Nephrotic-range proteinuria in type 2 diabetes: Effects of empagliflozin on kidney disease progression and clinical outcomes

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Summary

Background Diabetic kidney disease with nephrotic-range proteinuria (NRP) is commonly associated with rapid kidney function loss, increased cardiovascular risk, and premature mortality. We explored the effect of empagliflozin in patients with type 2 diabetes and cardiovascular disease, complicated by presence of this major risk factor for progressive kidney disease, in a *post-hoc* analysis of data from the EMPA-REG OUTCOME trial (NCT01131676).

Methods Cox proportional hazards models were used to investigate the risk of cardiovascular and kidney outcomes in participants with and without NRP, defined by urine albumin-to-creatinine ratio (UACR) ≥2200 mg/g at baseline. Annual loss of eGFR during chronic treatment (eGFR slopes) and hypothetical time to projected end-stage kidney disease (ESKD), conditioning upon linearity of eGFR change over time if a patient did not decease before projected ESKD, were calculated using a random-intercept random-coefficient model. Safety was described based on investigator-reported adverse events.

Findings 112 participants (pooled empagliflozin, $n = 70$; placebo, $n = 42$; median on-treatment follow-up of 1·9 years on placebo compared with 2·3 years on empagliflozin) presented with NRP at baseline; eGFR and UACR were balanced between treatments. Empagliflozin benefits on cardiovascular death, hospitalisation for heart failure, or kidney outcomes, were consistent in participants with and without NRP ($p_{interaction}$ >0·1). Treatment effects of empagliflozin on adjusted annual mean eGFR slope were more pronounced in participants with NRP versus those without ($p_{interaction}$ 0·005). Empagliflozin was estimated to double the median hypothetical time to projected ESKD in participants with NRP. The overall safety profile of empagliflozin was comparable between participants with and without NRP at baseline.

Interpretation Our data suggests that empagliflozin might slow kidney function loss and delay the estimated onset of projected ESKD in patients with type 2 diabetes and cardiovascular disease complicated by NRP.

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Research in context

Evidence before this study

When designing this analysis we searched PubMed with no language restrictions for peer-reviewed publications (excluding congress abstracts or presentations) using search terms "proteinuria", "kidney disease", and "nephrotic" in combination with "type 2 diabetes" or "SGLT2". Up to December 2017, studies of patients with type 2 diabetes mellitus (T2DM) and nephrotic-range proteinuria (NRP) have involved low numbers of cases and/or a short follow-up period. There had been no published controlle evidence of the efficacy of Sodium-glucose co-transporter-2 (SGLT2) inhibitors in patients with NRP.

Added value of this study

This *post-hoc* analysis represents one of the largest clinical data sets exploring potential beneficial interventions in patients with T2DM and NRP, with over 296 patient-years of clinical information for this relatively rare clinical condition. The safety profile and the beneficial effects of empagliflozin on cardiovascular (CV) death, hospitalisation for heart failure (HHF), or kidney outcomes were consistent in participants with and without NRP. However, we observe that the treatment effects of empagliflozin on adjusted annual mean changes in estimated glomerular filtration rate were greater in participants with NRP than those without, doubling the median hypothetical time to projected end-stage kidney disease (ESKD).

Implications of all the available evidence

Given that patients with T2DM and NRP have an extremely high dialysis risk, the beneficial effects of empagliflozin in terms of reduced mortality and morbidity could have major clinical implications for the treatment of this condition. These findings need confirmation in clinical trials.

Introduction

Nephrotic syndrome is a clinical entity defined by a triad of massive, nephrotic-range proteinuria (NRP), resulting hypoalbuminaemia and oedema, which is often accompanied by hyperlipidaemia and various complications such as thromboembolism and increased risk of infection.[1] NRP is caused by increased permeability of the glomerular basement membrane due to an underlying disease of the kidneys or secondary causes. One of the most common causes of secondary NRP in adults is type 2 diabetes mellitus (T2DM).[2] Unfortunately, prognosis of NRP in T2DM is poor,[3] especially in patients with diabetic nephropathy,[4] and it is a major risk factor for accelerated loss of kidney function leading to premature end-stage kidney disease (ESKD), increased healthcare utilisation (e.g., hospital admissions), cardiovascular disease,[5] and premature mortality.[6] Previous reports on treatments for patients with T2DM and NRP have mostly been limited by small numbers of cases and/or a short follow-up duration, and up to December 2017 when the present study was conceived, proven interventions were very limited; only angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers (ACEi/ARBs) have been shown to be effective, nearly 20 years ago.[7] Other treatment options, however, such as statins, have failed.[8]

Sodium-glucose co-transporter-2 (SGLT2) inhibitors have a kidney-targeted mechanism of action and have been shown to have nephroprotective effects, specifically in albuminuric patients.[9–12] Up to December 2017, there was no evidence on their efficacy in patients with NRP, but in a clinical case report, tofogliflozin was able to substantially reduce NRP in a patient with T2DM over 24 weeks of treatment.[13]

In EMPA-REG OUTCOME, empagliflozin, in addition to significantly reducing the risk of cardiovascular (CV) death and heart failure hospitalisation,[14] decreased clinically relevant kidney outcomes by 39% in participants with T2DM and established cardiovascular disease (CVD),[15] and by 47% in the participants with heart failure.[16] These findings are consistent with data from other SGLT2 inhibitors such as canagliflozin and dapagliflozin in patients with T2DM and CVD or CV risk.[17,18] Most recently, canagliflozin and dapagliflozin have also been shown to reduce CV and kidney events in patients with albuminuric chronic kidney disease (CKD), regardless of coexisting diabetes.[11,12] In the EMPA-REG OUTCOME trial, participants were followed over a median observation period of 3·1 years.[14] As no restrictions for albuminuria were applied at inclusion, it was also possible to study participants with albuminuria values in the nephrotic range. We therefore aimed to evaluate the potential of empagliflozin to slow kidney disease progression and to improve overall clinical outcomes burden in individuals with T2DM complicated by the presence of NRP, using data from EMPA-REG OUTCOME.

Methods

Trial design

As described in detail previously, the EMPA-REG OUTCOME trial (ClinicalTrials.gov identifier:

NCT01131676) was a double-blind, placebo-controlled, multinational trial.[19] The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines and was approved by local authorities. The study protocol was approved by the respective Institutional Review Boards, Independent Ethics Committees and Competent Authorities according to national and international regulations and all participants provided informed consent. Eligible study participants with T2DM, glycated haemoglobin (HbA1c) ≥7%, and established CVD were randomised in a 1:1:1 ratio to empagliflozin 10 mg, 25 mg, or placebo; all added to background standard of care. Participants were required to have an estimated glomerular filtration rate (eGFR) of ≥30 mL/min/1·73 m^2 (based on the Modification of Diet in Renal Disease study [MDRD] formula) at screening, but there were no specific study restrictions/requirements for levels of albuminuria or proteinuria at baseline. Serum creatinine and urine albumin-to-creatinine ratio (UACR) were measured by a central laboratory at the start of the placebo run-in period; randomisation; at 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 timepoints, except for week 4, urine dipstick was performed locally. For all glomerular filtration rate- (GFR-) based kidney assessments, serum creatinine was used to calculate eGFR using the MDRD formula. The primary CV endpoint of the trial, as well as results of the prespecified secondary kidney endpoint (defined as incident or worsening nephropathy), UACR changes over time, and a comprehensive analysis on eGFR slopes have been reported previously.[14,15,20,21]

Nephrotic-range proteinuria in EMPA-REG outcome

We conducted a *post-hoc* exploratory analysis of kidney, CV, and other relevant clinical outcomes in two subgroups from the overall population of EMPA-REG OUTCOME: participants with NRP (defined as UACR ≥2200 mg/g with any GFR based on previous results from the IDNT study[1,22]) at baseline and participants without NRP at baseline (non-NRP; UACR <2200 mg/g), and in accordance with the guideline recommendations as issued by KDIGO in 2012.[23]

Clinical outcomes

We compared the treatment effects of empagliflozin versus placebo in participants with NRP versus non-NRP for the clinical outcomes of 3P-MACE, all-cause mortality, CV death, combination of hospitalisation for heart failure (HHF) or CV death (excluding fatal stroke), and all-cause hospitalisation. Kidney endpoints were also evaluated, including incident or worsening nephropathy, sustained eGFR decline ≥40% (i.e., ≥2 consecutive measurements that were ≥28 days apart) from baseline, and the hard kidney composite outcome comprising events of doubling of serum creatinine accompanied by an eGFR of ≤45 mL/min/1·73 m^2, initiation of kidney replacement therapy (KRT), or death from kidney disease. Treatment for patients considered at risk for the various endpoints followed the rationale pre-specified for the study.[14,15] For the analyses of 3P-MACE, all-cause mortality, CV death, HHF or CV death (excluding fatal stroke), and all-cause hospitalization, all patients randomized and treated who had data available for the baseline covariates used in the model were included. All remaining 6953 patients with available baseline UACR data were included in the current analyses. For kidney endpoints, patients with missing baseline eGFR or no post-baseline eGFR measurement were excluded from the risk set for endpoints/components of doubling of serum creatinine or sustained eGFR decline ≥40% from baseline. For albuminuria changes, only patients with available baseline and at least one post-baseline UACR measurement were included in the analysis. For endpoints that required the condition to be sustained, if the condition occurred only with the last laboratory measurement, the patient was considered as not having an event.

Changes in albuminuria

Changes in albuminuria were assessed post hoc and analysed as time to new onset of sustained (i.e., ≥2 consecutive measurements that were ≥28 days apart) improvement in albuminuria status relative to baseline (sustained reduction ≥50% or ≥30% from baseline UACR). In addition, new onset of full remission (defined as sustained UACR <0·5 g/g), or partial remission (defined as sustained UACR <1·0 g/g) were assessed in participants not meeting the criterion at baseline.

eGFR slopes

Details on a prespecified slope analysis have been reported recently.[21] For slope analyses reported here, the main efficacy outcome was the average rate of change of eGFR in mL/min/1·73 m^2 per year during the trial period when participants received stable treatment with study drug (from week 4 until treatment cessation – i.e., the chronic treatment maintenance period). In addition, the average rate of change in eGFR per week in the first 4 weeks after treatment initiation (i.e., treatment initiation period) was assessed, as well as in the 30 days after stopping treatment (i.e., post-treatment cessation period).[21]

Hypothetical time to projected ESKD

Among the subgroup of participants with NRP, based on results from the random-intercept random-

coefficient model and utilising the individual participants' intercepts and slopes, we estimated the hypothetical time of reaching projected ESKD (defined as the time of first reaching eGFR-value ≤10 mL/min/1·73 m^2 that was maintained) if a patient does not die. Deaths occurring after hypothetically reaching ESKD were not considered for the primary ESKD evaluation, and any deaths occurring before projected ESKD were not accounted for.

We applied the random-intercept random-coefficient model to data from week 4 until treatment cessation and extrapolated the eGFR course, conditioning upon linearity, until 15 years from baseline. Hypothetical time to projected ESKD was determined by the individual intercept and slope for participants who reached it within 15 years. For all other NRP participants it was set to 15 years, assuming that any patient with a slower decline would have reached ESKD after 15 years, thereby potentially over-estimating the rate of ESKD particularly in the group with smaller eGFR decline (across both treatments), but to reflect the severe prognosis within this population studied. Any death in NRP patients within that 15-year time frame was not accounted for as a death-prediction was not performed. Comparison of the hypothetical time to projected ESKD between treatment groups was performed by providing median (interquartile range [IQR]) of individual participants' time and a log rank test.

Safety

Confirmed hypoglycaemia adverse events were defined as documented episodes with plasma glucose ≤70 mg/dL or requiring assistance. Events consistent with urinary tract infection, genital infection, volume depletion, oedema, bone fracture, hyperkalaemia, and acute kidney failure were based on searches of adverse events reported by investigators in accordance with previous reports. Investigator-reported venous-thrombotic events (VTE) and oedema were considered safety events of special interest for participants with NRP.

Effectiveness parameters

Effectiveness parameters of interest were changes from baseline over time in HbA1c, haematocrit, plasma albumin, uric acid, and systolic and diastolic blood pressure.

Analyses

Analyses were performed on the treated set (all participants who received ≥1 dose of study drug [modified intent-to-treat approach]) and compared the placebo and pooled empagliflozin (10 and 25 mg) groups. Treatment group differences in the risk of an outcome event were assessed using a Cox proportional hazards model with treatment, age, sex, baseline body mass index, baseline HbA1c, baseline eGFR, and region as factors. Subgroup analyses included additional factors for subgroup and treatment-by-subgroup interaction. Data for participants who did not have an event were censored on the last day they were known to be free of the outcome. Kaplan Meier estimates are shown. Differences in weekly or annual eGFR slopes were obtained using a random-intercept random-coefficient model, as described previously.[21] The same model was used to calculate the hypothetical time to projected ESKD, if a patient does not die before projected ESKD, conditioning upon linearity of eGFR change over time by utilising individual estimated intercepts and slopes from the chronic treatment maintenance phase for each participant within the NRP group. All effectiveness parameters were assessed using a mixed-model repeated measures (MMRM) analysis. All analyses were performed on a nominal two-sided α=0·05 without adjustment for multiplicity. Safety was assessed by means of frequency counts and incidence rates of adverse events.

Role of the funding source

The EMPA-REG OUTCOME trial was funded by the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance. The funder of the EMPA-REG OUTCOME trial had a role in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 7020 participants were randomised from September 2010 through April 2013, with a median duration of treatment of 2·6 years and a median observation time of 3·1 years.[14] Overall, 97% of participants completed the study, and final vital status was available for 99·2% of participants (Supplementary Figure S1). Less than 1% (n = 67) of participants were missing UACR at baseline and were omitted from the analyses. In the remaining 6953 (>99%) of all participants, UACR values at baseline were available, allowing for appropriate identification of prevalent NRP; 112 (1·6%) participants from EMPA-REG OUTCOME were identified as having NRP at baseline and 6841 (97·4%) had no evidence of NRP. Individuals with NRP had a median on-treatment follow-up of 1·9 years on placebo compared with 2·3 years on empagliflozin, yielding 83·8 patient-years on placebo and 151·0 patient-years on empagliflozin of drug exposure for this specific subgroup. Median observation time for participants with NRP was 2·9 years for participants receiving empagliflozin and 2·4 years for those receiving placebo.

Baseline characteristics and concomitant medications of participants with and without NRP are summarised in Table 1. As expected, several clinical

	NRP (UACR ≥2200 mg/g) *n* = 112	Non-NRP (UACR <2200 mg/g) *n* = 6841	*P* value
Age, years	62·1 ± 8·8	63·2 ± 8·6	0.1743
Male	75 (67·0)	4889 (71·5)	0.2957
Body mass index, kg/m^2	30·15 ± 5·67	30·62 ± 5·26	0.3505
Systolic blood pressure, mmHg	146·0 ± 20·6	135·3 ± 16·9	<0.0001
Diastolic blood pressure, mmHg	79·2 ± 10·6	76·6 ± 9·9	0.0058
Kidney function parameters			
eGFR, mL/min/1·73 m^2 (MDRD)	61·5 ± 21·1	74·2 ± 21·4	<0.0001
≥90	12 (10·7)	1507 (22·0)	
60 to <90	47 (42·0)	3583 (52·4)	
45 to <60	22 (19·6)	1216 (17·8)	
<45	31 (27·7)	534 (7·8)	
UACR, mg/g, median (Q1, Q3)	3532 (2707, 4879)	16·8 (6·2, 67·2)	<0.0001
Normal	0 (0)	4171 (61·0)	
Microalbuminuria	0 (0)	2013 (29·4)	
Macroalbuminuria	112 (100·0)	657 (9·6)	
Clinical laboratory parameters			
Plasma albumin, g/dL	3·81 ± 0·46	4·43 ± 0·30*	<0.0001
Haemoglobin, g/dL	12·74 ± 1·95	13·74 ± 1·46†	<0.0001
Haematocrit,%	38·6 ± 5·6	41·4 ± 4·4‡	<0.0001
HbA1c,%	8·24 ± 0·96	8·07 ± 0·84*	0.0329
Fasting plasma glucose, mg/dL	149 ± 54	153 ± 44§	0.2761
LDL cholesterol, mg/dL	111 ± 50·5	85 ± 35·3‖	<0.0001
HDL cholesterol, mg/dL	46·4 ± 12·6	44·4 ± 11·7¶	0.0690
Triglycerides, mg/dL	223 ± 230	170 ± 125¶	<0.0001
Time since diagnosis of diabetes			
≤1 year	1 (0·9)	179 (2·6)	0.0317
>1 to 5 years	11 (9·8)	1062 (15·5)	
>5 to 10 years	21 (18·8)	1704 (24·9)	
>10 years	79 (70·5)	3896 (57·0)	
History of CV high-risk factors			
Any CV high-risk factor	112 (100·0)	6785 (99·2)	
Coronary artery disease**	78 (69·6)	5178 (75·7)	0.1394
Stroke	35 (31·3)	1586 (23·2)	0.0453
PAD	38 (33·9)	1410 (20·6)	0.0006
HF	17 (15·2)	687 (10·0)	0.0739
Diabetic nephropathy	67 (59·8)	1290 (18·9)	<0.0001
Baseline medications			
Antihypertensive therapies	108 (96·4)	6498 (95·0)	0.4868
ACE inhibitors/ARBs	91 (81·3)	5521 (80·7)	0.8846
Beta-blockers	73 (65·2)	4435 (64·8)	0.9389
Diuretics	59 (52·7)	2946 (43·1)	0.0416
Calcium-channel blockers	57 (50·9)	2242 (32·8)	<0.0001
Statins	84 (75·0)	5272 (77·1)	0.6064

***Table 1*: Baseline characteristics in participants without (UACR <2200 mg/g) and with (UACR ≥2200 mg/g) nephrotic-range proteinuria (NRP).**

Participants treated with ≥1 dose of study drug. Data are *n* (%) or mean ± SD, unless otherwise indicated.

ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. CV=cardiovascular. eGFR=estimated glomerular filtration rate. HbA1c=glycated haemoglobin. HDL=high-density lipoprotein. HF=heart failure. LDL=low-density lipoprotein. MDRD=Modification of Diet in Renal Disease. PAD=peripheral artery disease. Q1=first quartile. Q3=third quartile. SD=standard deviation. UACR=urine albumin-to-creatinine ratio.

P value based on Chi−square test for categorical variables and analysis of variance for continuous variables

*Data available for *n* = 6840.

† data available for *n* = 6837.

‡ data available for *n* = 6821.

§ data available for *n* = 6810.

‖ data available for *n* = 6759.

¶ data available for *n* = 6762; **Defined as any history of myocardial infarction, coronary artery bypass graft, multivessel coronary artery disease or single-vessel coronary artery disease.

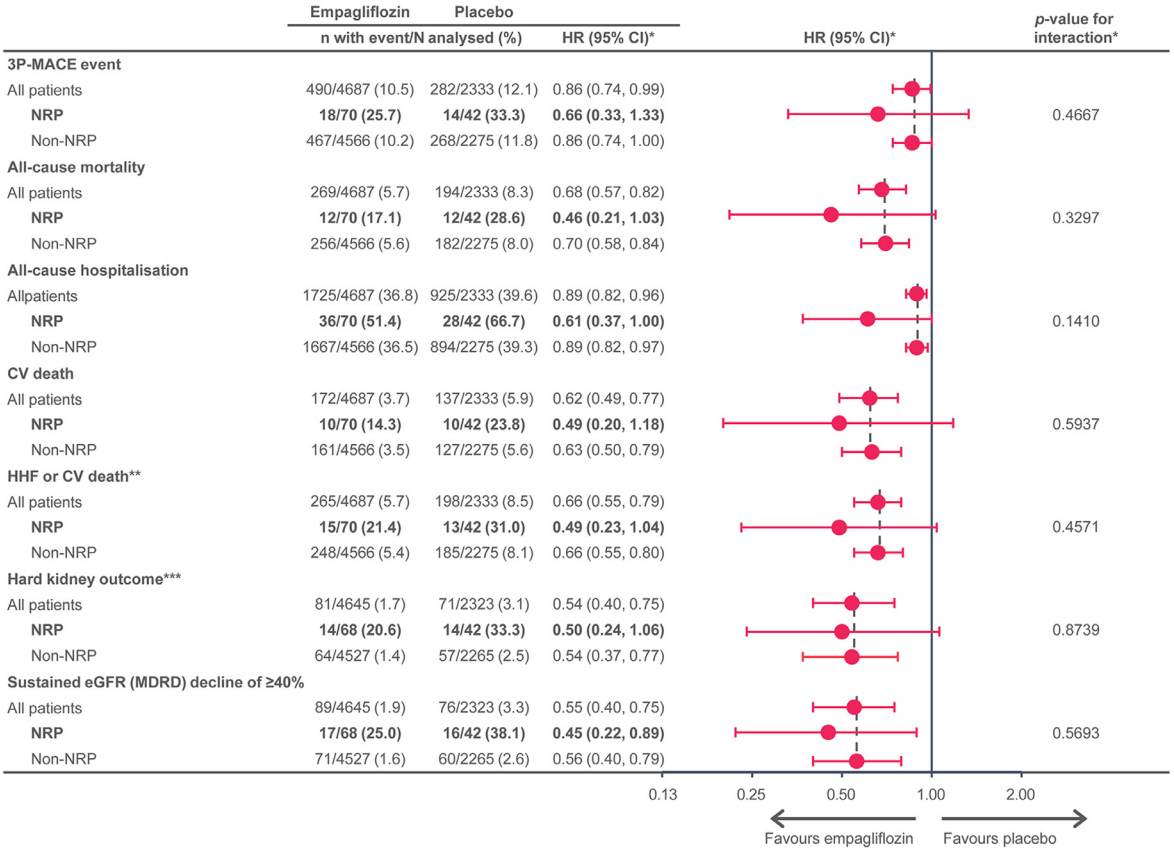

Figure 1. Cardiovascular and kidney outcomes by participants with NRP (UACR ≥2200 mg/g) and non-NRP (UACR <2200 mg/g)

3P-MACE=3-point major adverse cardiovascular event. CI=confidence interval. CV=cardiovascular. eGFR=estimated glomerular filtration rate. HHF=hospitalisation for heart failure. HR=hazard ratio for empagliflozin versus placebo. KRT=kidney replacement therapy. MDRD=Modification of Diet in Renal Disease. non-NRP=UACR <2200 mg/g. NRP=nephrotic-range proteinuria (UACR ≥2200 mg/g). UACR=urine albumin-to-creatinine ratio.

*Cox proportional hazards model with age as continuous covariate and factors for treatment, sex, baseline body mass index, baseline HbA1c, baseline eGFR, region, subgroup of NRP and subgroup-by-treatment interaction. **Excluding fatal stroke. ***Doubling of serum creatinine with eGFR (MDRD) ≤45 mL/min/1.73 m^2 or initiation of KRT or death from kidney disease.

characteristics of participants with NRP were different from those without NRP at baseline. Thus, eGFR, plasma albumin, haemoglobin levels, and haematocrit were lower, whereas levels of UACR and blood pressure were higher. In addition, this subgroup had an overall longer duration of T2DM and a higher frequency of reported history of stroke, heart failure, and peripheral artery disease. A history of diabetic nephropathy was reported in 59·8% of NRP compared with 18·9% of non-NRP participants. Moreover, a combined history of diabetic nephropathy and diabetic retinopathy, suggestive for overt diabetic microvascular complications, was reported in 7·6% (n = 521) of the overall study population, but in 33% (n = 37) of the NRP subgroup. Use of ACEi, ARBs or beta-blockers was balanced between participants with or without NRP at baseline, but use of diuretics and calcium-channel blockers was slightly more frequent in participants with NRP.

Of the 112 individuals with NRP at study entry, 70 were treated with empagliflozin and 42 with placebo following randomisation (2:1). Baseline (mean ± standard deviation) eGFR in the NRP subgroup was similar in the placebo (63·6 ± 23·5 mL/min/1·73 m^2) and empagliflozin (60·3 ± 19·5 mL/min/1·73 m^2) arms, as was median [interquartile range] UACR (placebo: 3676 [2713–4866] mg/g; empagliflozin: 3533 [2702–4893] mg/g) (Supplementary Table S1). Most other clinical characteristics were also similar between empagliflozin- and placebo-treated participants with NRP. However, heart failure history was numerically higher in placebo (21·4% [n = 9]) than in empagliflozin (11·4% [n = 8]). Moreover, use of some concomitant background medications differed slightly at baseline. Baseline treatment with calcium-channel-blockers was numerically lower in participants with NRP randomised to empagliflozin than to placebo (45·7% [n = 32] and 59·5% [n = 25],

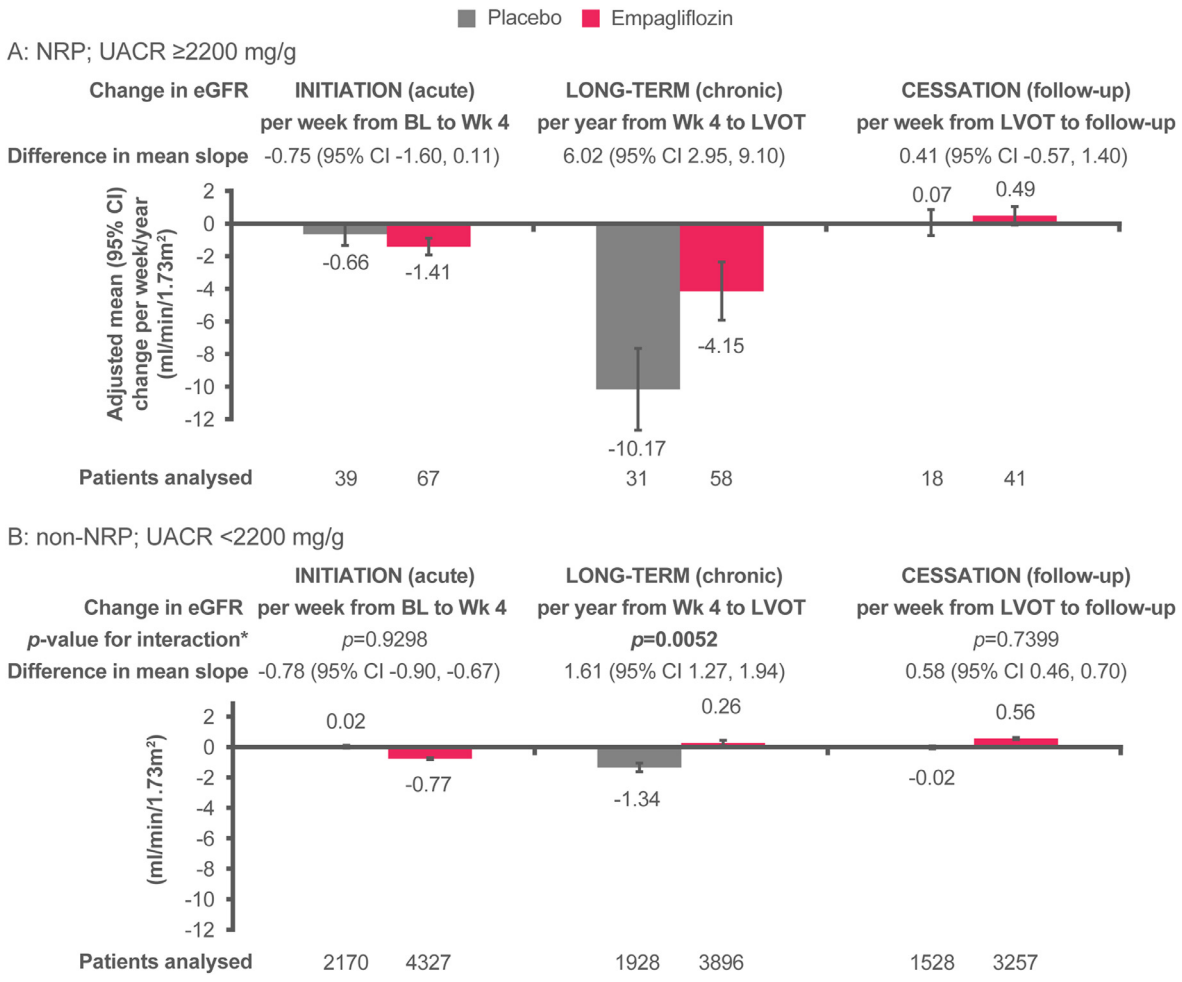

Figure 2. Change in eGFR per week/year during prespecified study periods

Participants treated with at least one dose of study drug. Adjusted mean slopes represent the average change in eGFR (MDRD) per mL/min/1.73 m^2 per week (for initiation and cessation) and per year (for chronic maintenance treatment) for prespecified study periods based on random intercept random coefficient model. p-value for interaction of subgroup (NRP/non-NRP) by treatment by time, All EMPA and placebo.

BL=baseline. CI=confidence interval. eGFR=estimated glomerular filtration rate. EMPA=empagliflozin. LVOT=last value on treatment. MDRD=Modification of Diet in Renal Disease. NRP=nephrotic-range proteinuria. UACR=urine albumin-to-creatinine ratio. Wk=week.

respectively), whereas use of ACEi/ARBs and statins tended to be numerically higher in the empagliflozin arm (for ACEi/ARBs: 87·1% [n = 61] on empagliflozin and 71·4% [n = 30] on placebo; for statins: 81·4% [n = 57] on empagliflozin and 64·3% [n = 27] on placebo).

Individuals with NRP had overall 1.4- to >10-fold higher frequencies of relevant CV and kidney outcomes compared with non-NRP participants; e.g., CV death occurred in 14·3 and 23·8% of participants with NRP in empagliflozin and placebo groups, respectively, versus 3·5% and 5·6%, respectively, of non-NRP participants. The composite hard kidney outcome occurred in 20·6% and 33·3% of NRP participants in the empagliflozin and placebo groups, respectively, versus 1·4% and 2·5%, respectively, in non-NRP participants. All-cause hospitalisation occurred in 51·4 and 66·7% of participants with NRP in empagliflozin and placebo groups, respectively, versus 36·5% and 39·3%, respectively, in non-NRP participants (Figure 1). More importantly, the risk for all CV and kidney outcomes were consistently reduced with empagliflozin treatment compared with placebo across participants with and without NRP at baseline (p-values for interaction 0·14–0·87; Figure 1). Additional analyses adjusting for concomitant ACEi/ARB and statin use at baseline (supplementary Figure S1) and accounting for all-cause mortality as competing risk (supplementary Figure S6) showed consistent results.

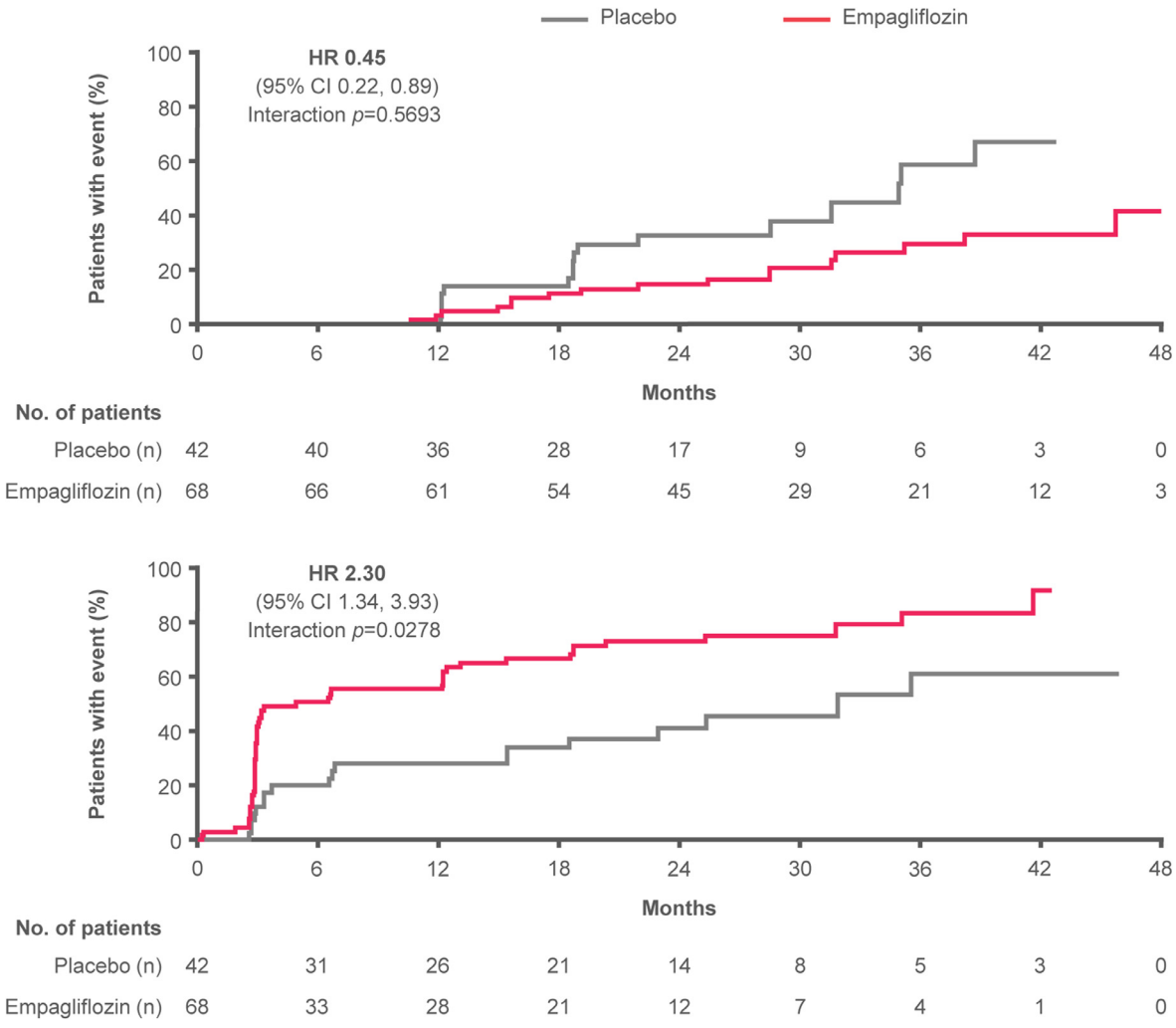

Figure 3. Time to first sustained eGFR decline ≥40% and sustained reduction in UACR of ≥30% in participants with NRP (UACR ≥2200 mg/g)

Kaplan Meier estimates. HR (95% CI) based on Cox Regression. Participants treated with at least one dose of study drug. Estimates for the sustained eGFR decline ≥40% and sustained reduction in UACR of ≥30% in the non-NRP (not shown) were HR 0.56 (0.40, 0.79) and 1.25 (1.16, 1.35), respectively.

CI=confidence interval. eGFR=estimated glomerular filtration rate. HR=hazard ratio. MDRD=Modification of Diet in Renal Disease. UACR=urine albumin-to-creatinine ratio.

Consistent with results of the overall trial population reported previously and consistent with non-NRP participants, participants with NRP on empagliflozin compared with placebo showed an initial decline in eGFR slope from baseline to week 4 (between group-difference in NRP −0·75 mL/min/1·73 m² per week, 95% CI −1·6 to 0·1; *p*-value for interaction with non-NRP 0·93, Figure 2A and B, INITIATION). During chronic maintenance therapy from week 4 until treatment cessation, the absolute treatment effect of empagliflozin on adjusted annual mean slope was significantly more pronounced in participants with NRP compared with non-NRP participants. Adjusted annual mean slope (95% CI) declined less in participants on empagliflozin versus placebo with a treatment difference of 6·0 (2·9 − 9·1) mL/min/1·73 m² per year in participants with NRP (i.e., −4·2 mL/min/1·73 m² per year with empagliflozin versus −10·2 mL/min/1·73 m² per year with placebo) compared with a treatment difference of 1·6 (1·3 − 1·9) mL/min/1·73 m² per year in non-NRP (i.e.,+0·3 mL/min/1·73 m² per year in empagliflozin versus −1·3 mL/min/1·73 m² per year in placebo; *p*-value for interaction 0·005, Figure 2A and B, LONG-TERM). The annualized eGFR change from baseline to last value on-treatment covering both the initial and chronic phase, consistently showed a more pronounced absolute treatment effect of

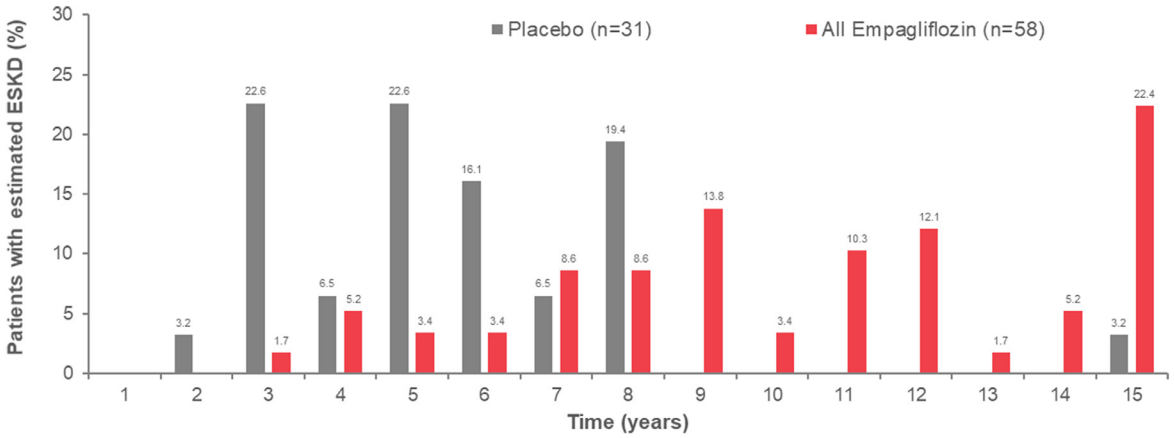

Figure 4. Distribution of hypothetical time (years) to projected ESKD for individual patients, NRP group

Median hypothetical time to projected ESKD: 5.0 [IQR 3.0, 6.9] years in placebo, 10.1 [IQR 7.4, 13.7] years in empagliflozin ($p < 0•0001$)

Bars represent the percentage of patients in each treatment group that are estimated to reach hypothetical time (years) to projected ESKD, if a patient does not die before projected ESKD. Hypothetical ESKD per year after initiation of randomised treatment (i.e., at 5 years, 22•6% of NRP patients on placebo versus 3•4% patients on empagliflozin treatment were estimated to reach hypothetical ESKD).

Patients treated with at least one dose of study drug. Hypothetical time to projected ESKD defined as time to eGFR (MDRD) reaching ≤ 10 mL/min/1•73 m^2 based on estimated eGFR using the random intercept random coefficient model applied to observations from week 4 to last week on treatment (conditioning upon linearity). At maximum of 15 years all patients are considered to projectably have reached hypothetical ESKD.

eGFR=estimated glomerular filtration rate. ESKD=end-stage kidney disease. NRP=nephrotic range proteinuria.

empagliflozin in NRP vs. non-NRP patients (data not shown). After drug cessation, the adjusted mean eGFR slope (mL/min/1·73 m^2 per week [95% CI]) consistently increased with empagliflozin versus placebo in NRP (between group-difference 0·4 [−0·6 to 1·4], Figure 2A, CESSATION) and non-NRP participants (between group-difference 0·6 [0·5 − 0·7], Figure 2B, CESSATION), *p*-value for interaction 0·74.

Individual slope distribution for the chronic maintenance period is shown in the supplementary material: NRP (Supplementary Figure S2A) and non-NRP (Supplementary Figure S2B).

Kidney function over time is presented in Figure S3A for participants with NRP and in Figure S3B for participants without NRP. The risk for sustained decline in eGFR of ≥40% from baseline was consistently reduced with empagliflozin versus placebo in participants with NRP (Figure 3A, hazard ratio [HR] 0·45; 95% CI 0·22−0·89) and non-NRP (*p*-value for interaction with the non-NRP group =0·57).

Remission of albuminuria was significantly higher in empagliflozin- compared with placebo-treated participants in both NRP and non-NRP subgroups. Full remission of NRP to <0·5 g urinary albumin/g creatinine was more likely to be achieved with empagliflozin as compared with placebo: HR 2·27 (95% CI 0·63−8·20) in NRP participants compared with HR 1·64 (95% CI 1·22−2·20) in non-NRP participants; *p*-value for interaction=0·63 for the NRP vs non-NRP treatment effect of empagliflozin, Figure S5). Similarly, partial remission of NRP to <1 g urinary albumin/g creatinine was consistently higher for empagliflozin compared with placebo: HR 2·31 (95% CI 0·98−5·42) in participants with NRP versus HR 1·31 (95% CI 0·86−2·00) in non-NRP participants, *p*-value for interaction=0·24, Figure S5**)**.

A sustained UACR reduction of ≥50% from baseline occurred more often on empagliflozin vs placebo treatment in participants with NRP (58·8% [*n* = 40] vs 26·2% [*n* = 11]): HR 2·48; 95% CI 1·27−4·84), and these effects were consistent with the non-NRP subgroup (*p*-value for interaction=0·09, Figure S6). When we applied a lower threshold for UACR reductions relative to baseline, we observed some heterogeneity suggesting augmented treatment effects of empagliflozin in participants with NRP compared with non-NRP participants. The sustained UACR reduction ≥30% from baseline occurred more frequently with empagliflozin versus placebo in participants with NRP (76·5% [*n* = 52] vs 42·9% [*n* = 18]; HR 2·30 [1·34−3·93]) compared with those without NRP; *p*-value for interaction=0·03; Figs. 3B, S8).

The median hypothetical time to projected ESKD derived from individual participants' intercepts and eGFR slopes by extrapolation (assuming a patient does not die before projected ESKD) was doubled from a

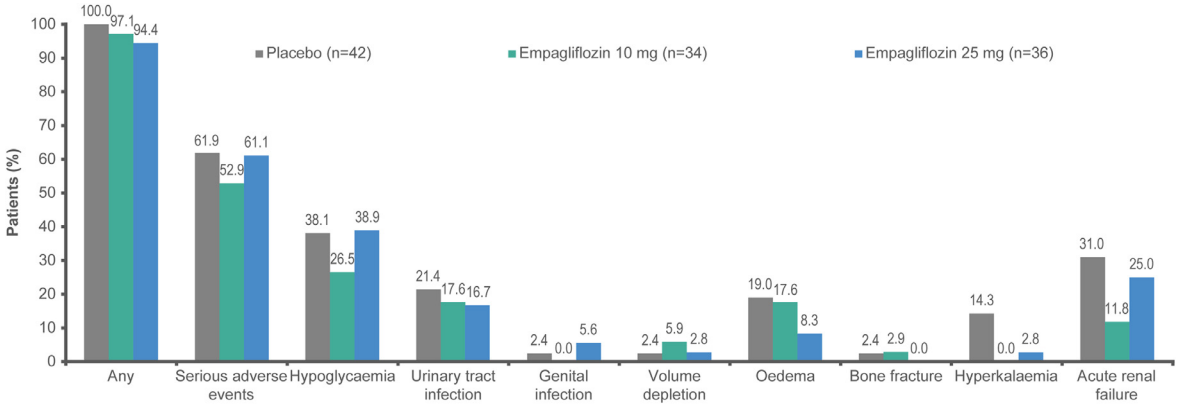

Figure 5. Adverse event profile in NRP patients

Analysis based on participants treated with at least one dose of study drug.

There were no episodes of venous embolic/thrombotic adverse events or diabetic ketoacidosis.

NRP=nephrotic-range proteinuria.

median [IQR] of 5·0 [3·0–6·9] years on placebo to 10·1 [7·4–13·7] years on empagliflozin ($p < 0·0001$). A histogram showing the distribution of the individual participants' hypothetical time to reach projected ESKD (defined as an eGFR of ≤10 mL/min/1·73 m², that is maintained) is shown in Figure 4. No patients had reached eGFR of ≤10 ml/min/1.73 m² by week 4 (data not shown).

Safety

Generally, adverse events occurred more frequently in participants with NRP than in non-NRP participants at baseline (Figure 5A and supplementary Figure S8). Notably, the adverse event profile of empagliflozin versus placebo was comparable in both subgroups. Rates of adverse events consistent with genital infections were higher with empagliflozin than placebo across the two subgroups (i.e., among participants with NRP, 2·4% in placebo vs 0% in empagliflozin 10 mg and 5·6% in empagliflozin 25 mg; Figure 6). Event rates of other relevant adverse events occurred at lower or similar rates with empagliflozin versus placebo in both subgroups (Figure 6 and supplementary Figure 8). Importantly, adverse events considered to be of particular clinical relevance for patients with NRP (such as oedema or acute kidney failure) were not increased with empagliflozin compared with placebo in either subgroup (Figure 5). There were no episodes of VTE or diabetic ketoacidosis in participants with NRP.

Effectiveness parameters

Changes in effectiveness parameters in participants with and without NRP are shown in Figure S7. In participants with NRP, a numerical increase in haematocrit (Figure S8A) and plasma albumin levels (Figure S8B) associated with empagliflozin treatment versus placebo was observed in a pattern comparable to non-NRP participants. Plasma uric acid levels were elevated over time in participants with NRP on placebo but appeared numerically lower on empagliflozin, resulting in a reduction comparable to the non-NRP population (Figure S8C). The reductions of HbA1c (Figure S8D) and systolic (Figure S8E) and diastolic (Figure S8F) blood pressure observed with empagliflozin treatment in the non-NRP group were less evident within the NRP group, likely a reflection of the group's reduced mean eGFR.

Discussion

In this *post-hoc* analysis of the EMPA-REG OUTCOME trial we suggest that empagliflozin had a protective effect against cardiovascular events, worsening of kidney function and albuminuria in T2DM patients with established CVD who had very high risk of accelerated kidney disease progression because of NRP. Treatment benefit was consistent between patients with or without NRP and tended to be statistically larger on regression (>30% reduction vs baseline) of albuminuria and eGFR slope in patients with NRP.

The NRP subgroup included highly vulnerable participants who were sicker overall compared with participants with non-nephrotic proteinuria. In line with this, the NRP subgroup experienced substantially increased rates of relevant clinical outcomes and most adverse events. Except for genital infections, adverse event rates were similar or lower with empagliflozin compared with placebo in both NRP and non-NRP groups, showing a reassuring safety profile in a very fragile population. But more importantly, empagliflozin slowed kidney function decline and consistently reduced albuminuria on top of concomitant treatment with ACE inhibitors or ARBs more effectivley in NRP than in non-NRP participants. Notably, empagliflozin also

improved clinical outcomes, reducing all-cause hospitalization by 39% in this sick subgroup of EMPA-REG OUTCOME participants. Finding that within both proteinuria strata main baseline characteristics were similar between treatment groups corroborated the hypothesis that study findings reflected a genuine effect of the SGLT2 inhibitor. Consistently, adjustments for the small differences in between-group distribution of renin-angiotensin-aldosterone-system (RAAS) inhibitors and statin therapy, confirmed the treatment benefits.

Empagliflozin benefits with respect to long-term kidney function and sustained reduction in albuminuria may at least partially be due to a reduction in intraglomerular pressure and glomerular hyperfiltration,[10,24] but emerging evidence indicates other potential contributing mechanisms, such as anti-inflammatory or antifibrotic effects of SGLT2 inhibitors [25,26]. As previously observed with ACE inhibitors in patients with non-diabetic proteinuric nephropathies,[27,28] the effect on UACR reduction appears to be more pronounced in participants with higher baseline glomerular protein traffic.[20] This is especially important as the degree of glomerular protein traffic is closely associated with adverse kidney and CV outcomes,[3] and remission of proteinuria is an indicator of risk reduction and nephroprotection in NRP.[28]

Almost 60% of the participants with NRP in EMPA-REG OUTCOME experienced a sustained ≥50% reduction in albuminuria, with roughly 1 in 6 achieving complete remission to <500 mg/g and more than one in three achieved partial remission to <1000 mg/g with empagliflozin treatment over the follow-up. Thus, the relevant reduction in albuminuria could have been a contributor to the overall benefits observed in the NRP population.

Our data suggest that empagliflozin may slow chronic loss of kidney function during the long-term treatment period, and that nominally the absolute effect is more pronounced in participants with NRP than those without. Indeed, empagliflozin reverted the annual eGFR loss of 10 mL/min per year seen with placebo to an eGFR decline comparable to the approximately −3·5 to −4 mL/min per year previously described for T2DM patients in the sub-nephrotic range.[29,30] Moreover, when extrapolating the individual estimated eGFR slopes beyond the treatment phase, these differences in loss of kidney function translated into a hypothetical median net benefit of approximately 5 years that may be gained before dialysis or transplantation would be required.

The kidney function data compares well to data from the REIN study (NCT02895425) in patients with NRP, even when we include the initial eGFR decline as done in REIN.[28] Thus, the treatment effect of empagliflozin appears comparable to the treatment effect of ramipril versus placebo in the REIN study, which was terminated prematurely due to the highly significant benefit on eGFR decline.[28] Nevertheless, the statistically larger treatment benefit in the NRP group needs to be interpreted with caution and put in perspective with the fact that empagliflozin treatment completely abolished the annual eGFR decline in the non-NRP participants.

The beneficial effects of empagliflozin were observed on top of similar background ACEi/ARB and beta-blocker treatment in NRP and non-NRP participants. Volume markers such as albumin and haematocrit were increased with empagliflozin compared with placebo treatment in patients with NRP, consistent with the non-NRP subgroup. Notably however, blood pressure (BP) control was insufficient in the NRP subgroup. As mean BP only slightly improved and mean HbA1c levels were comparable between treatment groups, the treatment effects of empagliflozin on eGFR chronic slopes in patients with NRP are less likely to be mediated by glycaemic control or changes in BP. Together, these findings suggest that the renoprotective effect of empagliflozin in NRP may have been mediated by other factors, such as haematocrit that mediated the treatment effect on a renal outcome in the overall population [31] or a reduction in albuminuria and glomerular protein traffic. Finding that the severity of proteinuria predicted more severe kidney disease outcomes, whereas proteinuria reduction was nephroprotective further corroborates the hypothesis that increased glomerular protein traffic plays a central pathogenic role in the progression of diabetic and non-diabetic chronic kidney disease (CKD).[32]

In this particularly frail population with a higher prevalence of concomitant diseases and more background treatment, empagliflozin was well tolerated, and its safety profile was comparable to that of placebo.

This *post-hoc* analysis represents one of the largest clinical data sets exploring potential beneficial interventions in patients with T2DM and NRP. Indeed, results of our study confirm and extend findings of a recent report of *post-hoc* analyses of the CREDENCE trial showing that canagliflozin safely reduced the relative risk for renal events and, to a lower extent, cardiovascular events in patients with T2DM and with or without severely increased albuminuria.[12] However, our findings should be interpreted in the context of several limitations. EMPA-REG OUTCOME was designed as a CV outcomes study [19] and thus all other endpoints, including kidney endpoints, have to be considered hypothesis-generating in nature. Additionally, the frequencies reported in the baseline characteristics might be unbalanced due to the low sample size of NRP patients. Particularly, slight imbalances in medical history (duration of T2DM, frequency of stroke, HF, and PAD history) and background medication (diuretic and CCB use) need to be interpreted with caution compared to the more striking differences seen for other characteristics (e.g. SBP, eGFR, UACR). Similarly, data on albuminuria

reduction in NRP vs non-NRP patients should be considered cautiously because albuminuria was just a surrogate endpoint of the study.

This study included only diabetic patients, and 60% of the NRP subgroup had been diagnosed with diabetic nephropathy. Hence, they represent one of the most susceptible populations — outcomes are significantly worse in patients with diabetic nephropathy than in patients with non-diabetic nephropathy.[4] Our results may therefore not be representative for patients with other causes of NRP.

As very low rates of actual ESKD were observed in EMPA-REG OUTCOME, we decided to estimate hypothetical time to projected ESKD based on individual participants' eGFR intercepts and slopes by extrapolation, conditioning upon linearity of eGFR change over time. This expands beyond the study observation time and may not exactly reflect the non-linear course of disease progression. Further, we assume that a patient does not die before projected ESKD, so any differences in mortality between the groups may have not been accounted for. Also, we considered all NRP patients to reach hypothetical projected ESKD at maximum at 15 years, potentially over-estimating the rate of ESKD particularly in NRP patients with slower eGFR decline. The use of slopes during the three prespecified study periods can lead to potential selection bias of patients with available data. Further, the EMPA-REG OUTCOME trial had a lower eGFR cut-off of 30 mL/min/1·73 m^2 at screening, and therefore our results are limited to T2DM patients with CKD stages 1–3 and may not be generalisable to more advanced stages of diabetic kidney disease. The first dedicated study of an SGLT2 inhibitor in a larger proteinuric population was the Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE, NCT02065791) trial.[12], followed by the Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD, NCT03036150).[11] Direct comparison of these trials with EMPA-REG OUTCOME should be made with caution owing to differences in study design, populations, and methodology. However, interestingly in the CREDENCE population, the treatment effect of canagliflozin on albuminuria (mean% difference vs placebo over study period −31% [95% CI: −26 to −35]) was very similar to the overall, less proteinuric EMPA-REG OUTCOME population (mean % difference at week 12 *vs* placebo −32% [95% CI −47 to −13]).[20]

The results of this *post-hoc* analysis of the EMPA-REG OUTCOME trial corroborate the hypothesis that empagliflozin could offer a safe and effective treatment option to slow kidney disease progression and improve clinical outcomes in a population of patients with T2DM who are at very high risk for rapid loss of kidney function due to residual NRP despite optimised conservative treatment. These findings need confirmation in other trials, including the ongoing randomised EMPA-KIDNEY (NCT03594110) trial on treatment effects of empagliflozin in adults with and without diabetes but with CKD at more advanced stages.

Author contributions

A literature search was performed by CW, PR, BJK, MvE, and AKW. Figures were developed by BJK, MM, and AKW. Study design was developed by CW, PR, BJK, MvE, AKW, and MM. Data analysis was performed by SH and MM. All authors were involved in the interpretation of the data. Writing: the initial draft of the manuscript was developed by PR, MvE, AKW, BJK and CW. All authors were involved at all subsequent stages of the manuscript development and are fully responsible for all content and editorial decisions, and have approved the final version.

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Declaration of interests

PR and GR have no conflicts to report. BJK is an employee of Boehringer Ingelheim, the University Hospital of Würzburg and has received grants from the IZKF (Interdisziplinaeres Zentrum fuer klinische Forschung) of the University of Wuerzburg, and from Boehringer Ingelheim. SI reports consulting fees and honoraria from Intarcia Therapeutics, Daiichi-Sankyo, Lexicon Pharmaceuticals, Janssen, Sanofi, AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. BZ has received grant support from Boehringer Ingelheim, AstraZeneca, and Novo Nordisk; and consulting fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, and Sanofi Aventis. SH, MM, MvE, and AKW are employees of Boehringer Ingelheim. CW reports honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Mitsubishi, and MSD.

Data sharing

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 Vivli centre for Global Clinical Research website (https://vivli.org/).

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.101240.

References

1 Stoycheff N, Stevens LA, Schmid CH, et al. Nephrotic syndrome in diabetic kidney disease: an evaluation and update of the definition. *Am J Kidney Dis* 2009;**54**(5):840–9.
2 Vassalotti JA, Stevens LA, Levey AS. Testing for chronic kidney disease: a position statement from the National Kidney Foundation. *Am J Kidney Dis* 2007;**50**(2):169–80.
3 Rossing K, Christensen PK, Hovind P, Parving HH. Remission of nephrotic-range albuminuria reduces risk of end-stage renal disease and improves survival in type 2 diabetic patients. *Diabetologia* 2005;**48**(11):2241–7.
4 Lee YH, Kim KP, Kim YG, et al. Clinicopathological features of diabetic and nondiabetic renal diseases in type 2 diabetic patients with nephrotic-range proteinuria. *Medicine* 2017;**96**(36):e8047.. Baltimore.
5 Gerstein HC, Mann JF, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001;**286**(4):421–6.
6 Hallan S, Astor B, Romundstad S, Aasarod K, Kvenild K, Coresh J. Association of kidney function and albuminuria with cardiovascular mortality in older vs younger individuals: the HUNT II Study. *Arch Intern Med* 2007;**167**(22):2490–6.
7 Jennings DL, Kalus JS, Coleman CI, Manierski C, Yee J. Combination therapy with an ACE inhibitor and an angiotensin receptor blocker for diabetic nephropathy: a meta-analysis. *Diabetes Med* 2007;**24**(5):486–93.
8 Qin X, Dong H, Fang K, Lu F. The effect of statins on renal outcomes in patients with diabetic kidney disease: a systematic review and meta-analysis. *Diabetes Metab Res Rev* 2017;**33**(6).
9 Cherney D, Lund SS, Perkins BA, et al. The effect of sodium glucose cotransporter 2 inhibition with empagliflozin on microalbuminuria and macroalbuminuria in patients with type 2 diabetes. *Diabetologia* 2016;**59**(9):1860–70.
10 Cherney DZ, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* 2014;**129**(5):587–97.
11 Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;**383**(15):1436–46.
12 Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;**380**(24):2295–306.
13 Tanaka A, Nakamura T, Sato E, Node K. Therapeutic potential of tofogliflozin on nephrotic syndrome secondary to diabetic nephropathy. *J Cardiol Cases* 2017;**16**(1):30–3.
14 Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**(22):2117–28.
15 Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;**375**(4):323–34.
16 Butler J, Zannad F, Fitchett D, et al. Empagliflozin improves kidney outcomes in patients with or without heart failure. *Circ Heart Fail* 2019;**12**(6):e005875.
17 Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**(7):644–57.
18 Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;**380**(4):347–57.
19 Zinman B, Inzucchi SE, Lachin JM, et al. Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME). *Cardiovasc Diabetol* 2014;**13**:102.
20 Cherney DZI, Zinman B, Inzucchi SE, et al. 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. *Lancet Diabetes Endocrinol* 2017;**5**(8):610–21.
21 Wanner C, Heerspink HJL, Zinman B, et al. Empagliflozin and kidney function decline in patients with type 2 diabetes: a slope analysis from the EMPA-REG OUTCOME trial. *J Am Soc Nephrol* 2018;**29**(11):2755–69.
22 Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;**345**(12):851–60.
23 KDIGO CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2013;**3**:1–150.
24 Skrtic M, Yang GK, Perkins BA, et al. Characterisation of glomerular haemodynamic responses to SGLT2 inhibition in patients with type 1 diabetes and renal hyperfiltration. *Diabetologia* 2014;**57**(12):2599–602.
25 Castoldi G, Carletti R, Ippolito S, et al. Renal anti-fibrotic effect of sodium glucose cotransporter 2 inhibition in angiotensin II-dependent hypertension. *Am J Nephrol* 2020;**51**(2):119–29.
26 Kim S, Jo CH, Kim GH. Effects of empagliflozin on nondiabetic salt-sensitive hypertension in uninephrectomized rats. *Hypertens Res* 2019;**42**(12):1905–15.
27 Ruggenenti P, Perna A, Gherardi G, et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet* 1999;**354**(9176):359–64.
28 The GISEN Group. Gruppo Italiano di Studi Epidemiologici in Nefrologia. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet* 1997;**349**(9069):1857–63.
29 Altemtam N, Russell J, El Nahas M. A study of the natural history of diabetic kidney disease (DKD). *Nephrol Dial Transplant* 2012;**27**(5):1847–54.
30 Hladunewich MA, Troyanov S, Calafati J, Cattran DC. Metropolitan Toronto glomerulonephritis Registry. The natural history of the non-nephrotic membranous nephropathy patient. *Clin J Am Soc Nephrol* 2009;**4**(9):1417–22.
31 Wanner C, Nangaku M, Kraus BJ, et al. Mediators of the improvement in kidney outcomes with empagliflozin in the EMPA-REG OUTCOME trial Presented at the. In: In: Proceedings of the European Renal Association - 58th Congress with the European Dialysis and Transplant Association; 2021.
32 Ruggenenti P, Cravedi P, Remuzzi G. Mechanisms and treatment of CKD. *J Am Soc Nephrol* 2012;**23**(12):1917–28.