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Articles

Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial

David Z I Cherney, Bernard Zinman, Silvio E Inzucchi, Audrey Koitka-Weber, Michaela Mattheus, Maximilian von Eynatten, Christoph Wanner

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Department of Medicine and Department of Physiology, Division of Nephrology, University Health Network, University of Toronto, Toronto, ON, Canada (D Z I Cherney MD); Toronto General Hospital, Toronto, ON, Canada (D Z I Cherney); Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada (Prof B Zinman MD); Section of Endocrinology, Yale School of Medicine, New Haven, CT, USA (S E Inzucchi MD); Boehringer Ingelheim Pharma GmbH and Co KG, Biberach, Germany (A Koitka-Weber PhD); Boehringer Ingelheim Pharma GmbH and Co KG, Ingelheim, Germany (M Mattheus MSc, M von Eynatten MD); and Division of Nephrology, Würzburg University Clinic, Würzburg, Germany (Prof C Wanner MD)

Correspondence to: Dr David Z I Cherney, Toronto General Hospital, Toronto, ON, M5G 2N2, Canada david.cherney@uhn.ca

Summary

Background In a pooled analysis of short-term trials, short-term treatment with the sodium-glucose co-transporter-2 (SGLT2) inhibitor empagliflozin reduced albuminuria in patients with type 2 diabetes and prevalent albuminuria. In this exploratory analysis of the EMPA-REG OUTCOME trial, we report the short-term and long-term effects of empagliflozin on albuminuria in patients with type 2 diabetes and established cardiovascular disease, according to patients' baseline albuminuria status.

Methods In this randomised, double-blind, placebo-controlled trial at 590 sites in 42 countries, we randomly assigned patients aged 18 years and older with type 2 diabetes and established cardiovascular disease (1:1:1) to empagliflozin 10 mg, empagliflozin 25 mg, or placebo in addition to standard of care until at least 691 patients experienced an adjudicated event included in the primary outcome. We did the randomisation with a computer-generated random-sequence and interactive voice-response and web-response system, stratified by HbA_{1c}, BMI, region, and estimated glomerular filtration rate. Patients, investigators, and individuals involved in analysis of trial data were masked to treatment assignment. The primary and secondary efficacy and safety endpoints of this trial have been reported previously. Here, we report urinary albumin-to-creatinine ratio (UACR) data for the pooled empagliflozin group versus placebo according to albuminuria status at baseline (normoalbuminuria: UACR <30 mg/g; microalbuminuria: UACR ≥30 to ≤300 mg/g; and macroalbuminuria: UACR >300 mg/g). We did the analysis with mixed-model repeated measures including prespecified and post-hoc tests. This study is completed and registered with ClinicalTrials.gov, number NCT01131676.

Findings Between Sept 1, 2010, and April 22, 2013, we randomly assigned 7028 patients to treatment groups and 7020 patients received treatment. At baseline, we had UACR data for 6953 patients: 4171 (59% of treated patients; 1382 assigned to placebo and 2789 assigned to empagliflozin) had normoalbuminuria, 2013 (29%; 675 assigned to placebo and 1338 assigned to empagliflozin) had microalbuminuria, and 769 (11%; 260 assigned to placebo and 509 assigned to empagliflozin) had macroalbuminuria. Median treatment duration was 2·6 years (IQR 2·0–3·4; 136 weeks) and median observation time was 3·1 years (2·2–3·6; 164 weeks). After short-term treatment at week 12, the placebo-adjusted geometric mean ratio of UACR change from baseline with empagliflozin was –7% (95% CI –12 to –2; p=0·013) in patients with normoalbuminuria, –25% (–31 to –19; p<0·0001) in patients with microalbuminuria, and –32% (–41 to –23; p<0·0001) in patients with macroalbuminuria. The reductions in UACR were maintained with empagliflozin in all three groups compared with placebo during long-term treatment when measured at 164 weeks. At follow-up, after cessation of treatment for a median of 34 or 35 days, UACR was lower in the empagliflozin versus placebo group in those with baseline microalbuminuria (placebo-corrected adjusted geometric mean ratio of relative change from baseline with empagliflozin: –22%, 95% CI –32 to –11; p=0·0003) or macroalbuminuria (–29%, –44 to –10; p=0·0048), but not for patients with baseline normoalbuminuria (1%, –8 to 10; p=0·8911). Patients treated with empagliflozin were more likely to experience a sustained improvement from microalbuminuria to normoalbuminuria (hazard ratio [HR] 1·43, 95% CI 1·22 to 1·67; p<0·0001) or from macroalbuminuria to microalbuminuria or normoalbuminuria (HR 1·82, 1·40 to 2·37; p<0·0001), and less likely to experience a sustained deterioration from normoalbuminuria to microalbuminuria or macroalbuminuria (HR 0·84, 0·74 to 0·95; p=0·0077). The proportions of patients with any adverse events, serious adverse events, and adverse events leading to discontinuation increased with worsening UACR status at baseline, but were similar between treatment groups. The proportion of patients with genital infections was greater with empagliflozin than placebo in all subgroups by UACR status.

Interpretation These results support short-term and long-term benefits of empagliflozin on urinary albumin excretion, irrespective of patients' albuminuria status at baseline.

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Research in context

Evidence before this study

In the EMPA-REG OUTCOME trial, empagliflozin reduced the risk of reaching the prespecified renal composite endpoint of new or worsening nephropathy and slowed the progression of kidney disease in patients with type 2 diabetes and cardiovascular disease. However, data for long-term effects of sodium-glucose co-transporter-2 (SGLT2) inhibition on the widely used renal surrogate albuminuria in a cardiorenal high-risk population are not available. We searched PubMed from Jan 1, 1990, to May 28, 2017 for all English-language publications with the search terms "SGLT2", "albuminuria", "kidney disease", "nephropathy", "hyperfiltration", "hemodynamic", and "GFR". Findings from previous short-term glycaemic control trials have shown that inhibition of SGLT2 reduces albuminuria in patients with type 2 diabetes, in both those with preserved estimated glomerular filtration rate (eGFR) and those with chronic kidney disease. Additionally, an analysis has reported that in patients with preserved renal function, SGLT2 inhibition prevents eGFR loss. However, data in patients with chronic kidney disease were scarce, the duration of follow-up for effects on proteinuria was short, especially in patients with chronic kidney disease, and previous studies did not include participants at elevated cardiorenal risk.

Added value of this study

Our analysis has several important novel aspects. This analysis is the first to show the effects of empagliflozin on urinary albumin-to-creatinine ratio (UACR) in a cohort at high cardiovascular risk. By using continuous data, we were able to better define both primary and secondary preventative effects of empagliflozin on UACR in this cohort of patients with type 2 diabetes and high cardiovascular risk. The reported eGFR change over time according to baseline UACR showed a greater effect of empagliflozin on preserving renal function in patients with baseline macroalbuminuria, which is an important potential area for future research. Finally, the only partial reversibility of the haemodynamic UACR effect in the microalbuminuric and macroalbuminuric cohorts after long-term treatment with empagliflozin and a subsequent washout period, might partly reflect underlying renal structural changes over time.

Implications of all the available evidence

On the basis of available evidence, SGLT2 inhibitors rapidly reduce UACR across the range of eGFR (chronic kidney disease stages 1–4) and in patients with normoalbuminuria, microalbuminuria, and macroalbuminuria. In our exploratory analysis with prespecified and post-hoc endpoints, this UACR-lowering effect was maintained with empagliflozin during long-term treatment of up to 192 weeks. Additionally, SGLT2 inhibitors prevent eGFR loss over time—for empagliflozin, this renal preservation effect might be greatest in patients with macroalbuminuria. Ultimately, the effect of SGLT2 inhibition on hard nephropathy endpoints is being examined in dedicated studies of renal endpoints.

Introduction

Empagliflozin, a potent and selective inhibitor of sodium-glucose co-transporter-2 (SGLT2), is used for the treatment of type 2 diabetes. SGLT2 inhibition blocks reabsorption of glucose and sodium at the renal proximal tubule. In patients with preserved renal function, the ensuing glucosuria lowers HbA_{1c} by around 0·7% and reduces weight by 2–3 kg.[1] In patients with type 2 diabetes and chronic kidney disease, however, the reduction in HbA_{1c} with SGLT2 inhibitors is attenuated because of reduced glomerular filtration and glucosuria.

SGLT2 inhibition also induces natriuresis and a small contraction in plasma volume—actions that are likely to contribute to antihypertensive effects in patients with type 2 diabetes.[1] Findings from short-term studies[2–6] have suggested that natriuresis was associated with SGLT2 inhibitor-mediated reductions in the urinary albumin-to-creatinine ratio (UACR) in patients with preserved renal function and patients with stage 2–4 chronic kidney disease. These effects were largely independent of decreases in blood pressure, weight, or HbA_{1c}, which suggests they were possibly intrarenal haemodynamic effects.[2,7] SGLT2 inhibitors augment renal tubulo-glomerular feedback signals in animals by increasing delivery of sodium to the macula densa, resulting in afferent renal arteriolar vasoconstriction, thereby reducing intraglomerular hypertension, hyperfiltration, and albuminuria.[1] In patients with type 1 diabetes, empagliflozin similarly reduces renal hyperperfusion and hyperfiltration[8]—an effect that might partly account for the acute decrease in the estimated glomerular filtration rate (eGFR) of 4–6 mL/min per 1·73 m² after initiation of treatment with empagliflozin in patients with type 2 diabetes.[9]

A high UACR is associated with all-cause and cardiovascular mortality, kidney failure, acute kidney injury, and progression of kidney disease.[10–13] Moreover, the reduction in UACR from blockade of the renin–angiotensin system (RAS) is associated with improved clinical renal outcomes.[14,15] In the EMPA-REG OUTCOME trial[16] involving 7020 patients with type 2 diabetes and established cardiovascular disease, empagliflozin reduced the risk of the primary outcome of three-point major adverse cardiovascular events (a composite outcome of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) versus placebo, driven by a reduction in cardiovascular death. Empagliflozin also reduced the risk of all-cause mortality, admissions to hospital for heart failure, new onset or worsening nephropathy (progression to macroalbuminuria, doubling of serum creatinine and

eGFR of 45 mL/min per 1·73 m² or less, initiation of renal-replacement therapy, or death from renal disease), and the composite renal outcome (doubling of serum creatinine and eGFR of 45 mL/min per 1·73 m² or less, initiation of renal replacement therapy, or death from renal disease).[9,16,17]

In this report, we present an analysis of the short-term and long-term effects of empagliflozin on UACR in EMPA-REG OUTCOME by baseline albuminuria status. We hypothesised that empagliflozin would reduce albuminuria across the range of baseline UACR in patients at high vascular risk.

Methods

Study design and participants

The design of the EMPA-REG OUTCOME trial has been published previously,[18] as has the full study protocol.[16] Briefly, we did a randomised, double-blind, placebo-controlled trial at 590 sites in 42 countries. 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.

Eligible participants were patients with type 2 diabetes aged 18 years and older with a BMI of 45 kg/m² or less and an eGFR (according to the Modification of Diet in Renal Disease [MDRD] formula) of 30 mL/min per 1·73 m² or higher. Participants were either treatment-naive (no glucose-lowering agents for ≥12 weeks before randomisation) with an HbA_{1c} of between 7·0% and 9·0% (53 and 75 mmol/mol), or on stable glucose-lowering therapy for 12 weeks or more before randomisation with an HbA_{1c} between 7·0% and 10·0% (53 and 86 mmol/mol), with established cardiovascular disease.

Randomisation and masking

After a 2-week, open-label, placebo run-in period, in which background glucose-lowering therapy was unchanged, we randomly assigned eligible patients (1:1:1) to either empagliflozin 10 mg, empagliflozin 25 mg, or placebo orally once daily in addition to standard care until at least 691 patients experienced an adjudicated event included in the primary outcome. Randomisation was done by Boehringer Ingelheim, one of the study funders, with a computer-generated random-sequence and interactive voice-response and web-response system, and was stratified according to HbA_{1c} at screening, BMI at randomisation, eGFR at screening, and region. The trial was done as a double-blind trial using matching placebos to the active treatment. Patients, investigators, and individuals involved in analysis of trial data were masked to treatment assignment.

See Online for appendix

Procedures

Background glucose-lowering therapy remained unchanged for the first 12 weeks after randomisation. After week 12, investigators were encouraged to adjust glucose-lowering therapy at their discretion to achieve glycaemic control according to local guidelines. Throughout the trial, investigators were encouraged to treat other cardiovascular risk factors to achieve an optimum standard of care according to local guidelines. The trial was to continue until at least 691 patients experienced an adjudicated event included in the primary outcome (three-point major adverse cardiovascular events). Patients who prematurely discontinued study medication were followed up until the end of the trial for ascertainment of cardiovascular outcomes, adverse events, and vital status. All patients were asked to attend a follow-up visit 30 days after the last intake of study medication.

Serum creatinine and UACR were measured by a central laboratory at the following timepoints: the start of the placebo run-in period; randomisation; weeks 4 (only serum creatinine), 12, 28, and 52; then every 14 weeks until the end-of-study visit; at the end-of-study visit; and 30 days after the end-of-study visit. At the same time points, except for week 4, urine dipstick was done locally. The timing of urine collection (eg, first morning void) was not specified. Events that were consistent with changes in albuminuria category (normoalbuminuria [UACR <30 mg/g], microalbuminuria [UACR ≥30 to ≤300 mg/g], or macroalbuminuria [UACR >300 mg/g]) were captured if any laboratory assessment fulfilled the criteria on one occasion. We used the MDRD formula to assess eGFR at baseline, as per the original protocol.[9,16] For this report, we also used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to report eGFR over time.

Outcomes

Results of the primary outcome (a composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke) and secondary outcomes of EMPA-REG OUTCOME have been reported previously.[16] In this report, we describe prespecified and post-hoc exploratory outcomes for this trial from an exploratory analysis of UACR (appendix). Prespecified outcomes were UACR over 192 weeks in subgroups by UACR status at baseline; time to new onset of sustained (ie, ≥2 consecutive measurements that were ≥4 weeks apart) normoalbuminuria in patients with microalbuminuria at baseline; time to new onset of sustained (ie, ≥2 consecutive measurements that were ≥4 weeks apart) normoalbuminuria or microalbuminuria in patients with macroalbuminuria at baseline; time to new onset of sustained (ie, ≥2 consecutive measurements that were ≥4 weeks apart) microalbuminuria or macroalbuminuria in patients with normoalbuminuria at baseline; occurrence of deterioration in UACR (shift from normoalbuminuria to microalbuminuria or macroalbuminuria or from microalbuminuria to macroalbuminuria) from baseline to the last value on treatment (LVOT); and occurrence of improvement in UACR status (shift from

microalbuminuria to normoalbuminuria or from macroalbuminuria to microalbuminuria or normoalbuminuria) from baseline to LVOT.

Post-hoc outcomes were UACR at LVOT and at follow-up in subgroups by UACR at baseline (normoalbuminuria, microalbuminuria, or macroalbuminuria); change from

	Normoalbuminuria at baseline (59% of patients treated)		Microalbuminuria at baseline (29% of patients treated)		Macroalbuminuria at baseline (11% of patients treated)	
	Placebo (n=1382)	Empagliflozin (n=2789)	Placebo (n=675)	Empagliflozin (n=1338)	Placebo (n=260)	Empagliflozin (n=509)
Age (years)	62·9 (8·9)	62·5 (8·5)	64·2 (8·7)	64·0 (8·6)	62·7 (8·2)	64·1 (8·5)
Sex						
Male	964 (70%)	1925 (69%)	499 (74%)	991 (74%)	204 (78%)	381 (75%)
Female	418 (30%)	864 (31%)	176 (26%)	347 (26%)	56 (22%)	128 (25%)
Race						
White	1021 (74%)	2094 (75%)	477 (71%)	938 (70%)	167 (64%)	328 (64%)
Asian	283 (20%)	527 (19%)	156 (23%)	331 (25%)	70 (27%)	141 (28%)
Black or African American	65 (5%)	148 (5%)	35 (5%)	57 (4%)	19 (7%)	31 (6%)
Other or missing data	13 (1%)	20 (1%)	7 (1%)	12 (1%)	4 (2%)	9 (2%)
Weight (kg)	86·8 (19·0)	86·8 (18·7)	86·8 (19·0)	85·7 (19·0)	84·9 (19·4)	84·0 (19·7)
BMI (kg/m²)	30·7 (5·3)	30·7 (5·3)	30·7 (5·2)	30·5 (5·2)	30·2 (5·3)	30·3 (5·5)
HbA_{1c}						
%	8·01% (0·80)	7·99% (0·82)	8·14% (0·88)	8·17% (0·88)	8·27% (0·93)	8·21% (0·86)
mmol/mol	64·1 (8·8)	63·8 (9·0)	65·5 (9·6)	65·8 (9·6)	66·9 (10·1)	66·2 (9·4)
Time since diagnosis of type 2 diabetes						
≤1 year	40 (3%)	92 (3%)	9 (1%)	23 (2%)	3 (1%)	13 (3%)
>1 to 5 years	246 (18%)	489 (18%)	98 (15%)	170 (13%)	26 (10%)	44 (9%)
>5 to 10 years	355 (26%)	738 (26%)	160 (24%)	332 (25%)	49 (19%)	91 (18%)
>10 years	741 (54%)	1470 (53%)	408 (60%)	813 (61%)	182 (70%)	361 (71%)
Systolic blood pressure (mm Hg)	132·9 (15·9)	132·1 (15·6)	138·8 (17·9)	138·6 (17·4)	143·6 (18·8)	143·6 (18·0)
Diastolic blood pressure (mm Hg)	76·2 (9·7)	75·9 (9·4)	77·4 (10·9)	77·5 (10·0)	78·7 (10·0)	77·8 (10·2)
Total cholesterol*						
mg/dL	158·7 (40·1)	161·0 (42·1)	163·4 (43·6)	164·4 (44·4)	175·3 (52·9)	174·2 (52·3)
mmol/L	4·1 (1·0)	4·2 (1·1)	4·2 (1·1)	4·3 (1·1)	4·5 (1·4)	4·5 (1·4)
LDL cholesterol†						
mg/dL	82·7 (33·7)	84·2 (34·4)	85·9 (35·4)	86·4 (36·5)	93·5 (41·3)	93·8 (41·7)
mmol/L	2·1 (0·9)	2·2 (0·9)	2·2 (0·9)	2·2 (0·9)	2·4 (1·1)	2·4 (1·1)
HDL cholesterol*						
mg/dL	44·4 (11·3)	44·5 (11·7)	43·1 (10·5)	44·7 (12·2)	44·6 (13·0)	44·6 (12·0)
mmol/L	1·1 (0·3)	1·2 (0·3)	1·1 (0·3)	1·2 (0·3)	1·2 (0·3)	1·2 (0·3)
Triglycerides*						
mg/dL	162·4 (105·9)	166·3 (126·8)	178·3 (125·7)	173·2 (125·5)	196·0 (172·9)	184·6 (154·1)
mmol/L	1·8 (1·2)	1·9 (1·4)	2·0 (1·4)	2·0 (1·4)	2·2 (2·0)	2·1 (1·7)
eGFR (mL/min per 1·73 m²)‡	76·4 (20·3)	76·7 (20·7)	71·9 (21·8)	72·3 (22·2)	64·7 (19·7)	65·0 (21·7)
eGFR‡						
>90 mL/min per 1·73 m²	321 (23%)	684 (25%)	131 (19%)	286 (21%)	29 (11%)	68 (13%)
60 to <90 mL per 1·73 m²	778 (56%)	1539 (55%)	339 (50%)	640 (48%)	116 (45%)	218 (43%)
30 to <60 mL per 1·73 m²	281 (20%)	556 (20%)	204 (30%)	405 (30%)	112 (43%)	218 (43%)
<30 mL/min per 1·73 m²	2 (<1%)	10 (<1%)	1 (<1%)	6 (<1%)	3 (1%)	5 (1%)
Medical history of diabetic retinopathy§	246 (18%)	489 (18%)	162 (24%)	348 (26%)	111 (43%)	170 (33%)

Baseline characteristics for patients treated with at least one dose of study drug. Data are n (%) or mean (SD). eGFR=estimated glomerular filtration rate. UACR=urine albumin-to-creatinine ratio. *Placebo n=1369 and empagliflozin n=2752 for patients with normoalbuminuria at baseline; placebo n=667 and empagliflozin n=1321 for patients with microalbuminuria at baseline; placebo n=258 and empagliflozin n=507 for patients with macroalbuminuria at baseline. †Placebo n=1369 and empagliflozin n=2749 for patients with normoalbuminuria at baseline; placebo n=667 and empagliflozin n=1321 for patients with microalbuminuria at baseline; placebo n=258 and empagliflozin n=507 for patients with macroalbuminuria at baseline. ‡Information was not available for one patient in the pooled empagliflozin group with microalbuminuria at baseline; eGFR was calculated using the Modification of Diet in Renal Disease formula. §Retinopathy information was based on investigator reporting without any further assessment. Normoalbuminuria=UACR <30 mg/g. Microalbuminuria=UACR ≥30 to ≤300 mg/g. Macroalbuminuria=UACR >300 mg/g.

***Table 1*: Baseline characteristics of patients with UACR data at baseline**

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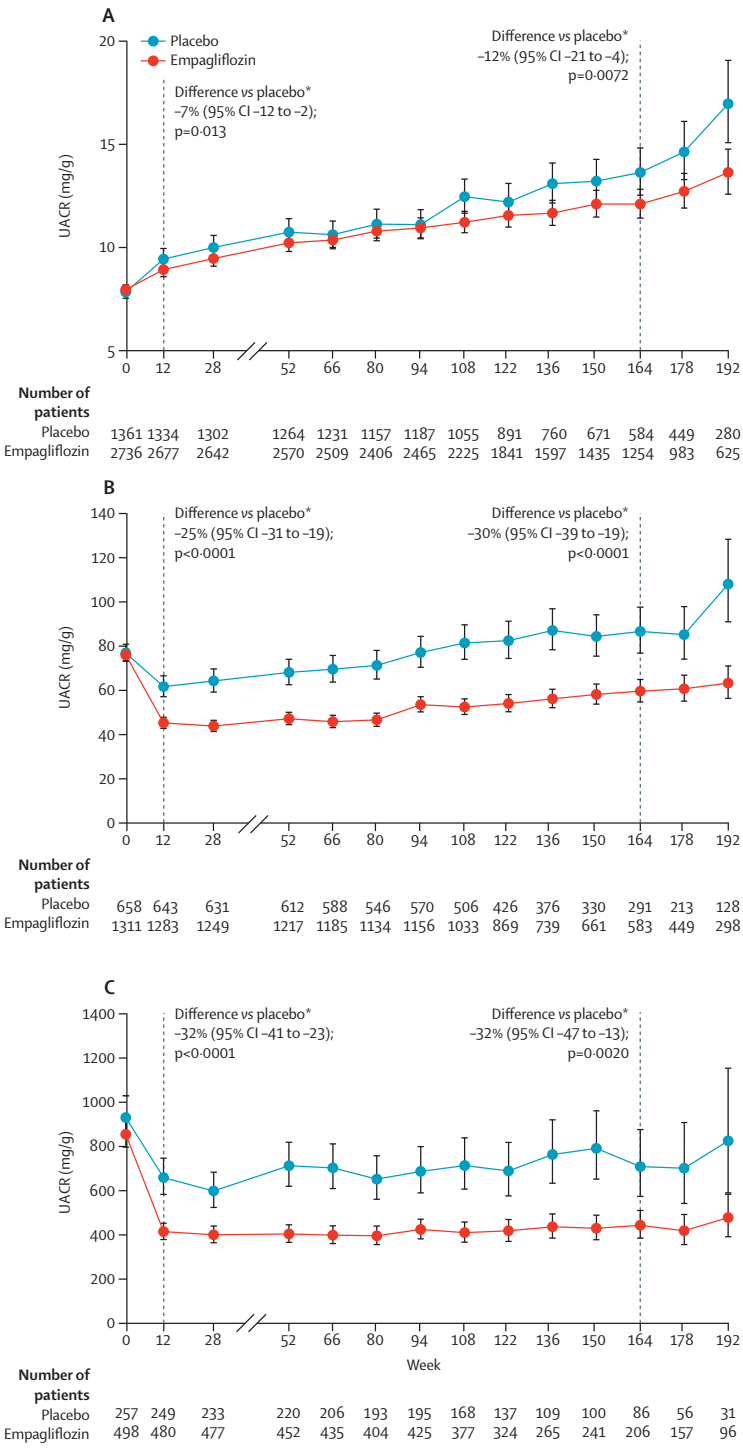
baseline in UACR at week 12 and week 164 (median observation time) by UACR status and HbA_{1c} or uric acid at baseline; the proportion of change in UACR mediated by concomitant changes in HbA_{1c}, systolic blood pressure, weight, uric acid, LDL cholesterol, and eGFR by baseline UACR status; new onset of sustained normoalbuminuria in patients with microalbuminuria at baseline or sustained normoalbuminuria or microalbuminuria in patients with macroalbuminuria at baseline categorised by use of angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) at baseline; and eGFR over 192 weeks in subgroups by UACR at baseline. We assessed safety on the basis of adverse events reported in subgroups by UACR and by use of ACE inhibitors or ARBs at baseline.



Statistical analysis

We analysed UACR over time in subgroups by UACR status at baseline using a mixed-model repeated measures (MMRM) analysis, with HbA_{1c} as a linear covariate and baseline eGFR, region, baseline BMI, the last week a patient could have had a UACR measurement, treatment, visit, baseline UACR, treatment-by-visit interaction, visit-by-baseline UACR interaction, treatment-by-baseline UACR interaction, treatment-by-visit by UACR interaction, and baseline HbA_{1c}-by-visit interaction as fixed effects, using all data obtained until study end from all patients treated with at least one dose of study drug (with a modified intention-to-treat [ITT] approach).

We also analysed changes in UACR at weeks 12 and 164 in subgroups by UACR status and HbA_{1c} at baseline, and in subgroups by UACR status and uric acid at baseline. Furthermore, we investigated the potential contribution of concomitant changes in HbA_{1c}, blood pressure, weight, uric acid, LDL cholesterol, and eGFR (separately and combined) to changes in UACR at week 12 and the median observation time of 164 weeks by UACR status at baseline using an MMRM model with additional factors for baseline UACR, baseline of the variable of interest, baseline UACR-by-visit interaction, baseline of the variable of interest-by-visit interaction, and the change from baseline in the variable of interest as linear covariates. Because of their non-normal distribution, UACR data were log-transformed before analysis, and adjusted least-square means, 95% CIs, and differences between treatments were back-transformed to the original scale. Percentage changes in adjusted geometric mean data and geometric mean ratios are presented.

***Figure 1*: Urinary albumin-to-creatinine ratio over 192 weeks**
Prespecified endpoint and post-hoc analyses in patients with (A) normoalbuminuria, (B) microalbuminuria, and (C) macroalbuminuria at baseline. Adjusted geometric mean values and 95% CIs are shown. Mixed-model repeated measures analysis using all data obtained until study end in patients treated with at least one dose of study drug. Normoalbuminuria: urinary albumin-to-creatinine ratio (UACR) <30 mg/g. Microalbuminuria: UACR ≥30 to ≤300 mg/g. Macroalbuminuria: UACR >300 mg/g. Only patients with post-randomisation measurements are included in the figure.
*Placebo-corrected adjusted geometric mean ratio (95% CI) of relative change from baseline with empagliflozin. 164 weeks (IQR 115–186) corresponds to the median observation period.

	Normoalbuminuria at baseline*		Microalbuminuria at baseline†		Macroalbuminuria at baseline‡	
	Independent (%)	Associated (%)	Independent (%)	Associated (%)	Independent (%)	Associated (%)
At week 12						
Change from baseline in HbA_{1c}	56·2%	43·8%	91·3%	8·7%	102·2%	−2·2%
Change from baseline in SBP	64·7%	35·3%	85·5%	14·5%	93·3%	6·7%
Change from baseline in HbA_{1c}, SBP, weight, uric acid, LDL cholesterol, and eGFR	73·3%	26·7%	77·4%	22·6%	86·5%	13·6%
At week 164						
Change from baseline in HbA_{1c}	87·9%	12·1%	98·0%	2·0%	100·0%	0
Change from baseline in SBP	89·5%	10·5%	93·9%	6·1%	97·7%	2·3%
Change from baseline in HbA_{1c}, SBP, weight, uric acid, LDL cholesterol, and eGFR	85·0%	15·0%	89·5%	10·6%	77·8%	22·3%

Data are based on the ratio of empagliflozin versus placebo-adjusted geometric mean ratio of the change from baseline to week 12 or week 164 from mixed-model repeated measures (MMRM) analyses using all data obtained until study end in patients treated with at least one dose of study drug. Each model (for week 12 and week 164) included baseline values for BMI, region, urine albumin-to-creatinine ratio (UACR), HbA_{1c}, systolic blood pressure (SBP), weight, uric acid, LDL cholesterol, and estimated glomerular filtration rate (eGFR) as linear covariates. Treatment; changes in HbA_{1c}, SBP, weight, uric acid, LDL cholesterol, eGFR; the last week a patient could have a UACR measurement, visit, treatment-by-visit interaction; and baseline UACR by visit interaction, baseline HbA_{1c}-by-visit interaction, baseline SBP-by-visit interaction, baseline weight-by-visit interaction, baseline uric acid-by-visit interaction, baseline LDL cholesterol-by-visit interaction, and baseline eGFR-by-visit interaction were included as fixed effects. In the MMRM analysis for week 12, the changes from baseline in HbA_{1c}, SBP, weight, uric acid and eGFR at week 12 were used. LDL was not collected at week 12; therefore, LDL change from baseline at week 4 was used. In the MMRM analysis for week 164, we used the changes from baseline in HbA_{1c}, SBP, weight, uric acid, LDL cholesterol and eGFR at week 164. Normoalbuminuria: UACR <30 mg/g. Microalbuminuria: UACR ≥30 to ≤300 mg/g. Macroalbuminuria: UACR >300 mg/g. *Number analysed at week 12 was 1056 in the placebo group and 2098 in the empagliflozin group; number analysed at week 164 was 567 in the placebo group and 1207 in the empagliflozin group. †Number analysed at week 12 was 520 in the placebo group and 996 in the empagliflozin group; number analysed at week 164 was 280 in the placebo group and 563 in the empagliflozin group. ‡Number analysed at week 12 was 191 in the placebo group and 374 in the empagliflozin group; number analysed at week 164 was 81 in the placebo group and 195 in the empagliflozin group.

***Table 2*: Proportion of the reduction in urinary albumin-to-creatinine ratio with empagliflozin that was independent of or associated with concomitant changes from baseline in covariates**

In an additional sensitivity analysis, UACR was analysed in patients treated with at least one dose of the study drug and who had a UACR measurement at baseline, LVOT, and follow-up visit after cessation of study treatment. Differences between empagliflozin and placebo in changes from baseline were based on adjusted geometric mean ratios from ANCOVA, with baseline HbA_{1c} as a linear covariate and baseline eGFR, region, baseline BMI, treatment, baseline UACR, and treatment-by-baseline UACR interaction as fixed effects.

Differences between empagliflozin and placebo in new onset of sustained normoalbuminuria in patients with microalbuminuria, in new onset of sustained normoalbuminuria or microalbuminuria in patients with macroalbuminuria, and in new onset of sustained microalbuminuria or macroalbuminuria in patients with normoalbuminuria at baseline were analysed using Cox regression analysis with terms for age, sex, baseline BMI, baseline HbA_{1c}, baseline eGFR, region and treatment in patients treated with at least one dose of study drug, and we present Kaplan-Meier estimates for these outcomes. Post-hoc analyses according to baseline use of ACE inhibitors or ARBs were also done for these outcomes.

With renal data obtained with the on-treatment approach—ie, in patients treated with at least one dose of study drug considering data obtained at the end of study drug intake (LVOT), we explored differences between empagliflozin and placebo in occurrence of deterioration and improvement in UACR status from baseline to LVOT using logistic regression. eGFR over 192 weeks was analysed using an MMRM analysis using all data obtained until study end in patients treated with a least one dose of study drug in subgroups by UACR status at baseline. Adverse events were assessed descriptively in subgroups by UACR status at baseline, and in subgroups by use of ACE inhibitors or ARBs at baseline.

All analyses were done for the pooled empagliflozin group versus placebo and for the individual empagliflozin doses versus placebo. All analyses were done at a nominal level of α=0·05 two-sided without adjustment for multiplicity. The present analyses regarding UACR are considered exploratory. Safety data were reviewed by an independent academic data monitoring committee. This trial is registered with ClinicalTrials.gov, number NCT01131676.

Role of the funding source

One of the funders of the study (Boehringer Ingelheim) had a role in study design, data collection, data analysis, data interpretation, and writing of the report. The other funder (Eli Lilly and Company) had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Sept 1, 2010, and April 22, 2013, of 7028 patients who underwent randomisation, 7020 patients received treatment (appendix). At baseline, we had UACR data for

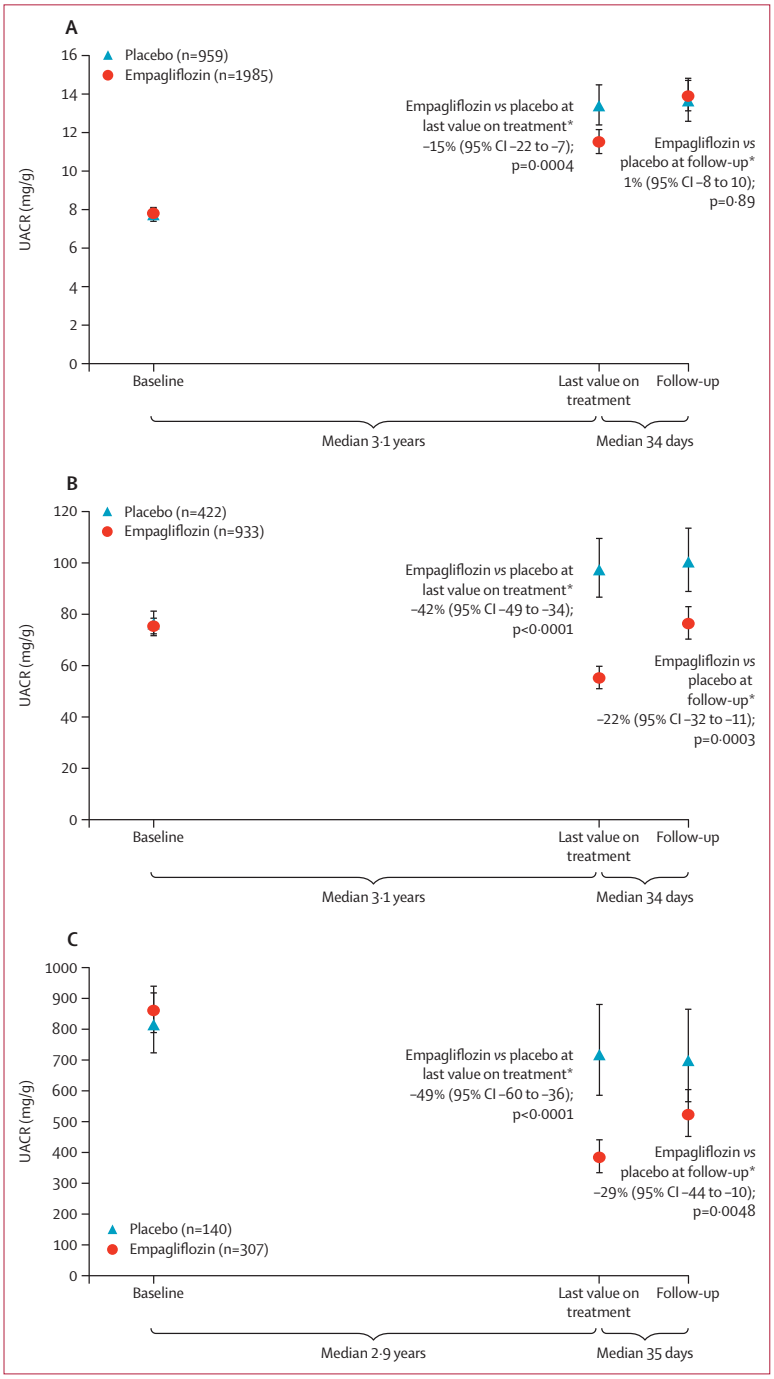


***Figure 2*: Urinary albumin-to-creatinine (UACR) ratio at baseline, last value on treatment, and follow-up**
Post-hoc analysis of covariance in patients with (A) normoalbuminuria, (B) microalbuminuria, and (C) macroalbuminuria at baseline treated with at least one dose of study drug who had a measurement at baseline, last value on treatment (using all data until last study medication intake plus 3 days), and follow-up. Adjusted geometric mean values and 95% CIs are shown. Normoalbuminuria: UACR <30 mg/g. Microalbuminuria: UACR ≥30 to ≤300 mg/g. Macroalbuminuria: UACR >300 mg/g. *Placebo-corrected adjusted geometric mean ratio (95% CI) of relative change from baseline with empagliflozin.

6953 patients: 4171 (59% of treated patients; 1382 assigned to placebo, 2789 assigned to empagliflozin) had normoalbuminuria, 2013 (29%; 675 assigned to placebo, 1338 assigned to empagliflozin) had microalbuminuria, and 769 (11%; 260 assigned to placebo and 509 assigned to empagliflozin) had macroalbuminuria (table 1). Mean baseline HbA_{1c}, the proportion of patients with more than 10 years since their diagnosis of type 2 diabetes, mean blood pressure, total cholesterol, LDL cholesterol, and triglyceride concentrations were higher in patients with microalbuminuria than in those with normoalbuminuria and highest in patients with macroalbuminuria (table 1). Mean baseline eGFR was lower in patients with microalbuminuria than normoalbuminuria and lowest in the patients with macroalbuminuria. Greater proportions of patients with macroalbuminuria were taking diuretics and calcium channel blockers at baseline compared with those with normoalbuminuria or microalbuminuria, but there was no apparent difference in the proportions of patients taking ACE inhibitors or ARBs at baseline between the three albuminuria subgroups (appendix).

The median treatment duration was 2·6 years (IQR 2·0–3·4; 136 weeks) and the median observation time was 3·1 years (2·2–3·6; 164 weeks), and similar among treatment groups. In patients with microalbuminuria or macroalbuminuria at baseline, there was a rapid reduction in UACR with empagliflozin compared with placebo, which was maintained over the course of the study, both at week 12 and week 164 (figure 1). In patients with normoalbuminuria at baseline, UACR increased from baseline in both the empagliflozin and placebo groups, but remained lower with empagliflozin than with placebo (figure 1).

At weeks 12 and 164, the albuminuria-lowering effect of empagliflozin was largely consistent across categories of baseline HbA_{1c} and across tertiles of baseline uric acid in patients in all three albuminuria subgroups (appendix). Treatment differences in UACR across patients with microalbuminuria or macroalbuminuria at baseline were largely independent of concomitant changes in other covariates (HbA_{1c}, systolic blood pressure, weight, uric acid, LDL cholesterol, and eGFR; table 2).

In patients with measurements at baseline, last value on treatment and follow-up, UACR was lower with empagliflozin versus placebo in all three albuminuria groups at end of study drug intake (LVOT; figure 2). At the follow-up visit, with a median of 34 days (IQR 31–37) for patients with normoalbuminuria or microalbuminuroia or 35 days (31–38) for patients with macroalbuminuria after the last intake of study drug, UACR remained unchanged in placebo-treated patients in each of the three groups (figure 2); by contrast, UACR increased from LVOT to follow-up in empagliflozin-treated patients in each of the three subgroups. At follow-up, UACR was no longer significantly different with empagliflozin compared with placebo in patients with normoalbuminuria at baseline (figure 2A), whereas

in patients with microalbuminuria or macroalbuminuria at baseline, UACR remained significantly lower in the empagliflozin group versus placebo.

New onset of sustained normoalbuminuria (in patients with microalbuminuria at baseline) and new onset of sustained normoalbuminuria or microalbuminuria (in patients with macroalbuminuria at baseline) occurred in greater proportions of patients treated with empagliflozin than placebo (figure 3, appendix). Results were consistent across subgroups by use of ACE inhibitors or ARBs at baseline (appendix). In a further analysis, the risk of new onset of sustained microalbuminuria or macroalbuminuria in patients with normoalbuminuria at baseline was attenuated with empagliflozin treatment (HR 0·84, 95% CI 0·74–0·95; p=0·0077; appendix).

In sensitivity analyses, a smaller proportion of patients assigned to empagliflozin had a deterioration in their UACR status compared with those assigned to placebo (OR 0·67 [95% CI 0·59–0·77, p<0·0001]; appendix), and a greater proportion of patients assigned to empagliflozin had improvements in their UACR status from baseline to LVOT (OR 1·61 [1·34–1·94, p<0·0001]; appendix). All UACR results with empagliflozin 10 mg and empagliflozin 25 mg were consistent with results from the pooled analyses (appendix).

In all empagliflozin subgroups by UACR at baseline, eGFR initially decreased until week 4; this decrease was followed by an increase and stabilisation of renal function within the first study year in patients with normoalbuminuria, with similar patterns seen in patients with microalbuminuria or macroalbuminuria (figure 4). By contrast, eGFR in the placebo group gradually decreased over time. During the second year of treatment, eGFR remained stable in the empagliflozin group and had decreased in the placebo-treated patients in each of the three subgroups, such that mean eGFR decreased below levels in empagliflozin-treated patients—a pattern that became more exaggerated over time (figure 4). eGFR results with empagliflozin 10 mg and empagliflozin 25 mg were consistent with the pooled analyses (appendix).

The proportions of patients with any adverse events, serious adverse events, and adverse events leading to discontinuation appeared to increase with worsening UACR status at baseline, but were similar between the empagliflozin and placebo groups (appendix). The proportion of patients with events consistent with genital infection was greater with empagliflozin than with placebo in all subgroups by UACR status (appendix). Numerically, smaller proportions of patients who were not taking ACE inhibitors or ARBs at baseline had serious adverse events compared with those who were (appendix).

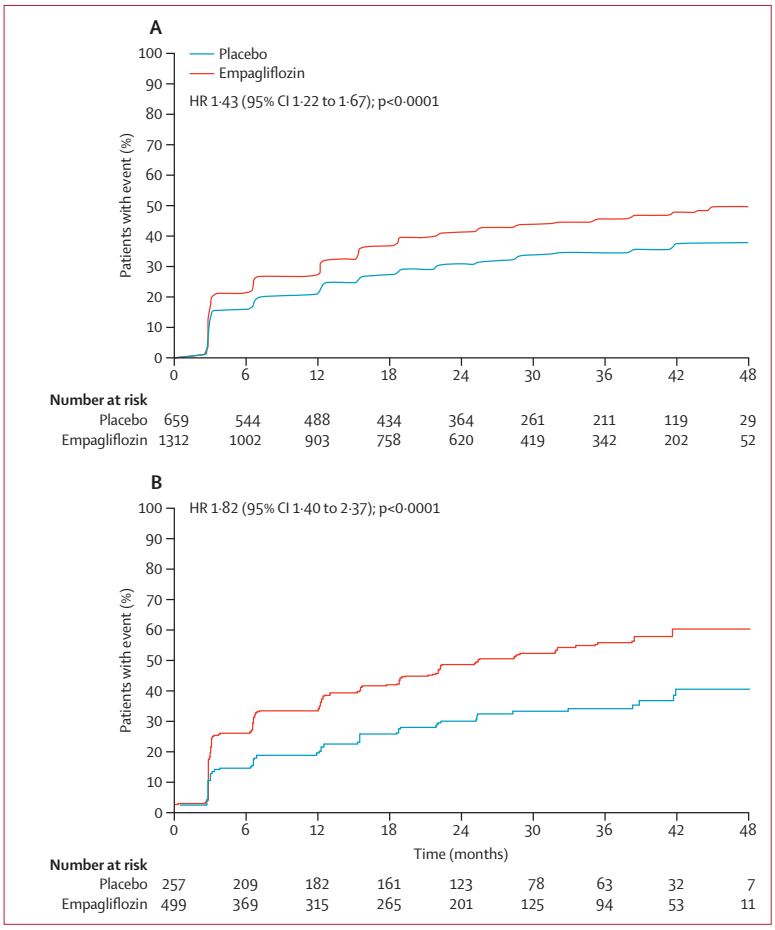
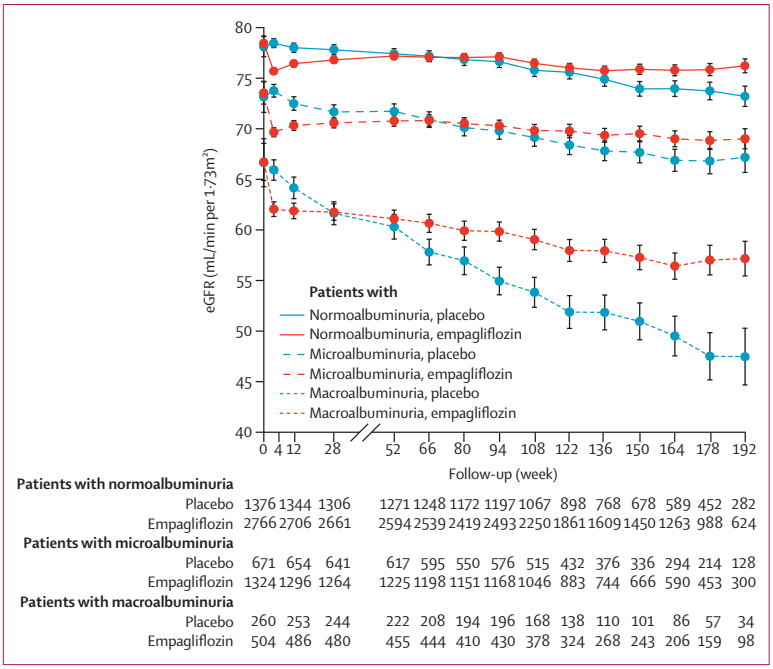


***Figure 3*: Sustained improvement in albuminuria status**
Prespecified analysis showing (A) new onset of sustained normoalbuminuria in patients with microalbuminuria at baseline, or (B) new onset of sustained normoalbuminuria or microalbuminuria in patients with macroalbuminuria at baseline. Kaplan-Meier estimate, hazard ratio (HR), and 95% CI in patients treated with at least one dose of study drug. Normoalbuminuria: urine albumin-to-creatinine ratio (UACR) <30 mg/g. Microalbuminuria: UACR ≥30 to ≤300 mg/g. Macroalbuminuria: UACR >300 mg/g.

Discussion

In this exploratory analysis from the EMPA-REG OUTCOME trial, empagliflozin reduced UACR in a cohort of patients with type 2 diabetes and established cardiovascular disease (of whom 26% had eGFR <60 mL/min per 1·73 m² at baseline),[16] regardless of their albuminuria status at baseline. Beyond its effect on glycaemic control, SGLT2 inhibition has important effects that might be related to changes in proximal tubular sodium reabsorption. These effects include reductions in blood pressure, and in intraglomerular hypertension that probably mediates the characteristic early small decrease in eGFR and the rapid and sustained reduction in albuminuria associated with SGLT2 inhibition. Additionally, cardiovascular benefits such as reduced hospital admissions for heart failure in EMPA-REG OUTCOME might have partly resulted from natriuresis and changes in intravascular volume.[2,7,19,20] The renal composite endpoint of incident or worsening nephropathy was also significantly reduced with empagiflozin treatment in this trial.[10]



Patients with normoalbuminuria														
Placebo	1376	1344	1306	1271	1248	1172	1197	1067	898	768	678	589	452	282
Empagliflozin	2766	2706	2661	2594	2539	2419	2493	2250	1861	1609	1450	1263	988	624
Patients with microalbuminuria														
Placebo	671	654	641	617	595	550	576	515	432	376	336	294	214	128
Empagliflozin	1324	1296	1264	1225	1198	1151	1168	1046	883	744	666	590	453	300
Patients with macroalbuminuria														
Placebo	260	253	244	222	208	194	196	168	138	110	101	86	57	34
Empagliflozin	504	486	480	455	444	410	430	378	324	268	243	206	159	98

Figure 4: **Estimated glomerular filtration rate over 192 weeks**
Post-hoc analysis of estimated glomerular filtration rate (eGFR), calculated according to CKD-EPI formula. Data are adjusted means; error bars show 95% CIs. Mixed-model repeated measures analysis using all data obtained until study end in patients treated with at least one dose of study drug. Only patients with baseline and post-randomisation measurements are included in the figure. Normoalbuminuria: urinary albumin-to-creatinine ratio (UACR) <30 mg/g. Microalbuminuria: UACR ≥30 to ≤300 mg/g. Macroalbuminuria: UACR >300 mg/g.

Following the results from EMPA-REG OUTCOME, the risk of three-point major adverse cardiovascular events was reduced in the CANVAS programme of an SGLT2 inhibitor and in the LEADER and SUSTAIN-6 trials of glucagon-like peptide-1 receptor agonists.[21-23] Progression of albuminuria and a composite renal endpoint of sustained 40% reduction in eGFR, requirement for renal-replacement therapy, or death from renal causes were reduced in the CANVAS program, although there was an increased risk of amputations and overall bone fractures.[23] The risk of new or worsening nephropathy was reduced in LEADER and SUSTAIN-6, but this reduction was mainly due to less progression to macroalbuminuria.[21,22] Importantly, the HbA_{1c} differences between treatment groups during the follow-up period in LEADER and SUSTAIN-6 were more substantial in comparison with differences in EMPA-REG OUTCOME, and no analyses have been reported that indicate to what extent effects on cardiovasular and renal outcomes are attributable to glycaemic control. Treatment with dipeptidyl peptidase-4 (DPP-4) inhibitors also reduces UACR, but without affecting the risk of doubling of serum creatinine, dialysis, or death, suggesting that effects on UACR might be beyond glycaemic control.[24,25] Given the association between UACR and renal outcomes in type 1 and type 2 diabetes,[26,27] a more detailed understanding of the UACR-lowering effects with newer antihyperglycaemic therapies is important.

From our analysis, the decrease in UACR with empagliflozin occurred as early as week 12 and was maintained under chronic treatment. These effects occurred across the spectrum of UACR—including in patients with normoalbuminuria at baseline—in a cohort with a high prevalent use (around 80%) of evidence-based therapies such as inhibitors of the RAS and other antihypertensive drugs. Findings from previous trials of patients with type 2 diabetes have shown that RAS inhibitors reduce the risk of developing albuminuria in patients with normoalbuminuria at baseline, and reduce the risk of progressive albuminuria in patients with baseline elevations in UACR.[28] The expected magnitude of the decrease in albuminuria with RAS inhibition is between 20% and 40%.[15] On the basis of analyses in patients at lower cardiovascular risk,[2,7] the effect size of empagliflozin on microalbuminuria and macroalbuminuria in this analysis seems to be at least equivalent to that of RAS inhibitors.

In our prespecified analyses, empagliflozin increased the likelihood of new onset of sustained normoalbuminuria in patients with microalbuminuria at baseline and also increased the likelihood of new onset of sustained normoalbuminuria or microalbuminuria in patients with macroalbuminuria at baseline. In patients with normoalbuminuria, empagliflozin reduced the risk of progressing to sustained albuminuria. This result adds further granularity to data showing no significant effect of empagliflozin on incidence of albuminuria based on a single UACR measurement.[9] We believe that confirmation of UACR events by applying criteria for sustainability reduces some of the natural background noise of the event and is therefore better suited to decipher treatment effects of empagliflozin in the early course of albuminuria deterioration.

A frequently cited physiological framework that best explains the lowering in UACR after SGLT2 inhibition is a reduction in intraglomerular pressure. With proximal tubular natriuresis and an increase in distal sodium delivery, more sodium chloride moves across the macula densa, increasing energy expenditure via ATP breakdown to adenosine monophosphate and adenosine.[1] Adenosine, in turn, acts at the adenosine type-1 receptor to cause vasoconstriction of the afferent arteriole; intraglomerular hypertension and, as a consequence, movement of albumin across the glomerular filtration barrier are reduced. In patients with macroalbuminuria, of the 41% reduction in UACR with empagliflozin in pooled phase 3 studies, less than 10% was attributable to the reduction in systolic blood pressure.[2] Additionally, the lowering in UACR was independent of decreases in weight and HbA_{1c}. A reduction in intraglomerular pressure is also probably responsible for the characteristic early dip in eGFR on treatment initiation with SGLT2 inhibitors in

patients with and without chronic kidney disease.[1] Similarly, SGLT2 inhibition with canagliflozin reduced the slope of eGFR over time and reduced UACR[29]—effects that were similarly independent of changes in weight, HbA_{1c}, or blood pressure. Consistent with previous observations, UACR-lowering effects in EMPA-REG OUTCOME in patients with microalbuminuria or macroalbuminuria were largely independent of concomitant changes in weight, HbA_{1c}, blood pressure, LDL cholesterol, uric acid, or eGFR. The data support a prominent role for the reduction in intraglomerular pressure as the dominant factor that slows the loss of renal function and lowers UACR in patients with type 2 diabetes treated with empagliflozin.

After cessation of empagliflozin for a median of 34 days at study end, the reduction in UACR at LVOT was completely reversible in patients with normoalbuminuria at baseline. In patients with microalbuminuria or macroalbuminuria at baseline, UACR increased after treatment cessation, but did not reach the levels of the placebo group. The reversibility of the treatment effect on UACR in the normoalbuminuric group strongly suggests that a haemodynamic mechanism was responsible for improvements in albuminuria over the course of the trial and that such a renal haemodynamic effect could be rapidly reversed upon drug discontinuation, even after long-term treatment. UACR effects in the micro-albuminuric and macroalbuminuric groups were only partly reversible during the period studied, suggesting that the haemodynamic effects in those patients are somehow sustained or that only a portion of the UACR reduction was haemodynamically induced. The remainder of the albuminuria benefit versus the placebo group might have been related to the prevention of the progression of diabetes-related structural changes in the kidney; however, biopsy data of the protective effect of SGLT2 inhibition has only been shown in animals, reflected by a reduction in glomerulosclerosis and tubulointerstitial fibrosis.[30–33]

On the basis of the primary cardiovascular outcomes reported in EMPA-REG OUTCOME,[16] clinical practice guidelines and regulatory agencies including Health Canada, the US Food and Drug Administration, and the European Medicines Agency have started to recognise the cardiovascular protective effects of empagliflozin in patients with type 2 diabetes and established cardio-vascular disease with suboptimal control on metformin, and heart failure guidelines have also noted its cardio-vascular benefits in patients with type 2 diabetes.[34–36] Although it seems unlikely that the secondary renal endpoints from EMPA-REG OUTCOME alone will modify clinical practice guidelines for diabetic kidney disease, the positive renal findings and the substantial reduction in UACR will probably make the use of empagliflozin, or more broadly SGLT2 inhibitors, more frequent in patients with diabetic kidney disease in clinical nephrology practice, as long as there is sufficient GFR to allow a drug effect. Clearly, however, a more formal preference for SGLT2 inhibitors as a potential renal protective therapy will require equally positive results from primary renal endpoint trials such as the dedicated outcomes trial of empagliflozin in patients with chronic kidney disease, both with and without type 2 diabetes, and trials such as CREDENCE (assessment of the effects of canagliflozin on renal and cardiovascular outcomes in participants with diabetic nephropathy; NCT02065791) and DAPA-CKD (a study to evaluate the effect of dapagliflozin on renal outcomes and cardiovascular mortality in patients with chronic kidney disease; NCT03036150). Renal data from the ongoing dapagliflozin cardiovascular outcome trial DECLARE-TIMI-58 (NCT01730534) will also likely inform this discussion.

The addition of empagliflozin to a background of RAS inhibition did not increase the risk of kidney relevant adverse events such as hypotension, hyperkalaemia, or acute kidney injury. For unclear reasons, the combination of an SGLT2 inhibitor with a RAS inhibitor therefore does not appear to portend the type of risk associated with dual RAS inhibition (eg, hyperkalaemia or acute kidney injury), even though both strategies probably act via a decrease in intraglomerular hypertension.

Our analysis had the following limitations. First, it was exploratory and partly post-hoc in nature. Second, the outcome measure in this exploratory analysis was UACR, which has limited use as a surrogate for long-term clinical renal risk,[37] partly because of the variability inherent in this marker.[38] Moreover, although other renal protection trials have used two or more UACR measures to define albuminuria status and EMPA-REG OUTCOME only required a single specimen, recent data have suggested that in large sample sizes, a single sample is sufficient.[39–41] Despite these limitations, in the absence of other novel and validated biomarkers, UACR continues to be the most common and accessible biomarker of renal risk used by clinicians to assess eligibility for, and gauge responses to, therapy such as RAS blockade. Furthermore, reductions in UACR with other drugs that target glomerular hypertension such as RAS inhibitors are associated with diminished renal risk.[14] The robust UACR-lowering effects in this trial despite the variability of UACR is reassuring, since a high signal-to-noise ratio would have tended to attenuate any beneficial effects. Therefore, if empagliflozin and other SGLT2 inhibitors are used more frequently by cardiologists and nephrologists in the future to target non-glycaemic parameters based on the EMPA-REG OUTCOME trial, UACR is also likely to be used as a surrogate, short-term marker of intraglomerular pressure and renal efficacy for these types of drugs. Although the acute dip in eGFR with SGLT2 inhibition has been attributed to decreased glomerular pressure, other factors such as changes in circulating volume leading to haemoconcentration might be involved, and the effect of SGLT2 inhibition on tubular handling of creatinine has not been fully elucidated. Although we

suggest that the partial rebound in UACR in the microalbuminuric and macroalbuminuric groups might have had mechanistic implications, we recognise that the median time between LVOT and follow-up was no more than 35 days, which might not be long enough to observe a complete rebound in UACR in these subgroups. Finally, for generalisability, mean HbA_{1c} values were suboptimal (around 8% [64 mmol/mol]) during the trial based on current guidelines.

In conclusion, in patients with type 2 diabetes and established cardiovascular disease, empagliflozin led to significant reductions in UACR from as early as week 12, which were sustained for at least 3 years, regardless of baseline albuminuria status and on top of RAS inhibition. The effect of empagliflozin on UACR appeared to be, in large part, beyond the effects on glycaemic control. These results suggest a persistent renal haemodynamic effect of empagliflozin, which may confer short-term and long-term renal effects on UACR when used in addition to current standard of care.

Contributors

All authors contributed to the interpretation of data; drafted, reviewed, and edited the report; were fully responsible for all content and editorial decisions, were involved at all stages of the development of the report, and approved the final submitted version. MvE is the guarantor of this work.

Declaration of interests

DZIC has been a paid consultant for and received speaker honoraria from Boehringer Ingelheim and Eli Lilly and Company, Merck, Janssen, Sanofi, and AstraZeneca, and has received research operating funds from Boehringer Ingelheim and Eli Lilly and Company, Merck, and AstraZeneca. BZ has received research grants awarded to his institution from Boehringer Ingelheim, AstraZeneca, and NovoNordisk, and has received honoraria for lectures and scientific advisory boards from Janssen, Sanofi, Boehringer Ingelheim, Eli Lilly and Company, NovoNordisk, and Merck. SEI participates in clinical trial steering committees for Boehringer-Ingelheim, Daiichi Sankyo, and AstraZeneca, and clinical trial data monitoring committees for Novo Nordisk and Intarcia; he is a consultant for Merck, Sanofi/Lexicon, Janssen, and vTv Pharmaceuticals. CW participates in clinical trial steering committees for Boehringer Ingelheim and Eli Lilly and Company, GlaxoSmithKline, Sanofi Genzyme, and clinical trial data monitoring committees for Janssen. He has received honoraria for lecturing from Boehringer Ingelheim and Eli Lilly and Company, and Sanofi Genzyme. AK-W, MM, and MvE are employees of Boehringer Ingelheim.

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