Cost-effectiveness of Empagliflozin in Chronic Kidney Disease (CKD) Management in the United Kingdom (UK)

EMPA-KIDNEY

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BACKGROUND

- Chronic kidney disease (CKD) can lead to severe outcomes with impact on survival and quality of life (QoL) and is associated with substantial public health and financial burden. Thus, prevention and measures to slow progression of CKD are key in reducing the overall morbidity burden and costs.[1-3]
- In the United Kingdom (UK) in 2023, the annual economic burden of CKD to the National Health Service (NHS) was estimated as £6.4 billion, accounting for approximately 3.2% of the NHS budget.[4]
- Empagliflozin, a sodium-glucose co-transporter-2 (SGLT2) inhibitor, demonstrated a significant reduction in kidney disease progression or cardiovascular (CV) death compared to standard of care (SoC) in adults with CKD in the EMPA-KIDNEY trial (a multi-center, double-blind, phase 3 clinical trial in approximately 6600 patients).[5]

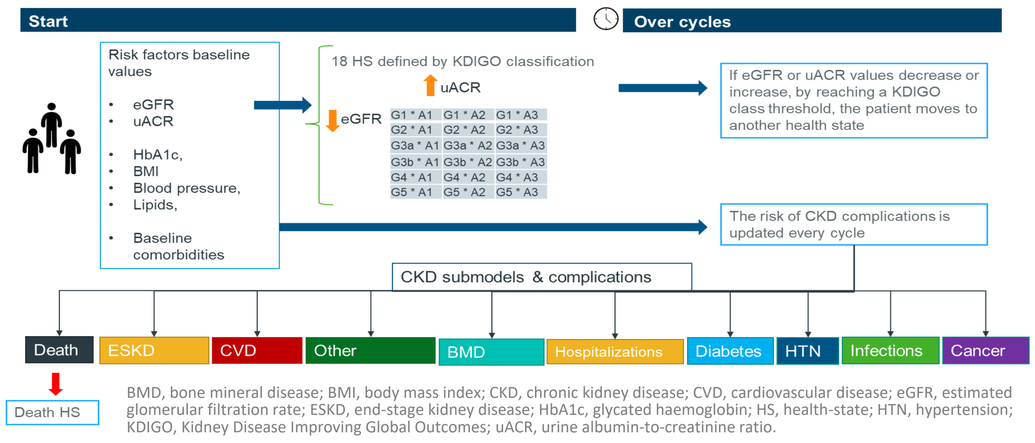
OBJECTIVE

- To evaluate the cost-effectiveness (CE) of empagliflozin on top of standard of care (SoC) versus SoC alone for the treatment of adults with CKD from the UK NHS and personal social services (PSS) perspective.

METHODS

- Our study used the Chronic Kidney Disease Progression Model (CKD-PM), its modeling properties have been published earlier.[6] This model is a patient-level (microsimulation) state-transition model with 18 health states based on Kidney Disease Improving Global Outcomes (KDIGO) categories which characterizes broad range of CKD severity and risk of complications (**Figure 1**).[7]
- The evolution of key risk factors are tracked in the model: estimated glomerular filtration rate (eGFR) and urine albumin-creatinine ratio (uACR). Other risk factors, like total cholesterol, high-density lipoproteins, systolic blood pressure (SBP), body mass index (BMI) and glycated haemoglobin (HbA1c) were also incorporated into the model. [6]
- The risk of complications is determined by the baseline characteristics and evolution of risk factors over time. Several CKD complications submodules are integrated in the CKD-PM: CVD, acute kidney injury (AKI), bone and mineral disorders (BMD), anemia in CKD, gout, metabolic acidosis, renal and urothelial cancer in non-functioning kidneys, infections, and prevalence of comorbidities like hypertension and diabetes (**Figure 1**).[6]

Figure 1. Chronic Kidney Disease Progression Model (CKD-PM) overview [6]



BMD, bone mineral disease; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HbA1c, glycated haemoglobin; HS, health-state; HTN, hypertension; KDIGO, Kidney Disease Improving Global Outcomes; uACR, urine albumin-to-creatinine ratio.

- The intention to treat (ITT) population of the EMPA-KIDNEY trial was used for patient baseline characteristics[5]. Baseline distribution across KDIGO health states and treatment effects on health state-dependent for eGFR and uACR were derived from EMPA-KIDNEY trial (*data in file*, *forthcoming January 2024*).
- Risk prediction engines and clinical data were derived from CKD registries, such as CKD-Prognosis Consortium (CKD-PC) and Chronic Renal Insufficiency Cohort Study (CRIC). These data are utilized to project risk over a lifelong modeling horizon. [6]
- Risk of all-cause mortality was predicted as the sum of CV mortality, kidney-related death, and other causes of death (**Table 1**).[6]
- UK health state utilities were used, with deduction of one-off disutilities per event/complication, based on published sources. [8-11]
- Health state costs were factored in for respective KDIGO health states until initiation of renal replacement therapy (RRT).[12] Complication costs were counted in, only if the risk of double counting with health state costs could be ruled out. Costs were representative of the UK healthcare payer perspective (NHS and PSS), informed by expert clinical opinion and sourced from published data.
- The model had an annual cycle, and lifelong analyses were run over a 50 years modelling horizon. An annual discount rate of 3.5% was applied on costs and outcomes in line with National Institute for Health and Care Excellence (NICE) guidelines.[13] The willingness-to-pay (WTP) thresholds of £20,000 and 30,000 were used.[13]
- Base case analyses were conducted to evaluate the CE of empagliflozin in addition to individually optimized SoC in adult patients with CKD, using the model settings detailed in **Table 1**; the comparator was SoC alone.
- Base case analyses were run in 1000 patients per arm, whereas probabilistic sensitivity analysis (PSA) was carried out 500 times using 1000 patients, to assess the effect of parameter uncertainties.

Table 1. Base case model setting

Model parameter	Option selected
Cohort characteristics	
Patient baseline characteristics	EMPA-KIDNEY trial cohort.[5]
eGFR and uACR distribution	EMPA-KIDNEY trial cohort.[5,6]
eGFR and uACR midpoints per KDIGO categories	EMPA-KIDNEY trial cohort.[5,6]
Risk factor progression/disease progression after treatment discontinuation	
eGFR progression	Fixed changes per eGFR and uACR classes.[14]
uACR progression	Lognormal distribution uACR fold.[15]
Risk prediction	
Risk of all cause of death	CVD death + non-specific cause death [16] + renal death [17]
Risk prediction of CVD mortality	CKD patch equations- Low risk countries.[18]
Risk of KRT	Tangri et 2016 [19] KRT 5-year risk equation, pooled with six variables (which includes DM and hypertension)
Upper age threshold for kidney transplant	80 years
Cost of complications (CVD, cancer, KT) Cost of ESKD, BMD and other complications Cost of events (infections, AKI, AEs, fractures)	Includes 1st and follow-up years Annual cost One-off costs
Cost applied in ESKD without RRT	Conservative therapy cost only (no ESKD health state cost)
Risk prediction of CVD	ASCVD from 'CKD patch' low risk countries[18] ; recurrent stroke[20] ; hospitalized HF[14] ; PAD hospitalizations.[21,22]

AE, adverse event; AKI, acute kidney injury; ASCVD, atherosclerotic cardiovascular disease; BMD, bone and mineral disorders; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR: Estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; KDIGO, Kidney Disease Improving Global Outcomes; KRT, kidney replacement therapy; KT, kidney transplant; PAD, peripheral artery disease; RRT; renal replacement therapy; RT, renal transplant; uACR, urine albumin-to-creatinine ratio

RESULTS

- Over a lifetime horizon, empagliflozin plus SoC compared with SoC alone resulted in an incremental gain in LYs (+1.04) and QALYs (+0.84) while decreasing costs by £6,019 per patient. Thus, empagliflozin was projected to be more effective and less costly than SoC alone, with a dominant ICER in deterministic analyses, and a NHB of 1.14 and 1.04 at the WTP threshold of £20,000 and £30,000 per QALY gained, respectively (**Table 2**).
- Although the cost of treatment was higher for empagliflozin (+£2,439), this was more than offset by reduced costs of renal replacement therapy (RRT:- £13,241); some costs, such as monitoring and CVD or CKD complications, were impacted by projected extended survival in the empagliflozin arm (**Table 2**).

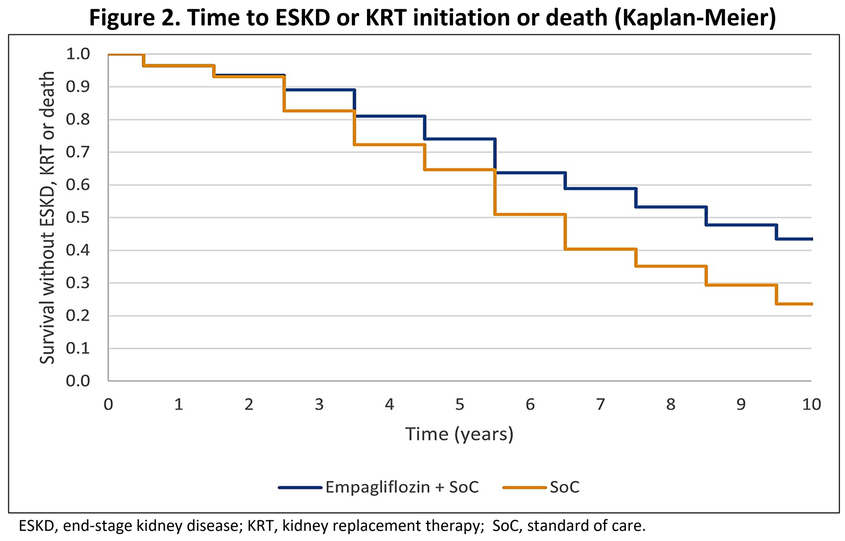
Table 2. Base case cost effectiveness analysis over a lifetime (50 years)

Outcome	Empagliflozin plus SoC	SoC	Incremental
Total discounted costs (£)	**89,911**	**95,930**	**-6,019**
Treatment (£)	2,571	132	2,439
Total KRT (£)	25,667	38,908	-13,241
ESKD conservative therapy (£)	2,546	2,696	-150
Monitoring (£)	20,610	19,903	707
CVD Complications (£)	7,223	6,541	681
Other CKD complications (£)	31,294	27,750	3,544
Total discounted LYs	9.59	8.55	1.04
Total discounted QALYs	7.12	6.28	0.84
ICER (£) per QALY gained	< 0	--	--
NHB at £20,000 (£) per QALY gained	1.14	--	--
NHB at £30,000 (£) per QALY gained	1.04	--	--

£, Great Britain Pound; CKD, chronic kidney disease; CVD, cardiovascular disease; ESKD, end-stage kidney disease; ICER, incremental cost effectiveness ratio; KRT, kidney replacement therapy; LY, life-year; NHB, net health benefit; QALY, quality-adjusted life-year; SoC, standard of care. Cost effectiveness was described in terms of the ICER and NHB. The ICER is the cost per additional unit of effectiveness gained for empagliflozin versus SoC (incremental total costs/incremental QALY). The NHB indicates the value of an intervention ([incremental QALY × WTP threshold] – incremental total cost).

- In the base case, the mean time to progression to ESKD or RRT or death was 9.7 and 7.0 years, respectively (p-value LogRank < 0.0001, **Figure 2**).

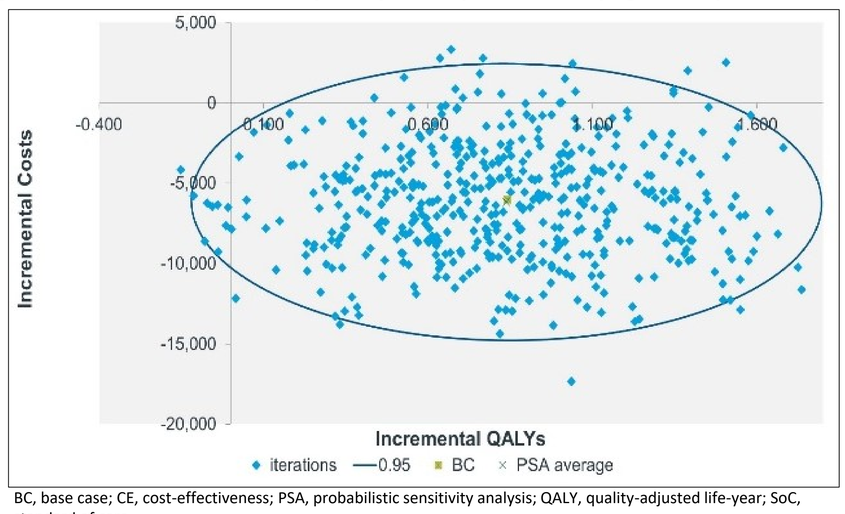
Figure 2. Time to ESKD or KRT initiation or death (Kaplan-Meier)



ESKD, end-stage kidney disease; KRT, kidney replacement therapy; SoC, standard of care.

- The CE plane displayed that most observations fell in the South-East (94%) quadrant of the scatterplot (**Figure 3**). The cost-effectiveness acceptability curve (CEAC) further indicated that at the defined WTP threshold of £20,000 and £30,000 per QALY gained, the probability of empagliflozin plus SoC to be cost-effective was 100% versus SoC alone.

Figure 3. Probabilistic sensitivity analysis: CE plane for empagliflozin plus SoC versus SoC



BC, base case; CE, cost-effectiveness; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; SoC, standard of care

CONCLUSIONS

- This de *novo* microsimulation CKD CE model suggested that treatment with empagliflozin, via slowing down CKD progression, may reduce the risk or delay the initiation of RRT and improve long term survival, compared to SoC alone.
- As a result, empagliflozin plus SoC was a cost-effective therapy, in comparison to SoC alone, representing a cost-effective use of NHS resources for treatment in adult patients with CKD in the UK.

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Disclosures

- The EMPA-KIDNEY trial was initiated, designed, and conducted by the University of Oxford in collaboration with a Steering Committee of experts and Boehringer Ingelheim. The presented analyses were initiated and conducted by Boehringer Ingelheim (BI) independently from the EMPA-KIDNEY Collaborative Group
- The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE).
- Mafalda Ramos, MSc, MEng, Laetitia Gerlier, MSc, and Mark Lamotte, MD, are/were full-time employees of IQVIA, were contracted by BI.
- Anastasia Uster, MD, Anna Rita Mazo, PhD, Louise Muttram, MSc are/were full-time employees of BI
- Andrew H Frankel, MD is associated with Imperial College Healthcare NHS Trust, London, UK
- Boehringer Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

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