Effects of Empagliflozin on Renal Outcomes Across KDIGO Risk Categories: Results from the EMPA-REG OUTCOME® Trial

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What's known

- In the EMPA-REG OUTCOME® trial in patients with type 2 diabetes mellitus (T2DM) and established cardiovascular (CV) disease, compared with placebo, empagliflozin, given in addition to standard of care, significantly reduced by 39% the risk of incident or worsening nephropathy (composite of progression to macroalbuminuria, doubling of serum creatinine level accompanied by estimated glomerular filtration rate [eGFR] of ≤45 mL/min/1.73 m², initiation of renal-replacement therapy, or death from renal disease).[1]

What's new

- Risk reductions in renal outcomes observed with empagliflozin treatment were consistent across the Kidney Disease: Improving Global Outcomes (KDIGO) risk categories.

INTRODUCTION

- Kidney disease occurs in around 40% of patients with type 2 diabetes mellitus (T2DM)[2] and can lead to increased mortality and morbidity.[2,3]
- Empagliflozin is a potent and selective sodium-glucose cotransporter-2 inhibitor used in the treatment of T2DM.
- The Kidney Disease: Improving Global Outcomes (KDIGO) chronic kidney disease (CKD) classification provides a renal risk prediction framework, using estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR).[3] Using this risk prediction framework, *post-hoc* we assessed renal outcomes in the EMPA-REG OUTCOME® trial in participants across each of the two-dimensional risk categories for progression of CKD.

OBJECTIVE

- To compare renal outcomes among participants in the EMPA-REG OUTCOME® trial according to the KDIGO risk categories at baseline.

METHODS

Study design and patients

- Adults with T2DM (with glycated haemoglobin [HbA1c] 7.0–10.0%), established CV disease, and eGFR (according to Modification of Diet in Renal Disease [MDRD]) ≥30 mL/min/1.73m² were randomised to receive empagliflozin 10 mg, empagliflozin 25 mg, or placebo once daily in addition to standard of care for T2DM and CV risk management.
- Investigators were encouraged to treat CV risk factors to achieve optimal standard of care according to local guidelines.
- Renal function at baseline was assessed using the creatinine-based GFR estimating equations, based on the MDRD formula.

Outcomes and analyses

- Prespecified renal outcomes in the current *post-hoc* analysis included incident or worsening nephropathy (composite of progression to macroalbuminuria, doubling of serum creatinine accompanied by estimated eGFR of ≤45 mL/min/1.73 m², initiation of renal replacement therapy, or death from renal disease) and progression to macroalbuminuria.
- The renal outcomes were analysed in subgroups by baseline KDIGO risk category, defined as follows:[2]

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (mL/min/1.73 m²) description and range				Persistent albuminuria categories description and range: A1 Normal to mildly increased <30 mg/g <3 mg/mmol	A2 Moderately increased 30–300 mg/g 3–30 mg/mmol	A3 Severely increased >300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk.
CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.

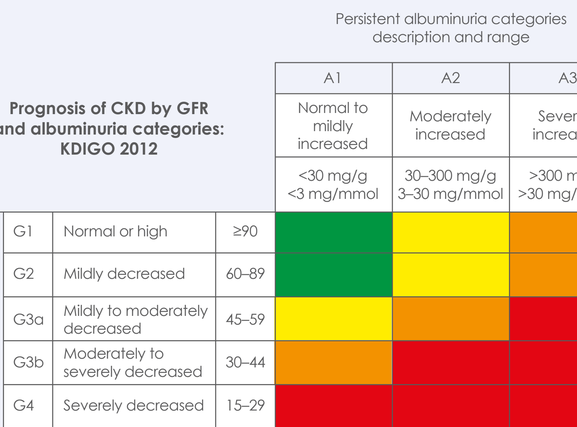
- Analyses were performed in patients treated with ≥1 dose of study drug and compared the pooled empagliflozin group versus the placebo group.
- A Cox proportional hazards model was used to investigate the consistency of treatment effect across subgroups.

RESULTS

Patients

- A total of 7020 patients were treated in 42 countries.
- The median observation time was 3.1 years.

Proportions of patients by KDIGO risk categories



Of all treated patients, baseline eGFR and UACR measurements were available for 4635 empagliflozin (98.9%) and 2317 placebo (99.3%) patients.
eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; UACR, urine albumin-to-creatinine ratio.

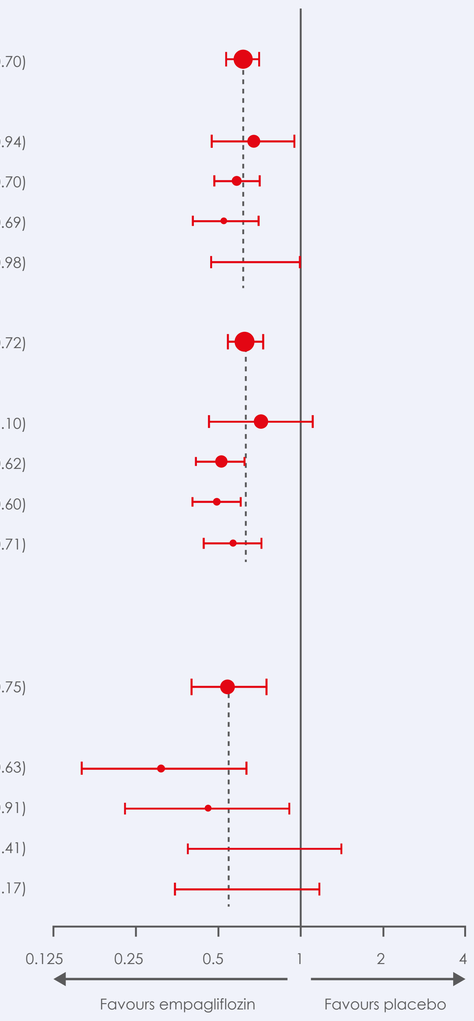
Baseline characteristics

	KDIGO Risk Category: Low		Moderately Increased		High		Very High	
	Placebo (n=1099)	Empagliflozin (n=2223)	Placebo (n=675)	Empagliflozin (n=1343)	Placebo (n=357)	Empagliflozin (n=710)	Placebo (n=186)	Empagliflozin (n=359)
Male	787 (72)	1571 (71)	490 (73)	970 (72)	254 (71)	500 (70)	136 (73)	255 (71)
Age, years	61.6 ± 8.7	61.4 ± 8.3	64.1 ± 8.6	63.7 ± 8.5	65.5 ± 8.9	65.6 ± 8.3	65.6 ± 8.0	67.0 ± 8.0
BMI, kg/m²	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, %	8.03 ± 0.81	7.98 ± 0.82	8.10 ± 0.85	8.14 ± 0.86	8.15 ± 0.86	8.16 ± 0.90	8.17 ± 0.94	8.12 ± 0.84
SBP, mmHg	133.0 ± 15.6	132.2 ± 15.4	137.6 ± 17.4	136.6 ± 17.2	138.9 ± 19.5	139.4 ± 18.6	140.4 ± 18.8	140.5 ± 17.9
DBP, mmHg	76.8 ± 9.5	76.6 ± 9.2	77.6 ± 10.9	77.3 ± 10.1	76.1 ± 10.6	76.2 ± 10.0	75.7 ± 10.2	74.8 ± 10.4
LDL-C, mg/dL	82.7 ± 33.8	85.1 ± 34.5	85.1 ± 34.2	85.3 ± 36.4	89.1 ± 39.1	87.5 ± 37.2	88.6 ± 39.1	89.8 ± 39.8
eGFR (MDRD), mL/min/1.73m²	83.4 ± 16.3	83.6 ± 16.9	73.5 ± 19.9	73.8 ± 20.2	60.1 ± 18.8	61.1 ± 19.6	44.4 ± 8.2	42.7 ± 8.6
≥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 to 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)
Background Medications								
ACE inhibitors/ARBs	846 (77)	1754 (79)	556 (82)	1119 (83)	305 (85)	585 (82)	147 (79)	299 (83)
Diruetics	405 (37)	841 (38)	295 (44)	605 (45)	172 (48)	360 (51)	110 (59)	216 (60)

Data are n (%) or mean ± SD in patients treated with ≥1 dose of study drug.
ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; KDIGO, Kidney Disease: Improving Global Outcomes; LDL-C, low-density lipoprotein cholesterol; MDRD, Modification of Diet in Renal Disease; SBP, systolic blood pressure; UACR, urine albumin-to-creatinine ratio.

Renal outcomes by KDIGO risk categories

	Empagliflozin n with event/N analysed (%)	Placebo n with event/N analysed (%)	Hazard ratio (95% CI)	p-value for subgroup by treatment interaction
Incident or worsening nephropathy				
All patients	525/4124 (12.7)	388/2061 (18.8)	0.61 (0.53, 0.70)	
KDIGO risk categories*				p=0.5968
Low	78/2180 (3.6)	56/1086 (5.2)	0.67 (0.47, 0.94)	
Moderately increased	254/1323 (19.2)	187/655 (28.5)	0.58 (0.48, 0.70)	
High	117/430 (27.2)	89/219 (40.6)	0.52 (0.40, 0.69)	
Very high	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*				p=0.4318
Low	50/2223 (2.2)	34/1099 (3.1)	0.71 (0.46, 1.10)	
Moderately increased	187/1343 (13.9)	160/675 (23.7)	0.51 (0.41, 0.62)	
High	225/710 (31.7)	174/357 (48.7)	0.49 (0.40, 0.60)	
Very high	161/359 (44.8)	122/186 (65.6)	0.56 (0.44, 0.71)	
Doubling of serum creatinine†, initiation of renal replacement therapy, or death from renal disease				
All patients	81/4645 (1.7)	71/2323 (3.1)	0.54 (0.40, 0.75)	
KDIGO risk categories*				p=0.2860
Low	13/2205 (0.6)	20/1094 (1.8)	0.31 (0.16, 0.63)	
Moderately increased	16/1334 (1.2)	17/671 (2.5)	0.46 (0.23, 0.91)	
High	25/704 (3.6)	15/356 (4.2)	0.74 (0.39, 1.41)	
Very high	24/352 (6.8)	19/186 (10.2)	0.64 (0.35, 1.17)	



Cox regression analysis in patients treated with ≥1 dose of study drug.
*68 patients were excluded as subgroup variable was missing.
†Accompanied by eGFR ≤45 mL/min/1.73 m².
Macroalbuminuria: UACR >300 mg/g.
CI, confidence interval; KDIGO, Kidney Disease: Improving Global Outcomes.

Renal outcomes

- The incidence of renal outcome events increased with increasing KDIGO risk category for both empagliflozin and placebo.

Safety

- The adverse event (AE) profile of empagliflozin versus placebo, respectively, was similar across KDIGO risk categories (percentage of patients with AE[s]: low risk, 88.4% vs 89.7%; moderately increased risk, 91.5% vs 92.4%; high risk, 92.0% vs 95.5%; very high risk, 91.9% vs 94.6%).
- Corresponding rates for serious AEs were also similar across categories (low risk, 33.2% vs 36.3%; moderately increased risk, 38.6% vs 43.1%; high risk, 44.8% vs 52.1%; very high risk, 53.2% vs 58.6%).
- Across KDIGO risk categories, rates of AEs consistent with genital infection were greater with empagliflozin than placebo, while urinary tract infection, volume depletion, acute renal failure, hyperkalemia, hypoglycaemia, and bone fracture occurred at similar or lower rates with empagliflozin compared with placebo.

CONCLUSIONS

- As expected, risk for renal outcome events increased with increasing KDIGO risk category in EMPA-REG OUTCOME®.
- However, the observed effects of empagliflozin versus placebo on incident or worsening nephropathy, progression to UACR >300 mg/g and the composite of hard renal endpoints (doubling of serum creatinine, initiation of renal replacement therapy, or death from renal disease) were consistent across the KDIGO risk categories.
- Empagliflozin, given in addition to standard of care, improved renal outcomes in patients with T2DM and established CV disease irrespective of KDIGO risk category at baseline.

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References

1. Wanner C, et al. *N Engl J Med*. 2016;375:323–334.
2. de Boer IH, et al. *JAMA*. 2011;305:2532–2539.
3. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int Suppl*. 2013;3:1–150.

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