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Frailty, multimorbidity and polypharmacy: exploratory analyses of the effects of empagliflozin from the EMPA-KIDNEY trial

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Abstract:	Background: Sodium-glucose co-transporter-2 (SGLT2) inhibitors are recommended treatment for adults with chronic kidney disease (CKD), but uncertainty exists regarding their use in patients with frailty and/or multimorbidity, among whom polypharmacy is common. We derived a multivariable logistic regression model to predict hospitalization (reflecting frailty) and assessed empagliflozin's risk-benefit profile in a post-hoc analysis of the double-blind, placebo-controlled EMPA-KIDNEY trial. Methods: The EMPA-KIDNEY trial randomized 6609 patients with CKD (estimated glomerular filtration rate [eGFR] ≥20<45 mL/min/1.73m2, or ≥45<90 mL/min/1.73m2 with urinary albumin-to-creatinine ratio ≥200 mg/g) to receive either empagliflozin 10 mg daily or matching placebo and followed for two years (median). Additional characteristics analysed in subgroups were multimorbidity, polypharmacy and health-related quality of life (HRQoL) at baseline. Cox regression analyses were performed with subgroups defined by approximate thirds of each variable. Results: The strongest predictors of hospitalization were N-terminal prohormone of brain natriuretic peptide, poor mobility and diabetes; then eGFR and other comorbidities. Empagliflozin was generally well-tolerated independent of predicted risk of hospitalization. In relative terms, allocation to empagliflozin reduced the risk of the primary outcome of kidney disease progression or cardiovascular death by 28% (hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.64-0.82); and all-cause hospitalization by 14% (HR 0.86, 95% CI 0.78-0.95); with broadly consistent effects across subgroups of predicted risk of hospitalization, multimorbidity, polypharmacy or HRQoL. In absolute terms, the estimated benefits of empagliflozin were greater in those at highest predicted risk of hospitalization (reflecting frailty) and outweighed potential serious harms. Conclusions: These findings support the use of SGLT2 inhibitors in CKD, irrespective of frailty, multimorbidity or polypharmacy.
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Frailty, multimorbidity and polypharmacy: exploratory analyses of the effects of empagliflozin from the EMPA-KIDNEY trial

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KEY POINTS

- Frailty, multimorbidity and polypharmacy overlap and are associated with higher risk of adverse health outcomes in chronic kidney disease (CKD)
- Empagliflozin was safe, well-tolerated and effectively reduced cardio-renal and hospitalization risk irrespective of these characteristics
- Absolute benefits appeared greater in the most frail participants in this *post-hoc* analysis of EMPA-KIDNEY

ABSTRACT

Background: Sodium-glucose co-transporter-2 (SGLT2) inhibitors are recommended treatment for adults with chronic kidney disease (CKD), but uncertainty exists regarding their use in patients with frailty and/or multimorbidity, among whom polypharmacy is common. We derived a multivariable logistic regression model to predict hospitalization (reflecting frailty) and assessed empagliflozin's risk-benefit profile in a *post-hoc* analysis of the double-blind, placebo-controlled EMPA-KIDNEY trial.

Methods: The EMPA-KIDNEY trial randomized 6609 patients with CKD (estimated glomerular filtration rate [eGFR] ≥20<45 mL/min/1.73m^2, or ≥45<90 mL/min/1.73m^2 with urinary albumin-to-creatinine ratio ≥200 mg/g) to receive either empagliflozin 10 mg daily or matching placebo and followed for two years (median). Additional characteristics analysed in subgroups were multimorbidity, polypharmacy and health-related quality of life (HRQoL) at baseline. Cox regression analyses were performed with subgroups defined by approximate thirds of each variable.

Results: The strongest predictors of hospitalization were N-terminal prohormone of brain natriuretic peptide, poor mobility and diabetes; then eGFR and other comorbidities. Empagliflozin was generally well-tolerated independent of predicted risk of hospitalization. In relative terms, allocation to empagliflozin reduced the risk of the primary outcome of kidney disease progression or cardiovascular death by 28% (hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.64-0.82); and all-cause hospitalization by 14% (HR 0.86, 95% CI 0.78-0.95); with broadly consistent effects across subgroups of predicted risk of hospitalization, multimorbidity, polypharmacy or HRQoL. In absolute terms, the estimated benefits of empagliflozin were greater in those at highest predicted risk of hospitalization (reflecting frailty) and outweighed potential serious harms.

Conclusions: These findings support the use of SGLT2 inhibitors in CKD, irrespective of frailty, multimorbidity or polypharmacy.

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INTRODUCTION

Sodium-glucose co-transporter-2 (SGLT2) inhibitors slow kidney disease progression and reduce cardiovascular risk in patients with chronic kidney disease (CKD).[1,2] These effects are broadly consistent across different subtypes of patient, including individuals with and without diabetes, and across the spectrum of estimated glomerular filtration rate (eGFR) studied,[2] irrespective of kidney disease etiology.[3] Uncertainty appears to exist surrounding the risk-benefit profile of disease-modifying drugs in older patients and particularly those with frailty, multimorbidity and/or polypharmacy which are increasingly common in clinical practice[4] but less well-represented in clinical trials.[5] Recent United Kingdom SGLT2 inhibitor clinical practice guidelines recommend "an approach to care that takes account of frailty and multimorbidity… [and] consideration of the balance of disease and treatment burden".[6]

Frailty, multimorbidity and polypharmacy are overlapping concepts.[7,8] Frailty is a syndrome reflecting a state of increased vulnerability to stressors (such as acute illness) due to decline in physiological reserve though there is no internationally accepted definition.[9] The relationship between frailty and CKD is bidirectional and frailty occurs more commonly in CKD relative to the general population,[10] particularly as CKD progresses.[11] Frailty is associated with increased burden of long-term conditions (i.e. multimorbidity)[7] and associated polypharmacy.[8] Multimorbidity is typically defined as the presence of two or more long-term conditions,[12] and polypharmacy is generally defined as the regular prescription of five or more drugs.[8] Frailty, multimorbidity and polypharmacy may confer an increased absolute risk of drug-related adverse effects.[6,13,14] Frailty and multimorbidity also confer poor

prognosis with greater risks of death, hospitalization and progression to kidney failure compared to non-frail adults with CKD.[11,15,16] Therefore, frailty, multimorbidity and polypharmacy may all be markers of higher absolute risk, and patients with such characteristics may conversely experience larger absolute benefits of SGLT2 inhibition relative to individuals without burden of frailty, multimorbidity or polypharmacy.

There are several different tools applied to quantify frailty in clinical practice and research.[17,18] Approaches in general populations include the Fried frailty phenotype,[7] the Clinical Frailty Scale[19] and the Rockwood Frailty Index.[20] The Rockwood Frailty Index was developed in community-dwelling adults aged over 70 years in the United States of America and applies weights to each comorbidity[20] which may not be generalizable across diseased populations. Considering this limitation, we developed a bespoke approach for the analysis of EMPA-KIDNEY data based on the established association of clinical frailty with hospitalization [15,24] which was a key secondary outcome in EMPA-KIDNEY.[1] Analyses assessing how the relative and net absolute effects of SGLT2 inhibitors might vary by indicators of frailty, multimorbidity and polypharmacy in a CKD population have not previously been reported and would help guide practical implementation of current SGLT2 inhibitor guidelines. We used predicted risk of hospitalization at baseline as a surrogate for clinical frailty to quantify how the absolute risk-benefit profile of SGLT2 inhibition varies, as well as separately assessing the impact of multimorbidity, polypharmacy and health-related quality of life in this *post-hoc* analysis of the EMPA-KIDNEY trial.

METHODS

The full methods of the EMPA-KIDNEY trial and the main results have been reported elsewhere (ClinicalTrials.gov number, NCT03594110).[1] Briefly, patients with CKD at risk of progression were identified based on historical and screening local laboratory measurements of an eGFR ≥20 but <45 mL/min/1.73m^2, or an eGFR ≥45 but <90 mL/min/1.73m^2 with a urinary albumin-to-creatinine ratio (UACR) ≥200 mg/g. All participants provided written informed consent. Regulatory authorities, as well as ethics committees in each region, approved the trial.

Definitions of frailty, multimorbidity, polypharmacy and health-related quality of life

In this *post-hoc* analysis, baseline predicted risk of hospitalization during follow-up was used as the primary frailty indicator based on the established association with frailty [15,24] and to maximise the number of events available for analysis (relative to mortality). A wide range of potential predictor variables measured at baseline were considered (Supplementary Table 1). These were then all entered into logistic regression models with first observed hospitalization during follow-up acting as the response variable to select the key independent predictors (see Supplementary Methods) and to estimate each participant's predicted risk of hospitalization (reflecting frailty).

Separate to analyses by predicted risk of hospitalization, we analysed multimorbidity, polypharmacy and health-related quality of life at baseline. Multimorbidity was established by the presence or absence of eight self-reported conditions (Supplementary Methods). Polypharmacy was derived from the number of

concomitant medications recorded at the randomization visit and health-related quality of life was assessed using the EuroQoL EQ-5D-5L tool [25-27] (Supplementary Methods).

Outcomes

The same pre-specified efficacy and safety outcomes which have previously been reported for the overall trial population[1] were assessed in these *post-hoc* analyses testing the impact of frailty, multimorbidity and polypharmacy. The primary composite outcome was time to first occurrence of progression of kidney disease (defined as end-stage kidney disease [ESKD; the initiation of maintenance dialysis or receipt of a kidney transplant], a sustained decrease in the eGFR to less than 10 mL/min/1.73m^2, a sustained decrease from baseline in the eGFR of at least 40%, or death from kidney failure) or death from cardiovascular causes. The pre-specified key secondary outcomes were a composite of hospitalization for heart failure or death from cardiovascular causes, hospitalization for any cause (including the first and any subsequent hospitalizations), and death from any cause. Other secondary outcomes were progression of kidney disease, death from cardiovascular causes, and a composite of ESKD or death from cardiovascular causes. Safety outcomes are defined in the Supplementary Methods.

Statistical analysis

Full details of prediction models for first hospitalization are provided in the Supplementary Methods. For time to first event outcomes, the effects of allocation to empagliflozin versus placebo were assessed using pre-specified Cox regression

models adjusted for age, sex, region, eGFR, UACR and diabetes status. Total hospitalizations were analysed using joint frailty models as previously described.[1] Effects on weight and blood pressure were analysed using a pre-specified mixed model repeated measures (MMRM) approach.[1] Evidence of any effect modification was assessed using standard tests for heterogeneity (for relative effects) or trend (for estimated absolute effects) across the frailty indicator subgroups (see Supplementary Methods for categorizations). Absolute events avoided per 1000 patients treated with empagliflozin per year (standard error) were estimated by applying hazard ratios, or their 95% confidence intervals (CI), to the event rate per 1000 patient-years in the placebo group; using the overall hazard ratio (or 95% CI) if no strong evidence of heterogeneity in relative effects of treatment was identified or the subgroup-specific hazard ratio (or 95% CI) if there was significant heterogeneity ($P<0.01$).[2] Analyses were performed using R Studio version 4.2.2 (RStudio: Integrated Development for R. RStudio, PBC, Boston, MA) and SAS version 9.4 (SAS Institute, Cary NC).

RESULTS

Predictors of frailty defined as risk of hospitalization

Median (Q1-Q3) follow-up of 6609 randomized participants was 2.0 years (1.5-2.4), during which time 1995 participants were hospitalized at least once (960 in the empagliflozin group and 1035 in the placebo group). The strongest predictors of hospitalization were N-terminal prohormone of brain natriuretic peptide (baseline median [Q1-Q3] 160 ng/L [69-419]); poor mobility (based on EQ-5D-5L) and the presence of diabetes (Table 1 & Supplementary Table 2). The final model which

additionally included eGFR and other comorbidities (Supplementary Table 3) adequately predicted risk of hospitalization (area under the receiver operating characteristic [AUROC] curve 0.70 [95% CI 0.69-0.71]) and separately, death from any cause (Supplementary Figure 1) with acceptable calibration. Median (Q1-Q3) predicted risk of hospitalization was 27% (18-40). Risk of hospitalization was positively correlated with multimorbidity, polypharmacy and inversely with health-related quality of life (Supplementary Figure 2) and consequently there was considerable overlap between these subgroups (Figure 1).

Baseline characteristics

In the description of results, use of the term frailty refers to predicted risk of hospitalization during follow-up. Those with the highest levels of frailty had lower levels of albuminuria (P<0.001) but greater 5-year risk of kidney failure (based on the four-variable Kidney Failure Risk Equation; P<0.001) owing to older age and lower eGFR (as would be expected based on the model; Tables 1 & 2; Supplementary Table 4). Five-year kidney failure risk was 14% (95% CI 5-37) versus 6% (95% CI 2-19) in those with the highest versus lowest levels of frailty. Participants with the highest level of frailty were also more likely to report cardiovascular disease and had higher body mass index (Table 2).

The median (Q1-Q3) number of comorbid conditions (excluding CKD) prior to randomization was 1 (0-2); range 0-7 (Supplementary Table 5). The median (Q1-Q3) number of concomitant medications recorded at randomization was 7 (5-10), range 0-36 (Table 2). At randomization, prescription of five or more concomitant

medications (i.e. polypharmacy) was present in 76% (5044/6609) of participants, and at least one condition in addition to CKD (i.e. multimorbidity) was present in 71% participants (4675/6609). Of 5635 participants who fulfilled these definitions of either polypharmacy or multimorbidity, 72% (4084/5635) were included in both groups (Supplementary Figure 3). Median (Q1-Q3) indexed EQ-5D value was 0.891 (0.773-0.987) and median (Q1-Q3) self-rated health score (visual analogue scale) was 80 (70-90) with scores ranging from 0 to 100.

Adherence to study treatment

Adherence to study treatment was reasonably high in all subgroups, but did inversely correlate with frailty at baseline. At 12 months of follow-up (the approximate midpoint of the trial), the proportion of surviving participants reportedly taking most (>80%) of their study treatment was highest in patients in the lowest frailty category (based on risk of hospitalization; 1830/1982, 92%) and lowest in those with the highest level of frailty (938/1090, 86%). Participants with greater levels of frailty (with similar patterns observed for polypharmacy) were more likely to discontinue study treatment (by the end of follow-up) in both the empagliflozin and placebo groups, but reasons for discontinuation were rarely attributed to serious adverse events (Supplementary Table 6).

Relative effects on the primary outcome and kidney disease progression

Overall, versus placebo, empagliflozin reduced the risk of the primary composite outcome of kidney disease progression or cardiovascular death by 28% (hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.64-0.82), with no significant difference in

relative effects by baseline level of frailty, multimorbidity, polypharmacy or health-related quality of life (P for heterogeneity all >0.05, Figure 2, Supplementary Tables 7-10). The majority of the 990 primary outcome events were due to kidney disease progression (888 events) and overall, empagliflozin reduced the risk of this secondary outcome by 29% (HR 0.71, 95% CI 0.62-0.81) and the risk of a composite of ESKD or cardiovascular death by 27% (HR 0.73, 95% CI 0.59-0.89), with no significant heterogeneity between subgroups (for frailty, multimorbidity, polypharmacy or health-related quality of life) for either outcome (Supplementary Tables 7-10).

Relative effects on key secondary outcomes

In total, 1611 hospitalizations occurred among 960 patients in the empagliflozin group, and 1895 hospitalizations occurred among 1035 patients in the placebo group during follow-up. Overall, there was a 14% reduction in total all-cause hospitalizations in participants allocated to empagliflozin versus placebo (HR 0.86, 95% CI 0.78-0.95) which was not clearly driven by a single cause of hospitalization (see previous reports).[1] On a relative scale, analyses by baseline measures of frailty showed no strong evidence of heterogeneity by baseline levels of frailty, multimorbidity or polypharmacy (Supplementary Figure 4). Considering the number of tests conducted, there was weak evidence of heterogeneity by baseline health-related quality of life (P=0.01, Supplementary Figure 4). These relative effects of empagliflozin on risk of all-cause hospitalization were also similar in those with and without diabetes, and were unmodified by baseline eGFR or baseline UACR (Supplementary Figure 5). No significant effect was observed overall on the

composite outcome of hospitalization for heart failure or death from cardiovascular causes (HR 0.84, 95% CI 0.67-1.07); or death from any cause (HR 0.87, 95% CI 0.70-1.08), with no evidence of significant heterogeneity between subgroups for either outcome (Supplementary Tables 7-10).

Relative effects on safety outcomes & physical measurements

Safety outcomes were more common in participants with indicators of higher frailty, but there was no evidence that these were increased by empagliflozin compared to placebo at any level of frailty. In particular, allocation to empagliflozin relative to placebo did not result in any excess of symptomatic dehydration or fractures (Supplementary Tables 11-14). Nor did the reported effects on body weight or blood pressure vary by baseline frailty (Supplementary Figure 6).

Absolute benefits and risks

There was evidence of larger estimated absolute benefits on the primary outcome of kidney disease progression or cardiovascular death, and on all-cause hospitalizations in participants in the top third of frailty (Figures 2 & 3; Supplementary Figure 4) compared to those with lesser degrees of frailty. Per 1000 participants treated, it was estimated that occurrences of kidney disease progression or cardiovascular death (i.e. primary outcomes) were avoided by empagliflozin in 35, 25 and 14 participants per year in the top, middle and lowest thirds of frailty, respectively. The total number of hospitalizations avoided annually by empagliflozin treatment were 74, 32 and 16 in the top, middle and lowest thirds of frailty, respectively (Figure 3). Low absolute excess risk of safety outcomes meant these

estimated absolute benefits of empagliflozin substantially outweighed the potential serious harms in the studied population (Figure 3).

DISCUSSION

The aims of these *post-hoc* exploratory analyses of EMPA-KIDNEY data were to characterize the risk-benefit profile of SGLT2 inhibition in CKD by differing levels of frailty (indicated by predicted risk of hospitalization), multimorbidity and polypharmacy. EMPA-KIDNEY studied a broader range of patients at risk of CKD progression than the other large SGLT2 inhibitor trials in CKD, including large numbers of participants with low levels of albuminuria and without diabetes.[1,28] Empagliflozin clearly reduced the risk of kidney disease progression or cardiovascular death with no evidence that the relative benefits were modified by levels of frailty, multimorbidity or polypharmacy. Furthermore, larger absolute benefits were observed in participants with the highest predicted risk of hospitalization (reflecting frailty). These absolute benefits were achieved safely and clearly outweigh the potential harms of SGLT2 inhibition in the studied population. Serious acute kidney injury occurred much more commonly in patients with the highest levels of frailty, multimorbidity or polypharmacy. Other data have shown SGLT2 inhibitors reduce risk of acute kidney injury meaning any effect of empagliflozin on acute kidney injury would mean larger absolute benefits among those these types of patient. These findings should encourage use of indicated SGLT2 inhibitor treatment in adults with CKD, irrespective of frailty, multimorbidity, polypharmacy or health-related quality of life. Whilst patient preference is important, SGLT2 inhibitor discontinuation simply to reduce tablet burden is not risk-free and

would be expected to increase the likelihood of several important and avoidable adverse health consequences.[29]

Our findings are consistent with reports from the DAPA-HF[22] and DELIVER[21] trials which used the general population-derived Rockwood Frailty Index approach in populations with heart failure. In these analyses, the beneficial effects of dapagliflozin in reducing risk of the composite primary outcome of worsening heart failure or cardiovascular death were apparent across the spectrum of frailty represented in the two trials, with larger absolute benefits in the participants with the highest levels of frailty.[21,22] The Rockwood Frailty Index approach was also applied in the DAPA-CKD trial which recruited patients with proteinuric CKD, about two-thirds of whom had diabetes.[30] The absolute benefits of dapagliflozin versus placebo were greatest among the most frail with respect to cardiovascular and mortality outcomes though effects on the primary composite kidney outcome did not differ on either a relative or absolute scale when participants were divided according to their Rockwood Frailty Index score.[23] Importantly, in each of these trials, and similarly in EMPA-KIDNEY, SGLT2 inhibitors were well-tolerated even at high levels of frailty.[21-23] We observed that patients at greater predicted risk of hospitalization were more likely to discontinue study treatment, whether allocated empagliflozin or placebo; yet there was no excess of discontinuation of empagliflozin relative to placebo irrespective of predicted risk of hospitalization. Since levels of discontinuation of study treatment were relatively low across all subgroups, the 28% relative risk reduction for the primary outcome reflects only a slight underestimate of the full effect in all participants, irrespective of level of frailty.

It has been suggested SGLT2 inhibitors may cause a degree of breakdown of skeletal muscle and loss of lean tissue mass,[31,32] due to upregulated gluconeogenesis, causing lipolysis and proteolysis of adipose and skeletal muscle tissue, respectively.[33] This may be a particular concern in underweight or malnourished patients however since glycosuric effects and body weight reduction are attenuated in those with lower eGFR, such concerns may be less relevant in patients with CKD. Indeed, other studies have not shown changes in muscle mass with SGLT2 inhibition, regardless of eGFR.[34] An EMPA-KIDNEY bioimpedance substudy conducted in a ~10% subset of the trial population corroborated these findings since there was no significant effect of empagliflozin versus placebo on either lean tissue or fat mass, with weight loss appearing to exclusively reflect reductions in total body water volume.[35] Furthermore, the effects of empagliflozin on the primary outcome of kidney disease progression or cardiovascular death in the EMPA-KIDNEY population of 6609 individuals were similar across the spectrum of studied body mass index.[1]

EMPA-KIDNEY has demonstrated clear benefits of SGLT2 inhibition on kidney disease progression in a wide range of patients with CKD at risk of progression.[1] These analyses benefit from the trial's sample size, median two-year follow-up duration, and randomized double-blind design. However, some limitations remain. First, since clinical trials typically recruit healthier patients, levels of "frailty" in EMPA-KIDNEY may not be representative of the general CKD population. Second, our assessment of "frailty" did not use an externally validated frailty assessment tool

since these largely depend on clinical assessments not conducted in large streamlined randomized trials like EMPA-KIDNEY. We chose not to use existing indices like the Rockwood Frailty Index which weight characteristics differentially and since the approach was developed in a general population, this approach to weighting may not be generalizable into diseased populations (e.g. CKD). We therefore developed a bespoke assessment of frailty using predicted risk of hospitalization as a marker of clinical frailty; accepting our model may not be broadly generalizable but is a scientifically robust approach for the studied population. Our model also performed well for prediction of death. Lastly, geographical variation in hospitalization patterns also might limit the generalizability of the absolute benefits for this outcome, but do not affect the overall pattern of increasing net absolute benefits among those with higher levels of frailty, multimorbidity or polypharmacy.

In conclusion, empagliflozin was safe, well-tolerated and effectively lowered the risk of progression of kidney disease or cardiovascular death (the primary outcome); and all-cause hospitalization in a broad range of patients studied in EMPA-KIDNEY, irrespective of indicators of frailty, multimorbidity or polypharmacy. The absolute benefits of empagliflozin were in fact greater in patients with the highest levels of frailty (indicated by predicted risk of hospitalization). Clinical guidelines should encourage evidence-based prescribing of SGLT2 inhibitors in individuals with CKD irrespective of frailty, multimorbidity or polypharmacy and emphasize that such patients may stand to gain most from treatment.

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DATA SHARING STATEMENT

The complete de-identified patient data set used for presented analyses will be available in due course and the application system to apply to use data will open 6 months after publication. Departmental policy details can be found here: https://www.ndph.ox.ac.uk/data-access. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data, typically, one year after the approval has been granted by major Regulatory Authorities or after termination of the development program. Researchers should use the https://vivli.org/ link to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.

Supplemental Material List:

Supplementary Table 12: Safety outcomes by multimorbidity

Supplementary Table 13: Safety outcomes by concomitant medication count

Supplementary Table 14: Safety outcomes by health-related quality of life (EQ-5D index value)

Supplementary Figure 1: Performance of the final multivariable logistic regression model in predicting hospitalization and all-cause death

Supplementary Figure 2: Associations between predicted risk of hospitalization and multimorbidity; polypharmacy; and health-related quality of life

Supplementary Figure 3: Number of participants in the highest level of frailty (defined as predicted risk of hospitalization >45%) in EMPA-KIDNEY showing overlap with conventional definitions of multimorbidity and polypharmacy (which differ from Figure 1)

Supplementary Figure 4: Effects of empagliflozin versus placebo on recurrent all-cause hospitalization by frailty (based on predicted risk of hospitalization), multimorbidity, polypharmacy and health-related quality of life

Supplementary Figure 5: Effects of empagliflozin versus placebo on recurrent all-cause hospitalization by key pre-specified subgroups

Supplementary Figure 6: Effects of empagliflozin versus placebo on weight and blood pressure by predicted risk of hospitalization

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Table 1: Multivariable logistic regression model used to derive predicted risk of hospitalization

	Participants N (%)*	Hospitalized during follow-up N (%)*	OR (95% CI)	P-value†
Age, per 10 year increase	-	-	1.09 (1.04-1.15)	0.001
Female sex	2192 (33)	615 (28)	0.84 (0.74-0.95)	0.004
Region				<0.001
Europe	2648 (40)	909 (34)	Ref	
North America	1717 (26)	492 (29)	0.67 (0.58-0.77)	
China & Malaysia	1632 (25)	424 (26)	1.14 (0.97-1.33)	
Japan	612 (9)	170 (28)	1.20 (0.97-1.48)	
Ln NT-proBNP, ng/L	-	-	1.26 (1.20-1.33)	<0.001
Mobility				<0.001
No problems	4411 (67)	1052 (24)	Ref	
Slight problems	1141 (17)	435 (38)	1.41 (1.21-1.64)	
Moderate problems	750 (11)	344 (46)	1.69 (1.41-2.02)	
Severe problems	282 (4)	149 (53)	1.93 (1.48-2.53)	
Unable to walk about	25 (0.4)	15 (60)	2.59 (1.11-6.07)	
Diabetes				<0.001
No diabetes	3569 (54)	851 (24)	Ref	
Diabetes without retinopathy	2375 (36)	853 (36)	1.27 (1.12-1.44)	
Diabetes with retinopathy	665 (10)	291 (44)	1.62 (1.34-1.96)	
Peripheral neuropathy‡	1316 (20)	557 (42)	1.34 (1.16-1.55)	<0.001
Heart failure‡	658 (10)	333 (51)	1.30 (1.08-1.57)	0.006
Estimated GFR, per 10 mL/min/1.73m^2 increase§	-	-	0.71 (0.60-0.84)	<0.001
Ischaemic heart disease‡	1095 (17)	494 (45)	1.30 (1.12-1.51)	0.001
Self-reported ankle swelling‡	1516 (23)	611 (40)	1.21 (1.06-1.38)	0.005

First occurrence of all-cause hospitalization was the response variable. All potential predictor variables assessed are reported in Supplementary Table 1 and were added using a forward stepwise approach based on significance in univariable models (Supplementary Table 2). Age, sex and region were forced to remain in the model. * Relevant for categorical variables only. †Wald test P value for continuous and binary outcomes; P value from likelihood ratio test comparing full model with and without the additional variable for categorical variables. ‡ Effect estimate for presence versus absence of. § Effect estimate for linear eGFR term, quadratic term also included in model due to non-linearity. Abbreviations: NT-proBNP = N-terminal pro B-type natriuretic peptide; GFR = glomerular filtration rate.

Table 2: Characteristics of participants at recruitment by predicted risk of hospitalization

	Predicted risk of hospitalization during follow-up (median 2 years)				
	≤20% (N=1988)	**>20% ≤35% (N=2504)**	**>35% ≤45% (N=968)**	**>45% (N=1149)**	**P**
DEMOGRAPHICS					
Age at randomization (years)					<0.001
Mean (SD)	52.8 (13.8)	65.6 (11.5)	71.4 (9.0)	72.6 (8.8)	
Sex					<0.001
Female	745 (38)	860 (34)	294 (30)	293 (26)	
Country					<0.001
UK	311 (16)	429 (17)	159 (16)	234 (20)	
Germany	210 (11)	415 (17)	220 (23)	424 (37)	
Italy	72 (4)	95 (4)	40 (4)	39 (3)	
USA	384 (19)	486 (19)	201 (21)	158 (14)	
Canada	149 (8)	195 (8)	71 (7)	73 (6)	
Malaysia	167 (8)	261 (10)	120 (12)	98 (9)	
China	503 (25)	346 (14)	81 (8)	56 (5)	
Japan	192 (10)	277 (11)	76 (8)	67 (6)	
PRIOR DISEASE					
Prior diabetes*					<0.001
Yes	329 (17)	1168 (47)	645 (67)	898 (78)	
Diabetes without retinopathy	308 (16)	980 (39)	478 (49)	609 (53)	
Diabetes with retinopathy	21 (1)	188 (8)	167 (17)	289 (25)	
No	1659 (83)	1336 (53)	323 (33)	251 (22)	
History of cardiovascular disease†					<0.001
Yes	101 (5)	503 (20)	395 (41)	766 (67)	
No	1887 (95)	2001 (80)	573 (59)	383 (33)	
Number of comorbid conditions (excluding CKD), median (Q1-Q3)	0 (0-1)	1 (0-2)	2 (1-3)	3 (2-4)	<0.001
CLINICAL MEASUREMENTS					
Blood pressure (mmHg)					
Mean systolic (SD)	132 (15)	138 (18)	140 (19)	138 (20)	<0.001
Mean diastolic (SD)	82 (11)	79 (12)	75 (11)	73 (12)	<0.001
Body mass index (kg/m^2)					<0.001
Mean (SD)	28.3 (6.3)	29.4 (6.5)	30.8 (7.0)	32.1 (7.1)	
LABORATORY MEASUREMENTS					
Estimated GFR (mL/min/1.73m^2)					<0.001
Mean (SD)	45.1 (15.6)	36.2 (13.7)	33.1 (11.2)	30.0 (9.3)	
Urinary albumin-to-creatinine ratio (mg/g)					<0.001
Geometric mean (95% CI)	299 (277-323)	210 (194-227)	177 (154-202)	183 (162-206)	
Median (Q1-Q3)	440 (133-1056)	314 (43-1062)	220 (29-1060)	193 (34-1118)	
CONCOMITANT MEDICATION USE					
RAS inhibitor	1791 (90)	2100 (84)	790 (82)	947 (82)	<0.001
Any diuretic therapy	507 (26)	925 (37)	548 (57)	835 (73)	<0.001
Lipid-lowering therapy	968 (49)	1699 (68)	745 (77)	966 (84)	<0.001
Count of concomitant medications at randomization, median (Q1-Q3)	5 (3-7)	7 (5-9)	9 (6-11)	10 (8-13)	<0.001
5-YEAR RISK OF KIDNEY FAILURE (KFRE, %), median (Q1-Q3)	6 (2-19)	10 (3-32)	11 (4-34)	14 (5-37)	<0.001
CAUSE OF KIDNEY DISEASE					<0.001
Diabetic kidney disease	203 (10)	773 (31)	460 (48)	621 (54)	
Hypertension/renovascular	348 (18)	627 (25)	233 (24)	237 (21)	
Glomerular	987 (50)	545 (22)	81 (8)	56 (5)	
Other/unknown	450 (23)	559 (22)	194 (20)	235 (20)	
HEALTH-RELATED QUALITY OF LIFE					
Visual analogue scale rating, median (Q1-Q3)	85.0 (80.0-90.0)	80.0 (70.0-90.0)	80.0 (68.8-85.0)	70.0 (50.0-80.0)	<0.001
EQ-5D index value, median (Q1-Q3)	0.99 (0.87-0.99)	0.90 (0.80-0.99)	0.84 (0.72-0.99)	0.72 (0.60-0.87)	<0.001

Figures are n (%) or mean (SD) or median (Q1-Q3). Predicted risk of hospitalization was derived from multivariable logistic regression models adjusted for age, sex and region assessing the association of all potential predictor variables with recorded hospitalization (first event; see Supplementary Methods). * Prior diabetes defined as: participant-reported history of diabetes of any type, use of glucose-lowering medication or baseline HbA1c ≥48 mmol/mol at randomization visit. † Defined as self-reported history of myocardial infarction, heart failure, stroke,

transient ischaemic attack, or peripheral arterial disease. P values are from Chi squared tests for categorical variables; one-way ANOVA for normally distributed and Kruskal-Wallis tests for non-normally distributed continuous variables, respectively. Abbreviations: CKD = chronic kidney disease; GFR = glomerular filtration rate; KFRE = kidney failure risk equation; RAS = renin-angiotensin system.

Figure legends

The figure legend (title) is in bold with footnote text underneath.

Figure 1: Number of participants in the top thirds of predicted risk of hospitalization (>35%), multimorbidity (≥3 conditions excluding chronic kidney disease) and polypharmacy (≥9 concomitant medications) showing degrees of overlap

Figure presents numbers of participants (%) in the top approximate third of each category applied in subgroup analyses (Supplementary Tables 7-14; Figure 3). An alternative presentation showing overlap between the highest level of frailty defined in EMPA-KIDNEY (predicted risk of hospitalization >45%) and conventional definitions of multimorbidity (≥2 conditions) and polypharmacy (≥5 medications) is shown in Supplementary Figure 3.

Figure 1: Number of participants in the top thirds of predicted risk of hospitalization (>35%), multimorbidity (≥3 conditions excluding chronic kidney disease) and polypharmacy (≥9 concomitant medications) showing degrees of overlap

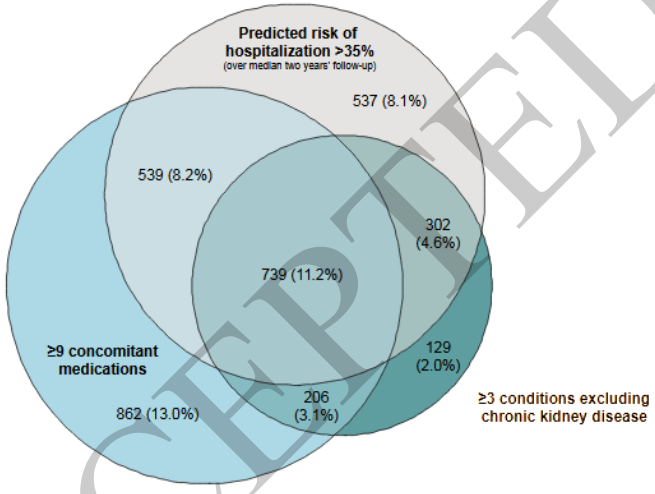

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Figure 2: Effects of empagliflozin on the primary outcome of kidney disease progression or cardiovascular death by frailty (based on predicted risk of hospitalization), multimorbidity, polypharmacy and health-related quality of life

Predicted risk of hospitalization during follow-up (median two years) was derived from multivariable logistic regression models (first event; see Supplementary Methods). Multimorbidity was determined based on the presence/absence of 8 patient-reported comorbidities at randomization (see Supplementary Table 5) excluding chronic kidney disease. The EQ-5D index value is a weighted index of the 5 EQ-5D domain scores (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) derived using established methodology (see Supplementary Methods); lower values indicate poorer quality of life. Due to absence of any evidence of effect modification by the presented characteristics, absolute events avoided per 1000 patients treated with empagliflozin per one year (95% CI) were estimated by applying the overall hazard ratio (or 95% CI) to the event rate per 1000 patient-years in the placebo group.

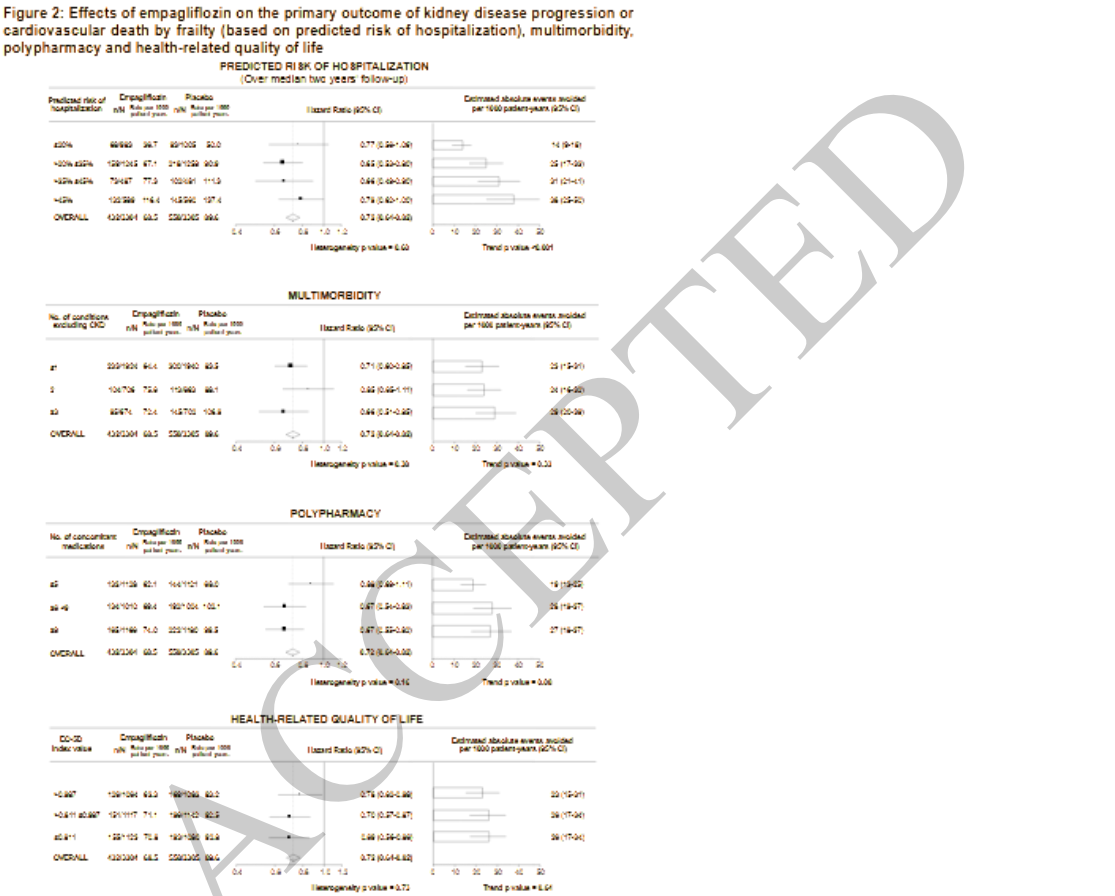
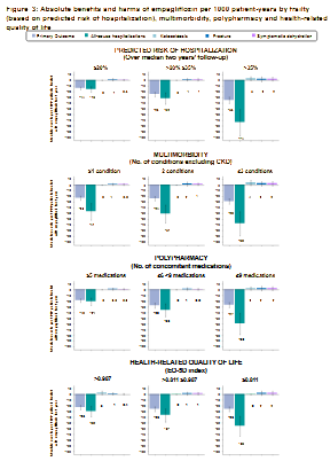


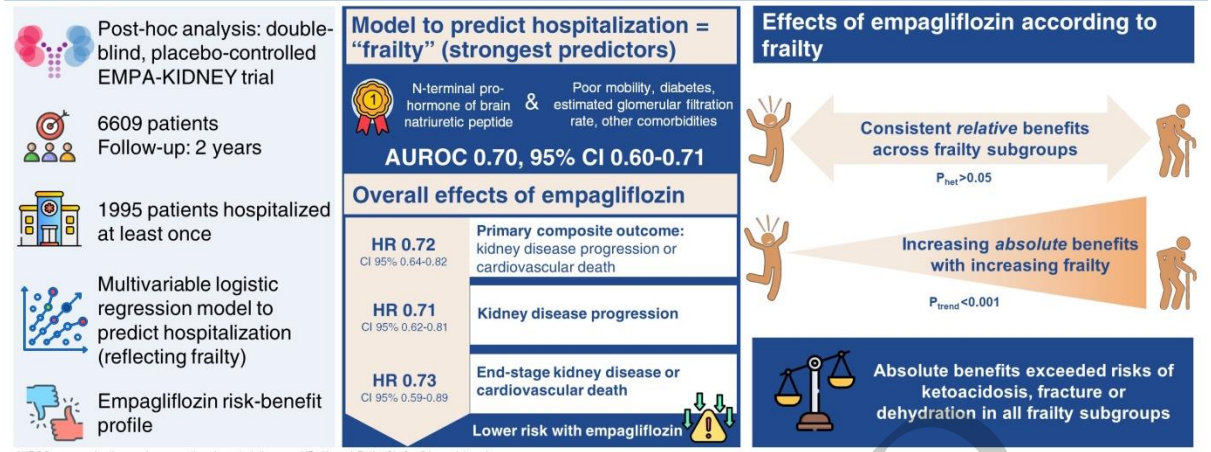
Figure 3: Absolute benefits and harms of empagliflozin per 1000 patient-years by frailty (based on predicted risk of hospitalization), multimorbidity, polypharmacy and health-related quality of life

Predicted risk of hospitalization during follow-up (median two years) was derived from multivariable logistic regression models adjusted for age, sex and region assessing the association of all potential predictor variables with recorded hospitalization (first event; see Supplementary Methods). Multimorbidity was determined based on the presence/absence of 8 patient-reported comorbidities at randomization (see Supplementary Table 5) in addition to chronic kidney disease. The EQ-5D index value is a weighted index of the 5 EQ-5D domain scores (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) derived using established methodology (see Supplementary Methods); lower values indicate poorer quality of life. Absolute events avoided per 1000 patients treated with empagliflozin per one year (and SE represented by error bars) were estimated by applying the overall hazard ratio or 95% CI (since no significant heterogeneity was observed across subgroups) to the event rate per 1000 patient-years in the placebo group. If subgroup-specific hazard ratios (or CIs) were used to estimate absolute effects on all-cause hospitalization by health-related quality of life, based on P for heterogeneity = 0.01 for relative effects, the numbers of estimated absolute events avoided would be one, 87 and 39 respectively (rather than 30, 37 and 56 as plotted). Ketoacidosis was infrequent occurring in 6 participants in the empagliflozin group and one allocated to placebo; six out of seven had diabetes and five of these six reported insulin use at baseline. Pre-specified analyses of all-cause hospitalizations include first and recurrent events; all other events are time-to-first event analyses.



EMPA-KIDNEY: Does empagliflozin continue to show beneficial effects in frail patients with chronic kidney disease?

CJASN
Clinical Journal of the American Society of Nephrology



Conclusions: The findings support the use of SGLT2 inhibitors in CKD, irrespective of frailty. Absolute benefits clearly exceeded any potential harm across the spectrum of frailty in EMPA-KIDNEY.

Kaitlin J. Mayne, Rebecca J. Sardell, Natalie Staplin, et al. **Frailty, multimorbidity, and polypharmacy: exploratory analyses of the effects of empagliflozin from the EMPA-KIDNEY trial**. 2024,CJASN DOI 10.2215/CJN.0000000000000498
Visual abstract by Cristina Popa, MD

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C. Baigent reports the following:
Employer: University of Oxford; Research Funding: Boehringer Ingelheim; Advisory or Leadership Role: I have served as Chair of the European Society of Cardiology Clinical Practice Guidelines Committee 2020-22; and Other Interests or Relationships: I am a trustee of the UK charity alport-uk, which supports patients and families with Alport Syndrome.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Colin Baigent
Manuscript ID: CJASN-2024-000275R2
Manuscript Title: Frailty, multimorbidity and polypharmacy: exploratory analyses of the effects of empagliflozin from the EMPA-KIDNEY trial
Date of Completion: May 29, 2024
Disclosure Updated Date: May 14, 2024

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D. Cherney reports the following:
Employer: Toronto General Hospital; Consultancy: Boehringer Ingelheim-Lilly, Merck, AstraZeneca, Sanofi, Mitsubishi-Tanabe, Abbvie, Janssen, Bayer, Prometic, Lexicon, BMS, Maze, CSL-Behring, Otsuka, Novartis, Yeungene and Novo-Nordisk; Research Funding: Boehringer Ingelheim-Lilly, Merck, Novo Nordisk and AstraZeneca, CSL-BEHRING; Honoraria: Boehringer Ingelheim-Lilly, Merck, AstraZeneca, Sanofi, Mitsubishi-Tanabe, Abbvie, Janssen, Bayer, Prometic, BMS, Maze, CSL-Behring, Otsuka, Novartis, Yeungene and Novo-Nordisk; and Advisory or Leadership Role: Boehringer Ingelheim-Lilly, Merck, AstraZeneca, Lexicon, Janssen, Bayer, BMS, Maze, CSL-Behring, Novartis, Novo-Nordisk.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: David Cherney
Manuscript ID: CJASN-2024-000275R2
Manuscript Title: EMPA-KIDNEY frailty manuscript
Date of Completion: May 29, 2024
Disclosure Updated Date: January 6, 2024

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A. Cheung reports the following:
Employer: University of Utah; Consultancy: Boehringer-Ingelheim, CSL Behring, 3D Communications, Alucent, Nova Nordisk.; Ownership Interest: Merck; Patents or Royalties: Uptodate; and Advisory or Leadership Role: KDIGO.

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Name: Alfred K. Cheung
Manuscript ID: CJASN-2024-000275R2
Manuscript Title: Frailty, multimorbidity and polypharmacy: exploratory analyses of the effects of empagliflozin from the EMPA-KIDNEY trial
Date of Completion: June 18, 2024
Disclosure Updated Date: June 18, 2024

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J. Emberson reports the following:
Employer: University of Oxford; and Research Funding: Boehringer Ingleheim.

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Name: Jonathan Emberson
Manuscript ID: CJASN-2024-000275R1
Manuscript Title: Frailty, multimorbidity and polypharmacy: exploratory analyses of the effects of empagliflozin in CKD from the EMPA-KIDNEY trial
Date of Completion: April 22, 2024
Disclosure Updated Date: October 9, 2023

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R. Haynes reports the following:
Employer: University of Oxford

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Name: Richard Haynes
Manuscript ID: CJASN-2024-000275
Manuscript Title: Frailty, multimorbidity and polypharmacy: exploratory analyses of the effects of empagliflozin in CKD from the EMPA-KIDNEY trial
Date of Completion: April 22, 2024
Disclosure Updated Date: April 22, 2024

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W. Herrington reports the following:
Employer: University of Oxford; Research Funding: Boehringer Ingelheim & Eli Lilly to conduct renal trials (including EMPA-KIDNEY); and Advisory or Leadership Role: NDT subject editor; UK Kidney Association, European Society of Cardiology & KDIGO guideline committee roles. UK Renal Trial Network Chair. I decline all honoraria from the pharmaceutical or food industry, except for reasonable travel expenses.

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Name: William G. Herrington
Manuscript ID: CJASN-2024-000275R1
Manuscript Title: Frailty, multimorbidity and polypharmacy: exploratory analyses of the effects of empagliflozin in CKD from the EMPA-KIDNEY trial.
Date of Completion: April 18, 2024
Disclosure Updated Date: March 22, 2024

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K. Ihara reports the following:
Employer: Nippon Boehringer Ingelheim Co., Ltd.

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Name: Katsuhito Ihara
Manuscript ID: CJASN-2024-000275R2
Manuscript Title: Frailty, multimorbidity and polypharmacy: exploratory analyses of the effects of empagliflozin from the EMPA-KIDNEY trial
Date of Completion: June 18, 2024
Disclosure Updated Date: May 20, 2024

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T. Iwata reports the following:
Employer: Boehringer Ingelheim GmbH & Co. KG

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Name: Tomoko Iwata
Manuscript ID: CJASN-2024-000275R2
Manuscript Title: Frailty, multimorbidity and polypharmacy: exploratory analyses of the effects of empagliflozin from the EMPA-KIDNEY trial
Date of Completion: June 4, 2024
Disclosure Updated Date: June 4, 2024

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P. Judge reports the following:
Employer: University of Oxford; and Research Funding: The UK HARP-III trial was funded by a grant to the University of Oxford from Novartis.; The EMPA-KIDNEY trials was funded by a grant to the University of Oxford from Boehringer Ingelheim & Eli Lily; The EASi-KIDNEY trial is funded by a grant to the University of Oxford from Boehringer Ingelheim.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Parminder K. Judge
Manuscript ID: CJASN-2024-000275R1
Manuscript Title: Frailty, multimorbidity and polypharmacy: exploratory analyses of the effects of empagliflozin in CKD from the EMPA-KIDNEY trial
Date of Completion: April 18, 2024
Disclosure Updated Date: April 18, 2024

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M. Landray reports the following:
Employer: University of Oxford; and Research Funding: Boehringer Ingelheim; Novartis; Regeneron; Sanofi; Moderna; Apollo Tx; GSK; Vaxxinity.

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Name: Martin J. Landray
Manuscript ID: CJASN-2024-000275R1
Manuscript Title: Frailty, multimorbidity and polypharmacy: exploratory analyses of the effects of empagliflozin in CKD from the EMPA-KIDNEY trial
Date of Completion: April 29, 2024
Disclosure Updated Date: April 29, 2024

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A. Maggioni reports the following:
Employer: Heart Care Foundation; Research Funding: Boehringer Ingelheim; and Advisory or Leadership Role: Bayer, Novartis (DSMB member); AstraZeneca, Novartis and Sanofi (Steering Committee member).

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Name: Aldo Pietro Maggioni
Manuscript ID: CJASN-2024-000275R1
Manuscript Title: Frailty, multimorbidity and polypharmacy: exploratory analyses of the effects of empagliflozin in CKD from the EMPA-KIDNEY trial
Date of Completion: April 19, 2024
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K. Mayne reports the following:
Research Funding: Boehringer Ingelheim and Eli Lilly - grant to institution to design and conduct EMPA-KIDNEY trial & EASi-KIDNEY trial; MRC-UK - core funding paid to department

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Name: Kaitlin J. Mayne
Manuscript ID: CJASN-2024-000275R2
Manuscript Title: Frailty, multimorbidity and polypharmacy: exploratory analyses of the effects of empagliflozin from the EMPA-KIDNEY trial
Date of Completion: June 18, 2024
Disclosure Updated Date: April 18, 2024

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M. Nangaku reports the following:
Employer: the University of Tokyo Graduate School of Medicine; Consultancy: Kyowa-Kirin, Tanabe-Mitsubishi, Boehringer-Ingelheim; Research Funding: Kyowa-Kirin, Chugai, Boehringer-Ingelheim; and Honoraria: Kyowa-Kirin, Tanabe-Mitsubishi.

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Name: Masaomi Nangaku
Manuscript ID: CJASN-2024-000275R2
Manuscript Title: Frailty, multimorbidity and polypharmacy: exploratory analyses of the effects of empagliflozin from the EMPA-KIDNEY trial
Date of Completion: June 18, 2024
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D. Preiss reports the following:
Employer: University of Oxford; and Research Funding: Boehringer Ingelheim, Novartis, Novo Nordisk.

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Name: David Preiss
Manuscript ID: CJASN-2024-000275R1
Manuscript Title: Frailty, multimorbidity and polypharmacy: exploratory analyses of the effects of empagliflozin in CKD from the EMPA-KIDNEY trial
Date of Completion: April 23, 2024
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X. Rossello reports the following:
Other Interests or Relationships: European Society of Cardiology (ESC) Clinical Practice Guideline Committee member

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Name: Xavier Rossello
Manuscript ID: CJASN-2024-000275R2
Manuscript Title: Frailty, multimorbidity and polypharmacy: exploratory analyses of the effects of empagliflozin from the EMPA-KIDNEY trial
Date of Completion: May 28, 2024
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E. Sammons reports the following:
Research Funding: Institutional awards from the following companies and charities have supported the EMPA-KIDNEY trial: Boehringer Ingelheim, Eli Lilly, UK Medical Research Council, British Heart Foundation, National Institute for Health and Care Research Biomedical Research Council, Health Data Research UK.

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Name: Emily Sammons
Manuscript ID: CJASN-2024-000275R1
Manuscript Title: Frailty, multimorbidity and polypharmacy: exploratory analyses of the effects of empagliflozin in CKD from the EMPA-KIDNEY trial
Date of Completion: April 18, 2024
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R. Sardell has nothing to disclose.

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Name: Rebecca J. Sardell
Manuscript ID: CJASN-2024-000275R2
Manuscript Title: Frailty, multimorbidity and polypharmacy: exploratory analyses of the effects of empagliflozin from the EMPA-KIDNEY trial
Date of Completion: May 29, 2024
Disclosure Updated Date: May 22, 2024

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N. Staplin reports the following:
Employer: Clinical Trial Service Unit, University of Oxford; Research Funding: Boehringer Ingelheim; Novo Nordisk; and Advisory or Leadership Role: Associate Editor for Nephrology Dialysis Transplant.

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Name: Natalie Staplin
Manuscript ID: CJASN-2024-000275R1
Manuscript Title: Frailty, multimorbidity and polypharmacy: exploratory analyses of the effects of empagliflozin in CKD from the EMPA-KIDNEY trial
Date of Completion: April 23, 2024
Disclosure Updated Date: May 16, 2023

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K. Tuttle reports the following:
Employer: Providence Medical Research Center/Providence Inland Northwest Health; Consultancy: Boehringer Ingelheim, Novo Nordisk, Bayer, ELi Lilly; Research Funding: Bayer, Travere; Honoraria: Bayer, Novo Nordisk; and Advisory or Leadership Role: Chair, Diabetic Kidney Disease Collborative, American Society of Nephrology (unpaid).

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Katherine R. Tuttle
Manuscript ID: CJASN-2024-000275R2
Manuscript Title: Frailty, multimorbidity and polypharmacy: exploratory analyses of the effects of empagliflozin from the EMPA-KIDNEY trial
Date of Completion: May 28, 2024
Disclosure Updated Date: March 20, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

ASN Journal Disclosure Form

As per ASN journal policy, I have disclosed any financial relationships or commitments I have held in the past 36 months as included below. I have listed my Current Employer below to indicate there is a relationship requiring disclosure. If no relationship exists, my Current Employer is not listed.

C. Wanner reports the following:
Employer: University Hospital; Consultancy: Alexion, AstraZeneca, Bayer, Boehringer-Ingelheim, GSK, Idorsia, MSD, NovoNordisk, CSL-Vifor; Research Funding: University of Oxford; Honoraria: Amgen, Amicus, Astellas, AstraZeneca, Bayer, Boehringer-Ingelheim, Chiesi, FMC, Eli-Lilly, GSK, Novartis, Sanofi, Stadapharm, Takeda, CSL-Vifor; and Other Interests or Relationships: European Renal Association.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Christoph Wanner
Manuscript ID: 2024-000275R2
Manuscript Title: Frailty
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ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
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CJASN Clinical Journal of the American Society of Nephrology

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As per ASN journal policy, I have disclosed any financial relationships or commitments I have held in the past 36 months as included below. I have listed my Current Employer below to indicate there is a relationship requiring disclosure. If no relationship exists, my Current Employer is not listed.

D. Zhu reports the following:
Employer: Oxford Population Health, University of Oxford

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Doreen Zhu
Manuscript ID: CJASN-2024-000275R2
Manuscript Title: Frailty, multimorbidity and polypharmacy: exploratory analyses of the effects of empagliflozin from the EMPA-KIDNEY trial
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