Received: 7 September 2020 | Revised: 14 January 2021 | Accepted: 23 January 2021

DOI: 10.1111/dom.14326

ORIGINAL ARTICLE

WILEY

Impact of polyvascular disease with and without co-existent kidney dysfunction on cardiovascular outcomes in diabetes: A post hoc analysis of EMPA-REG OUTCOME

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Funding information
The EMPA-REG OUTCOME trial was sponsored by the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance.

Abstract

Aim: To determine the relationship between polyvascular disease and risk of hospitalization for heart failure (HHF) and cardiovascular (CV) death in the EMPA-REG OUTCOME population, and the relationship of kidney dysfunction co-existent with polyvascular disease on CV/heart failure (HF) outcomes.

Materials and Methods: Patients with type 2 diabetes and atherosclerotic CV (ASCVD) received empagliflozin 10, 25 mg or placebo. Post hoc, subgroups were analyzed by one versus two or more vascular beds, and the estimated glomerular filtration rate ([eGFR] < vs. ≥60 mL/min/1.73 m^2) at baseline. The empagliflozin arms were pooled. Time to CV death, HHF, CV death (excluding fatal stroke) or HHF, all-cause mortality (ACM) and 3-point major adverse CV events (3P-MACE) were assessed using multivariable Cox regression models.

Results: Baseline characteristics (N = 6959) within subgroups were balanced between treatment groups. In the placebo group, two or more versus one vascular bed increased HHF risk (1.59 [95% confidence interval 1.02, 2.49]), CV death (2.17 [1.52, 3.09]), CV death/HHF (1.79 [1.32, 2.43]), ACM (1.95 [1.44, 2.64]) and 3P-MACE (1.76 [1.36, 2.27]). Hazard ratios for those with polyvascular disease/kidney dysfunction (vs. 1 vascular bed/eGFR ≥60 mL/min/1.73 m^2) were HHF 2.80 (1.46, 5.36), CV death 3.10 (1.87, 5.13), CV death/HHF 2.71 (1.74, 4.23), ACM 2.59 (1.67, 4.02) and 3P-MACE 2.62 (1.82, 3.77). Empagliflozin reduced the risk of all outcomes across subgroups.

Conclusions: Polyvascular disease with/without kidney dysfunction markedly increases the risk of HF/CV events. Empagliflozin consistently reduces risk, regardless of vascular bed and kidney function status.

KEYWORDS
CV outcomes, empagliflozin, kidney dysfunction, kidney outcomes, polyvascular disease, type 2 diabetes

1 | INTRODUCTION

Individuals with clinically manifest atherosclerotic cardiovascular disease (ASCVD) are at high or very high risk of recurrent cardiovascular (CV) events.[1] International guidelines[1–6] for the prevention of CV disease use different clinical criteria to identify those patients who are at very high risk of recurrent CV events.[1] These guidelines include those of the American College of Cardiology (ACC)/American Heart Association (AHA).[4] Polyvascular disease and kidney dysfunction (reflected by low estimated glomerular filtration rate [eGFR]) place a patient at very high risk of recurrent CV events. Separately, they have both been shown to perform as well as ACC/AHA 'very high risk' criteria in identifying patients at risk.[1] Previous analyses of contemporary CV outcomes trials have shown that polyvascular disease is also a marker of enhanced CV risk in patients with type 2 diabetes (T2D).[7–9] However, these trials did not consider concomitant kidney dysfunction. Furthermore, whether the risk of heart failure (HF) outcomes is influenced by polyvascular disease and co-existing kidney dysfunction is not fully established.

Empagliflozin is a sodium-glucose co-transporter-2 (SGLT2) inhibitor approved as a glucose-lowering agent for patients with T2D. In the EMPA-REG OUTCOME trial empagliflozin, given in addition to standard of care and compared with placebo, reduced the risk of CV death by 38% and hospitalization for heart failure (HHF) by 35% in patients with T2D and established ASCVD.[10–12]

The primary aim of the current analysis was to investigate, post hoc, the association of polyvascular disease (defined as coronary artery disease [CAD], peripheral artery disease [PAD] and cerebrovascular disease), with or without co-existing kidney dysfunction, with the risk of HF and CV outcomes as well as mortality in patients from the EMPA-REG OUTCOME trial. Our secondary objective was to explore the treatment effect of empagliflozin across the spectrum of baseline polyvascular disease and kidney dysfunction.

2 | MATERIALS AND METHODS

2.1 | Study design

The EMPA-REG OUTCOME trial (ClinicalTrials.gov: NCT01131676) was a randomized, double-blind, placebo-controlled trial, as described previously.[13] The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines and was approved by local authorities. An independent ethics committee or institutional review board approved the clinical protocol at each participating centre. All patients provided written informed consent before study entry.

Patients in the trial were adults (aged ≥18 years) with T2D (HbA1c 7.0%–9.0% for treatment-naïve patients and 7.0%–10.0% for patients on stable glucose-lowering therapy) and established CV disease.[12,13] For inclusion, patients had to have an eGFR of 30 mL/min/1.73 m^2 or higher (calculated with the Modification of Diet in Renal Disease formula).[14] Patients were randomized (1:1:1) to receive oral, once-daily treatment with empagliflozin 10, 25 mg or placebo in addition to standard-of-care therapies. The trial was designed to continue until 691 or more patients had a primary outcome event (3-point major adverse CV events [3P-MACE]), namely, CV death, non-fatal myocardial infarction (MI) or non-fatal stroke. All CV outcomes and mortality events were prospectively adjudicated by independent expert committees.

2.2 | Polyvascular disease/kidney dysfunction population

For this report, four subgroups were defined according to the number of vascular beds involved at baseline (1 vs. ≥2) and baseline eGFR (≥60 vs. <60 mL/min/1.73 m^2). Vascular bed disease was defined as investigator-reported CAD, PAD and cerebrovascular disease at baseline. CAD was defined as any of the components of history of MI, coronary artery bypass graft, multivessel CAD and single vessel CAD. PAD and cerebrovascular disease were assessed using the inclusion criterion of high CV risk. PAD was defined as documented by any of the following: limb angioplasty, stenting or bypass surgery; limb or foot amputation because of circulatory insufficiency; evidence of significant peripheral artery stenosis (>50% on angiography or >50% or haemodynamically significant via non-invasive methods) in one limb; or ankle brachial index less than 0.9 in one or more ankle. Cerebrovascular disease was defined as a history of stroke (ischaemic or haemorrhagic) more than 2 months prior to consent. In this post hoc analysis, the empagliflozin arms were pooled. Safety was assessed descriptively by evaluation of adverse events (AEs) across subgroups.

2.3 | Statistical analyses

All analyses were performed post hoc and were not adjusted for multiplicity. These postanalyses are hypothesis-generating only and the presented *p*-values are explorative in nature. Continuous variables are given as mean ± standard deviation, and categorical as number and proportion n (%). We first explored, in the placebo and empagliflozin groups, the association of the number of vascular beds involved with the risk of CV death, HHF, the composite of CV death (excluding fatal stroke) or HHF, all-cause mortality (ACM) and 3P-MACE using a multivariable Cox regression model. In a second approach, we repeated these analyses using four subgroups that also took into account eGFR status at baseline (eGFR ≥60 vs. <60 mL/min/1.73 m^2). The models for the first approach included age, sex, baseline body mass index, baseline HbA1c, baseline eGFR, geographical region, treatment, vascular beds category at baseline (two categories) and the interaction of treatment*vascular beds category at baseline. Models for the second approach combined the vascular beds and baseline eGFR in a single variable with four categories instead of using two separate variables. Incidence rates were

calculated and given as patients with events per 1000 years at risk. In addition, we calculated absolute risk reductions (ARRs), defined as incidence rate differences and number needed to treat (NNT). NNTs were derived as the reciprocal of the difference between the control and treatment groups in the proportion of patients who experienced a CV event within 3 years of treatment with empagliflozin, assuming exponential distribution of time to events. Poisson regression models were used to calculate the ARR, including treatment with a log-link applied by each subgroup. In the model log (days at risk) for the time-to-first event, censoring was used as offset. Interaction *p*-values were calculated by *t*-tests, using the estimated interaction effect and variance of the interaction, as determined from the delta method following Poisson regression.

We also examined the treatment effect of empagliflozin versus placebo by the number of vascular beds involved and eGFR status using the same Cox regression model as in the second approach described above. All *p*-values reported are nominal. Statistical analyses were performed with SAS version 9.4.

3 | RESULTS

3.1 | Patient disposition

A total of 7020 patients received one or more doses of the study drug; the median observation time was 3.1 years. Sixty-one patients were excluded from these post hoc analyses because of missing baseline information on vascular beds and/or eGFR.

3.2 | Baseline characteristics

Of 6959 evaluable patients at baseline, 5630 (80.9%) had involvement of one vascular bed, of whom 1341 (23.8%) had an eGFR of less than 60 mL/min/1.73 m^2. The 1329 (19.1%) patients who had involvement of two or more vascular beds included a higher proportion of patients (34.8%) with an eGFR of less than 60 mL/min/1.73 m^2. The distribution and overlap of involvement of the three vascular territories (CAD, PAD and cerebrovascular disease) at baseline in patients in EMPA-REG OUTCOME are shown in Figure 1.

Baseline characteristics were generally balanced between the treatment groups. Across the four subgroups, based on the number of vascular beds and eGFR status, patients with disease in two or more vascular beds and an eGFR of less than 60 mL/min/1.73 m^2 were slightly older, had a T2D duration of longer than 10 years more often, and had a higher prevalence of HF compared with those with two or more vascular beds/eGFR of 60 mL/min/1.73 m^2 or higher, and with patients with only one vascular bed regardless of kidney function (Table 1). As expected, regardless of eGFR status, at baseline a considerably higher proportion of patients with disease in two or more versus one vascular bed had previous stroke (approximately 50% vs. 17%, respectively), PAD (approximately 65% vs. 10%, respectively) and MI (approximately 53% vs. 45%, respectively) (Table 1).

3.3 | Association of polyvascular disease and eGFR status with CV, HF and mortality outcomes

In the placebo group, when kidney function was not taken into account, the presence of polyvascular disease (≥2 vascular beds involved vs. 1 vascular bed as reference) was strongly associated with an increased risk of all CV, HF and mortality outcomes (Table S1). The pattern seen in the placebo group remained when we also considered an eGFR of less than 60 or of 60 mL/min/1.73 m^2 or higher and assessed four subgroups. In the placebo group, patients with disease in two or more vascular beds involved had event rates approximately twice those reported for patients with only one vascular bed involved within the respective eGFR subgroups, across all CV outcomes: CV death, HHF, CV death or HHF, ACM and 3P-MACE, although the pattern was less clear for HHF, with smaller differences in event rates across subgroups. Similarly, the event rates of all outcomes, including HHF, for patients with an eGFR of less than 60 mL/min/1.73 m^2 were approximately 1.5-fold higher compared with patients with an eGFR of 60 mL/min/1.73 m^2 or higher, in both the one vascular bed and two or more vascular bed cohorts. The event rates in the placebo group were highest in patients with disease in two or more vascular

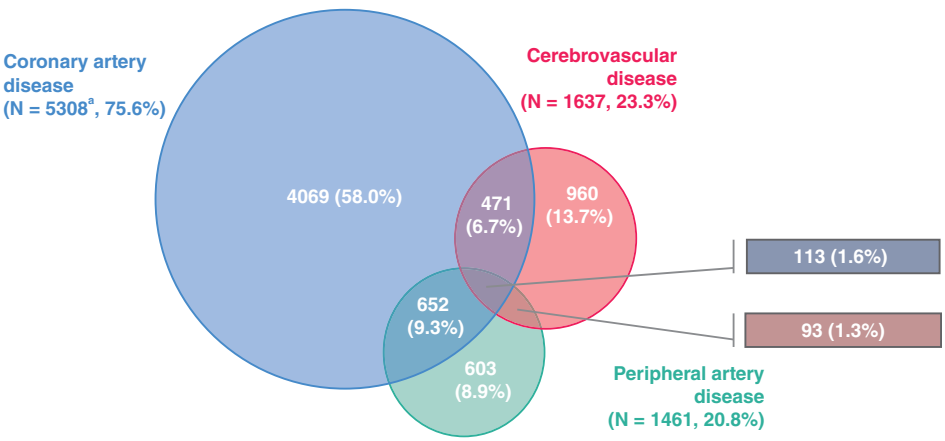

FIGURE 1 Overlap of vascular beds at baseline in patients in EMPA-REG OUTCOME. Each patient is counted only once. [a]Includes three patients who had missing data for one of the other diseases: one patient missing for cerebrovascular disease; two patients missing for peripheral artery disease. Coronary artery disease: any of the components of history of myocardial infarction, coronary artery bypass graft, multivessel coronary artery disease or single vessel coronary artery disease

TABLE 1 Baseline characteristics

	1 vascular bed involved (N = 5630)		≥2 vascular beds involved (N = 1329)	
	eGFR ≥60 mL/min/1.73 m^2	eGFR <60 mL/min/1.73 m^2	eGFR ≥60 mL/min/1.73 m^2	eGFR <60 mL/min/1.73 m^2
Characteristic	**n = 4289**	**n = 1341**	**n = 866**	**n = 463**
Female	1200 (28.0)	456 (34.0)	202 (23.3)	125 (27.0)
Age, years	61.3 ± 8.5	66.7 ± 7.8	64.3 ± 7.7	68.2 ± 7.7
BMI, kg/m^2	30.5 ± 5.2	30.8 ± 5.5	30.6 ± 5.3	31.5 ± 5.3
HbA1c, %	8.07 ± 0.84	8.08 ± 0.87	8.10 ± 0.85	8.01 ± 0.83
LDL-C, mg/dL	[a]86.5 ± 35.9	[b]85.2 ± 36.3	[c]83.2 ± 35.0	[d]82.5 ± 34.6
SBP, mmHg	134.7 ± 16.2	135.7 ± 18.2	137.4 ± 18.2	137.8 ± 17.9
DBP, mmHg	77.7 ± 9.5	74.6 ± 10.0	76.0 ± 10.3	74.4 ± 10.2
Smoking status				
Never smoked	1780 (41.5)	645 (48.1)	267 (30.8)	164 (35.4)
Ex-smoker	1878 (43.8)	601 (44.8)	445 (51.4)	259 (55.9)
Current smoker	631 (14.7)	95 (7.1)	154 (17.8)	40 (8.6)
Time since T2D diagnosis, years				
≤1	135 (3.1)	29 (2.2)	13 (1.5)	3 (0.6)
>1–5	785 (18.3)	148 (11.0)	114 (13.2)	26 (5.6)
>5–10	1147 (26.7)	296 (22.1)	192 (22.2)	94 (20.3)
>10	2222 (51.8)	868 (64.7)	547 (63.2)	340 (73.4)
eGFR mL/min/1.73 m^2	83.5 ± 17.0	48.9 ± 8.0	80.4 ± 16.6	47.3 ± 8.3
Previous MI	1981 (46.2)	574 (42.8)	465 (53.7)	249 (53.8)
Previous stroke	741 (17.3)	219 (16.3)	447 (51.6)	230 (49.7)
PAD	469 (10.9)	133 (9.9)	547 (63.2)	311 (67.2)
Cardiac failure	346 (8.1)	172 (12.8)	96 (11.1)	90 (19.4)
Retinopathy	816 (19.0)	324 (24.2)	241 (27.8)	152 (32.8)
Neuropathy	1182 (27.6)	443 (33.0)	338 (39.0)	221 (47.7)
Background medications				
ACEi/ARBs	3384 (78.9)	1116 (83.2)	714 (82.4)	404 (87.3)
Statins	3230 (75.3)	1044 (77.9)	713 (82.3)	373 (80.6)
Anticoagulants	3767 (87.8)	1193 (89.0)	813 (93.9)	431 (93.1)
Metformin	3416 (79.6)	820 (61.1)	657 (75.9)	247 (53.3)
Insulin	1828 (42.6)	736 (54.9)	482 (55.7)	314 (67.8)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; BMI, body mass index; CAD, coronary artery disease; CABG, coronary artery bypass graft; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral artery disease; SBP, systolic blood pressure; T2D, type 2 diabetes.

Data are n (%) or mean ± SD in patients treated with ≥1 dose of study drug and non-missing baseline information on vascular beds and/or eGFR.

[a]n = 4240; [b]n = 1327; [c]n = 850; [d]n = 457. Vascular bed disease was defined as investigator-reported CAD, PAD and cerebrovascular disease at baseline. CAD was defined as any of the components of history of MI, coronary artery bypass graft, multivessel CAD and single vessel CAD. PAD was defined as documented by any of the following: limb angioplasty, stenting or bypass surgery; limb or foot amputation because of circulatory insufficiency; evidence of significant peripheral artery stenosis (>50% on angiography or >50% or haemodynamically significant via non-invasive methods) in one limb; ankle brachial index <0.9 in ≥1 ankle. Cerebrovascular disease was defined as a history of stroke (ischaemic or haemorrhagic) >2 months prior to consent.

beds involved and an eGFR of less than 60 mL/min/1.73 m^2 (Figure 2).

The presence of polyvascular disease and kidney impairment was strongly associated with an increased risk of all outcomes in the placebo and empagliflozin treatment groups compared with involvement of one vascular bed and no kidney impairment (Table 2).

3.4 | Relative and absolute treatment effect of empagliflozin

Empagliflozin consistently reduced the risk of all mortality, CV and HF outcomes versus placebo, regardless of the number of vascular beds affected and eGFR status, as evident by the non-significant

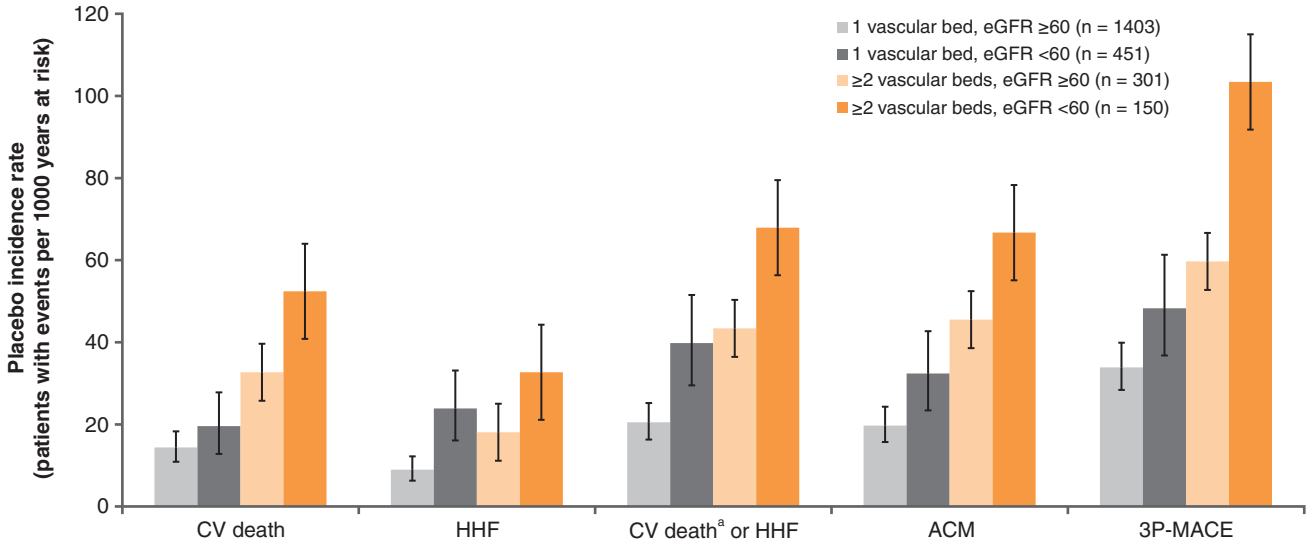

FIGURE 2 Incidence rates in the placebo group across outcomes by number of vascular beds involved and estimated glomerular filtration rate (eGFR) status. [a]Excluding fatal stroke. Error bars are ± confidence interval (CI). 3P-MACE, 3-point major adverse cardiovascular events; ACM, all-cause mortality; CV, cardiovascular; HHF, hospitalization for heart failure

interaction *p*-values (Figure 3). Table S2 shows the ARRs for number of events per 1000 patient-years and the NNT to prevent one event (CV death, HHF, CV death or HHF, and ACM) over 3 years of treatment with empagliflozin versus placebo. In the analysis of subgroup interactions with treatment effect for the ARRs, we found higher ARRs for CV death for one vascular bed/eGFR of 60 mL/min/1.73 m^2 or higher (p = .0440) and one vascular bed/eGFR of less than 60 mL/min/1.73 m^2 (p = .0212), both versus two or more vascular beds/eGFR of 60 mL/min/1.73 m^2 or higher. No significant interactions were observed among subgroups for the four outcomes, all with interaction *p*-values of more than .05.

3.5 | Safety

In general, the rates of AEs were similar across treatment arms. The rates of AEs across subgroups are shown in Table S3. Within each treatment group, among patients with an eGFR of 60 mL/min/1.73 m^2 or higher, we observed a pattern of higher rates of AEs in those with two or more vascular beds involved compared with those with one vascular bed, whereas individuals with an eGFR of less than 60 mL/min/1.73 m^2 tended to have higher AE rates, regardless of the number of vascular beds involved.

4 | DISCUSSION

This post hoc analysis from the EMPA-REG OUTCOME trial showed that, for patients with established ASCVD and T2D, the presence of polyvascular disease, alone or with co-existing eGFR of less than 60 mL/min/1.73 m^2, was strongly associated with an increased risk for all CV outcomes, including HHF. As expected, patients with involvement of two or more vascular beds and an eGFR of less than 60 mL/min/1.73 m^2 were at greater risk of CV events. Empagliflozin consistently lowered the risk for all outcomes, including HHF, regardless of the number of vascular beds involved and eGFR status.

These findings emphasize the importance of polyvascular disease and kidney impairment as risk factors for HF as well as ischaemic events in patients with T2D. Furthermore, these results support the ACC/AHA guidelines for prevention of CV disease, in which polyvascular disease, diabetes and an eGFR of less than 60 mL/min/1.73 m^2 are all identified as markers of very high CV risk. Interestingly, Van den Berg et al. showed that polyvascular disease alone or low eGFR alone performed better than the ACC/AHA risk score in discriminating risk for future CV events in patients with ASCVD.[1] However, we found that combining these risk factors identified subgroups with a dissimilar risk of CV, HF and mortality outcomes among patients with T2D and ASCVD. This variation in CV risk across subgroups is in line with a previous analysis showing that the patients included in the EMPA-REG OUTCOME trial, although they all had T2D and ASCVD, displayed a broad risk spectrum for CV events.[15] Other CV outcomes trials have shown that the co-existence of polyvascular disease and T2D is linked to an increased risk of CV events and mortality,[7–9] but these did not take kidney dysfunction into account. In an analysis of patients from the COMPASS trial, however, risk stratification identified subsets of patients at a higher risk of recurrent vascular events, including patients with kidney insufficiency (defined as eGFR <60 mL/min/1.73 m^2) as well as disease in two or more vascular beds affected, HF and diabetes.[16]

The relationship between polyvascular disease and HF in diabetes is complex, with numerous common underlying pathophysiological features.[17] Furthermore, the evidence regarding an association between polyvascular disease and risk of clinical HF outcomes in patients with T2D is scarce: the post hoc analysis from the IMPROVE-IT

TABLE 2 Association of number of vascular beds involvement and estimated glomerular filtration rate (eGFR) status to outcomes in the placebo and empagliflozin groups

	Placebo								Empagliflozin							
	1 vascular bed involved				≥2 vascular beds involved				1 vascular bed involved				≥2 vascular beds involved			
	eGFR ≥60 mL/min/1.73 m^2 (n = 1403)		eGFR <60 mL/min/1.73 m^2 (n = 451)		eGFR ≥60 mL/min/1.73 m^2 (n = 301)		eGFR <60 mL/min/1.73 m^2 (n = 150)		eGFR ≥60 mL/min/1.73 m^2 (n = 2886)		eGFR <60 mL/min/1.73 m^2 (n = 890)		eGFR ≥60 mL/min/1.73 m^2 (n = 565)		eGFR <60 mL/min/1.73 m^2 (n = 313)	
	Patients with event, n (%)	HR (95% CI)	Patients with event, n (%)	HR (95% CI)[a]	Patients with event, n (%)	HR (95% CI)[a]	Patients with event, n (%)	HR (95% CI)[a]	Patients with event, n (%)	HR (95% CI)	Patients with event, n (%)	HR (95% CI)[a]	Patients with event, n (%)	HR (95% CI)[a]	Patients with event, n (%)	HR (95% CI)[a]
CV death	59 (4.2)	Ref.	26 (5.8)	1.26 (0.79, 2.02)	28 (9.3)	2.08 (1.32, 3.27)	22 (14.7)	3.10 (1.87, 5.13)	75 (2.6)	Ref.	49 (5.5)	1.96 (1.35, 2.83)	21 (3.7)	1.34 (0.82, 2.18)	25 (8.0)	2.88 (1.81, 4.57)
HHF	36 (2.6)	Ref.	30 (6.7)	2.12 (1.29, 3.48)	15 (5.0)	1.85 (1.01, 3.38)	13 (8.7)	2.80 (1.46, 5.36)	50 (1.7)	Ref.	30 (3.4)	1.60 (1.01, 2.54)	25 (4.4)	2.30 (1.41, 3.73)	21 (6.7)	3.19 (1.89, 5.37)
CV death[b] or HHF	82 (5.8)	Ref.	50 (11.1)	1.69 (1.18, 2.41)	36 (12.0)	1.96 (1.32, 2.90)	27 (18.0)	2.71 (1.74, 4.23)	110 (3.8)	Ref.	71 (8.0)	1.84 (1.35, 2.50)	42 (7.4)	1.79 (1.25, 2.56)	40 (12.8)	2.99 (2.06, 4.33)
ACM	81 (5.8)	Ref.	43 (9.5)	1.39 (0.96, 2.03)	39 (13.0)	2.06 (1.40, 3.02)	28 (18.7)	2.59 (1.67, 4.02)	115 (4.0)	Ref.	74 (8.3)	1.75 (1.30, 2.36)	38 (6.7)	1.54 (1.06, 2.22)	40 (12.8)	2.73 (1.89, 3.95)
3P-MACE	133 (9.5)	Ref.	60 (13.3)	1.33 (0.97, 1.81)	48 (15.9)	1.64 (1.17, 2.28)	39 (26.0)	2.62 (1.82, 3.77)	241 (8.4)	Ref.	110 (12.4)	1.39 (1.10, 1.75)	72 (12.7)	1.45 (1.11, 1.89)	65 (20.8)	2.43 (1.83, 3.22)

Abbreviations: 3P-MACE, 3-point major adverse cardiovascular events; ACM, all-cause mortality; BMI, body mass index; CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio.

Cox regression model includes age, sex, baseline BMI, baseline HbA1c, geographical region, treatment, vascular beds with eGFR status category at baseline (four categories) and the interaction of treatment*vascular beds with eGFR status category at baseline.

[a]Comparison vs. one vascular bed and eGFR ≥60 mL/min/1.73 m^2 as the reference (Ref.) value.

[b]Excluding fatal stroke.

trial mentioned above also explored the risk of investigator-reported congestive HF in relation to polyvascular disease and T2D.[7] The authors found that the presence of concomitant polyvascular disease and T2D identified patients with a particularly high risk of both CV and HF outcomes.[7] Likewise, in COMPASS, the higher risk patient subsets (≥2 vascular beds, HF, diabetes or kidney insufficiency) had a 2-fold higher 30-month incidence risk compared with the patient subsets without these high-risk features.[16] Our results show a similar pattern: if we compare patients with polyvascular disease versus those with only one vascular bed involved with similar eGFR (either ≥60 or <60 mL/min/1.73 m^2), those with polyvascular disease have a higher prevalence of HF at baseline and higher rates of HHF (Figure 2). The highest rates of HHF and CV outcomes are seen among those with polyvascular disease and reduced eGFR: the composite endpoint of HHF or CV death (excluding fatal stroke) occurred in 18.0% and 12.8% of patients in the placebo and empagliflozin groups, respectively (Table 2). Interestingly, the rates of HHF are comparable across the two subgroups of two or more vascular beds/eGFR of 60 mL/min/1.73 m^2 or higher and one vascular bed/eGFR of less than 60 mL/min/1.73 m^2 (Figure 2). It thus appears that involvement of two or more versus one vascular bed approximately doubles the rate of HHF, whereas an eGFR of less than 60 versus 60 mL/min/1.73 m^2 or higher increases the rate by 1.5. This suggests that polyvascular disease and kidney impairment may be similarly strong risk factors for HHF in individuals with T2D and ASCVD.

In the current analysis, the treatment effect of empagliflozin was consistent across all outcomes, including HHF, regardless of the extent of vascular disease and kidney function status. This consistency of treatment effect has also been reported for a number of subgroup analyses from EMPA-REG OUTCOME, including those that have explored the effect of empagliflozin by the presence of different manifestations of ASCVD at baseline.[12,13] For example, in subgroups of patients with or without a prior MI or stroke at baseline,[15] and with or without PAD at baseline,[18] there was a similar reduction in risk of CV, HF and mortality outcomes with empagliflozin versus placebo.[15,18]

The beneficial effects of empagliflozin on the primary outcome (first occurrence of CV death, non-fatal MI or non-fatal stroke) were driven by the reduction in risk of CV death, with no significant differences seen with risk of MI or stroke.[12] However, in a recent analysis of the totality of CV events, that is, first plus recurrent events, a significant reduction in fatal or non-fatal MI was observed (rate ratio [RR]: 0.79 [0.62-0.998]; p = .049), as well as the composite of fatal or non-fatal MI/coronary revascularization (RR: 0.80 [0.67-0.95]; p = .012).[19] The finding regarding stroke risk was confirmed in a separate prespecified, comprehensive analysis showing no impact in those with or without a prior stroke.[20]

Analyses have also shown that empagliflozin and another SGLT2 inhibitor, canagliflozin, reduced CV outcomes in patients with an eGFR down to 30 mL/min/1.73 m^2,[21,22] and trials investigating CV and kidney effects of SGLT2 inhibitors in patients with kidney impairment with or without diabetes are ongoing (i.e. EMPA-KIDNEY [NCT03594110]), or have recently been completed and will report in the near future (i.e. DAPA-CKD [NCT03036150]).

Analysis group	Empagliflozin	Placebo	Hazard ratio (95% CI)	p-value for interaction
	n with event/N analyzed (%)			
CV death				
All patients	172/4687 (3.7)	137/2333 (5.9)	0.62 (0.49, 0.77)	
1 vascular bed involved				.1306
eGFR ≥60 mL/min/1.73 m²	75/2886 (2.6)	59/1403 (4.2)	0.61 (0.43, 0.85)	
eGFR <60 mL/min/1.73 m²	49/890 (5.5)	26/451 (5.8)	0.94 (0.58, 1.51)	
≥2 vascular beds involved				
eGFR ≥60 mL/min/1.73 m²	21/565 (3.7)	28/301 (9.3)	0.39 (0.22, 0.69)	
eGFR <60 mL/min/1.73 m²	25/313 (8.0)	22/150 (14.7)	0.56 (0.32, 1.00)	
HHF				
All patients	126/4687 (2.7)	95/2333 (4.1)	0.65 (0.50, 0.85)	
1 vascular bed involved				.6256
eGFR ≥60 mL/min/1.73 m²	50/2886 (1.7)	36/1403 (2.6)	0.67 (0.43, 1.02)	
eGFR <60 mL/min/1.73 m²	30/890 (3.4)	30/451(6.7)	0.50 (0.30, 0.83)	
≥2 vascular beds involved				
eGFR ≥60 mL/min/1.73 m²	25/565 (4.4)	15/301 (5.0)	0.83 (0.44, 1.57)	
eGFR <60 mL/min/1.73 m²	21/313 (6.7)	13/150 (8.7)	0.76 (0.38, 1.52)	
CV death[a] or HHF				
All patients	265/4687 (5.7)	198/2333 (8.5)	0.66 (0.55, 0.79)	
1 vascular bed involved				.9225
eGFR ≥60 mL/min/1.73 m²	110/2886 (3.8)	82/1403 (5.8)	0.64 (0.48, 0.86)	
eGFR <60 mL/min/1.73 m²	71/890 (8.0)	50/451 (11.1)	0.70 (0.49, 1.01)	
≥2 vascular beds involved				
eGFR ≥60 mL/min/1.73 m²	42/565 (7.4)	36/301 (12.0)	0.59 (0.38, 0.92)	
eGFR <60 mL/min/1.73 m²	40/313 (12.8)	27/150 (18.0)	0.71 (0.43, 1.16)	
ACM				
All patients	269/4687 (5.7)	194/2333 (8.3)	0.68 (0.57, 0.82)	
1 vascular bed involved				.3744
eGFR ≥60 mL/min/1.73 m²	115/2886 (4.0)	81/1403 (5.8)	0.68 (0.51, 0.90)	
eGFR <60 mL/min/1.73 m²	74/890 (8.3)	43/451 (9.5)	0.85 (0.59, 1.24)	
≥2 vascular beds involved				
eGFR ≥60 mL/min/1.73 m²	38/565 (6.7)	39/301 (13.0)	0.51 (0.32, 0.79)	
eGFR <60 mL/min/1.73 m²	40/313 (12.8)	28/150 (18.7)	0.71 (0.44, 1.16)	
3P-MACE				
All patients	490/4687 (10.5)	282/2333 (12.1)	0.86 (0.74, 0.99)	
1 vascular bed involved				.9023
eGFR ≥60 mL/min/1.73 m²	241/2886 (8.4)	133/1403 (9.5)	0.87 (0.71, 1.08)	
eGFR <60 mL/min/1.73 m²	110/890 (12.4)	60/451 (13.3)	0.91 (0.67, 1.25)	
≥2 vascular beds involved				
eGFR ≥60 mL/min/1.73 m²	72/565 (12.7)	48/301 (15.9)	0.77 (0.53, 1.11)	
eGFR <60 mL/min/1.73 m²	65/313 (20.8)	39/150 (26.0)	0.81 (0.54, 1.21)	

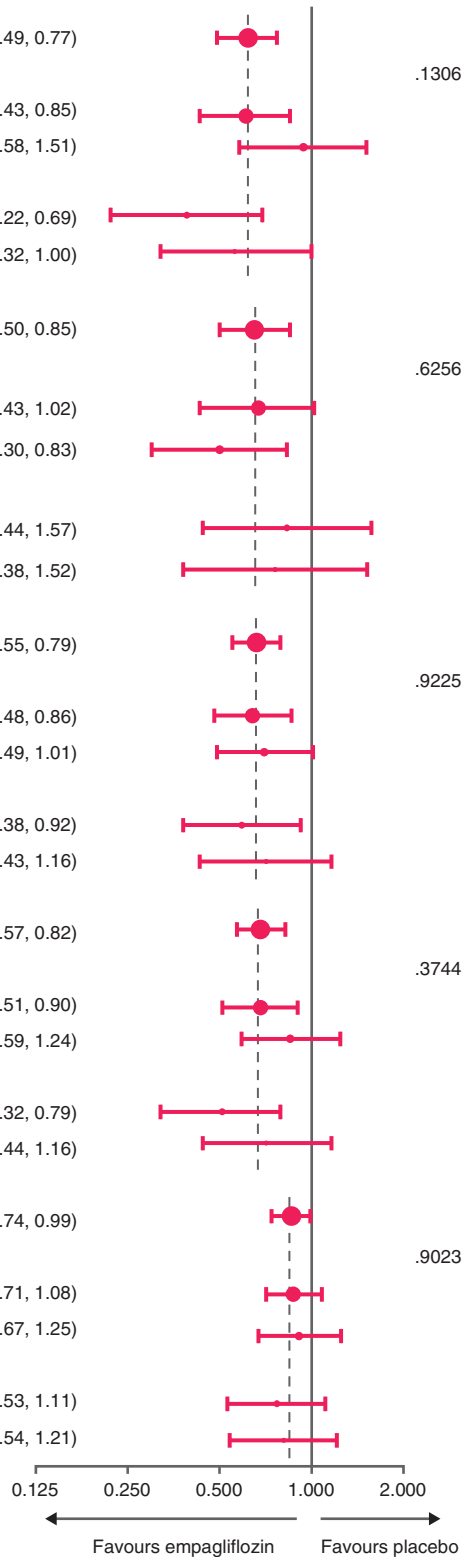

FIGURE 3 Treatment effect of empagliflozin versus placebo by number of vascular beds involved and estimated glomerular filtration rate (eGFR) status. [a]Excluding fatal stroke. Cox regression model includes age, sex, baseline body mass index (BMI), baseline HbA1c, geographical region, treatment, vascular beds with eGFR status category (four categories), and the interaction of treatment by vascular beds with eGFR status category at baseline. 3P-MACE, 3-point major adverse cardiovascular events; ACM, all-cause mortality; CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure

In the analysis of subgroup interactions with treatment effect for ARRs, there were higher ARRs for CV death (1 vascular bed with eGFR ≥60 mL/min/1.73 m^2 or eGFR <60 mL/min/1.73 m^2, both vs. ≥2 vascular beds/eGFR ≥60 mL/min/1.73 m^2). No significant interactions were observed across subgroups for the four outcomes, including for the highest (≥2 vascular beds/eGFR <60 mL/min/1.73 m^2) versus lowest (1 vascular bed/eGFR ≥60 mL/min/1.73 m^2) risk groups. This may be attributable to the comparatively low number of patients and events in the highest versus lowest risk groups (number of patients, n = 463 vs. n = 4289, respectively).

The safety profile of empagliflozin in these vulnerable subgroups of patients with polyvascular disease and impaired kidney function at baseline was consistent with that reported previously.[11,12] Notably, the rates of reported AEs appeared to be determined more by kidney function than by the number of vascular beds involved.

These analyses have some limitations: first, their post hoc nature makes them hypothesis-generating only. Second, because of the low number of patients and CV events we were not able to discriminate between those that have two or three vascular beds affected in our analyses. However, the key strengths of these analyses are the long period of follow-up as well as prospective adjudication of outcomes.

In conclusion, the current analysis shows that, in addition to being a marker for ischaemic events, the presence of polyvascular disease is strongly associated with the risk of HF events in patients with T2D. Furthermore, co-existing polyvascular disease and kidney dysfunction (eGFR <60 mL/min/1.73 m^2) markedly increases CV risk. Treatment with empagliflozin, compared with placebo, led to consistent reductions in the risk of these CV, mortality and HF outcomes, regardless of vascular bed and kidney function status, in these patient subgroups.

ACKNOWLEDGEMENTS

The authors thank the patients who participated in this trial. Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Charlie Bellinger of Elevate Scientific Solutions, during the preparation of this article. The authors are fully responsible for all content and editorial decisions and were involved at all stages of manuscript development and have approved the final version. The EMPA-REG OUTCOME trial was sponsored by the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance.

CONFLICT OF INTEREST

SV holds a Tier 1 Canada Research Chair in Cardiovascular Surgery; has received grants and personal fees for speaker honoraria and advisory board participation from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, EOCI Pharmacomm Ltd, HLS Therapeutics, Janssen, Merck, Novartis, Novo Nordisk, Sanofi, Sun Pharmaceuticals and the Toronto Knowledge Translation Working Group; and serves as President of the Canadian Medical and Surgical Knowledge Translation Research Group. CDM has received consulting fees from Amgen, AstraZeneca, Boehringer Ingelheim and Octapharma. SEI has received honoraria for lectures, advisory work and/or clinical trial leadership from AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Sanofi/Lexicon, VTV Therapeutics, Merck and Abbott/Alere. CW reports honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme and Sanofi. APO and IZ are employees of Boehringer Ingelheim. JTG was employed by Boehringer Ingelheim at the time of this analysis, and is now an employee of Novo Nordisk Limited, Gatwick, UK. OEJ was employed by Boehringer Ingelheim at the time of this analysis, and is now an employee of Nestlé Health Science, Epalinges, Switzerland. JB has received research support from the National Institutes of Health, Patient Centered Outcomes Research and the European Union, and has served as a consultant for Abbott, Adrenomed, Amgen, Array, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, CVRx, G3 Pharmaceutical, Innolife, Janssen, LinaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Roche, Sanofi, V-Wave and Vifor Pharma. BZ has received research grants awarded to his institution from Boehringer Ingelheim, AstraZeneca and Novo Nordisk, and honoraria from Janssen, Sanofi, Eli Lilly, Boehringer Ingelheim, Novo Nordisk and Merck Sharp & Dohme.

AUTHOR CONTRIBUTIONS

SV conceived the idea, and SV, APO and OEJ contributed to the interpretation of data and drafted the manuscript. CDM, SEI, CW, JTG, JB and BZ contributed to the interpretation of data and the development of the manuscript. IZ contributed to the analysis and interpretation of data and the development of the manuscript, and provided statistical expertise. IZ and SV are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

DATA AVAILABILITY STATEMENT

The sponsor of the EMPA-REG OUTCOME trial (Boehringer Ingelheim) is committed to responsible sharing of clinical study reports, related clinical documents, and patient-level clinical study data. Researchers are invited to submit inquiries via the following website (https://trials.boehringer-ingelheim.com/).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Verma S, Mazer CD, Inzucchi SE, et al. Impact of polyvascular disease with and without co-existent kidney dysfunction on cardiovascular outcomes in diabetes: A post hoc analysis of EMPA-REG OUTCOME. *Diabetes Obes Metab*. 2021;23:1173–1181. https://doi.org/10.1111/dom.14326