Consistent effects of empagliflozin on cardiovascular and kidney outcomes irrespective of diabetic kidney disease categories: Insights from the EMPA-REG OUTCOME trial

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Abstract

Aim: To explore the cardiovascular (CV) and kidney effects of empagliflozin in patients with different clinical phenotypes of diabetic kidney disease (DKD) (i.e. with the presence or absence of overt albuminuria) participating in the EMPA-REG OUTCOME trial.

Materials and methods: EMPA-REG OUTCOME randomized participants (1:1:1) to empagliflozin 10 mg, 25 mg or placebo, added to standard of care. Post hoc, patients with different clinical phenotypes of DKD at baseline were categorized in three subgroups: (a) overt DKD (overt albuminuria [urinary albumin-to-creatinine ratio of >300 mg/g] with any estimated glomerular filtration rate [eGFR]; n = 769); (b) non-overt DKD (kidney impairment [eGFR < 60 mL/min/1.73 m²] without overt albuminuria [urinary albumin-to-creatinine ratio of ≤300 mg/g]; n = 1290); and (c) ‘all others’ (eGFR ≥ 60 mL/min/1.73 m² without overt albuminuria; n = 4893). Analyses included CV (death, hospitalization for heart failure, all-cause hospitalization) and selected kidney outcomes, change in eGFR and kidney safety. Cox proportional hazards models assessed the consistency of treatment effect across subgroups.

Results: Empagliflozin significantly reduced the risk of CV and kidney outcomes across all subgroups (P-values for interaction >.05), consistent with the overall trial population findings. Empagliflozin also significantly reduced the yearly loss of eGFR.
assessed by chronic slopes, in all subgroups. The adverse event profile of empagliflozin was similar across all subgroups.

Conclusions: Empagliflozin may improve CV and kidney outcomes and slow the progression of kidney disease in type 2 diabetes patients with DKD, irrespective of its clinical form, both with or without the presence of overt albuminuria.

KEYWORDS
cardiovascular disease, clinical trial, diabetic nephropathy, empagliflozin, sodium-glucose co-transporter-2 inhibitor, type 2 diabetes

1 | INTRODUCTION

Diabetes is the leading cause of kidney failure in industrialized countries, and macroalbuminuria (i.e. overt albuminuria) has historically been considered its hallmark, commonly referred to as diabetic nephropathy (DN).1 DN evolves from chronic glomerular damage caused by hyperglycaemia and was previously commonly used as a synonym for chronic kidney disease (CKD) in diabetes.2 This concept, however, has been challenged, initially by elegant studies in the late 1990s, showing that biopsy-proven evidence of classical DN was only present in approximately one-third of patients with type 2 diabetes and concomitant microalbuminuria.3 In fact, the majority of patients showed extra-glomerular, interstitial injury. Consequently, the term diabetic kidney disease (DKD) was introduced to describe alterations of kidney function (glomerular filtration rate [GFR]) and/or kidney damage (albuminuria) associated with diabetes.4 Interestingly, recent epidemiological studies from the United States identified a change in the kidney phenotype of patients with diabetes and reported a shift from overt albuminuric toward non-overt forms, the latter now felt to represent the most common form of DKD.5 However, very few treatments have been proven to slow the progression of all forms of DKD.

Furthermore, DKD is commonly associated with an elevated risk of cardiovascular (CV) disease.6 Notably, an increased risk of CV outcomes and mortality has been reported to be independent of the presence of albuminuria in patients with type 2 diabetes and DKD, although it remains unclear how the various DKD phenotypes differ regarding the pathogenesis, prognosis and potential treatment responses.7 Based on the stage of DKD, one study has reported that the risks of myocardial infarction (MI) and stroke were ~85% and ~65% higher, respectively, in stage 3 kidney disease, compared with no disease.8 The relationship of congestive heart failure (CHF) with kidney disease stage was even stronger: DKD stage 3 was associated with an ~3-fold risk of CHF, and stage 4 to 5 disease with a greater than 5.5-fold risk.8 The precise mechanisms are not well known: while traditional risk factors such as poor glycaemic control and hypertension are common to both conditions, other pathophysiological mechanisms probably exist that may explain the clinical phenomenon of increased CVD risk in patients with DKD and vice versa.6,9 Non-traditional factors believed to contribute to CVD risk include arterial stiffening, anaemia, hyperaldosteronism, chronic inflammation, endothelial dysfunction and platelet dysfunction.9 Landmark studies utilizing renin-angiotensin system (RAS) inhibitors have historically been conducted exclusively in patients with overt DKD.10,11 As clinical evidence is scarce across the spectrum of albuminuria, there is a need for studies exploring the cardio/kidney effects of therapies, also including DKD stages without overt albuminuria.

The effects of empagliflozin on CV outcomes in the EMPA-REG OUTCOME trial, including a 38% reduction in the relative risk of CV death, as well as a 39% reduction in the prespecified secondary kidney endpoint of incident or worsening nephropathy, have been reported previously in the overall trial population.12-14 In this post hoc analysis, we aimed to explore the CV and kidney effects of empagliflozin in patients with different clinical phenotypes of DKD (i.e. with the presence or absence of overt albuminuria) participating in EMPA-REG OUTCOME, as this trial included approximately one-third of patients (n = 2059/7020) with prevalent DKD at study entry.15

2 | MATERIALS AND METHODS

2.1 | EMPA-REG OUTCOME

As described in detail previously, the EMPA-REG OUTCOME trial (ClinicalTrials.gov identifier: NCT01131676) was a double-blind, placebo-controlled, multinational trial in which adults with type 2 diabetes, an HbA1c of 7%–10% and established CVD were randomized in a 1:1:1 ratio to empagliflozin 10 mg, 25 mg or placebo, all added to background standard of care.14,16 Patients were required to have an estimated GFR (eGFR) of 30 mL/min/1.73 m² or higher (based on the Modification of Diet in Renal Disease [MDRD] study formula) at screening, but there were no specific study restrictions/requirements for levels of albuminuria at baseline. Serum creatinine and urinary albumin-to-creatinine ratio (UACR) were measured by a central laboratory using standardized procedures.17 For GFR-based kidney outcomes, serum creatinine was used to calculate eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; one component of the incident or worsening nephropathy kidney endpoint (doubling of serum creatinine level accompanied by an eGFR of ≤ 45 mL/min/1.73 m²) was based on the MDRD formula.
2.2 | Overt and non-overt DKD population

For this report, we defined three subgroups from the overall population of EMPA-REG OUTCOME: (a) patients with overt albuminuria (overt DKD [UACR > 300 mg/g] with any eGFR [CKD-EPI] at baseline); (b) patients with non-overt DKD (eGFR < 60 mL/min/1.73 m² without overt albuminuria [UACR ≤ 300 mg/g] at baseline); and (c) all other participants (eGFR ≥ 60 mL/min/1.73 m² without overt albuminuria [UACR ≤ 300 mg/g] at baseline).

2.3 | CV and kidney outcomes

The present exploratory analysis focused on the CV and kidney outcomes mentioned above among patients with different clinical phenotypes of DKD at baseline (i.e. with the presence or absence of overt albuminuria). The following CV outcomes were measured: CV death, hospitalization for heart failure (HHF), the composite of HHF or CV death (excluding fatal stroke), all-cause hospitalization, all-cause mortality and three-point major adverse cardiovascular events (3P-MACE).

The kidney outcome of incident or worsening nephropathy was defined as: progression to macroalbuminuria (UACR > 300 mg/g; a doubling of the serum creatinine level, accompanied by an eGFR of <45 mL/min/1.73 m², as calculated by the MDRD formula); the initiation of kidney-replacement therapy; or death from kidney disease (previously reported by Wanner et al.13). Initiation of kidney replacement therapy was considered to be ‘sustained’ when investigators reported ‘long-term treatment’ or the intervention had no definitive stopping date.18 We also defined two additional post hoc composite kidney endpoints not previously reported: (a) a hard kidney endpoint, defined as kidney failure (initiation of kidney replacement therapy, a sustained eGFR of <15 mL/min/1.73 m²), sustained doubling of serum creatinine from baseline or kidney death (this is identical to a secondary outcome tested in the recent CRESCENDO trial [NCT02065791])15, and (b) an alternative kidney endpoint, defined as a sustained eGFR of less than 10 mL/min/1.73 m², a sustained eGFR decline of 40% from baseline, initiation of kidney replacement therapy (not required to be sustained) or kidney death (this is the composite kidney endpoint included in the primary outcome in the EMPA-KIDNEY study; NCT03594110).20 All three composite kidney endpoints were also analysed when CV death was added as an outcome component (i.e. as composite cardio/kidney endpoints).

For the incident or worsening nephropathy endpoint, patients with overt DKD were not considered in the subgroup analyses as the criterion of a UACR of more than 300 mg/g was as per definition already fulfilled at baseline. Hospitalizations were recorded as part of adverse events (AEs) reporting (as one of the qualifying criteria for having a serious AE). Hospitalization events as such were not to be confirmed by adjudication, but the outcome of all-cause hospitalization included hospitalization events that fulfilled the criteria for adjudication as other types of outcomes (e.g. CV outcomes, which were sent for adjudication).

For eGFR slope analyses reported herein, because of the acute haemodynamic effect, eGFR slopes were separately calculated for the prespecified study periods: treatment initiation from baseline to week 4, the chronic maintenance phase from week 4 to last value on treatment, and the post-treatment phase (last value on treatment to follow-up). The main efficacy outcome was the average rate of change of eGFR per year during the trial period when patients received stable treatment with study drug (from week 4 until treatment cessation, i.e. the chronic maintenance treatment period) and results are expressed as annual changes in eGFR in accordance with previously published prespecified analysis.21

Safety has already been reported in the overall population,13,14 and was assessed in the current analysis based on AEs reported in relevant subgroups. AE data were based on investigator reports without any formal adjudication.

2.4 | Analyses

Analyses were performed in the treated set (patients who received at least one dose of study drug [modified intent-to-treat approach]). We compared treatment effects of empagliflozin versus placebo on CV and kidney outcomes across subgroups. Treatment group differences in the risk of an outcome were assessed using a Cox proportional hazards model with treatment, age, sex, baseline body mass index, baseline HbA1c, region, subgroup and subgroup-by-treatment interaction as factors. Changes in eGFR per year, further referred to as eGFR slope, were obtained using a random-intercept/random-coefficient model, as described previously.21 For safety, first events were analysed as event rates by a Poisson model with factors for treatment, subgroup and subgroup-by-treatment interaction. This was performed to obtain rate ratios based on the first event for all subgroups. All analyses were performed on a nominal two-sided α = 0.05 without adjustment for multiplicity.

3 | RESULTS

3.1 | Patient disposition

A total of 7020 patients were randomized; the median duration of treatment was 2.6 years and the median observation time was 3.1 years. Overall, 97.0% of patients completed the study, and final vital status was available for 99.2%. UACR and eGFR values at baseline were available for 6952 (99.0%) patients (68 [1.0%] individuals had missing kidney data at baseline and were excluded from the subgroup analyses), allowing for appropriate subgroup allocation. Based on our selected subgroup definitions for clinical phenotypes of DKD, 769 (11.0%) participants from EMPA-REG OUTCOME were identified to have overt DKD at baseline, 1290 (18.4%) had non-overt DKD at baseline, and 4893 (69.7%) met neither of the two clinical phenotypes of DKD criteria and were classified as ‘all others’. Figure 1 illustrates the distribution of the three subgroups across the Kidney Disease Improving Global Outcomes heat map for identifying patients at increased cardio/kidney risk.
3.2 | Baseline characteristics

Baseline clinical characteristics and concomitant medications of the three patient subgroups (overt DKD vs. non-overt DKD vs. ‘all others’) are shown in Table 1. Data below, if not indicated otherwise, are mean ± standard deviation in patients treated with at least one dose of study drug. As expected, baseline eGFR was lowest for patients with non-overt DKD (64.9 ± 21.0 vs. 47.7 ± 7.5 vs. 82.4 ± 17.3 mL/min/1.73 m²), whereas UACR levels (geometric mean) were highest in those with overt DKD (877.12 vs. 22.99 vs. 15.16 mg/g). Patients with non-overt DKD tended to be the oldest out of the three subgroups (63.6 ± 8.4 vs. 68.5 ± 7.5 vs. 61.7 ± 8.4 years) and were more often female (n: 184 [23.9%] vs. 425 [32.9%] vs. 1380 [28.2%]). By contrast, at baseline, patients with overt DKD had long-standing type 2 diabetes (n > 10 years: 543 [70.6%] vs. 862 [66.8%] vs. 2569 [52.5%]), higher systolic blood pressure (143.6 ± 18.3 vs. 134.7 ± 17.8 vs. 134.3 ± 16.2 mmHg) and higher total cholesterol values (174.6 ± 52.5 vs. 160.6 ± 42.3 vs. 161.7 ± 42.4 mg/dL) out of the three subgroups. A total of 260, 440 and 1617 patients received placebo in the overt DKD, non-overt DKD and all other subgroups, respectively, while 509, 850 and 3276 patients received empagliflozin in the three subgroups, respectively.

Regarding macrovascular complications, the presence of established coronary artery disease or coronary artery bypass graft tended to be more frequent in those with non-overt DKD at baseline compared with the overt DKD and the ‘all others’ groups. By contrast, microvascular complications (diabetic retinopathy) were reported more frequently in those with overt DKD at baseline compared with the non-overt and ‘all others’ groups. Overall, more than 90% of patients were taking antihypertensive therapies at baseline, most commonly angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (>80%), with similar frequencies across the three subgroups.

3.3 | Empagliflozin and effects on CV and kidney outcomes

Overall, individuals with overt DKD had the highest incidence rates for CV outcomes, followed by patients with non-overt DKD and the ‘all others’ group (Figure 2A). Among the total trial population, empagliflozin significantly reduced the risk of CV death [hazard ratio (HR), 0.62; 95% CI, 0.49, 0.77], HHF (HR, 0.65; 95% CI, 0.50, 0.85) and all-cause hospitalization (HR, 0.89; 95% CI, 0.82, 0.96). These effects were consistent across the three subgroups (all P-values for interaction >.05; Figure 3A).

In the overall trial population, there were no effects of empagliflozin on MI [hazard ratio (HR), 0.87; 95% CI, 0.70, 1.09] or stroke (HR, 1.18; 95% CI, 0.89, 1.56) and these results were consistent across the three subgroups (all P-values for interaction >.05).

Overall, individuals with overt DKD had the highest incidence rates for kidney as well as combined cardio/kidney outcomes, followed by patients with non-overt DKD and the ‘all others’ group (Figure 2B,C). For incident or worsening nephropathy, incidence rates were higher for the non-overt DKD group versus the ‘all others’ group, while overt DKD patients were not considered in the analysis of this endpoint. Among the total trial population, empagliflozin...
|                                            | Overt DKD (N = 769) | Non-overt DKD (N = 1290) | All others (N = 4893) |
|-------------------------------------------|---------------------|--------------------------|-----------------------|
| **Age, y**                                | 63.6 ± 8.4          | 68.5 ± 7.5               | 61.7 ± 8.4            |
| **Male**                                  | 585 (76.1)          | 865 (67.1)               | 3513 (71.8)           |
| **Race**                                  |                     |                          |                       |
| White                                     | 495 (64.4)          | 985 (76.4)               | 3545 (72.5)           |
| Black/African American                    | 50 (6.5)            | 55 (4.3)                 | 250 (5.1)             |
| Asian                                     | 211 (27.4)          | 244 (18.9)               | 1053 (21.5)           |
| Native Hawaiian or other Pacific          | 0                   | 0                        | 10 (0.2)              |
| American Indian or Alaska native          | 13 (1.7)            | 6 (0.5)                  | 35 (0.7)              |
| **Ethnicity**                             |                     |                          |                       |
| Not Hispanic or Latino                    | 579 (75.3)          | 1091 (84.6)              | 4024 (82.2)           |
| Hispanic or Latino                        | 190 (24.7)          | 197 (15.3)               | 863 (17.6)            |
| Missing                                   | 0                   | 2 (0.2)                  | 6 (0.1)               |
| **Region**                                |                     |                          |                       |
| Europe                                    | 242 (31.5)          | 461 (35.7)               | 2146 (43.9)           |
| North America                             | 146 (19.0)          | 383 (29.7)               | 851 (17.4)            |
| Latin America                             | 156 (20.3)          | 166 (12.9)               | 748 (15.3)            |
| Africa                                    | 29 (3.8)            | 72 (5.6)                 | 206 (4.2)             |
| Asia                                      | 196 (25.5)          | 208 (16.1)               | 942 (19.3)            |
| **BMI, kg/m²**                            | 30.25 ± 5.44        | 31.0 ± 5.4               | 30.6 ± 5.2            |
| **SBP, mmHg**                             | 143.6 ± 18.3        | 134.7 ± 17.8             | 134.3 ± 16.2          |
| **DBP, mmHg**                             | 78.1 ± 10.2         | 73.8 ± 10.1              | 77.2 ± 9.6            |
| **Total cholesterol, mg/dL**              | 174.6 ± 52.5        | 160.6 ± 42.3             | 161.7 ± 42.4          |
| **Low-density lipoprotein cholesterol, mg/dL** | 93.7 ± 41.5        | 82.7 ± 34.2              | 85.0 ± 35.0           |
| **High-density lipoprotein cholesterol, mg/dL** | 44.6 ± 12.3        | 43.9 ± 11.9              | 44.5 ± 11.5           |
| **Triglycerides, mg/dL**                  | 188.5 ± 160.7       | 174.6 ± 110.6            | 166.5 ± 124.9         |
| **eGFR, mL/min/1.73 m² (MDRD)**           | 64.9 ± 21.0         | 47.7 ± 7.5               | 82.4 ± 17.3           |
| **UACR, mg/g (gmean [Q1, Q3, %])**        | 877 [441, 1461]     | 23 [8, 67]               | 15 [6, 37]            |
| **History of cardiovascular disease**      |                     |                          |                       |
| CAD                                       | 536 (69.7)          | 1032 (80.0)              | 3687 (75.4)           |
| CABG                                      | 187 (24.3)          | 437 (33.9)               | 1095 (22.4)           |
| MI                                        | 324 (42.1)          | 588 (45.6)               | 2332 (47.7)           |
| PAD                                       | 226 (29.4)          | 292 (22.6)               | 930 (19.0)            |
| Stroke                                    | 211 (27.4)          | 313 (24.3)               | 1097 (22.4)           |
| Cardiac failure                           | 90 (11.7)           | 190 (14.7)               | 424 (8.7)             |
| **Diabetic retinopathy**                  | 281 (36.5)          | 302 (23.4)               | 942 (19.3)            |
| **Diabetic nephropathy**                  | 354 (46.0)          | 435 (33.7)               | 567 (11.6)            |
| **Diabetic neuropathy**                   | 301 (39.1)          | 474 (36.7)               | 1404 (28.7)           |
| **HbA1c, %**                              | 8.23 ± 0.88         | 8.03 ± 0.84              | 8.06 ± 0.84           |
| **Time since diagnosis of T2D, y**         |                     |                          |                       |
| ≤1                                        | 16 (2.1)            | 21 (1.6)                 | 143 (2.9)             |
| >1 to 5                                   | 70 (9.1)            | 123 (9.5)                | 880 (18.0)            |
| >5 to 10                                  | 140 (18.2)          | 284 (22.0)               | 1301 (26.6)           |
| >10                                       | 543 (70.6)          | 862 (66.8)               | 2569 (52.5)           |
| **Glucose-lowering therapy**              |                     |                          |                       |
| Metformin                                 | 522 (67.9)          | 751 (58.2)               | 3871 (79.1)           |
| Insulin                                   | 478 (62.2)          | 731 (56.7)               | 2142 (43.8)           |
significantly reduced the risk of incident or worsening nephropathy (HR, 0.61; 95% CI, 0.53, 0.70),13 the ‘hard’ kidney composite endpoint (HR, 0.40; 95% CI, 0.25, 0.65) and the ‘alternative’ kidney composite endpoint (HR, 0.59; 95% CI, 0.45, 0.78). These effects were consistent across the three subgroups of patients with overt DKD, patients with non-overt DKD and ‘all others’ (all P-values for interaction >.05; Figure 3B). Results were similar when CV death was added as an additional component to all three composite kidney endpoints in the overall trial population, with consistent effects across all three subgroups studied. Among the total trial population, empagliflozin significantly reduced the risk of incident or worsening nephropathy or CV death (HR, 0.61; 95% CI, 0.55, 0.69),13 the ‘hard’ kidney composite endpoint or CV death (HR, 0.57; 95% CI, 0.47, 0.70) and the ‘alternative’ kidney composite endpoint or CV death (HR, 0.61; 95% CI, 0.51, 0.73). Again, these effects were consistent across the three subgroups (all P-values >.05; Figure 3C).

3.4 | Kidney function

Figure S1 shows the change in eGFR over time for the three subgroups. Figure 4 shows the adjusted mean change in eGFR per week/year over the three prespecified study periods. Empagliflozin significantly reduced the yearly loss of eGFR, as assessed by chronic slopes from week 4 onward, in all three subgroups (Figure 4). Adjusted annual mean eGFR slopes (eGFR change per year [95% CI]) with empagliflozin during chronic maintenance treatment were significantly less decreased versus placebo in all three subgroups (overt DKD: −1.60 [−2.10, −1.10] vs. −6.00 [−6.91, −5.10]; non-overt DKD: 0.55 [0.19, 0.92] vs. −0.74 [−1.31, −0.16]; ‘all others’: −0.20 [−0.37, −0.03] vs. −1.48 [−1.76, −1.20] mL/min/1.73 m² per year, respectively; P < .001 for all within-group comparisons). The corresponding data for eGFR change per week for the acute and post-treatment periods are shown in Figure 4.
FIGURE 2  Incidence rates of cardiovascular, kidney and cardio/kidney endpoints with empagliflozin and placebo in EMPA-REG OUTCOME and among subgroups of patients with overt diabetic kidney disease (DKD), patients with non-overt DKD and ‘all others’ at baseline. A, cardiovascular (CV) outcomes; B, kidney outcomes; C, cardio/kidney outcomes. Incident or worsening nephropathy was defined as: progression to macroalbuminuria (urinary albumin-to-creatinine ratio [UACR] > 300 mg/g); a doubling of serum creatinine, accompanied by an estimated glomerular filtration rate (eGFR) of ≤ 45 mL/min/1.73 m² (modification of diet in renal disease [MDRD] study formula); initiation of kidney replacement therapy (KRT); or kidney death. *Sustained eGFR < 15 mL/min/1.73 m², sustained doubling of serum creatinine from baseline, initiation of KRT or kidney death. †Sustained eGFR < 10 mL/min/1.73 m², sustained eGFR (chronic kidney disease epidemiology collaboration [CKD-EPI]) decline of 40% from baseline, initiation of KRT or kidney death. Overt DKD defined as UACR > 300 mg/g with any eGFR (CKD-EPI); non-overt DKD defined as eGFR > 60 mL/min/1.73 m² and UACR ≤ 300 mg/g; “all others” defined as eGFR ≥ 60 mL/min/1.73 m² and UACR ≤ 300 mg/g. HHF, hospitalization for heart failure; n/a, not analysed (patients with macroalbuminuria at baseline were not analysed as ‘progression to macroalbuminuria’ was a component of this endpoint)
The effect of empagliflozin versus placebo on AEs by albuminuric status, as incidence rate ratios, is shown in Figure S2. The AE profile of empagliflozin was similar across patients with overt DKD, patients with non-overt DKD and the ‘all others’ group. In all subgroups, rates of AEs consistent with genital infection were greater with empagliflozin than with placebo (incidence rate ratios [95% CI] for overt DKD, non-overt DKD and all others were 7.26 [1.73, 30.37], 3.39 [1.53, 7.52] and 3.30 [2.29, 4.76], respectively). All other AEs (AEs leading to discontinuation, serious AEs, confirmed hypoglycaemia, urinary tract infection, decreased renal function, acute kidney injury, volume depletion, hyperkalaemia, oedema and bone fracture) occurred at lower or similar rates with empagliflozin compared with placebo. The interaction P-values were >.05 for all AEs assessed except for the incidence of confirmed hypoglycaemia.

4 | DISCUSSION

Reduced kidney function and increased albuminuria are both independently associated with CV risk and premature mortality in individuals with and without diabetes. The overt albuminuric form of DKD in particular is highly predictive for the risk of kidney failure. Although historically DKD was considered to be characterized by high levels of proteinuria (i.e. albuminuria), recently the spectrum of DKD has undergone a significant shift, with non-overt forms of kidney disease now being the most prevalent form in the United States. The authors of a recent comprehensive epidemiological study speculated that frequent use of RAS inhibition may have contributed, at least in part, to this phenomenon. Conversely, a recent small biopsy study in individuals with type 2 diabetes reported that typical structural changes in the kidneys associated with diabetes are less common in patients with kidney impairment (eGFR ≤ 60 mL/min/1.73 m²) in the absence of normo-albuminuria. Instead, the study results suggest that in these individuals a multi-factorial pathogenesis for DKD is probable, with additional contributions from ageing, hypertension and intra-kidney vascular disease. Currently, there is no approved treatment for non-overt forms of DKD and clinical evidence in this important patient population is scarce.

We provide novel insights from the EMPA-REG OUTCOME trial in patients with type 2 diabetes and established CVD by reporting clinical outcome effects of the sodium-glucose co-transporter-2 (SGLT2) inhibitor empagliflozin in patients with different clinical phenotypes of DKD at baseline. We defined three subgroups from the overall population of the trial, namely, patients with overt albuminuria (overt DKD [UACR > 300 mg/g] with any eGFR [CKD-EPI] at baseline; N = 769), patients with non-overt DKD (eGFR < 60 mL/min/1.73 m² without overt albuminuria [UACR ≤ 300 mg/g] at baseline; N = 1290) and all other participants (eGFR ≥ 60 mL/min/1.73 m² without overt albuminuria [UACR ≤ 300 mg/g] at baseline; N = 4893).

Results suggest that empagliflozin treatment leads to clinically meaningful improvements in CV, as well as in hard kidney outcomes, irrespective of the presence of DKD and/or the accompanying degree of albuminuria at baseline. The observed treatment effects with empagliflozin were consistent and robust across the three defined subgroups for the relative risk reductions in CV, kidney and combined cardio/kidney outcomes compared with placebo when given in addition to standard of care. Similar findings have been observed by the CANVAS investigators, who have reported that canagliflozin produced beneficial effects on the risk of kidney and CV outcomes that were mostly consistent across patients with different levels of albuminuria, although the absolute benefits were greatest among those with overt DKD. The current study also builds on the findings from a meta-analysis in 2019 of major SGLT2 inhibitor trials, which showed consistent treatment effects across different levels of albuminuria.

Almost one-third of the EMPA-REG OUTCOME population had some level of DKD at baseline, providing adequate numbers to facilitate further analyses for subgroups of DKD. Hence, our analyses provide one of the largest clinical datasets exploring potential beneficial interventions in patients with non-overt DKD, and our hypothesis-generating findings may encourage future research in this field. As an example, the ongoing EMPA-KIDNEY study with empagliflozin is recruiting patients with and without diabetes, as well as individuals with kidney impairment or CKD stages but without overt albuminuria. This trial is therefore uniquely designed to expand the existing and/or upcoming evidence from canagliflozin and dapagliflozin in patients with albuminuric DKD (CREDENCE trial) and albumuric CKD (DAPA-CKD trial) by generating additional interventional evidence for patients with forms of kidney disease across the spectrum of albuminuria.

Our subgroup findings from EMPA-REG OUTCOME in patients with overt DKD are in line with the recently published results from the CREDENCE trial. The latter study explored the cardio/kidney effects of the SGLT2 inhibitor canagliflozin in type 2 diabetes patients with overt albuminuria (UACR > 300 mg/g) and CKD stages 1 to 3 (i.e. GFR 30-90 mL/min/1.73 m²). Canagliflozin reduced the risk of the primary cardio/kidney endpoint by 30% (HR, 0.70; 0.59, 0.82; P < .001). In a post hoc approach, we applied the primary composite endpoint of CREDENCE to our dataset, and the respective treatment effect with empagliflozin in patients with overt DKD appeared overall to be in line with the findings from CREDENCE (HR, 0.49; 95% CI, 0.34, 0.72). Notably, our analyses expand the clinical evidence beyond overt DKD by further analysing patients with kidney impairment or CKD stages but without overt albuminuria. EMPA-REG OUTCOME had no specific enrichment or exclusion criteria based on albuminuria levels, which allowed a broad representation of DKD forms within the overall trial population. Our results show the consistency of the effects of empagliflozin across the subgroups of patients with and without DKD and thus indicate that the cardio/kidney benefits of empagliflozin may be present across the spectrum of kidney disease in type 2 diabetes, irrespective of accompanying levels of albuminuria.

Our results are also interesting from a mechanistic perspective. Previous experimental and clinical studies have suggested that a potentially key mechanism by which SGLT2 inhibition may confer kidney protection is by activation of tubulo-glomerular feedback (TGF). SGLT2 inhibitors block glucose-sodium co-transport at the
luminal site of proximal tubules, thereby leading to increased delivery of sodium (and chloride) to the macula densa, resulting in TGF activation/increase in urinary adenosine, which have both been reported in type 1 diabetes and type 2 diabetes. This eventually causes a reduction in glomerular pressure, thereby reducing glomerular hypertension and single-nephron hyperfiltration. According to the

| A | Empagliflozin | Placebo | Hazard ratio (95% CI) | Hazard ratio (95% CI) | Interaction P-value |
|---|---|---|---|---|---|
| CV death |  |  |  |  |  |
| All patients | 172/4687 3.7 | 137/2333 5.9 | 0.62 (0.49, 0.77) |  | .2567 |
| Overt DKD | 42/509 8.3 | 36/260 13.8 | 0.54 (0.35, 0.85) |  | .7087 |
| Non-overt DKD | 47/850 5.5 | 29/440 6.6 | 0.86 (0.54, 1.37) |  | .3408 |
| All others | 82/3276 2.5 | 72/1617 4.5 | 0.55 (0.40, 0.76) |  | .5750 |
| HHF |  |  |  |  |  |
| All patients | 126/4687 2.7 | 95/2333 4.1 | 0.65 (0.50, 0.85) |  | .7368 |
| Overt DKD | 32/509 6.3 | 24/260 9.2 | 0.58 (0.34, 0.99) |  | .3841 |
| Non-overt DKD | 31/850 3.6 | 29/440 6.6 | 0.57 (0.34, 0.95) |  |  |
| All others | 62/3276 1.9 | 42/1617 2.6 | 0.72 (0.49, 1.07) |  |  |
| HHF or CV death* |  |  |  |  |  |
| All patients | 265/4687 5.7 | 198/2333 8.5 | 0.66 (0.55, 0.79) |  |  |
| Overt DKD | 67/509 13.2 | 50/260 19.2 | 0.59 (0.41, 0.85) |  |  |
| Non-overt DKD | 67/850 7.9 | 49/440 11.1 | 0.72 (0.50, 1.05) |  |  |
| All others | 129/3276 3.9 | 99/1617 6.1 | 0.64 (0.49, 0.83) |  |  |
| All-cause mortality |  |  |  |  |  |
| All patients | 269/4687 5.7 | 194/2333 8.3 | 0.68 (0.57, 0.82) |  | .2343 |
| Overt DKD | 63/509 12.4 | 41/260 15.8 | 0.71 (0.48, 1.05) |  | .3408 |
| Non-overt DKD | 74/850 8.7 | 50/440 11.4 | 0.78 (0.55, 1.12) |  | .3841 |
| All others | 131/3276 4.0 | 103/1617 6.4 | 0.62 (0.48, 0.80) |  |  |
| All-cause hospitalization |  |  |  |  |  |
| All patients | 1725/4687 36.8 | 925/2333 39.6 | 0.89 (0.82, 0.96) |  |  |
| Overt DKD | 237/509 46.6 | 139/260 53.5 | 0.77 (0.62, 0.94) |  |  |
| Non-overt DKD | 373/850 43.9 | 208/440 47.3 | 0.88 (0.74, 1.05) |  |  |
| All others | 1093/3276 33.4 | 575/1617 35.6 | 0.91 (0.82, 1.01) |  |  |
| 3P-MACE |  |  |  |  |  |
| All patients | 490/4687 10.5 | 282/2333 12.1 | 0.86 (0.74, 0.99) |  |  |
| Overt DKD | 86/509 16.9 | 58/260 22.3 | 0.69 (0.49, 0.96) |  |  |
| Non-overt DKD | 114/850 13.4 | 67/440 15.2 | 0.90 (0.67, 1.22) |  |  |
| All others | 285/3276 8.7 | 157/1617 9.7 | 0.89 (0.73, 1.08) |  |  |

**FIGURE 3** Cardiovascular, kidney and cardio/kidney endpoints in empagliflozin versus placebo overall and by subgroups of patients with overt diabetic kidney disease (DKD), patients with non-overt DKD and ‘all others’ at baseline. A, cardiovascular (CV) outcomes; B, kidney outcomes; C, cardio/kidney outcomes. Cox regression analyses in patients treated with at least one dose of study drug. Interaction P-value is for test of homogeneity of treatment group difference between subgroups with no adjustment for multiple tests. Data for patients who did not have an event were censored on the last day they were known to be free of the outcome. *excludes fatal stroke. **defined as: progression to macroalbuminuria (urinary albumin-to-creatinine ratio [UACR] > 300 mg/g); a doubling of serum creatinine, accompanied by an estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73 m² (modification of diet in renal disease [MDRD] study formula); initiation of kidney replacement therapy (KRT); or kidney death. †Defined as an eGFR of <15 mL/min/1.73 m², sustained doubling of serum creatinine from baseline, initiation of KRT or kidney death. ‡Defined as a sustained eGFR of <10 mL/min/1.73 m², sustained eGFR decline of 40% from baseline, initiation of KRT or kidney death. Overt DKD defined as UACR > 300 mg/g with any eGFR [chronic kidney disease epidemiology collaboration [CKD-EPI]]; non-overt DKD defined as an eGFR of <60 mL/min/1.73 m² and UACR of ≤300 mg/g; ‘all others’ defined as eGFR ≥60 mL/min/1.73 m² and UACR ≤300 mg/g. 3P-MACE, three-point major adverse cardiovascular events; CI, confidence interval; HHF, hospitalization for heart failure; NA, not analysed (patients with macroalbuminuria at baseline were not analysed as ‘progression to macroalbuminuria’ was a component of this endpoint); NC, not calculated
The single-nephron hypothesis, the latter is being considered as a key pathophysiological factor in the progression of CKD. Elevated levels of proteinuria, in particular in the range of macro-molecular proteins such as albumin, are considered a surrogate for increased glomerular pressure. Hence, the beneficial effects of SGLT2 inhibitors in patients with overt DKD may at least in part be explained by the haemodynamic concept of lowering intra-glomerular pressure.

However, our findings of consistent effects of empagliflozin in subgroups of patients irrespective of the presence of albuminuria support recent hypotheses that additional cardio/kidney mechanisms may be involved. Improved cellular energy status with altered cellular substrate utilization, increased kidney tissue oxygenation and kidney anti-inflammatory and antifibrotic effects with this class of drugs have been postulated. Putative cardio/kidney protective mechanisms have recently been discussed thoroughly in a dedicated review article by Cherney et al.

Our study has important limitations. EMPA-REG OUTCOME was designed as a CV outcomes study and thus all kidney endpoints (either prespecified or post hoc) have to be considered hypothesis-generating in nature: only patients with type 2 diabetes and established CVD were enrolled in the trial, so this may limit the generalizability of the findings. In addition, the current analysis is post hoc, rather than prespecified in nature, and the majority of patients (nearly 5000) were in the ‘all others’ group and only ~800 and ~1300 patients were categorized as having overt DKD and non-overt DKD, respectively. Moreover, this study had a lower-bound eGFR cut-off of

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### Table A

| Incident or worsening nephropathy** | All patients | Overt DKD | Non-overt DKD | All others |
|-----------------------------------|-------------|-----------|---------------|-----------|
| Empagliflozin | 525/4124 | 12.7 | 388/2061 | 18.8 | 0.61 (0.53, 0.70) |
| Placebo | 388/2061 | NA | NA | NA | NC |
| Hazard ratio | 0.61 (0.53, 0.70) | NA | NA | NA | NC |
| Interaction | .1145 | NA | NA | NA | NC |

### Table B

| Hard kidney endpoint† | All patients | Overt DKD | Non-overt DKD | All others |
|-----------------------|-------------|-----------|---------------|-----------|
| Empagliflozin | 31/4645 | 0.7 | 37/2323 | 1.6 | 0.40 (0.25, 0.65) |
| Placebo | 17/504 | 3.4 | 19/260 | 7.3 | 0.40 (0.21, 0.77) |
| Hazard ratio | 0.40 (0.25, 0.65) | NA | NA | NA | NC |
| Interaction | .4462 | NA | NA | NA | NC |

### Table C

| Alternative kidney endpoint‡ | All patients | Overt DKD | Non-overt DKD | All others |
|-----------------------------|-------------|-----------|---------------|-----------|
| Empagliflozin | 108/4645 | 2.3 | 87/2323 | 3.7 | 0.59 (0.45, 0.78) |
| Placebo | 49/504 | 9.7 | 36/260 | 13.8 | 0.56 (0.36, 0.86) |
| Hazard ratio | 0.59 (0.45, 0.78) | NA | NA | NA | NC |
| Interaction | .9858 | NA | NA | NA | NC |

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**Incident or worsening nephropathy**

†Hard kidney endpoint

‡Alternative kidney endpoint

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**FIGURE 3** (Continued)
In conclusion, the clinical phenotype of patients with DKD is changing, with non-overt DKD forms emerging to the forefront. Previous clinical evidence for DKD, however, has exclusively focused on patients with overt albuminuria. The present results from the EMPA-REG OUTCOME trial expand clinical data beyond overt DKD and suggest that SGLT2 inhibition with empagliflozin may improve CV and kidney outcomes and slow the progression of kidney disease in type 2 diabetes patients with and without DKD, and notably, irrespective of the clinical phenotype of DKD in the presence or absence of overt albuminuria.

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**CONFLICT OF INTEREST**

A.K.-W., M.M., J.T.G. and S.J.H. are employees of Boehringer Ingelheim. M.v.E. was an employee of Boehringer Ingelheim at the time of the study.

**DATA SHARING**

The initial draft of the manuscript was developed by C.W., M.v.E. and S.J.H. All authors were fully responsible for all content and editorial decisions and were involved at all stages of manuscript development and have approved the final version. C.W. serves as the guarantor for the content of this work.

**AUTHOR CONTRIBUTIONS**

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**FIGURE 4** Change in estimated glomerular filtration rate (eGFR) (chronic kidney disease epidemiology collaboration [CKD-EPI] formula) per week or year during prespecified study periods. Adjusted mean eGFR slopes across selected subgroups (overt diabetic kidney disease (DKD), non-overt DKD, ‘all others’) are shown. All patients treated with at least one dose of study drug. Adjusted mean slopes represent the average change in eGFR per week or per year assessed using a random-intercept/random-coefficient model as reported previously.\(^{21}\) CI, confidence interval; LVOT, last value on-treatment.
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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

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