Article

Empagliflozin and Cardiovascular and Kidney Outcomes across KDIGO Risk Categories

Post Hoc Analysis of a Randomized, Double-Blind, Placebo-Controlled, Multinational Trial

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Abstract

Background and objectives In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG Outcome), empagliflozin, in addition to standard of care, significantly reduced risk of cardiovascular death by 38%, hospitalization for heart failure by 35%, and incident or worsening nephropathy by 39% compared with placebo in patients with type 2 diabetes and established cardiovascular disease. Using EMPA-REG Outcome data, we assessed whether the Kidney Disease Improving Global Outcomes (KDIGO) CKD classification had an influence on the treatment effect of empagliflozin.

Design, setting, participants, & measurements Patients with type 2 diabetes, established atherosclerotic cardiovascular disease, and eGFR≥30 ml/min per 1.73 m² at screening were randomized to receive empagliflozin 10 mg, empagliflozin 25 mg, or placebo once daily in addition to standard of care. *Post hoc*, we analyzed cardiovascular and kidney outcomes, and safety, using the two-dimensional KDIGO classification framework.

Results Of 6952 patients with baseline eGFR and urinary albumin-creatinine ratio values, 47%, 29%, 15%, and 8% were classified into low, moderately increased, high, and very high KDIGO risk categories, respectively. Empagliflozin showed consistent risk reductions across KDIGO categories for cardiovascular outcomes (*P* values for treatment by subgroup interactions ranged from 0.26 to 0.85) and kidney outcomes (*P* values for treatment by subgroup interactions ranged from 0.16 to 0.60). In all KDIGO risk categories, placebo and empagliflozin had similar adverse event rates, the notable exception being genital infection events, which were more common with empagliflozin for each category.

Conclusions The observed effects of empagliflozin versus placebo on cardiovascular and kidney outcomes were consistent across the KDIGO risk categories, indicating that the effect of treatment benefit of empagliflozin was unaffected by baseline CKD status.

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Introduction

CKD occurs in approximately 40% of patients with type 2 diabetes (1) and leads to a higher risk of mortality and morbidity (2,3). CKD is also a strong risk factor for cardiovascular disease (4). For example, in a large Canadian general population cohort of >900,000 individuals, the proportion of deaths from cardiovascular disease was higher with decreasing eGFR, from 28% in individuals with normal kidney function to 58% in patients with kidney failure (5). As such, treatment of CKD places a major burden on health care systems in terms of resources and costs (6,7). Therefore, there is a strong health and economic imperative to improve clinical outcomes in people with CKD and type 2 diabetes (8). Despite the introduction of novel treatment strategies for type 2 diabetes, it remains uncertain if these approaches can positively affect the course of cardiovascular and kidney disease in patients with type 2 diabetes (9).

In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), a large cardiovascular outcome study in patients with type 2 diabetes and established cardiovascular disease (10), the sodium-glucose cotransporter-2 (SGLT2) inhibitor empagliflozin significantly reduced the risk of cardiovascular death by 38%, risk of hospitalization for heart failure by 35% (10), and risk of incident or worsening nephropathy by 39%, and it decreased progression of kidney disease (11). The urinary albumin-

creatinine ratio (UACR) also improved, irrespective of baseline UACR levels, although these improvements were of greatest clinical relevance in patients with elevated baseline UACR levels (12).

The Kidney Disease Improving Global Outcomes (KDIGO) CKD classification system provides a two-dimensional framework for categorizing patients on the basis of eGFR and UACR as markers of kidney function and damage (3). These guidelines have evolved over time to include an increasingly detailed description of the relationship between GFR, albuminuria, and prognosis, which has improved our understanding of CKD in multiple populations (3). Patients with low eGFR levels and higher urinary albumin excretion rates are at higher risk of both adverse kidney and adverse cardiovascular outcomes, allowing the KDIGO CKD classification system to be adapted into a risk "heat map" as used in this analysis.

The 2012 KDIGO classification framework is a useful tool for assessing severity of kidney disease. However, it is not known whether this classification system is associated with treatment response. Here, we report a *post hoc* comparison of cardiovascular and kidney outcomes in participants in EMPA-REG OUTCOME using the KDIGO classification to determine the effect of baseline KDIGO risk category on treatment effect.

Materials and Methods
Study Design
EMPA-REG OUTCOME was a randomized, double-blind, placebo-controlled, multinational trial (NCT01131676; registration date May 27, 2010). Patients entered a 2-week, open-label, placebo run-in prior to randomization (1:1:1) to empagliflozin 10 mg, empagliflozin 25 mg, or placebo once daily in addition to standard of care for type 2 diabetes and cardiovascular risk management. Randomization was performed with the use of a computer-generated random sequence and interactive voice and web response system, and it was stratified according to the glycated hemoglobin (HbA1c) level at screening (<8.5% or ≥8.5%), body mass index at randomization (<30 or ≥30), kidney function at screening (eGFR of 30–59, 60–89, or ≥90 ml/min per 1.73 m²), and geographic region. Investigators were encouraged to treat cardiovascular risk factors in order to achieve optimal standard of care according to local guidelines (10,13).

The EMPA-REG OUTCOME trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines, and it was approved by local authorities. An independent ethics committee or institutional review board approved the clinical protocol at each participating center. All of the patients provided written informed consent before study entry.

Cardiovascular outcome events and deaths were prospectively adjudicated by clinical events committees. Kidney events were reported by investigators and were not adjudicated. The trial continued until at least 691 patients experienced an adjudicated event included in the primary composite outcome: first occurrence of three-point major adverse cardiovascular event (MACE; composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke). Kidney function at baseline was assessed using the creatinine-based GFR estimating equations on the basis of the Modification of Diet in Renal Disease (MDRD) formula.

Participants
Eligible patients were adults with type 2 diabetes (HbA1c≥7.0% and ≤9.0% for treatment-naïve patients and HbA1c≥7.0% and ≤10.0% for patients on background glucose-lowering therapy), a body mass index of ≤45 kg/m², established cardiovascular disease, and eGFR≥30 ml/min per 1.73 m² (according to MDRD).

Outcomes and Analyses
Prespecified cardiovascular outcomes included three-point MACE and its individual components (*i.e.*, myocardial infarction, stroke, and cardiovascular death), hospitalization for heart failure, and all-cause mortality.

Prespecified kidney outcomes have been previously described in detail and included incident or worsening nephropathy (composite of progression to macroalbuminuria, doubling of serum creatinine accompanied by eGFR of ≤45 ml/min per 1.73 m², initiation of KRT, or death from kidney disease) and progression to macroalbuminuria (11). Additionally, a *post hoc* analysis looked at the composite of doubling of serum creatinine, initiation of KRT, or death from kidney disease.

Cardiovascular and kidney outcomes were analyzed in subgroups by baseline KDIGO risk category (3).

Changes in eGFR values were assessed over time alongside a prespecified eGFR slope analysis for three prespecified study periods (treatment initiation effects from baseline to week 4; chronic maintenance treatment effects from week 4 to last value on treatment; and post-treatment effects from last value on treatment to follow-up) (14).

Analyses were performed in patients treated with at least one dose of study drug, and they compared the placebo and pooled empagliflozin groups. A Cox proportional hazards model was used to investigate the consistency of treatment effect on cardiovascular and kidney outcomes across subgroups. The model included terms for age, sex, baseline HbA1c category, baseline body mass index category, geographical region, treatment, baseline KDIGO risk category, and treatment by baseline KDIGO risk category interaction.

Calculation of eGFR slopes within the three prespecified study periods was performed by applying a separate random coefficient model for each period, allowing for random intercept and random slope per patient (14).

Safety data were analyzed by Poisson regression of first event using log of time at risk as offset and including factors for treatment, KDIGO risk category, and treatment by baseline KDIGO risk category interaction, yielding incidence rate ratios to assess differences between the empagliflozin and placebo groups across KDIGO risk categories.

All analyses were performed on a nominal two-sided $\alpha=0.05$ without adjustment for multiplicity.

Results
The EMPA-REG OUTCOME trial has been described previously (10,13). A total of 7028 patients were randomized to study treatment from September 2010 to April 2013; 7020 patients at 590 sites in 42 countries received one or more doses of study drug (placebo, $n=2333$; empagliflozin

Table 1. Baseline characteristics and concomitant medications of participants were similar between treatment groups across Kidney Disease Improving Global Outcomes risk categories

Parameter	Kidney Disease Improving Global Outcomes Risk Category[a]							
	Low		Moderately Increased		High		Very High	
	Placebo, $n=1099$	Empagliflozin,[b] $n=2223$	Placebo, $n=675$	Empagliflozin,[b] $n=1343$	Placebo, $n=357$	Empagliflozin,[b] $n=710$	Placebo, $n=186$	Empagliflozin,[b] $n=359$
Men	787 (72)	1571 (71)	490 (73)	970 (72)	254 (71)	500 (70)	136 (73)	255 (71)
Age, yr	62±9	61±8	64±9	64±9	66±9	66±8	66±8	67±8
BMI, kg/m^2	30.5±5.2	30.5±5.2	31.0±5.2	30.7±5.3	30.7±5.4	30.6±5.3	30.2±5.3	30.6±5.7
HbA1c, %	8.0±0.8	8.0±0.8	8.1±0.9	8.1±0.9	8.2±0.9	8.2±0.9	8.2±0.9	8.1±0.8
Systolic BP, mm Hg	133±16	132±15	138±17	137±17	139±20	139±19	140±19	141±18
Diastolic BP, mm Hg	77±10	77±9	77±11	77±10	76±11	76±10	76±10	75±10
LDL cholesterol, mg/dl	83±34	85±35	85±34	85±36	89±39	88±37	89±39	90±40
eGFR (MDRD), ml/min per 1.73 m^2	83±16	84±17	74±20	74±20	60±19	61±20	44±8	43±9
≥60	1099 (100)	2223 (100)	470 (70)	926 (69)	145 (41)	286 (40)	0	0
<60	0	0	205 (30)	417 (31)	212 (59)	424 (60)	186 (100)	359 (100)
UACR, mg/g								
<30	1099 (100)	2223 (100)	205 (30)	417 (31)	76 (21)	139 (20)	2 (1)	10 (3)
30–300	0	0	470 (70)	926 (69)	136 (38)	285 (40)	69 (37)	126 (35)
>300	0	0	0	0	145 (41)	286 (40)	115 (62)	223 (62)
UACR, median (IQR), mg/g	7.1 (4.4−14.1)	8.0 (5.3−14.1)	43.3 (16.8−94.6)	43.3 (17.7−89.3)	141.4 (37.1−630.3)	134.4 (39.8−484.4)	406.2 (110.5−908.8)	422.6 (114.0−1067.0)
Background medications								
ACE inhibitors/ARBs	846 (77)	1754 (79)	556 (82)	1119 (83)	305 (85)	585 (82)	147 (79)	299 (83)
Diuretics	405 (37)	841 (38)	295 (44)	605 (45)	172 (48)	360 (51)	110 (59)	216 (60)
History of heart failure	95 (9)	181 (8)	77 (11)	146 (11)	48 (13)	84 (12)	23 (12)	50 (14)
Smoking status								
Never smoked	464 (42)	902 (41)	260 (39)	556 (41)	144 (40)	288 (41)	80 (43)	164 (46)
Ex-smoker	489 (45)	967 (44)	326 (48)	623 (46)	169 (47)	353 (50)	85 (46)	164 (46)
Currently smokes	146 (13)	354 (16)	89 (13)	164 (12)	44 (12)	69 (10)	21 (11)	31 (9)
Duration of diabetes, yr								
≤1	35 (3)	78 (4)	11 (2)	31 (2)	2 (1)	14 (2)	4 (2)	5 (1)
>1–5	216 (20)	424 (19)	103 (15)	189 (14)	41 (12)	65 (9)	10 (5)	25 (7)
>5–10	301 (27)	597 (27)	159 (24)	344 (26)	69 (19)	156 (22)	35 (19)	64 (18)
>10	547 (50)	1124 (51)	402 (60)	779 (58)	245 (69)	475 (67)	137 (74)	265 (74)
Metformin use	885 (81)	1752 (79)	514 (76)	1022 (76)	219 (61)	476 (67)	104 (56)	172 (48)
Insulin use	447 (41)	933 (42)	338 (50)	648 (48)	211 (59)	412 (58)	130 (70)	232 (65)

BMI, body mass index; HbA1c, glycated hemoglobin; MDRD, Modification of Diet in Renal Disease; UACR, urinary albumin-creatinine ratio; IQR, interquartile range; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
[a]Sixty-eight patients were excluded as the subgroup variable was missing.
[b]Pooled. Data are n (%) or mean ± SD unless otherwise indicated.

10 mg, $n=2345$; empagliflozin 25 mg, $n=2342$) (11). The median duration of treatment was 2.6 years (interquartile range, 1.9–3.4), and the median observation time was 3.1 years (interquartile range, 2.2–3.6); 97% of patients completed the trial.

Baseline Characteristics

The distribution of patients across the KDIGO risk categories is shown in Table 1. Among 7020 participants, baseline eGFR and UACR measurements were available for 6952 patients (99%; empagliflozin, $n=4635$; placebo, $n=2317$). Baseline characteristics and concomitant medications were similar between the placebo and empagliflozin groups across the KDIGO risk categories.

The proportions of patients by KDIGO risk category in the overall study population are shown in Figure 1. As expected, randomization led to similar distributions of all patients between placebo and treatment groups within each KDIGO category (approximately 47%, 29%, 15%, and 8% in each treatment group for the low, moderately increased, high, and very high KDIGO risk categories, respectively).

Cardiovascular Outcomes Stratified by Kidney Disease Improving Global Outcomes Risk Status at Baseline

The event rates for all outcomes presented were higher with higher KDIGO risk category for both the empagliflozin- and placebo-treated groups (Figure 2). However, for each of the cardiovascular outcomes (three-point MACE; fatal/nonfatal myocardial infarction and fatal/nonfatal stroke cardiovascular death; hospitalization for heart failure; and all-cause mortality), the reductions in risk with empagliflozin versus placebo were consistent for patients with low, moderately increased, high, and very high KDIGO risk category at baseline (the P values for treatment by subgroup interactions across all cardiovascular outcomes ranged from 0.26 to 0.85) (Figure 2).

Kidney Outcomes Stratified by Kidney Disease Improving Global Outcomes Risk Status at Baseline

As observed with cardiovascular outcomes, the incidence of kidney outcome events was higher with higher KDIGO risk categories for both the empagliflozin and placebo groups (Figure 3). However, for each of the three kidney outcomes (incident or worsening nephropathy; progression to UACR$>$300 mg/g; and the composite of hard kidney end points [doubling of serum creatinine, initiation of KRT, or death from kidney disease]), empagliflozin was associated with a consistent and lower relative risk versus placebo across the KDIGO risk categories (the P values for treatment by subgroup interactions across all kidney outcomes ranged from 0.16 to 0.60) (Figure 3).

Estimated Glomerular Filtration Rate Slopes

The adjusted mean eGFR slopes for the three prespecified study periods are shown in Figure 4. Over the initial 4 weeks of treatment, the weekly mean adjusted eGFR decrease was numerically greater in the empagliflozin versus placebo groups for all KDIGO risk subgroups. During the chronic maintenance treatment period, however, the annual adjusted change in mean eGFR was stable in all empagliflozin subgroups but declined in the placebo subgroups. Finally, during the post-treatment follow-up, the adjusted mean eGFR in the empagliflozin subgroups increased, whereas little change was observed in eGFR levels in the placebo groups.
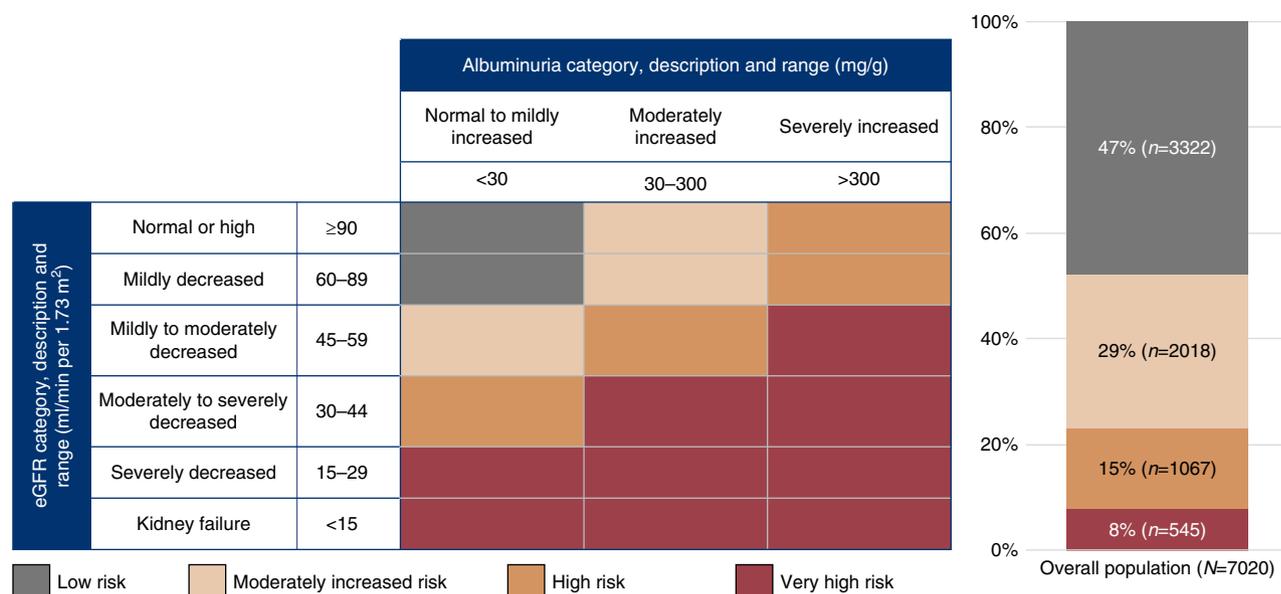

Figure 1. | **Proportions of patients by Kidney Disease Improving Global Outcomes (KDIGO) risk category in the overall trial population, showing that almost half of patients (47%) were in the low-risk category.** The KDIGO "heat map" showing prognosis of CKD by GFR and albuminuria category is shown for reference (3). Of all treated patients, baseline eGFR and urine albumin-creatinine ratio measurements were available for 4635 patients on empagliflozin (98.9%) and 2317 patients on placebo (99.3%). Reprinted from ref. 3, with permission.

	Empagliflozin	Placebo	Hazard ratio (95% CI)	Hazard ratio (95% CI)	P-value for interaction
	n with event/N analyzed (%)				
3-point MACE					
All patients	490/4687 (10.5)	282/2333 (12.1)	0.86 (0.74, 0.99)		
KDIGO risk categories*					0.52
Low risk	175/2223 (7.9)	97/1099 (8.8)	0.89 (0.69, 1.14)		
Moderately increased risk	146/1343 (10.9)	79/675 (11.7)	0.93 (0.71, 1.23)		
High risk	99/710 (13.9)	69/357 (19.3)	0.69 (0.51, 0.94)		
Very high risk	65/359 (18.1)	37/186 (19.9)	0.88 (0.59, 1.32)		
Fatal/nonfatal MI					
All patients	223/4687 (4.8)	126/2333 (5.4)	0.87 (0.70, 1.09)		
KDIGO risk categories*					0.54
Low risk	84/2223 (3.8)	46/1099 (4.2)	0.89 (0.62, 1.28)		
Moderately increased risk	62/1343 (4.6)	37/675 (5.5)	0.85 (0.56, 1.27)		
High risk	43/710 (6.1)	30/357 (8.4)	0.70 (0.44, 1.11)		
Very high risk	32/359 (8.9)	13/186 (7.0)	1.26 (0.66, 2.40)		
Fatal/nonfatal stroke					
All patients	164/4687 (3.5)	69/2333 (3.0)	1.18 (0.89, 1.56)		
KDIGO risk categories*					0.26
Low risk	61/2223 (2.7)	22/1099 (2.0)	1.37 (0.84, 2.24)		
Moderately increased risk	55/1343 (4.1)	18/675 (2.7)	1.51 (0.88, 2.57)		
High risk	30/710 (4.2)	18/357 (5.0)	0.84 (0.47, 1.51)		
Very high risk	16/359 (4.5)	11/186 (5.9)	0.72 (0.33, 1.56)		
Cardiovascular death					
All patients	172/4687 (3.7)	137/2333 (5.9)	0.62 (0.49, 0.77)		
KDIGO risk categories*					0.85
Low risk	53/2223 (2.4)	40/1099 (3.6)	0.65 (0.43, 0.98)		
Moderately increased risk	46/1343 (3.4)	39/675 (5.8)	0.59 (0.39, 0.91)		
High risk	39/710 (5.5)	35/357 (9.8)	0.54 (0.34, 0.85)		
Very high risk	33/359 (9.2)	23/186 (12.4)	0.73 (0.43, 1.24)		
Hospitalization for heart failure					
All patients	126/4687 (2.7)	95/2333 (4.1)	0.65 (0.50, 0.85)		
KDIGO risk categories*					0.46
Low risk	35/2223 (1.6)	20/1099 (1.8)	0.87 (0.50, 1.50)		
Moderately increased risk	34/1343 (2.5)	30/675 (4.4)	0.56 (0.34, 0.92)		
High risk	34/710 (4.8)	23/357 (6.4)	0.72 (0.42, 1.22)		
Very high risk	22/359 (6.1)	22/186 (11.8)	0.48 (0.26, 0.86)		
All-cause mortality					
All patients	269/4687 (5.7)	194/2333 (8.3)	0.68 (0.57, 0.82)		
KDIGO risk categories*					0.50
Low risk	84/2223 (3.8)	61/1099 (5.6)	0.68 (0.49, 0.94)		
Moderately increased risk	69/1343 (5.1)	57/675 (8.4)	0.61 (0.43, 0.86)		
High risk	61/710 (8.6)	47/357 (13.2)	0.63 (0.43, 0.92)		
Very high risk	54/359 (15.0)	29/186 (15.6)	0.93 (0.59, 1.46)		

0.125   0.25   0.5   1   2   4

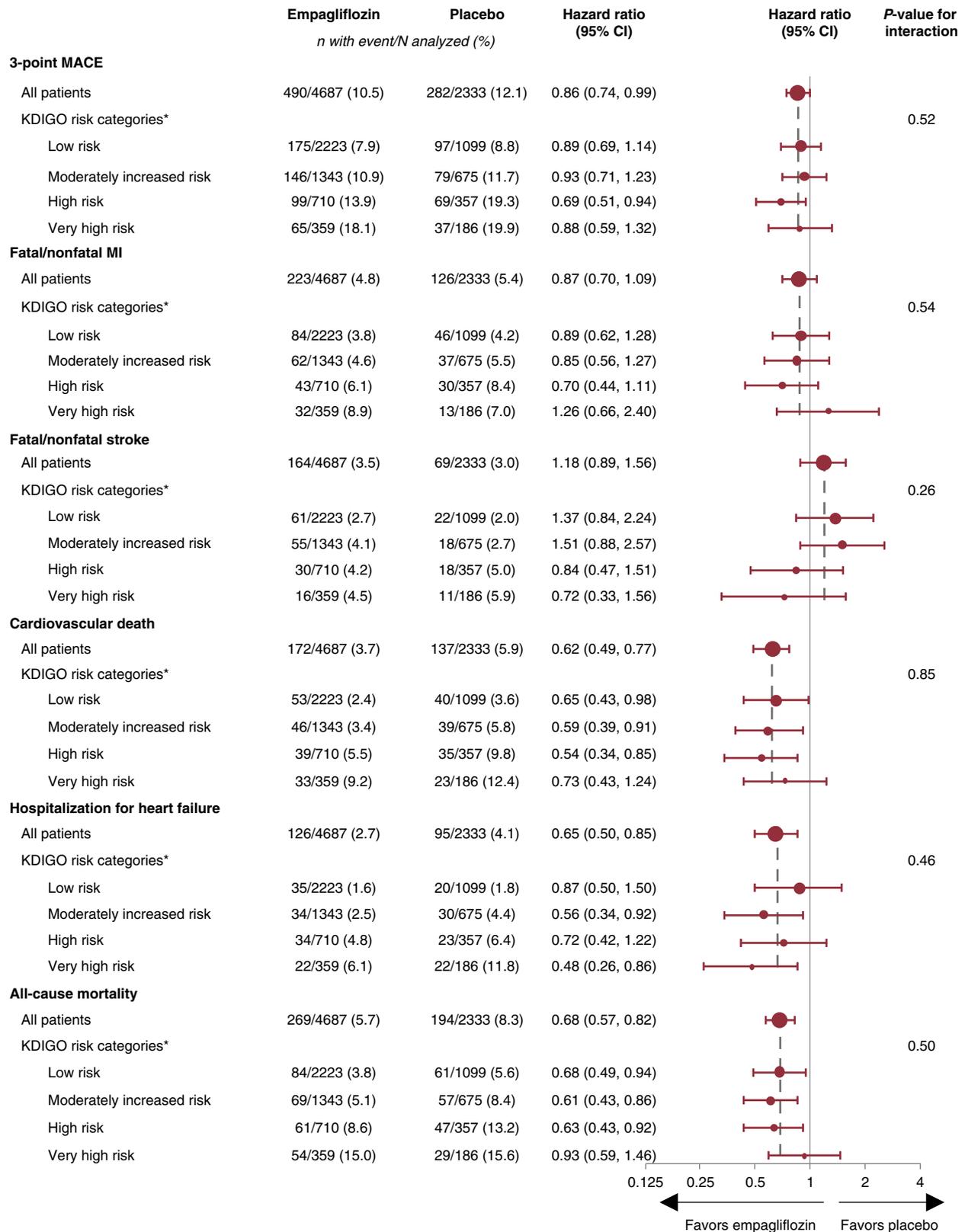Favors empagliflozin   Favors placebo

Figure 2. | Forest plot showing that the risk reduction of cardiovascular outcomes with empagliflozin versus placebo is consistent across KDIGO risk categories. *Sixty-eight patients were excluded as the subgroup variable was missing. 95% CI, 95% confidence interval; MACE, major adverse cardiovascular event; MI, myocardial infarction.
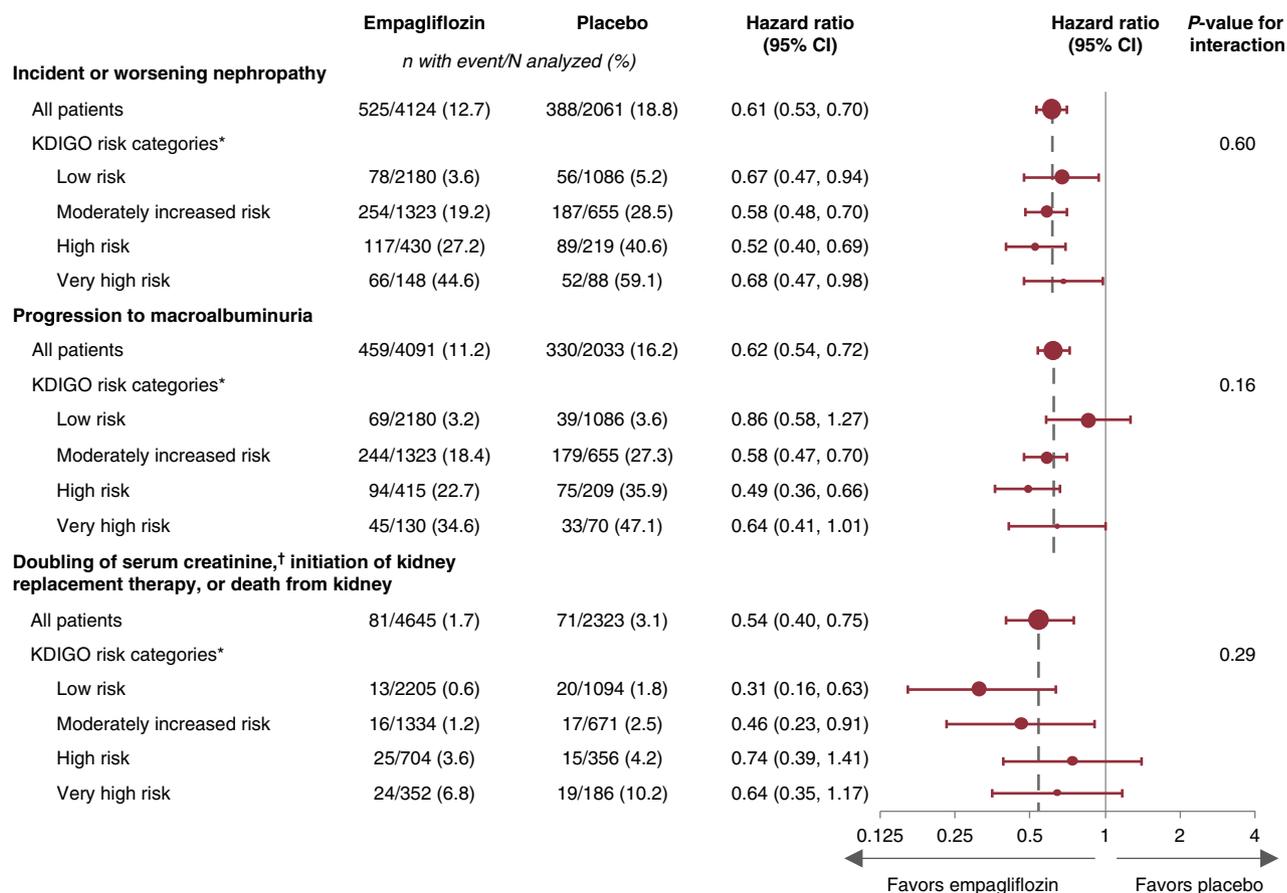
	Empagliflozin	Placebo	Hazard ratio (95% CI)		Hazard ratio (95% CI)	P-value for interaction
	n with event/N analyzed (%)					
Incident or worsening nephropathy						
All patients	525/4124 (12.7)	388/2061 (18.8)	0.61 (0.53, 0.70)			
KDIGO risk categories*						0.60
Low risk	78/2180 (3.6)	56/1086 (5.2)	0.67 (0.47, 0.94)			
Moderately increased risk	254/1323 (19.2)	187/655 (28.5)	0.58 (0.48, 0.70)			
High risk	117/430 (27.2)	89/219 (40.6)	0.52 (0.40, 0.69)			
Very high risk	66/148 (44.6)	52/88 (59.1)	0.68 (0.47, 0.98)			
Progression to macroalbuminuria						
All patients	459/4091 (11.2)	330/2033 (16.2)	0.62 (0.54, 0.72)			
KDIGO risk categories*						0.16
Low risk	69/2180 (3.2)	39/1086 (3.6)	0.86 (0.58, 1.27)			
Moderately increased risk	244/1323 (18.4)	179/655 (27.3)	0.58 (0.47, 0.70)			
High risk	94/415 (22.7)	75/209 (35.9)	0.49 (0.36, 0.66)			
Very high risk	45/130 (34.6)	33/70 (47.1)	0.64 (0.41, 1.01)			
Doubling of serum creatinine,[†] initiation of kidney replacement therapy, or death from kidney						
All patients	81/4645 (1.7)	71/2323 (3.1)	0.54 (0.40, 0.75)			
KDIGO risk categories*						0.29
Low risk	13/2205 (0.6)	20/1094 (1.8)	0.31 (0.16, 0.63)			
Moderately increased risk	16/1334 (1.2)	17/671 (2.5)	0.46 (0.23, 0.91)			
High risk	25/704 (3.6)	15/356 (4.2)	0.74 (0.39, 1.41)			
Very high risk	24/352 (6.8)	19/186 (10.2)	0.64 (0.35, 1.17)			

Scale: 0.125 0.25 0.5 1 2 4
Favors empagliflozin   Favors placebo

Figure 3. | **Forest plot showing that the risk reduction of kidney outcomes with empagliflozin versus placebo is consistent across KDIGO risk categories.** Cox regression analysis in patients treated with one or more doses of study drug. *Sixty-eight patients were excluded as the subgroup variable was missing. [†]Accompanied by eGFR≤45 ml/min per 1.73 m^2. Macroalbuminuria: urine albumin-creatinine ratio >300 mg/g.

Safety

The effect of empagliflozin versus placebo on adverse events by baseline KDIGO risk category, as incidence rate ratios, is shown in Figure 5. The incidence rate ratios were similar for empagliflozin versus placebo across the adverse events assessed, with interaction P values of >0.05 for all except for the incidence of any adverse event and hyperkalemia. Except for genital infections, all incidence rates were similar or lower with empagliflozin versus placebo, indicated by the 95% confidence intervals of the incidence rate ratios below or including unity. As reported in other trials of empagliflozin and in trials of other SGLT2 inhibitors, the rates of adverse events consistent with genital infection were greater with empagliflozin than with placebo; this was seen across KDIGO risk categories (Figure 5).

Discussion

In this *post hoc* analysis of EMPA-REG OUTCOME, the overall numbers of cardiovascular and kidney events were higher with the degree of KDIGO risk categories in both empagliflozin and placebo groups, as reported previously in both diabetic and nondiabetic populations (15). Randomization to empagliflozin versus placebo (both given in addition to standard of care) resulted in a reduction in risk of cardiovascular outcomes (three-point MACE, cardiovascular death, hospitalization for heart failure, and all-cause mortality). This reduction in risk associated with active treatment was similar in relative terms, irrespective of baseline KDIGO risk category, and consistent with what was previously observed in the overall trial population and across patients with or without prevalent kidney disease at baseline (10,16).

In addition, empagliflozin versus placebo also lowered the risk of incident or worsening nephropathy, progression to UACR>300 mg/g, and the composite of hard kidney end points (doubling of serum creatinine, initiation of KRT, or death from kidney disease). These findings, which were seen across all baseline KDIGO risk categories, support previously reported kidney effects in the overall trial population, as well as across eGFR and albuminuria subgroups (11). The treatment effect of SGLT2 inhibitors on eGFR slopes has been shown to be a viable surrogate for clinical end points in CKD trials (17,18). The acute and chronic eGFR slopes in the EMPA-REG OUTCOME trial have previously been published (14), with similar analyses reported from the Canagliflozin Cardiovascular Assessment Study (CANVAS) and the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study (19,20). Given the acute
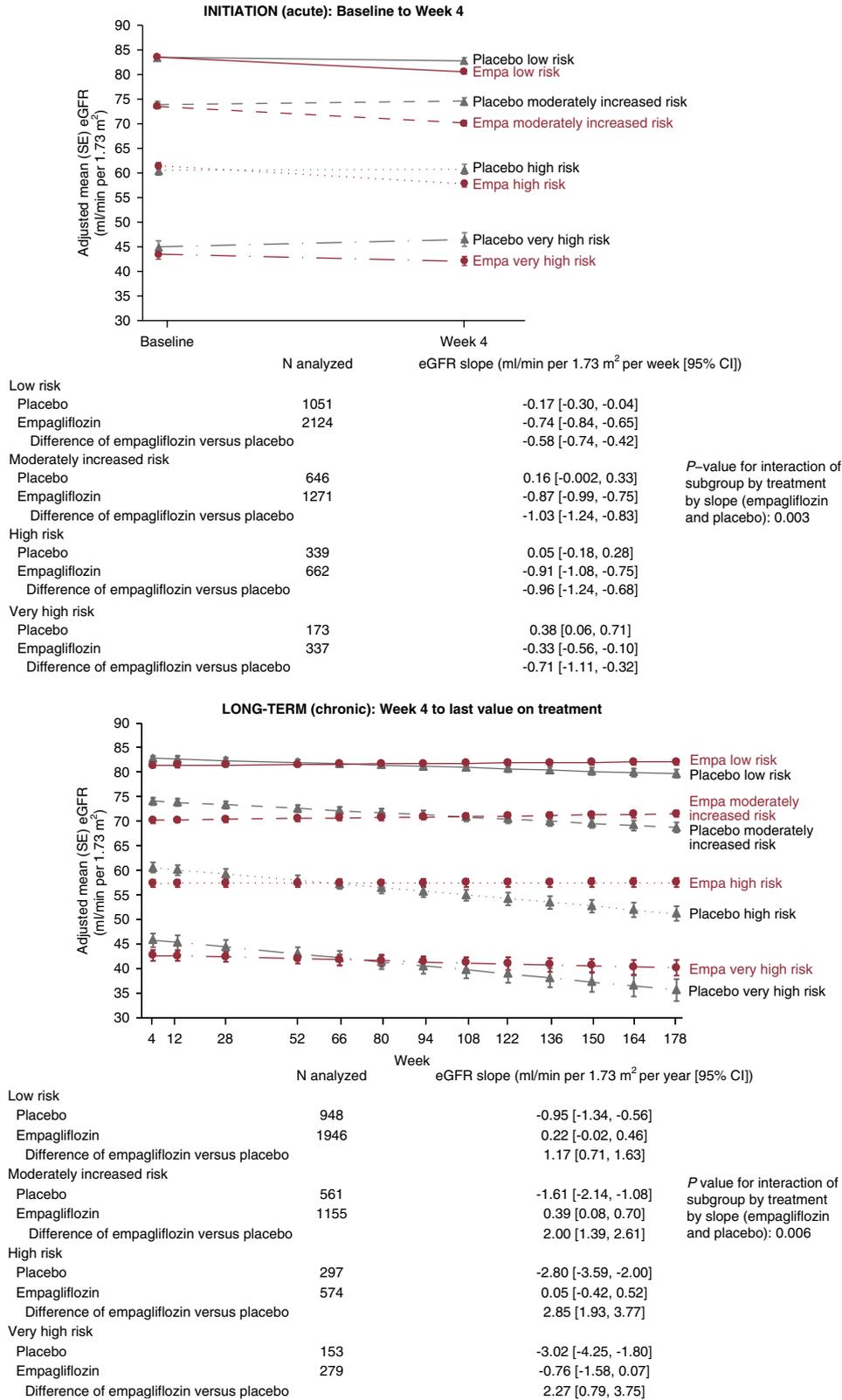
INITIATION (acute): Baseline to Week 4

	N analyzed	eGFR slope (ml/min per 1.73 m^2 per week [95% CI])	
Low risk			
Placebo	1051	-0.17 [-0.30, -0.04]	
Empagliflozin	2124	-0.74 [-0.84, -0.65]	
Difference of empagliflozin versus placebo		-0.58 [-0.74, -0.42]	
Moderately increased risk			
Placebo	646	0.16 [-0.002, 0.33]	*P*–value for interaction of subgroup by treatment by slope (empagliflozin and placebo): 0.003
Empagliflozin	1271	-0.87 [-0.99, -0.75]	
Difference of empagliflozin versus placebo		-1.03 [-1.24, -0.83]	
High risk			
Placebo	339	0.05 [-0.18, 0.28]	
Empagliflozin	662	-0.91 [-1.08, -0.75]	
Difference of empagliflozin versus placebo		-0.96 [-1.24, -0.68]	
Very high risk			
Placebo	173	0.38 [0.06, 0.71]	
Empagliflozin	337	-0.33 [-0.56, -0.10]	
Difference of empagliflozin versus placebo		-0.71 [-1.11, -0.32]	

LONG-TERM (chronic): Week 4 to last value on treatment

	N analyzed	eGFR slope (ml/min per 1.73 m^2 per year [95% CI])	
Low risk			
Placebo	948	-0.95 [-1.34, -0.56]	
Empagliflozin	1946	0.22 [-0.02, 0.46]	
Difference of empagliflozin versus placebo		1.17 [0.71, 1.63]	
Moderately increased risk			
Placebo	561	-1.61 [-2.14, -1.08]	*P* value for interaction of subgroup by treatment by slope (empagliflozin and placebo): 0.006
Empagliflozin	1155	0.39 [0.08, 0.70]	
Difference of empagliflozin versus placebo		2.00 [1.39, 2.61]	
High risk			
Placebo	297	-2.80 [-3.59, -2.00]	
Empagliflozin	574	0.05 [-0.42, 0.52]	
Difference of empagliflozin versus placebo		2.85 [1.93, 3.77]	
Very high risk			
Placebo	153	-3.02 [-4.25, -1.80]	
Empagliflozin	279	-0.76 [-1.58, 0.07]	
Difference of empagliflozin versus placebo		2.27 [0.79, 3.75]	

Figure 4. | Empagliflozin consistently slowed the long-term annual decline in eGFR across all patient subgroups regardless of KDIGO risk category, as assessed by mean eGFR (Modification of Diet in Renal Disease [MDRD]) slopes on the basis of random intercept/random coefficient models. Adjusted mean eGFR across subgroups of KDIGO risk category. Empa, empagliflozin.

CESSATION (post-treatment): Last value on treatment to follow-up

	N analyzed	eGFR slope (ml/min per 1.73 m² per week [95% CI])	
Low risk			
Placebo	792	-0.07 [-0.21, 0.07]	
Empagliflozin	1644	0.55 [0.46, 0.65]	
Difference of empagliflozin versus placebo		0.62 [0.46, 0.79]	
Moderately increased risk			
Placebo	440	0.06 [-0.12, 0.23]	P value for interaction of
Empagliflozin	976	0.51 [0.39, 0.63]	subgroup by treatment
Difference of empagliflozin versus placebo		0.46 [0.24, 0.67]	by slope (empagliflozin
High risk			and placebo): 0.559
Placebo	209	0.05 [-0.20, 0.31]	
Empagliflozin	461	0.63 [0.46, 0.81]	
Difference of empagliflozin versus placebo		0.58 [0.27, 0.89]	
Very high risk			
Placebo	105	-0.08 [-0.44, 0.27]	
Empagliflozin	217	0.66 [0.41, 0.91]	
Difference of empagliflozin versus placebo		0.74 [0.31, 1.18]	

Figure 4. | *Continued.*

hemodynamic effect of SGLT2 inhibitors, the treatment effect of empagliflozin on eGFR slope by baseline KDIGO risk categories was investigated. We showed that, over the initial 4 weeks of treatment, the weekly mean adjusted eGFR decrease was numerically greater in the empagliflozin versus placebo groups across all risk subgroups; however, during chronic maintenance treatment, the adjusted

mean eGFR stabilized with empagliflozin but declined with placebo. In the post-treatment follow-up phase, the adjusted mean eGFR with empagliflozin returned toward mean baseline eGFR levels, whereas little change was seen with placebo.

The cardiovascular benefits in this study are also in line with more recently reported outcomes from SGLT2 inhibitor trials
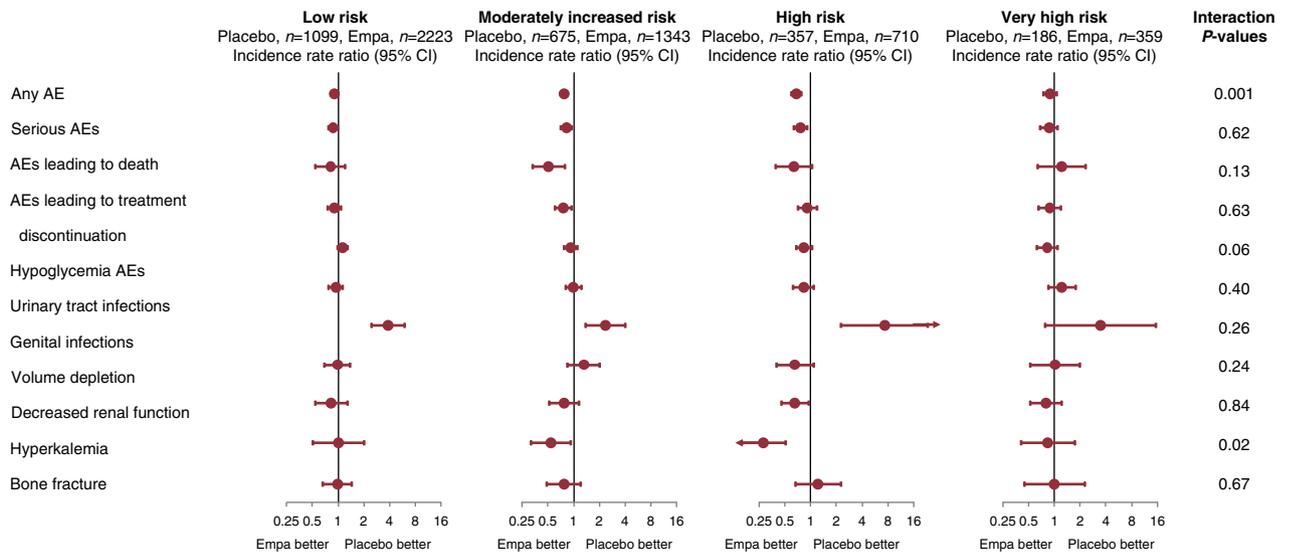
Figure 5. | **Adverse event (AE) incidence rate ratios were similar or lower with empagliflozin compared with placebo except for genital infections.** Data are from patients treated with one or more doses of study drug, including all events that occurred within 7 days after the last receipt of the study drug. Medical Dictionary for Drug Regulatory Activities version used for reporting: 18.0.

(CANVAS, Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events) that have shown reduction in the risk of cardiovascular outcomes in patients with high risk of cardiovascular events (19,21). Kidney benefits of canagliflozin were suggested in CANVAS and confirmed in CREDENCE (20). In CREDENCE, improvement in a specified kidney outcome—ESKD, doubling of serum creatinine, or death from kidney disease— was consistent across eGFR and UACR subgroups with canagliflozin versus placebo (20). Furthermore, the positive effects of SGLT2 inhibition are seen in addition to the benefits of background therapy with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers and so, are particularly important.

In this analysis, the risk reductions seen with empagliflozin versus placebo were similar across the four risk category groups for each of the cardiovascular and kidney outcomes, with no attenuation of effect with higher KDIGO risk categories. The proposed mechanisms by which SGLT2 inhibition may lower the risk of cardiovascular and kidney outcomes are most likely multifactorial and may include improvements in BP control, reduction in total body sodium and water, and weight loss, all of which are associated with improved outcomes in patients with type 2 diabetes. The restoration of tubuloglomerular feedback is likely to be an important contributor to the mechanism of action of the kidney-protective effect of SGLT2 inhibitors, although this is not yet fully understood (22). Additional kidney mechanisms (e.g., tubular protection, reduced hypoxia and inflammation, and long-term effects of natriuresis) may also contribute to these kidney-protective effects (23).

Furthermore, it has been reported that reduction in HbA1c from baseline with empagliflozin was smaller in patients with versus without CKD (24). Similar data have been reported for canagliflozin (25) and dapagliflozin (26). However, the effects of empagliflozin on other cardiovascular parameters, such as systolic BP, were similar regardless of kidney function (24). Attenuation of HbA1c lowering with empagliflozin in patients with CKD is not surprising given its mechanism of action in the kidney (27). A similar finding was reported with canagliflozin (28). Additional research is required to explore the effects of SGLT2 inhibitors on cardiovascular and kidney outcomes in a broader population of patients with CKD, beyond type 2 diabetes. To this end, clinical outcomes trials investigating these agents are underway, including the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial of patients with heart failure and reduced ejection fraction with or without type 2 diabetes. The study included a kidney composite secondary end point, for which no difference between dapagliflozin and placebo was reported (29); this finding was encouraging, although the trial was relatively short (median follow-up 18.2 months). More recently, the Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) (NCT03036150) has investigated the effect of dapagliflozin on kidney and cardiovascular events in a broad range of patients with CKD, importantly including those with and without type 2 diabetes (30). In this regard, although DAPA-CKD and CREDENCE both included patients with albuminuria, DAPA-CKD differs from CREDENCE

as the latter included only patients with type 2 diabetes (20). DAPA-CKD has been stopped early as the treatment benefits of dapagliflozin occurred earlier than anticipated (31). A large clinical outcomes trial investigating empagliflozin for heart and kidney protection in patients with CKD with or without type 2 diabetes, EMPA-KIDNEY, is underway, with plans to enroll approximately 6000 people, including those with and without albuminuria (NCT03594110) (32). The results of these studies will help to further define the role of new treatment therapies in the management of patients with CKD, including the effects on cardiovascular disease and premature death.

The adverse event profile of empagliflozin versus placebo was similar across KDIGO risk categories, with interaction P values for incidence rate ratios of >0.05 except for the incidence of any adverse event and hyperkalemia. Except for genital infections, rates of adverse events were similar or lower with empagliflozin versus placebo across all KDIGO risk groups. Rates of adverse events consistent with genital infections, as reported in previous trials of empagliflozin and other SGLT2 inhibitors, were greater with empagliflozin versus placebo across risk categories, with the 95% confidence interval for very high risk crossing unity (interaction P value =0.26).

The limitations of our data include the post hoc exploratory nature of the analyses and the relatively low number of patients with advanced CKD: only 8.0% (n=186) and 7.7% (n=359) of patients on placebo and patients on empagliflozin, respectively, were in the very high KDIGO risk category at baseline. Indeed, this analysis may be underpowered to detect differences in treatment effect across subgroups by virtue of the small proportions of patients in high and very high risk categories. In addition, EMPA-REG OUTCOME was not powered or designed to robustly assess kidney outcomes, and these were not adjudicated. However, the consistency of effect size across various definitions of kidney outcomes, and across SGLT2 trials, suggests that this limitation may be inconsequential (33,34).

Early detection of CKD and appropriate interventions are key to slowing disease progression and reducing the risk of adverse cardiovascular and kidney outcomes. For the small proportion of people with CKD and kidney failure who require dialysis and/or kidney transplantation, the economic effect of these interventions on health care budgets can be disproportionately high (3). Hence, identifying individuals at highest risk early in the disease course would enable earlier referral of those patients who will most likely gain benefit from specialist kidney services. This could lead to greater clinical and economic benefits (3). Furthermore, as CKD is a risk factor for cardiovascular disease, earlier intervention will also reduce the risk of cardiovascular and all-cause mortality. Evidence shows that the clinical presentation of CKD among adults with diabetes in the United States has evolved: low eGFR (<60 ml/min per 1.73 m^2) in the absence of albuminuria (UACR<30 mg/g) is becoming the most common phenotype, with an associated higher mortality (35). Therefore, any treatment strategies will also need to address the high mortality rates associated with this trend (35).

In conclusion, the overall number of cardiovascular and kidney events was higher numerically with higher KDIGO risk categories in the empagliflozin and placebo groups. However, the observed cardiovascular and kidney benefits of empagliflozin versus placebo were consistent across KDIGO risk categories, indicating that the treatment benefit of empagliflozin was unaffected by baseline CKD status.

Data Sharing 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.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.14901219/-/DCSupplemental.

Supplemental Material. List of EMPA-REG OUTCOME investigators.

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