Vascular Disease Burden, Outcomes and Benefits with Empagliflozin in Heart Failure: Insights From the EMPEROR-Reduced Trial

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ABSTRACT

Background: The presence of ischemic heart disease impacts prognosis in patients affected by heart failure and reduced ejection fraction (HFrEF). It is not well known how the extent of vascular disease impacts prognoses and responses to therapy in this setting.

Methods: In this post hoc analysis of the EMPEROR-Reduced trial, outcomes and the effects of empagliflozin, were assessed in study participants according to the extent (none vs mono[1] vs poly [$\geq$ 2] vascular bed) of vascular disease. Vascular disease was defined as investigator-reported coronary artery disease (CAD), peripheral artery disease (PAD) and cerebrovascular disease at baseline. Cox proportional-hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Incidence rates are presented per 100 person-years (py) of follow-up.

Results: Of the 3730 study participants enrolled, 1324 (35.5%) had no vascular disease, 1879 (50.4%) had monovascular disease, and 527 (14.1%) had polyvascular disease. Participants with polyvascular disease tended to be older and male and to have had histories of hypertension, diabetes and smoking. In the placebo arm, a significantly higher risk for cardiovascular death existed in those with polyvascular disease (HR 1.57, 95% CI1.02, 2.44, compared to those with no vascular disease). In adjusted analysis, the benefit of empagliflozin in cardiovascular death or hospitalization due to HF, HF hospitalization, cardiovascular death, renal composite endpoint, estimated glomerular filtration slope changes, and health status scores were seen across the 3 groups (interaction $P > 0.05$ for all) but were attenuated in those with polyvascular disease. Adverse events were higher in those with polyvascular disease, but no major differences were noted between empagliflozin or placebo assignment in the 3 groups.

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Conclusion: In patients with HFrEF, the extent of vascular disease is associated with the risk for adverse cardiovascular outcomes. Empagliflozin offers cardiovascular and renal benefits in HFrEF across the extent of vascular disease, but this benefit is attenuated in those with polyvascular disease. (*J Cardiac Fail 2023;29:1345−1354*)

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a class I guideline-directed medical therapy (GDMT) for patients with heart failure with reduced ejection fraction (HFrEF).[1-4] In both the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction) trials, dapagliflozin and empagliflozin improved the outcomes of study participants with HFrEF independent of diabetes status.[5,6] A better understanding of how GDMT reduces risk across the HF spectrum is important, including understanding the benefit of medical therapies relative to the presence and severity of risk factors causing HF or contributing to its outcome.

A dominant risk factor for HF onset and its complications is atherosclerotic cardiovascular disease. Persons with atherosclerotic vascular disease are at higher risk for poorer outcomes in general[7−13]; data are mixed with respect to whether this may be particularly the case for those with HF.[14] However, the natural history and outcomes of those with HFrEF as well as the benefit of HF therapies across the extent of vascular disease are not clearly known. It was recently reported that empagliflozin offered cardiovascular and renal benefits in persons with HFrEF, regardless of ischemic or nonischemic etiology of HF.[15] In the prior analysis, the extent of vascular disease, including presence in other vascular territories, was not considered.

In this post hoc analysis of the EMPEROR-Reduced trial, we sought to investigate how the extent of vascular disease burden affects prognosis as well as the effect of empagliflozin on cardiovascular and renal outcomes according to the extent of vascular disease in individuals with HFrEF.

Methods

Trial Design and Patient Population

The EMPEROR-Reduced trial was a randomized, double-blind, placebo-controlled trial that enrolled 3730 participants. The design and results of the trial have been published previously.[2,16] Briefly, patients with chronic HF, New York Heart Association class II−IV symptoms with left ventricular ejection fraction (LVEF) $\leq$ 40% were enrolled. To be eligible, participants had either a hospitalization due to HF within 12 months or an LVEF of $\leq$ 30% and an N-terminal pro B-type natriuretic peptide (NT-proBNP) levels of $>$ 600 pg/mL. For patients with an LVEF of 31%−35% or 36%−40%, NT-proBNP had to be $>$ 1000 pg/mL or $>$ 2500 pg/mL, respectively, for inclusion. Persons with systolic blood pressure of $<$ 100 mmHg or symptomatic hypotension or an estimated glomerular filtration rate (eGFR) $<$ 20 mL/min/1.73m^2 or requiring dialysis were excluded. Study participants were randomized (1:1) to receive once-daily empagliflozin 10 mg or placebo.

Presence, Type and Extent of Vascular Disease

Vascular disease type was defined as investigator-reported coronary artery disease (CAD), peripheral artery disease (PAD) and cerebrovascular disease at baseline. CAD was defined as history of myocardial infarction, prior revascularization, documented history of CAD, or acute coronary syndrome during the past 6 months. Cerebrovascular disease was defined as a history of stroke (ischemic or hemorrhagic) or transient ischemic attack or cerebrovascular disease other than stroke or transient ischemic attack. PAD was defined as peripheral artery occlusive disease according to the investigator`s judgment or prior lower-limb amputation. Extent of vascular disease was defined according to number of vascular beds involved: 0 (none), 1 (monovascular) or $\geq$ 2 (polyvascular) disease.

Outcomes

Multiple cardiorenal endpoints were studied across the 3 groups of patients based on the extent of vascular disease burden at baseline, including (1) time to cardiovascular death or HF hospitalization; (2) time to HF hospitalization; (3) time to cardiovascular death; (4) changes in eGFR slope; (5) renal composite endpoint; and (6) changes in health status. The renal composite endpoint was defined as the need for chronic dialysis or renal transplantation or a $\geq$ 40% decrease in eGFR (by the Chronic Kidney Disease Epidemiology Collaboration formula) or a sustained eGFR $<$ 15 mL/min/1.73m^2 (if the baseline eGFR was $\geq$ 30) or $<$ 10 mL/min/1.73m^2 (if the baseline eGFR was $<$ 30 mL/min/1.73m^2). Health status was assessed using Kansas City Cardiomyopathy Questionnaire clinical summary score change from baseline to weeks 12, 32 and 52.

Statistical Analysis

Continuous variables are reported as mean (standard deviation) or median (interquartile ranges), and categorical variables are reported as frequencies and proportions. Baseline patients' characteristics were stratified according to extent of vascular disease. Incidence rates for each outcome of interest are presented per 100 person-years (py) of follow-up. To determine the natural history of patients with HFrEF with respect to vascular disease, incidence rates for (1) time to cardiovascular death or HF hospitalization; (2) time to HF hospitalization; (3) time to cardiovascular death; and (4) renal composite endpoint were assessed in the placebo arm by using Cox proportional hazards models. Results were adjusted for smoking, age, sex, region, baseline eGFR, body mass index, diabetes status, medical therapy, systolic blood pressure, ejection fraction, New York Heart Association class, baseline log (NT-proBNP), history of HF hospitalization, hypertension, and atrial fibrillation. To assess the effects of empagliflozin, outcomes according to the extent of vascular involvement were evaluated using Cox proportional hazards models. Hazard ratios (HRs), 95% confidence intervals (CIs), and 2-sided *P* values were calculated. The HRs were adjusted for age, sex, region, ejection fraction, diabetes status, and baseline eGFR. Between-group differences in the chronic slope of change in eGFRs were analyzed using a random intercept random slope model. The difference between treatment groups in the changes in Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score from baseline to weeks 12, 32 and 52 were assessed using a mixed model repeated measures analysis with the same covariates as for Cox proportional hazard models. To evaluate whether there was a linear trend across the groups of vascular disease, we used the trend test to investigate a continuous category rank according to treatment interaction. Stroke and acute myocardial infarction events were also assessed in the various groups, but due to the small number of events in subgroups, only descriptive statistics were performed . Safety events up to 7 days after end of treatment were also compared among the various groups. Lower-limb amputations were compared until completion of the trial. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA). A *P* value of < 0.05 was considered significant.

Results

Baseline Characteristics

Of the 3730 study participants, 1324 (35.5%) had no vascular disease, 1879 (50.4%) had monovascular disease, and 527 (14.1%) had polyvascular disease. The distribution and overlap of the presence of CAD, PAD and cerebrovascular disease are shown in Fig. 1. CAD was approximately 4 times more common than cerebrovascular disease, which, in turn, was approximately twice as common as PAD. Almost 80% of the patients with monovascular disease had CAD. Table 1 shows the baseline characteristics of the study's participants stratified according to the extent of vascular disease. Those with polyvascular disease were more likely to be older (69.6 vs 68.1 vs 64.0 years), to be male (82% vs 80% vs 68%) and to have histories of diabetes (60% vs 53% vs 41%), hypertension (84% vs 76% vs 63%) and smoking (64% vs 57% vs 47%) than those with monovascular and no vascular disease, respectively. There was no difference in LVEF (27.4% vs 27.6% vs 27.3%) or NT-proBNP levels (median 2077 vs 1842 vs 1938 pg/mL) among the 3 groups.

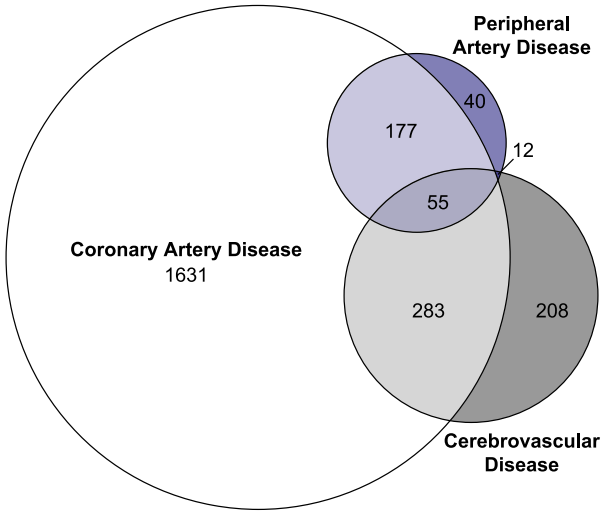

Fig. 1. Venn diagram for the presence of coronary artery disease, peripheral artery disease and cerebrovascular disease at baseline.

Outcomes in the Placebo Arm

The rate of cardiovascular death or HF hospitalization (20.2 vs 20.8 vs 24.9 events/100 py, respectively; $P = 0.87$), HF hospitalization (15.5 vs 14.9 vs 18.5 events/100 py, respectively; $P = 0.92$), cardiovascular death (7.5 vs 7.9 vs 11.9 events/100 py, respectively; $P = 0.06$), and renal composite outcome (2.9 vs 3.0 vs 4.1 events/100 py, respectively; $P = 0.80$) in patients with no, mono-, or polyvascular disease were not statistically significantly different; however, they were numerically higher in patients with polyvascular disease. Patients with polyvascular

Table 1. Baseline patient characteristics according to the extent of vascular disease

Variable	No Vascular Disease (n = 1324)	Monovascular (n = 1879)	Polyvascular (n = 527)
Age, yearsr	64 (12)	68 (10)	70 (9)
Female, n (%)	418 (31.6)	383 (20.4)	92 (17.5)
White	850 (64.2)	1372 (73.0)	407 (77.2)
Black	142 (10.7)	92 (4.9)	23 (4.4)
Asian	266 (20.1)	330 (17.6)	76 (14.4)
Other or missing	54 (4.1)	51 (2.7)	21 (4.0)
North America	111 (8.4)	223 (11.9)	91 (17.3)
Latin America	605 (45.7)	562 (29.9)	119 (22.6)
Europe	339 (25.6)	768 (40.9)	246 (46.7)
Asia	202 (15.3)	330 (17.6)	63 (12.0)
Other	67 (5.1)	51 (2.7)	8 (1.5)
NYHA class I/II	1028 (77.6)	1413 (75.2)	359 (68.1)
NYHA class III/IV	296 (22.4)	466 (24.8)	168 (31.9)
Body mass index (kg/m^2)	28.0 (5.8)	27.8 (5.2)	27.9 (5.2)
Ex-smoker	492 (37)	893 (48)	268 (51)
Current smoker	131 (10)	185 (10)	71 (14)
Heart rate, beats/min	73 (12)	70 (11)	71 (12)
Systolic blood pressure, mmHg	121.1 (15.7)	122.0 (15.5)	124 (16)
Diabetes (%)	547 (41.3)	991 (52.7)	308 (60.3)
Coronary artery disease (%)	0	1631 (86.8)	515 (97.7)
Peripheral arterial disease (%)	0	40(2.1)	244 (46.3)
Cerebrovascular disease (%)	0	208 (11.1)	350 (66.4)
History of myocardial infarction	0	1239 (65.9)	384 (72.9)
History of PCI or CABG	0	1150 (61.2)	373 (70.8)
Ejection fraction (%)	27.3 (6.1)	27.6 (5.9)	27.4 (6.4)
Median NT-proBNP-pg/mL	1938 (1144–3466)	1843 (1061–3274)	2077 (1292–4351)
Atrial fibrillation	307 (23.2)	316 (16.8)	110 (20.9)
Hypertension	836 (63.1)	1422 (75.7)	440 (83.5)
eGFR mean, mL/min/1.73 m^2	66.6 (22.7)	60.4 (20.8)	56.3 (19.5)
eGFR $<$ 60 mL/min/1.73 m^2; n (%)	537 (40.6)	960 (51.1)	305 (57)
Implantable defibrillator	272 (20.5)	693 (36.9)	206 (39.1)
ACEi/ARB	958 (72.4)	1299 (69.1)	343 (65.1)
ARNI	240 (18.1)	379 (20.2)	108 (20.5)
Loop diuretic	1128 (85.2)	1574 (83.8)	448 (85.0)
Mineralocorticoid receptor antagonist	1007 (76.1)	1316 (70.0)	338 (64.1)
Beta-blocker	1240 (93.7)	1785 (95.0)	508 (96.4)

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; NT-proBNP, N terminal pro brain natriuretic peptide; PCI, percutaneous coronary intervention.

disease had significantly higher risks of cardiovascular death than those with no vascular disease (HR 1.57; 95%CI1.02, 2.44; $P = 0.04$) (Table 2). The mean slope of change in eGFR was -2.34, -2.29 and -2.11 mL/min/1.73 m^2/year among patients with no, mono-, and polyvascular disease, respectively.

Effect of Empagliflozin on Outcomes

The effect of empagliflozin on cardiovascular death or HF hospitalization was seen across the spectrum of baseline vascular disease (no vascular disease HR 0.63 [0.49–0.81]; monovascular disease HR

Table 2. Outcomes according to the extent of vascular disease at baseline in the placebo group

	Polyvascular Disease (n = 250)	Monovascular Disease (n = 928)	No Vascular Disease (n = 689)	*P* trend*
Time to First Event of CV Death or HHF				
Incidence rates per 100 py	24.9 (19.4, 31.0)	20.8 (18.1, 23.6)	20.2 (17.1, 23.5)	0.65
Comparison vs no VD (HR and 95% CI)	1.06 (0.78–1.45)	1.06 (0.85–1.32)	-	
Time to First HHF				
Incidence rates per 100 py	18.5 (13.8, 23.8)	14.9 (12.7, 17.4)	15.5 (12.8,18.4)	0.71
Comparison vs no VD (HR and 95% CI)	0.94 (0.66, 1.35)	0.96 (0.74, 1.23)	-	
Time to CV Death				
Incidence rates per 100 py	11.9 (8.4, 15.9)	7.86 (6.4, 9.5)	7.47 (5.8, 9.4)	0.06
Comparison vs no VD (HR and 95% CI)	1.57 (1.02, 2.44)	1.11 (0.79,1.55)	-	
Time to First Renal Composite Outcome				
Incidence rates per 100 py	4.07 (2.0, 6.9)	2.99 (2.0, 4.2)	2.85 (1.7, 4.3)	0.60
Comparison vs no VD (HR and 95% CI)	1.31 (0.55–3.11)	1.03 (0.55–1.93)	-	

CI, confidence interval; CV, cardiovascular; HHF, heart failure hospitalization; HR, hazard ratio; VD, vascular disease.
*P value from Cox proportional hazards test for a linear trend of the outcome across the groups of vascular disease.

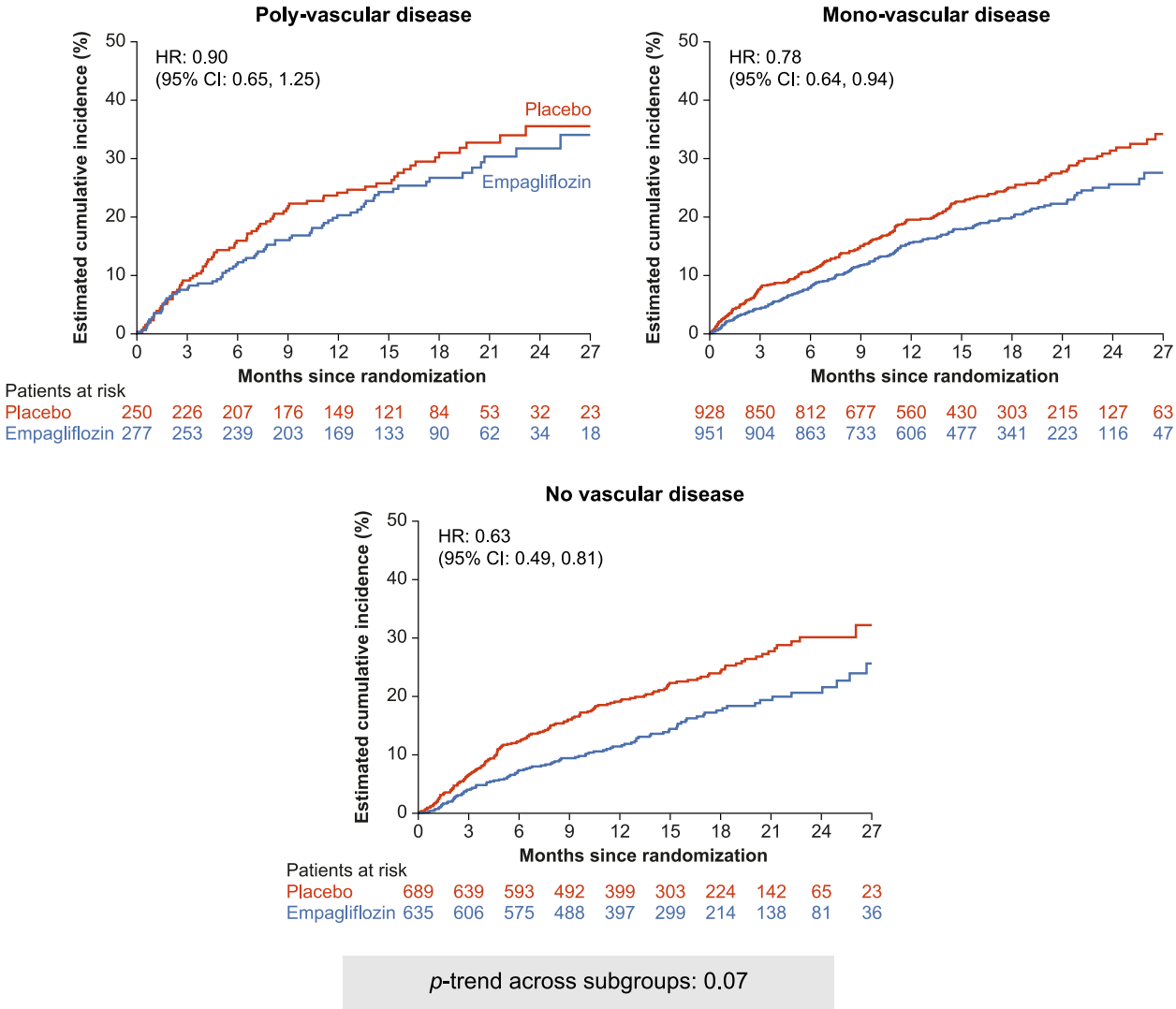

Fig. 2. Kaplan-Meier curve regarding the effect of empagliflozin on hospitalization due to heart failure or cardiovascular death, according to extent of baseline vascular disease.

0.78 [0.64–0.94]; polyvascular disease HR = 0.90 [0.65–1.25]; *P* trend = 0.07), with an attenuated effect in patients with polyvascular disease (Fig. 2). The effects of empagliflozin compared with placebo on other outcomes are shown in Fig. 3 and Table 3.

Stroke and Acute Myocardial Infarction

The incidence of stroke events was higher in the group with polyvascular disease (total: 18 [3.4%]; placebo = 8 [3.2%]; empagliflozin = 10 [3.6%]) compared with those with monovascular disease (total: 38 [2.0%]; placebo = 20 [2.2%], empagliflozin = 18 [1.9%]) and no vascular disease (total: 19 [1.4%]; placebo = 7 [1.0%]; empagliflozin = 12 [1.9%]). Similarly, the incidence of acute myocardial infarction events was higher in those with polyvascular disease (total: 12 [2.3%]; placebo = 3 [1.2%]; empagliflozin = 9 [3.2%]) compared with those with monovascular disease (total: 21 [1.1%]; placebo = 12 [1.3%], empagliflozin = 9 [0.9%]) and no vascular disease (total: 6 [0.5%]; placebo = 5 [0.7%]; empagliflozin = 1 [0.2%]).

Safety

The frequencies of severe adverse events were similar in patients receiving empagliflozin vs placebo in the group with polyvascular disease (33.2% vs 34.9%), monovascular disease (24.8% vs 27.1%) and no vascular disease (20.6% vs 23.8%). In the group with polyvascular disease, there were 9 (1.7%) lower-limb amputations, of which 6 (2.2%) occurred in the empagliflozin group and 3 (1.2%) in the placebo group. In the group with monovascular disease, there were 11 (0.6%) lower-limb amputations, of which 7 (0.7%) occurred in the empagliflozin group and 4 (0.4%) in the placebo group. In patients with no vascular disease, there were 3

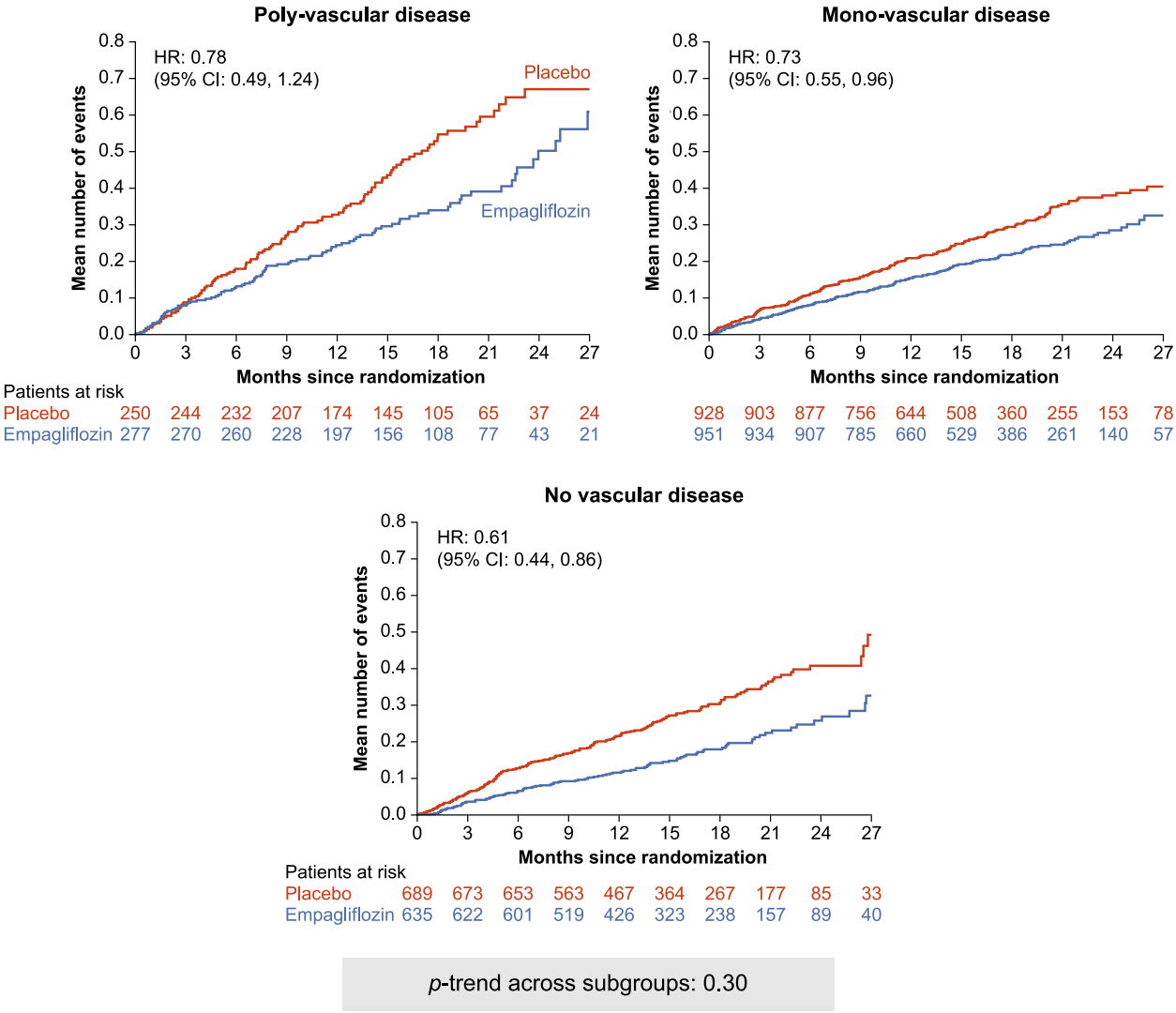

Fig. 3. Kaplan-Meier curve regarding the effect of empagliflozin on total hospitalizations due to heart failure according to extent of baseline vascular disease.

(0.2%) lower-limb amputations, all of which occurred in the placebo group.

Discussion

In this analysis of the EMPEROR-Reduced trial, we report several key findings. Those with polyvascular disease were generally at higher risk and had incidence rates of cardiovascular death that were statistically significantly higher in study participants with polyvascular disease compared to those with no vascular disease. The beneficial effects of empagliflozin on cardiovascular, renal and health-status outcomes were seen across the spectrum of baseline vascular disease. No statistical interaction was present; however, the effect of empagliflozin was numerically smaller in those with polyvascular disease. These results provide new insights regarding the impact of the extent of baseline vascular disease on prognosis and response to therapy in patients with HFrEF.

Our results emphasize the importance of polyvascular disease as a significant risk factor for patients with HFrEF. Previous studies have shown that polyvascular disease is associated with increased risk, especially in patients with diabetes and baseline atherosclerotic cardiovascular disease, but this was not well documented for patients with HFrEF.[10–13] It is also consistent with the American College of Cardiology/American Heart Association guidelines, which have identified polyvascular disease as a marker for very high cardiovascular risk.[17] Interestingly, monovascular disease did not confer a substantially higher risk of adverse outcomes compared with no vascular disease. This is similar to the results observed in the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose) trial.

Table 3. Effect of empagliflozin on outcomes according to extent of baseline vascular disease

	Empagliflozin (n = 1863) n/N (%)	Placebo (n = 1867) n/N (%)	HR (95% CI)/slope difference (95% CI)	*P* trend*
Time to First Event of CV Death or HHF				
No vascular	102/635 (16.1)	161/689 (23.4)	0.63 (0.49–0.81)	0.07
Monovascular	186/951 (19.6)	226/928 (24.4)	0.78 (0.64–0.94)	
Polyvascular	73/277 (26.4)	75/250 (30)	0.90 (0.65–1.25)	
First and Recurrent HHF				
No vascular	106/635	191/689	0.61 (0.44–0.86)	0.30
Monovascular	191/951	247/928	0.73 (0.55–0.96)	
Polyvascular	91/277	115/250	0.78 (0.49–1.24)	
Time to First HHF				
No vascular	72/635 (11.3)	124/689 (18.0)	0.58 (0.43–0.77)	0.20
Monovascular	122/951 (12.8)	163/928 (17.6)	0.71 (0.56–0.90)	
Polyvascular	52/277 (18.8)	55/250 (22.0)	0.89 (0.61–1.30)	
Time to First Renal Composite Outcome				
No vascular	9/635 (1.4)	20/689 (2.9)	0.48 (0.22–1.05)	0.94
Monovascular	15/951 (1.6)	27/928 (2.9)	0.52 (0.27–0.97)	
Polyvascular	6/277 (2.2)	11/250 (4.4)	0.48 (0.18–1.31)	
Mean Slope of Change in eGFR: mL/min/1.73 m^2/year				
No vascular	−0.44	−2.34	1.90 (0.82–2.97)	0.26
Monovascular	−0.29	−2.29	2.00 (1.12–2.88)	
Polyvascular	−1.70	−2.11	0.41 (−1.29–2.10)	
Time to CV Death				
No vascular	52/635 (8.2)	66/689 (9.6)	0.84 (0.58–1.21)	0.81
Monovascular	97/951 (10.2)	95/928 (10.2)	0.99 (0.74–1.31)	
Polyvascular	38/277 (13.7)	41/250 (16.4)	0.87 (0.56–1.35)	
Change in KCCQ-CSS	Change from baseline empagliflozin group	Change from baseline placebo group	Difference in change (95% CI)	
12 weeks				
No vascular	5.17 (0.61)	2.75 (0.60)	2.42 (0.76–4.08)	0.45
Monovascular	5.83 (0.50)	3.80 (0.51)	2.03 (0.65–3.42)	
Polyvascular	3.97 (0.93)	3.54 (0.98)	0.43 (−2.20–3.06)	
32 weeks				
No vascular	6.15 (0.66)	3.79 (0.65)	2.37 (0.57–4.17)	0.19
Monovascular	5.22 (0.53)	3.93 (0.55)	1.29 (−0.21–2.79)	
Polyvascular	3.32 (1.01)	4.07 (1.07)	−0.75 (−3.62–2.12)	
52 Weeks				
No vascular	6.03 (0.77)	3.78 (0.74)	2.25 (0.18–4.33)	0.18
Monovascular	5.86 (0.61)	3.89 (0.63)	1.98 (0.26–3.69)	
Polyvascular	4.12 (1.16)	5.36 (1.22)	−1.24 (−4.53–2.06)	

CI, confidence interval; CV, cardiovascular; eGFR,estimated glomerular filtration rate; HHF, heart failure hospitalization; HR, hazard ratios; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score.

**P* value testing for a linear trend of the treatment effect across the groups of patients with vascular disease.

Empagliflozin reduces mortality rates in patients with type 2 diabetes who are at high cardiovascular risk; involvement of ≥ 2 vs 1 vascular bed approximately doubled the rates of hospitalization due to HF.[13] It is also important to highlight that previous studies have shown that polyvascular disease is independently associated with cardiovascular events in patients with heart failure with preserved ejection fraction (HFpEF) as well.[18]

Previous post hoc analyses of HF trials have generally assessed the effect modification of GDMT by ischemic vs nonischemic etiology.[9,19] All the foundational HF therapies, such as beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid antagonists, and sacubitril/valsartan, have shown no evidence of treatment heterogeneity based on the etiology of HF. Moreover, the recent post hoc analysis of DAPA-HF, also showed improved cardiovascular outcomes and quality of life, regardless of the etiology of HFrEF.[19] Our results validate these findings and further extend the observations that empagliflozin has beneficial effects on cardiovascular and renal outcomes and quality of life across the extent of vascular disease, but they were, nevertheless, attenuated in those with polyvascular disease. This is in contrast to lipid-lowering drugs, where the beneficial effect is generally higher in patients with polyvascular disease than in those with monovacular or no vascular disease.[20] The attenuation of effect on patients with HFrEF and polyvascular disease may or may not be seen in patients with HFpEF; further studies of this possibility are needed.

It was recently reported that benefits of empagliflozin in the EMPEROR-Reduced trial were observed, regardless of the etiology of HFrEF (ischemic vs

nonischemic).[15] As a natural extension of this initial finding, we wished to evaluate whether the presence of extracardiac vascular disease modified background risk for cardiac and renal events or reduced response to empagliflozin. This is important, because the increased burden of vascular disease not only increases risk for more severe coronary artery disease itself, it also raises the potential for common underlying mechanisms of cardiac and renal complications.[21–23] Thus, individuals with polyvascular disease may require consideration for study in clinical trials and better understanding of existing GDMT for their care. Our results establish the graded risk that exists between the presence and extent of vascular disease in patients with HFrEF as well in other patients. Also, it is important that clinicians explore the presence of extracardiac vascular disease in patients with HFrEF, even if the classic symptoms are not evident; they may be masked by salient functional limitations due to dyspnea.

Limitations

There are some limitations in this study that need to be considered. Because of the post hoc nature of this analysis, these results should be considered exploratory, and due to the relatively lower number of patients in the polyvascular group, the estimates may be underpowered. The numbers of patients with PAD were much lower than those with CAD. Last, these results were not adjusted for multiplicity testing.

Conclusion

In conclusion, the risk of adverse clinical outcomes is higher in patients with HFrEF and with polyvascular disease than in patients who had no vascular disease, whereas the incidence rate is comparable among patients with monovascular disease and no history of vascular disease. Empagliflozin offers cardiovascular and renal benefits in patients with HFrEF across the extent of baseline vascular disease, but these benefits seem to be attenuated in those with polyvascular disease.

Lay Summary

In this post hoc analysis of the EMPEROR-Reduced trial, outcomes and the effect of empagliflozin were assessed in study participants according to the extent (none vs mono[1] vs poly [≥ 2] vascular bed) of vascular disease. Of the 3730 study participants enrolled, 1324 (35.5%) had no, 1879 (50.4%) had mono, and 527 (14.1%) had polyvascular disease. Incidence rates of cardiovascular death were significantly higher in patients with polyvascular disease compared to those with no vascular disease. The beneficial effects of empagliflozin were seen across the spectrum of baseline vascular disease; however, the effect of empagliflozin was numerically smaller in those with polyvascular disease.

Data Transparency Statement

To ensure independent interpretation of clinical study results and enable authors to fulfill their roles and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data after publication of the primary manuscript and secondary analyses in peer-reviewed journals and regulatory and reimbursement activities are completed, normally within 1 year after the marketing application has been granted by major regulatory authorities. Researchers should use the https://vivli.org/link to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.

Javed Butler.

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References

1. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995–2008.
2. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al., EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with Empagliflozin in heart failure. N Engl J Med 2020;383:1413–24. https://doi.org/10.1056/NEJMoa2022190.
3. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al., SOLOIST-WHF Trial Investigators. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med 2021;384:117–28. https://doi.org/10.1056/NEJMoa2030183.
4. Butler J, Usman MS, Khan MS, Greene SJ, Friede T, Vaduganathan M, et al. Efficacy and safety of SGLT2 inhibitors in heart failure: systematic review and meta-analysis. ESC Heart Fail 2020;7:3298–309. https://doi.org/10.1002/ehf2.13169.
5. Anker SD, Butler J, Filippatos G, Khan MS, Marx N, Lam CSP, et al. Effect of empagliflozin on cardiovascular and renal outcomes in patients with heart failure by baseline diabetes status: results from the EMPEROR-Reduced Trial. Circulation 2021;143:337–49. https://doi.org/10.1161/CIRCULATIONAHA.120.051824.
6. Petrie MC, Verma S, Docherty KF, Inzucchi SE, Anand I, Belohlávek J, et al. Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes. JAMA 2020;323:1353–68. https://doi.org/10.1001/jama.2020.1906.
7. Frazier CG, Alexander KP, Newby LK, Anderson S, Iverson E, Packer M, et al. Associations of gender and etiology with outcomes in heart failure with systolic dysfunction. a pooled analysis of 5 randomized control trials. J Am Coll Cardiol 2007;49:1450–8.
8. Martínez-Sellés M, Doughty RN, Poppe K, Whalley GA, Earle N, Tribouilloy C, et al. Gender and survival in patients with heart failure: interactions with diabetes and aetiology: results from the MAGGIC individual patient meta-analysis. Eur J Heart Fail 2012;14:473–9.
9. Balmforth C, Simpson J, Shen L, Jhund PS, Lefkowitz M, Rizkala AR, et al. Outcomes and effect of treatment according to etiology in HFrEF: an analysis of PARADIGM-HF. JACC Hear Fail 2019;7:457–65.
10. Bonaca MP, Gutierrez JA, Cannon C, Giugliano R, Blazing M, Park JG, et al. Polyvascular disease, type 2 diabetes, and long-term vascular risk: a secondary analysis of the IMPROVE-IT trial. Lancet Diabetes Endocrinol 2018;6:934–43.
11. Gutierrez JA, Scirica BM, Bonaca MP, Steg PG, Mosenzon O, Hirshberg B, et al. Prevalence and outcomes of polyvascular (coronary, peripheral, or cerebrovascular) disease in patients with diabetes mellitus (from the SAVOR-TIMI 53 trial). Am J Cardiol 2019;123:145–52.
12. Verma S, Bhatt DL, Bain SC, Buse JB, Mann JFE, Marso SP, et al. Effect of liraglutide on cardiovascular events in patients with type 2 diabetes mellitus and polyvascular disease: results of the LEADER trial. Circulation 2018;137:2179–83.
13. Verma S, Mazer CD, Inzucchi SE, Wanner C, Ofstad AP, Johansen OE, et al. Impact of polyvascular disease with and without coexistent kidney dysfunction on cardiovascular outcomes in diabetes: a post hoc analysis of EMPA-REG OUTCOME. Diabetes Obes Metab 2021;23(5):1173–81. https://doi.org/10.1111/dom.14326.
14. Khan H, Kalogeropoulos AP, Zannad F, Marti CN, Wilson PW, Georgiopoulou VV, et al., Health ABC Study. Incident heart failure in relation to vascular disease: insights from the Health, Aging, and Body Composition study. Eur J Heart Fail 2014;16:526–34. https://doi.org/10.1002/ejhf.69.
15. Khan MS, Butler J, Anker SD, Filippatos G, Ferreira JP, Pocock SJ, et al. Impact of empagliflozin in heart failure with reduced ejection fraction in patients with ischemic versus nonischemic cause. J Am Heart Assoc 2022: e027652. https://doi.org/10.1161/JAHA.122.027652. Epub ahead of print.
16. Packer M, Butler J, Filippatos GS, Jamal W, Salsali A, Schnee J, et al., EMPEROR-Reduced Trial committees and investigators. Evaluation of the effect of sodium-glucose co-transporter 2 inhibition with empagliflozin

on morbidity and mortality of patients with chronic heart failure and a reduced ejection fraction: rationale for and design of the EMPEROR-Reduced trial. Eur J Heart Fail 2019;21:1270–8. https://doi.org/10.1002/ejhf.1536.
17. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, RS, Blumenthal RS, et al. 2018 guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. J Am Coll Cardiol 2019;73:e285–350.
18. Fujisue K, Tokitsu T, Yamamoto E, Sueta D, Takae M, Nishihara T, et al. Prognostic significance of polyvascular disease in heart failure with preserved left ventricular ejection fraction. Medicine (Baltimore) 2019;98:e15959.
19. Butt JH, Nicolau JC, Verma S, Docherty KF, Petrie MC, Inzucchi SE, et al. Efficacy and safety of dapagliflozin according to aetiology in heart failure with reduced ejection fraction: insights from the DAPA-HF trial. Eur J Heart Fail 2021;23(4):601–13. https://doi.org/10.1002/ejhf.2124.
20. Ikhalil M, Kuzemczak M, Whitehead N, Kavvouras C, Džavík V. Meta-analysis of intensive lipid-lowering therapy in patients with polyvascular disease. J Am Heart Assoc 2021;10:e017948.
21. Bauersachs R, Zeymer U, Brière JB, Marre C, Bowrin K, Huelsebeck M. Burden of coronary artery disease and peripheral artery disease: a literature review. Cardiovasc Ther 2019:8295054. https://doi.org/10.1155/2019/8295054.
22. Samsky MD, Hellkamp A, Hiatt WR, Fowkes FGR, Baumgartner I, Berger JS, et al. Association of heart failure with outcomes among patients with peripheral artery disease: insights from EUCLID. J Am Heart Assoc 2021;10:e018684. https://doi.org/10.1161/JAHA.120.018684.
23. Garimella PS, Hirsch AT. Peripheral artery disease and chronic kidney disease: clinical synergy to improve outcomes. Adv Chronic Kidney Dis 2014;21:460–71. https://doi.org/10.1053/j.ackd.2014.07.005.