBJECTIVES

- To describe the clinical features of participants with and without PAD enrolled in the EMPEROR clinical trial program and evaluate cardiorenal outcomes and the efficacy of empagliflozin in these patients.

METHODS

- EMPEROR-Pooled was a combined analysis of 9718 patients with HF across the spectrum of left ventricular ejection fraction (LVEF) from the EMPEROR-Reduced and EMPEROR-Preserved trials. Participants were randomized to 10 mg empagliflozin or placebo.
- Outcomes assessed included total hospitalizations for HF (HHF), time to first HHF or CV death, time to first HHF, time to CV death, and all-cause mortality. Additional outcomes were an extended composite outcome of time to first CV death, HHF equivalent event, or intensification of diuretic therapy along with renal endpoints including the slope of estimated glomerular filtration rate (eGFR) change and a composite renal endpoint.
- CV outcomes in this analysis were stratified by presence or absence of a history of PAD at baseline and were assessed using a Cox regression model with adjustment for prespecified baseline covariates of age, baseline eGFR, baseline LVEF, region, diabetes at baseline, sex, study, treatment, history of PAD, and treatment by history of PAD interaction.

RESULTS

- A total of 821 patients with, and 8897 patients without, PAD were included. Participants with PAD were more likely to be men (70.5% vs. 62.6%), White (83.9% vs. 72.9%), and older (72.2 ± 8.3 vs. 69.7 ± 10.5 years) than those without PAD (**Table 1**).

Table 1. Baseline characteristics from EMPEROR-Pooled by history of PAD

Baseline characteristic	Without PAD (N=8897)	With PAD (N=821)	p-value*
Men, n (%)	5570 (62.6)	579 (70.5)	<0.0001
Race, n (%)			
White	6482 (72.9)	689 (83.9)	<0.0001
Black	481 (5.4)	34 (4.1)	
Asian	1423 (16.0)	73 (8.9)	
Other	459 (5.2)	17 (2.1)	
Missing	52 (0.6)	8 (1.0)	
Age, years (SD)	69.7 (10.5)	72.2 (8.3)	<0.0001
Diabetic, n (%)	4259 (47.9)	535 (65.2)	<0.0001
LVEF %, mean (SD)	43.9 (15.3)	45.6 (14.5)	0.0014
SBP [mmHg], mean (SD)	127.8 (16.3)	131.1 (17.1)	<0.0001
eGFR [ml/min/1.73 m²], mean (SD)	61.7 (20.6)	55.6 (19.4)	<0.0001
History of hypertension, n (%)	7378 (82.9)	744 (90.6)	<0.0001
Ischemic cause of HF, n (%)	3549 (39.9)	497 (60.5)	<0.0001
History of Hypercholesterolemia, n (%)	5598 (62.9)	696 (84.8)	<0.0001
NYHA class, n (%)			
II	7088 (79.7)	595 (72.5)	<0.0001
III/IV	1806 (20.3)	225 (27.4)	
KCCQ-CSS, mean (SD)	70.9 (21.4)	66.7 (21.3)	<0.0001
Background therapies			
ACEi/ARB/ARNI	7451 (83.7)	674 (82.1)	0.22
Beta-blockers	7957 (89.4)	743 (90.5)	0.34
MRA	4551 (51.2)	354 (43.1)	<0.0001
Other antihypertensives	1861 (20.9)	247 (30.1)	<0.0001
Lipid lowering therapies	6149 (69.1)	706 (86.0)	<0.0001
Anti-platelet therapies	4296 (48.3)	531 (64.7)	<0.0001

*t-test for continuous variables and chi-squared test for categorical variables.
ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; PAD peripheral arterial disease; SBP, systolic blood pressure; SD, standard deviation.

- In participants randomized to placebo, a history of PAD was associated with an increased risk of CV outcomes when compared with those with no history of PAD. Specifically, the hazard ratios for total HHF, time to CV death, and time to all-cause mortality were higher in people with PAD. Renal outcomes were similar in participants with and without PAD (**Figure 1**).

Figure 1. Risk of CV outcomes in participants with and without PAD in the placebo population

Outcome	Without PAD n/N	Without PAD Events/100 py	With PAD n/N	With PAD Events/100 py	Hazard ratio (95% CI)	p-value
Total HHF	957/4455	–	137/403	–	1.51 (1.12, 2.03)*	0.007
Time to CV death	391/4455	4.82	55/403	7.07	1.40 (1.05, 1.87)†	0.021
Time to all-cause mortality	601/4455	7.41	92/403	11.83	1.42 (1.14, 1.78)†	0.002
Composite of CV death and time to first HHF	871/4455	11.78	101/403	14.62	1.21 (0.98, 1.49)†	0.077
Extended composite outcome‡	1465/4455	22.10	169/403	28.24	1.27 (1.08, 1.50)†	0.003
Time to first HHF	623/4455	8.42	71/403	10.28	1.18 (0.92, 1.51)†	0.20
Time to composite renal outcome	84/4455	1.32	11/403	1.86	1.25 (0.66, 2.38)†	0.49

*Based on a joint frailty model with terms for age, baseline eGFR, baseline LVEF, history of PAD, region, diabetes at baseline, sex, study. †Based on a Cox regression model with terms for age, baseline eGFR, baseline LVEF, region, diabetes at baseline, sex, study, and history of PAD. ‡CV death or HHF equivalent events or reported intensification of diuretic since last visit.
CV, cardiovascular, eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; LVEF, left ventricular ejection fraction; PAD peripheral arterial disease; py, patient-years.

- There was no excess in adverse events (AEs) with empagliflozin in people with PAD. Specifically, AEs leading to lower limb amputations were similar in both treatment groups (**Table 2**).

Table 2. AEs from EMPEROR-Pooled by history of PAD

	Without PAD		With PAD	
	Empagliflozin	Placebo	Empagliflozin	Placebo
Any AEs, %	81.5	82.9	89.2	89.1
SAEs, %	44.4	49.1	56.0	62.9
Lower limb amputations, %	0.4	0.4	2.9	3.5

AEs, adverse events; PAD, peripheral arterial disease; SAEs, serious AEs.

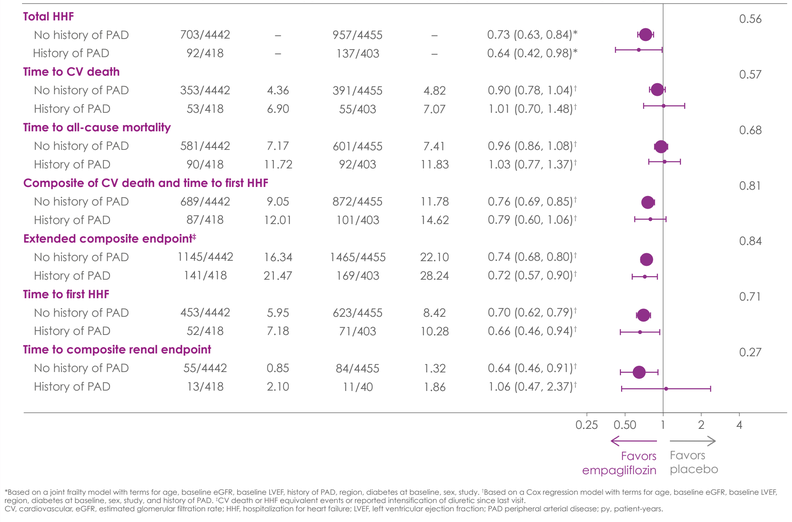
CONCLUSIONS

- Coexistent PAD in EMPEROR trial participants with HF (either HFrEF or HFpEF) is associated with a higher risk of CV outcomes compared with participants without PAD.
- While empagliflozin was efficacious in both populations, participants with PAD had a higher absolute risk reduction in total HHF events compared with those without PAD.
- There was no excess in AEs or lower limb amputations with empagliflozin in participants with PAD.

- Empagliflozin reduced the risk of total HHF (PAD: HR 0.64 [95% CI 0.42–0.98]; no PAD: HR 0.73 [95% CI 0.63–0.84]; $P_{interaction}$=0.56) in both participants with and without a history of PAD. The absolute risk reduction (ARR) for total HHF events was 6.0% amongst participants with PAD and 3.2% amongst participants without PAD. There was no significant interaction between PAD history and the efficacy of empagliflozin on CV or renal outcomes (**Figures 2** and **3**).

Figure 2. The effect of empagliflozin on CV and renal outcomes by history of PAD

Endpoint	Empagliflozin n/N	Empagliflozin Events/100 py	Placebo n/N	Placebo Events/100 py	Hazard ratio (95% CI)	Interaction p-value
Total HHF						0.56
No history of PAD	703/4442	–	957/4455	–	0.73 (0.63, 0.84)*	
History of PAD	92/418	–	137/403	–	0.64 (0.42, 0.98)*	
Time to CV death						0.57
No history of PAD	353/4442	4.36	391/4455	4.82	0.90 (0.78, 1.04)†	
History of PAD	53/418	6.90	55/403	7.07	1.01 (0.70, 1.48)†	
Time to all-cause mortality						0.68
No history of PAD	581/4442	7.17	601/4455	7.41	0.96 (0.86, 1.08)†	
History of PAD	90/418	11.72	92/403	11.83	1.03 (0.77, 1.37)†	
Composite of CV death and time to first HHF						0.81
No history of PAD	689/4442	9.05	872/4455	11.78	0.76 (0.69, 0.85)†	
History of PAD	87/418	12.01	101/403	14.62	0.79 (0.60, 1.06)†	
Extended composite endpoint‡						0.84
No history of PAD	1145/4442	16.34	1465/4455	22.10	0.74 (0.68, 0.80)†	
History of PAD	141/418	21.47	169/403	28.24	0.72 (0.57, 0.90)†	
Time to first HHF						0.71
No history of PAD	453/4442	5.95	623/4455	8.42	0.70 (0.62, 0.79)†	
History of PAD	52/418	7.18	71/403	10.28	0.66 (0.46, 0.94)†	
Time to composite renal endpoint						0.27
No history of PAD	55/4442	0.85	84/4455	1.32	0.64 (0.46, 0.91)†	
History of PAD	13/418	2.10	11/40	1.86	1.06 (0.47, 2.37)†	



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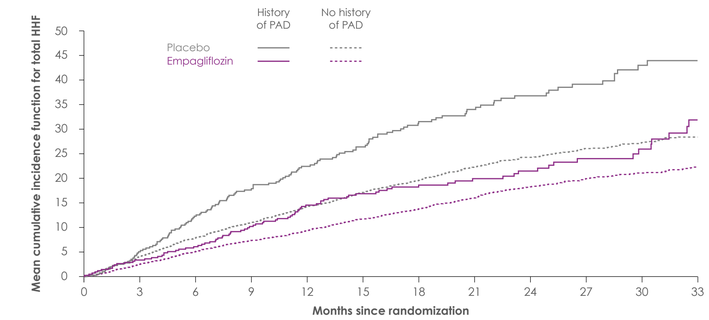
CV, cardiovascular, eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; LVEF, left ventricular ejection fraction; PAD peripheral arterial disease; py, patient-years.

Figure 3. The effect of empagliflozin on the cumulative incidence function for total HHF by history of PAD



Participants at risk, n												
History of PAD												
Placebo	403	393	382	366	342	310	264	229	186	153	107	78
Empagliflozin	418	412	398	380	361	319	254	214	176	136	101	70
No history of PAD												
Placebo	4455	4372	4281	4015	3759	3325	2726	2266	1784	1396	983	673
Empagliflozin	4442	4376	4283	4021	3739	3293	2725	2258	1780	1411	1001	698

HHF, hospitalization for heart failure; PAD, peripheral arterial disease.

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Disclosures

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Nitish K. Dhingra declares no competing interests.

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