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 m²) 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 m²) 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. International guidelines for the prevention of CV disease use different clinical criteria to identify those patients who are at very high risk of recurrent CV events. These guidelines include those of the American College of Cardiology (ACC)/American Heart Association (AHA). 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. 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). 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 (ClinicalTrials.gov: NCT01131676) was a randomized, double-blind, placebo-controlled trial, as described previously. 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. For inclusion, patients had to have an eGFR of 30 mL/min/1.73 m² or higher (calculated with the Modification of Diet in Renal Disease formula). 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 | MATERIALS AND METHODS

2.1 | Study design

The EMPA-REG OUTCOME trial was a randomized, double-blind, placebo-controlled trial, as described previously. 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.

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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 m²). 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 history of peripheral artery disease (CAD, PAD and cerebrovascular disease) 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 m²). 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 m². 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 m². 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 m² 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 m² 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 m² 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 m² were approximately 1.5-fold higher compared with patients with an eGFR of 60 mL/min/1.73 m² 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 beds.
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
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 m² or higher (p = .0440) and one vascular bed/eGFR of less than 60 mL/min/1.73 m² (p = .0212), both versus two or more vascular beds/eGFR of 60 mL/min/1.73 m² 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 m² 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 m² 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 m², 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 m² 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 m² 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. 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. 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, 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 m²) as well as disease in two or more vascular beds affected, HF and diabetes.

The relationship between polyvascular disease and HF in diabetes is complex, with numerous common underlying pathophysiological features. 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 1 vascular bed involved | Placebo ≥2 vascular beds involved | Empagliflozin 1 vascular bed involved | Empagliflozin ≥2 vascular beds involved |
|--------------------------|---------------------------------|----------------------------------|--------------------------------------|----------------------------------------|
| eGFR ≥60 mL/min/1.73 m²  | Patients with event, n (%)      | HR (95% CI)                       | Patients with event, n (%)            | HR (95% CI)                            |
|                         |                                 |                                  | (n = 1400)                           | (n = 451)                              |
| CV death                | 59 (4.2) Ref.                   | 1.26 (0.79, 2.02)                | 28 (9.3)                             | 3.10 (1.87, 5.13)                      |
| HHF                     | 36 (2.6) Ref.                   | 1.22 (1.12, 3.48)                | 15 (5.0)                             | 2.10 (1.40, 3.13)                      |
| CV death or HHF         | 82 (5.8) Ref.                   | 1.69 (1.18, 2.41)                | 36 (12.0)                            | 2.71 (1.74, 4.23)                      |
| ACM                     | 81 (5.8) Ref.                   | 1.39 (0.96, 2.03)                | 39 (13.0)                            | 2.59 (1.67, 4.02)                      |
| 3P-MACE                 | 133 (9.5) Ref.                  | 1.33 (0.97, 1.81)                | 48 (15.9)                            | 2.62 (1.82, 3.77)                      |
| eGFR <60 mL/min/1.73 m² | Patients with event, n (%)      | HR (95% CI)                       | Patients with event, n (%)            | HR (95% CI)                            |
|                         |                                 |                                  | (n = 301)                            | (n = 150)                              |
| CV death                | 26 (5.8)                        | 1.20 (0.73, 2.02)                | 22 (14.7)                            | 3.16 (1.83, 5.43)                      |
| HHF                     | 30 (6.7)                        | 1.15 (0.98, 1.34)                | 13 (8.7)                             | 1.78 (1.06, 3.00)                      |
| CV death or HHF         | 50 (11.1)                       | 1.56 (1.40, 3.00)                | 27 (18.0)                            | 2.18 (1.25, 3.80)                      |
| ACM                     | 43 (9.5)                        | 1.39 (0.96, 2.03)                | 30 (20.0)                            | 2.59 (1.67, 4.02)                      |
| 3P-MACE                 | 60 (13.3)                       | 1.33 (0.97, 1.81)                | 40 (13.3)                            | 2.62 (1.82, 3.77)                      |

**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.

*Comparison vs. one vascular bed and eGFR ≥60 mL/min/1.73 m² as the reference (Ref.) value.

**Excluding fatal stroke.
### Table

| Analysis group | Empagliflozin | Placebo | Hazard ratio (95% CI) | Hazard ratio (95% CI) | p-value for interaction |
|----------------|---------------|---------|-----------------------|-----------------------|-------------------------|
| **CV death**   |               |         |                       |                       |                         |
| All patients   | 172/4687 (3.7)| 137/2333 (5.9)| 0.62 (0.49, 0.77)     |                       |                         |
| 1 vascular bed involved | 75/2886 (2.6) | 59/140 (4.2) | 0.61 (0.43, 0.85) |                       | .1306                   |
| 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 | 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)     |                       | .6256                   |
| 1 vascular bed involved | 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 | 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 or HHF** |          |         |                       |                       |                         |
| All patients   | 265/4687 (5.7)| 198/2333 (8.5)| 0.66 (0.55, 0.79)     |                       | .9225                   |
| 1 vascular bed involved | 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 | 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)     |                       | .3744                   |
| 1 vascular bed involved | 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 | 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)     |                       | .9023                   |
| 1 vascular bed involved | 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 | 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. *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 ARR, there were higher ARRs for CV death (1 vascular bed with eGFR ≥ 60 mL/min/1.73 m²) or eGFR <60 mL/min/1.73 m², both vs. ≥2 vascular beds/eGFR ≥60 mL/min/1.73 m²). No significant interactions were observed across subgroups for the four outcomes, including for the highest (≥2 vascular beds/eGFR < 60 mL/min/1.73 m²) versus lowest (1 vascular bed/eGFR ≥ 60 mL/min/1.73 m²) 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. 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 m²) 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 Apen, 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 Apen, 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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REFERENCES
1. van den Berg MJ, Bhatt DL, Kappelle LJ, et al. Identification of vascular patients at very high risk for recurrent cardiovascular events: validation of the current ACC/AHA very high risk criteria. Eur Heart J. 2017;38:3211-3218.
2. Authors/Task Force Members, Piepoli MF, Hoes AW, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur J Prev Cardiol. 2016;23:NP1-NP96.
3. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227-239.

4. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/ABC/ACP/M/AGS/APhA/ASP/NLA/P- CNA 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- e350.

5. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41:111-188.

6. World Health Organization. Prevention of cardiovascular disease guidelines for assessment and management of total cardiovascular risk. http://apps.who.int/iris/bitstream/10665/43685/1/9789241 547178_eng.pdf. Accessed April 9, 2020.

7. Bonaca MP, Gutierrez JA, Cannon C, et al. Polyvascular disease, type 2 diabetes, and long-term vascular risk: a secondary analysis of the IMPROVE-IT trial. *Lancet Diabetes Endocrinol*. 2018;6:934-943.

8. Gutierrez JA, Scirica BM, Bonaca MP, 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;123:145-152.

9. Verma S, Bhatt DL, Bain SC, 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- 2183.

10. Fitchett D, Zinman B, Lachin JM, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME trial. *Eur Heart J*. 2016;37:1526-1534.

11. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375: 323-334.

12. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373: 2117-2128.

13. Zinman B, Inzucchi SE, Lachin JM, et al. Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME). *Cardiovasc Diabetol*. 2014;13:102.

14. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in renal disease study group. *Ann Intern Med*. 1999;130:461-470.

15. Fitchett D, Inzucchi SE, Cannon CP, et al. Empagliflozin reduced mortality and hospitalization for heart failure across the spectrum of cardiovascular risk in the EMPA-REG OUTCOME trial. *Circulation*. 2019;139:1384-1395.

16. Anand SS, Eikelboom JW, Dyal L, et al. Rivaroxaban plus aspirin versus aspirin in relation to vascular risk in the COMPASS trial. *J Am Coll Cardiol*. 2019;73:3271-3280.

17. Low Wang CC, Hess CN, Hiatt WR, Goldfine AB. Clinical update: cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus - mechanisms, management, and clinical considerations. *Circulation*. 2016;133:2459- 2502.

18. Verma S, Mazer CD, Al-Omran M, et al. Cardiovascular outcomes and safety of Empagliflozin in patients with type 2 diabetes mellitus and peripheral artery disease: a subanalysis of EMPA-REG OUTCOME. *Circulation*. 2018;137:405-407.

19. McGuire DK, Zinman B, Inzucchi SE, et al. Effects of empagliflozin on first and recurrent clinical events in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a secondary analysis of the EMPA-REG OUTCOME trial. *Lancet Diabetes Endocrinol*. 2020;8: 949-959.

20. Zinman B, Inzucchi SE, Lachin JM, et al. Empagliflozin and cerebrovascular events in patients with type 2 diabetes mellitus at high cardiovascular risk. *Stroke*. 2017;48:1218-1225.

21. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380: 2295-2306.

22. Wanner C, Lachin JM, Inzucchi SE, et al. Empagliflozin and clinical outcomes in patients with type 2 diabetes mellitus, established cardiovascular disease, and chronic kidney disease. *Circulation*. 2018;137:119-129.

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](https://doi.org/10.1111/dom.14326)