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Cost-Effectiveness of Empagliflozin in Patients With Diabetic Kidney Disease in the United States: Findings Based on the EMPA-REG Outcome Trial

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ABSTRACT

**Rationale & Objective:** Benefits of sodium-glucose co-transporter 2 inhibitors on kidney outcomes have been demonstrated in clinical trials. Among patients with type 2 diabetes and established cardiovascular (CV) disease enrolled in EMPA-REG Outcome Study (NCT01131676), empagliflozin added to standard of care (SoC) reduced the risk of incident or worsening nephropathy compared to SoC alone. This analysis evaluated the cost-effectiveness of empagliflozin versus SoC alone in the subpopulation with diabetic kidney disease (DKD) from the perspective of United States (US) commercial insurers and Medicare.

**Study Design:** Discrete event simulation model.

**Setting & Population:** Patients with DKD in a US healthcare system.

**Interventions:** Empagliflozin 10 or 25 mg with SoC versus SoC alone. SoC included glucose-lowering therapies and medications to treat CV risk factors.

**Outcomes:** Incremental cost-effectiveness ratios (ICERs, 2020 US dollars per quality-adjusted life-year [QALY] gained). Costs and QALYs were discounted 3.0%/year.

**Model, Perspective, & Timeframe:** Cost-effectiveness analysis, commercial insurers and Medicare perspective, lifetime horizon.

**Results:** The ICER of empagliflozin with SoC versus SoC alone was $25,974/QALY. Empagliflozin added 0.67 QALYs and $17,322/patient over a lifetime horizon. Results were driven by fewer clinical events (including CV death, heart failure [HF] hospitalization, albuminuric progression, and a composite kidney outcome) experienced by patients receiving empagliflozin with SoC versus SoC alone. Results were sensitive to rates of CV death, non-fatal...
MI, and HF hospitalization, as well as to drug costs, and time horizon. Probabilistic sensitivity analyses indicated 91% of simulations falling below $50,000/QALY.

**Limitations:** The EMPA-REG Outcome Study was not powered to assess treatment benefits in a subgroup and excluded patients with estimated glomerular filtration rate <30 mL/min/1.73m².

**Conclusion:** Based on EMPA-REG Outcome Study, this cost-effectiveness analysis suggests that for commercial insurers and Medicare, adding empagliflozin to SoC may be a cost-effective treatment option for patients with DKD.

**Index or Key Words**

cost-effectiveness; diabetic kidney disease; empagliflozin; sodium-glucose co-transporter 2 inhibitor; type 2 diabetes; United States
Plain-Language Summary

Kidney injury is a common complication of type 2 diabetes, associated with increased risk of cardiovascular events and death in this population. Empagliflozin demonstrated slower kidney disease progression and lower kidney event rates than placebo when combined with standard care in the EMPA-REG Outcome Trial. A health economic model was used to predict long-term treatment effects and costs for patients with diabetic kidney disease at baseline in the EMPA-REG Outcome Trial. Treatment with empagliflozin combined with standard care for US patients with diabetic kidney disease may lead to health benefits and be cost-effective versus standard care alone for commercial insurers and Medicare. These results will help guide patients, clinicians, and decision makers in selecting a regimen for management of diabetic kidney disease.
INTRODUCTION

A common complication of type 2 diabetes (T2D) is kidney injury, affecting more than one-third of the 27 million people living with diabetes in the United States (US). Diabetic kidney disease (DKD) is itself costly to treat while also being associated with increased risks of cardiovascular (CV) events and death. The humanistic, economic, and societal burden of DKD is substantial and expected to grow over the coming years as the number of Americans living with T2D increases.

 Originally developed as a glucose-lowering therapy for T2D, sodium-glucose cotransporter-2 inhibitors (SGLT2i) have demonstrated beneficial effects in kidney disease. Clinical trials of SGLT2i including T2D patients with relatively preserved kidney function (EMPA-REG OUTCOME [NCT01131676], CANVAS Program, and DECLARE-TIMI 58), individuals with overt DKD (CREDENCE), and chronic kidney disease (CKD) with or without T2D (DAPA-CKD; NCT03036150) have demonstrated risk reductions for both incident and progressive kidney and CV endpoints. The ongoing EMPA-KIDNEY trial will provide further evidence in patients with CKD, including those with and without T2D (NCT03594110, Clinicaltrials.gov).

The effects of empagliflozin (Jardiance®; 10 or 25 mg) in patients with T2D, established CV disease (CVD), and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73m² who were receiving standard of care (SoC) were demonstrated in EMPA-REG OUTCOME (N=7,020). SoC was a combination of drugs, used at trial initiation or escalated over the study duration according to local guidelines, for glycemic management and control of CV risk factors. Empagliflozin with SoC reduced incident or worsening nephropathy by 39% (hazard ratio [HR]: 0.61; 95% confidence interval [CI]: 0.53–0.70) compared to SoC, with a consistent benefit in
patients with DKD at baseline (32%; DKD defined as eGFR <60 mL/min/1.73m² and/or urine albumin-to-creatinine ratio [UACR] >300mg/g) across all Kidney Disease Improving Global Outcomes (KDIGO) risk categories.¹⁵⁻¹⁷

Given likely increases in DKD prevalence and recent proliferation of promising treatment options for those affected, evaluating the cost-effectiveness of empagliflozin in patients with DKD is important to guide optimal allocation of healthcare system resources. This study assessed the cost-effectiveness of empagliflozin with SoC versus SoC alone in patients with DKD over a lifetime horizon from the perspective of US commercial insurers and Medicare. A model was previously published to assess patients with T2D and CVD in the United Kingdom based on the EMPA-REG OUTCOME intent-to-treat population data.¹⁸ This model incorporates new risk equations and population characteristics from a sub-analysis of patients with baseline DKD in EMPA-REG OUTCOME and US-specific costs and utilities.

**METHODS**

**Model Overview**

A discrete-event simulation (DES) approach was used to predict CV and kidney events associated with T2D progression and estimate the cost-effectiveness of empagliflozin with SoC versus SoC alone for the management of patients with DKD in the US. DES is less restrictive versus Markovian approaches as it can track change in characteristics and patients’ CV/kidney history, captures interdependencies between multiple events as patients evolve with no *a priori* restrictions (i.e., future event times depend on patient history), and uses the trial data more directly. DES was used previously for cost-effectiveness analyses in T2D and CVD.¹⁸⁻²¹
At start of the simulation (Figure 1), baseline characteristics of individual patients were assigned and a series of risk equations based on analyses of EMPA-REG OUTCOME DKD subpopulation data were used to draw random times from event-specific time-to-event distributions. Modeled clinical events were treated as competing risks. For each simulated patient, the earliest event occurred and associated quality-adjusted life years (QALYs) and direct medical costs were accrued. The patient exited the model if a fatal event occurred or the time horizon exhausted. Otherwise, the patient remained in the model, clinical history was updated, and the time to the next event was updated. The process repeated for every simulated patient. Once all patients had been subjected to this process in each treatment arm, outcomes of individuals were aggregated. The model tabulated the cumulative number of events, event rates per 100 person years (PY), mean life years (LYs), QALYs, costs, and the incremental cost-effectiveness ratio (ICER) per QALY. Analyses discounted future costs and QALYs at 3.0% annual rate.\textsuperscript{22}

**Baseline Patient Characteristics**

The modeled population was specified using demographics, physiological parameters (e.g., baseline metabolic risk factors), and clinical event history of EMPA-REG OUTCOME participants with DKD at baseline.\textsuperscript{17} Based on EMPA-REG OUTCOME’s inclusion criteria, all patients had T2D and atherosclerotic CVD.\textsuperscript{8} Individuals with DKD at baseline exhibited either eGFR (Modification of Diet in Renal Disease equation) <60 mL/min/1.73m\textsuperscript{2} (80.8% of patients with baseline DKD) or UACR >300 mg/g (34.2% of patients), or both (15.0% of patients). This subgroup had a mean (standard deviation [SD]) age of 66.2 (8.2) years, body mass index of 30.8 (5.4) kg/m\textsuperscript{2}, glycated hemoglobin (HbA1c) of 8.10% (0.87%), eGFR of 54.4 (20.4) mL/min/1.73m\textsuperscript{2}, and 31% were female. Compared to patients without DKD, those with baseline
DKD tended to be older and had T2D for a longer time; they were also more likely to have multi-vessel coronary artery disease, coronary artery bypass graft, or cardiac failure.

Patient characteristics were generated by sampling with replacement 5,000 complete profiles from the observed data of EMPA-REG OUTCOME participants with DKD at baseline, accounting for natural correlation in characteristics. Every patient profile was cloned, and identical cohorts of individuals were assigned to empagliflozin with SoC and SoC alone.

**Clinical Inputs**

Effectiveness was assessed with reference to occurrence of albuminuria progression, a composite kidney outcome, CV death, non-fatal myocardial infarction (MI), non-fatal stroke, hospitalization for heart failure (HF), hospitalization for unstable angina (UA), transient ischemic attack, and revascularization. Simulated patients could also experience non-CV death. Definitions of CV events in EMPA-REG OUTCOME have been published. Albuminuria was measured using UACR. Participants in EMPA-REG OUTCOME were categorized as having normoalbuminuria (UACR <30 mg/g), microalbuminuria (UACR ≥30 mg/g and ≤300 mg/g), or macroalbuminuria (UACR >300 mg/g) at baseline. Progression of albuminuria was defined as a ≥30% increase from baseline in UACR and a shift in albuminuria category: (a) from baseline normoalbuminuria to microalbuminuria or macroalbuminuria, or (b) from baseline microalbuminuria to macroalbuminuria. Progression of albuminuria was evaluated in 1,481 participants with normoalbuminuria or microalbuminuria at baseline. The composite kidney outcome was a sustained ≥40% eGFR reduction, development of end-stage kidney disease, or kidney death. A sustained 40% decline in eGFR from baseline was defined as being present on ≥2 consecutive measurements >30 days apart. End-stage kidney disease was based on initiation
of kidney replacement therapy (dialysis treatment for ≥30 days or kidney transplant). Kidney death reflects death attributed to kidney disease.

Post-hoc analyses of individual patient data from the EMPA-REG OUTCOME trial DKD subpopulation were performed to quantify time to the next clinical event (Item S1). Risk equations were derived by fitting parametric distributions to the trial data and conducting parametric proportional hazards regression analysis, considering baseline and time-dependent variables as potential predictors that impact the risk of each event. The final risk equations used in the model are shown in Item S2 and the time-to-event estimation is described in Item S3. Treatment allocation (empagliflozin with SoC or SoC alone) was a predictor in each equation. As clinical literature suggests increased CV events in patients with kidney disease,23-25 kidney events were potential predictors of the risk of future CV events in the model, but CV events were not used to predict kidney events. When the model time horizon exceeded the trial duration, the risk equations were extrapolated. Non-fatal CV events were permitted to occur repeatedly, but kidney events were non-recurrent. Expected time to non-CV death was derived by fitting Gompertz distributions to age- and sex-specific probabilities from US life tables (Item S2).26 The base case analysis included all modeled events.

The risk equations were applied in the model over the three-year mean trial duration and validated by estimating event rates and HRs for empagliflozin with SoC versus SoC alone and comparing the resultant outcomes against those observed in EMPA-REG OUTCOME’s DKD subpopulation (Item S4).

Quality of Life Inputs
Cost-effectiveness analyses commonly use utility weights—a construct ranging from zero (representing death) to one (full health)—to adjust survival and estimate QALYs for simulated patients with different health status. Utility weights employed in the model (Table 1) originated primarily from Sullivan and Ghushchyan, who derived US-specific EQ-5D scores for diabetes-related chronic conditions from data for 20,705 patients with diabetes (56% reported at least one diabetes-related chronic condition) who participated in the 2000–2011 Medical Expenditure Panel Survey. A utility reduction for composite kidney outcome was based on published analysis of EQ-5D data for nephropathy among respondents with T2D to the US SHIELD study. Because no US-specific utility weight for revascularization was available, non-US utility reduction data was used. To reflect the impact of clinical events on patients’ health-related quality of life, the model applied a permanent, event-specific utility decrement to their baseline utility (see Item S5).

Cost Inputs

The analysis adopts the perspective of US commercial insurers (non-governmental agencies who provide health insurance) and Medicare. All costs are expressed in 2020 US dollars, adjusted for inflation by applying the medical component of the US Consumer Price Index, where applicable. Costs constitute weighted averages for Medicare and commercial insurers, with the weights determined by the proportions of EMPA-REG OUTCOME DKD subgroup participants who were at least 65 years of age (59%) or younger (41%) when the trial began.

Drug costs were limited to empagliflozin, regarded as add-on to SoC, since participants in both treatment groups of EMPA-REG OUTCOME used SoC. The wholesale acquisition cost (WAC) of empagliflozin ($529.68/month for 10mg or 25mg tablets) from RED BOOK® represented the drug cost...
parameter following principles for economic evaluations published by the Institute for Clinical and Economic Review.\textsuperscript{32} WAC is the most commonly used benchmark in pharmacy purchasing of drugs. The wholesaler acquires branded drugs from the manufacturer at a certain price (typically based on WAC) and then re-sells them to pharmacies for around the same price (based on WAC). The pharmacy sells to their customers at that price plus a mark-up. However, pharmacies are reimbursed differently based on the plan and rates negotiated with a payer, influenced by various factors. Thus, as a proxy, WAC is considered a close approximation of the price to most payers. All modeled patients were assumed to be insured for medication. The model applied a $35 patient co-pay (based on median $10/$35/$55 co-pays for three-tier plans),\textsuperscript{33} and assumed a weighted average rebate discount (52\% of the WAC) for Medicare (53\%) and commercial insurers (50\%). Patients remained on the same regimen for the simulation duration.

Payers were assumed to incur a one-time cost of acute care for each clinical event (Table 2). These inputs represent weighted averages of the national cost per admission by specific diagnosis codes and payer status, based on the Healthcare Cost and Utilization Project’s (HCUP) National Inpatient Sample (N=35,675,421) using the International Classification of Diseases, Tenth Revision diagnostic codes on inpatient discharges.\textsuperscript{34} Published literature furnished clinical event costs not available from HCUP.\textsuperscript{35, 36} Since clinical events can indirectly impose longer-term costs by increasing the risk of subsequent CV events, the model avoids double counting by abstaining from explicit consideration of post-acute event costs.

**Sensitivity Analyses**

Parameter uncertainty was explored in deterministic sensitivity analysis (DSA) scenarios assessing treatment effect, payer perspective, exclusion of certain CV or kidney events, costs, utilities, time horizon, and discount rates (Item S6). Probabilistic sensitivity analysis (PSA) was
performed with random sampling from distributions assigned to input parameters, and risk equation coefficients varied using Cholesky decomposition (Item S7).

RESULTS

Base Case Analysis

Simulated patients in the EMPA-REG OUTCOME DKD subgroup who received empagliflozin with SoC versus SoC alone experienced lower lifetime rates of progression of albuminuria, composite kidney outcome, hospitalization for HF, CV death, revascularization, non-fatal MI, non-fatal stroke, and transient ischemic attack, but a similar rate of hospitalization for UA (Figure 2). Over the lifetime horizon, 185 progression of albuminuria and 364 composite kidney outcome events were avoided. A higher rate of non-CV death was estimated in simulated patients receiving empagliflozin with SoC versus SoC alone, contradictory to the trial. Since all patients experienced a fatal event in the lifetime analysis and empagliflozin with SoC reduces CV death, more simulated patients in the empagliflozin with SoC group were predicted to have non-CV death. However, a lower rate of all-cause mortality was still estimated for empagliflozin with SoC versus SoC alone, due to the large reduction in CV deaths.

Reduced frequency of clinical events among simulated patients receiving empagliflozin with SoC versus SoC alone culminated in lifetime incremental gains of 1.27 LYs and 0.67 discounted QALYs (Table 3). Patients using empagliflozin with SoC incurred higher lifetime drug treatment costs but lower lifetime clinical event costs (driven by reduced CV deaths, hospitalizations for HF, and revascularizations), equivalent to $17,322/patient in additional average lifetime discounted costs for US commercial insurers and Medicare. The resultant ICER was $25,974/QALY.
Sensitivity Analyses

Results of the DSA top 10 drivers are presented in Table 4. The strongest drivers were the highest net empagliflozin price in the Federal Supply Schedule (FSS), short time horizons (3, 5, and 10 years), CV death, non-fatal MI and hospitalization for HF risk (no empagliflozin benefit or treatment effect using 95% CIs), and manufacturer rebate for empagliflozin drug cost (no rebate, ±20% variation). Among these scenarios, ICERs ranged from $17,440–$143,333/QALY. Results were relatively insensitive to changes in other parameters (Item S6). Varying model parameters through DSA did not affect conclusions about the cost-effectiveness of empagliflozin with SoC versus SoC alone, considering a $150,000/QALY cost-effectiveness threshold.37

Results of the PSA generated a mean ICER of $29,750/QALY (95% CI: $13,410–$88,301/QALY). The PSA produced relatively broad 95% CIs around mean event rates for both empagliflozin with SoC and SoC alone, which was expected given EMPA-REG OUTCOME (from which the modeled time-to-event estimates were derived) was not powered to assess treatment benefits in the DKD subgroup (Item S7). Nonetheless, the probabilities of obtaining an ICER that does not exceed $50,000/QALY and $150,000/QALY were 90.9% and 99.8%, respectively. These results (Figure 3) indicate that QALYs and costs are typically higher with empagliflozin with SoC than SoC alone (reflecting both increased drug costs and longer life expectancy among patients receiving empagliflozin)—as exemplified by most ICERs falling into the upper right quadrant of the cost-effectiveness plane—and imply that empagliflozin with SoC is likely to exhibit cost-effectiveness for most plausible combinations of input values.

DISCUSSION
This study summarizes the results of a health economic evaluation from the perspective of US commercial insurers and Medicare examining the cost-effectiveness of empagliflozin with SoC versus SoC alone in T2D patients concurrently managing CVD and DKD. While one cost model in patients with T2D and nephropathy based on the CREDENCE trial has been published, and EMPA-REG OUTCOME has yielded several cost-effectiveness analyses of trial participants or subgroups, this is the first study to focus specifically on the subset of EMPA-REG OUTCOME trial participants with baseline DKD.

Results of the lifetime analysis indicate that, relative to those receiving SoC alone, patients with baseline DKD for whom SoC was supplemented with empagliflozin experienced more LYs (1.27) and discounted QALYs (0.67), and accrued greater average discounted costs ($17,322/patient). The ICER was $25,974/QALY, which falls well beneath the lower range of cost-effectiveness thresholds ($50,000–$150,000/QALY) recommended by the Institute for Clinical and Economic Review. Sensitivity analyses results reinforce the base case analysis, suggesting that, for this patient subgroup, the cost-effectiveness of empagliflozin with SoC versus SoC alone is sustained for most plausible ranges of parameter values.

Analyses were performed from third-party payer (default) and healthcare sector (scenario) perspectives. The payer perspective included medical costs incurred by the payer related to inpatient management of clinical events and pharmacies, while the healthcare sector perspective also included copayments paid as out-of-pocket expenses by patients. From the perspective of healthcare reimbursement by US commercial insurers or Medicare, use of empagliflozin with SoC is cost-effective versus SoC alone, with higher pharmacy costs of empagliflozin partially offset by reduced event costs. From the perspective of the clinical care of DKD patients, using empagliflozin with SoC showed benefits in terms of reduced risks of CV and kidney events.
The model offers several advantages. First, the model utilized hard CV and kidney endpoint data from EMPA-REG OUTCOME, sidestepping methodological issues that result from relying on surrogate measures to estimate mediated treatment effects. Second, model-generated simulation results align closely with event rates and HRs observed for this subgroup in EMPA-REG OUTCOME. Third, non-CV death rates were taken from US life tables and therefore specific to the US population.

However, the model did not account for costs or utility losses attributable to adverse events (AEs) associated with empagliflozin with SoC. Clinical trials have demonstrated an overall favorable safety profile for empagliflozin, although genital mycotic infection (GMI) occurred more frequently in the empagliflozin group than the control group. Unnikrishnan and colleagues, who reviewed management strategies for GMI in patients with T2D using SGLT2i therapies, found that episodes of GMI with empagliflozin were mild to moderate, infrequent (typically one episode), and many patients were self-treated. AEs are not expected to materially affect analytical findings.

Because the model focuses on incremental differences between treatments that ultimately drive the ICER, it does not include expenditures expected to be similar across treatment regimens—costs related to regular disease management and monitoring. This is conservative in estimating the cost-effectiveness of empagliflozin with SoC, as patients using SoC alone would be expected to accrue more ongoing management costs.

The EMPA-REG OUTCOME trial was not powered to assess treatment benefits in the DKD subgroup, manifesting in non-significant differences for some events, including those with large point estimates, and variability in PSA-derived ICERs. A scenario analysis restricted to events
with statistically significant differences between treatment groups in the DKD subgroup (hospitalization for HF, revascularization, albuminuria progression, composite kidney outcome, and CV death) modestly impacted the ICER ($34,337/QALY).

The model does not include costs of SoC or allow treatment intensification over time, conservatively assuming empagliflozin does not impact SoC utilization. More EMPA-REG OUTCOME trial participants (16%) in the placebo versus empagliflozin group added therapy to their antihyperglycemic regimen after week 12. However, simulated patients using empagliflozin with SoC versus SoC alone experienced longer survival times and thus longer duration on SoC. Furthermore, US pharmaceuticals have a wide range of prices, influenced by proprietary negotiations for rebates/discounts between payers, manufacturers, and distributors that are influenced by a variety of factors. Several scenarios were run to test the uncertainty in the drug cost of the empagliflozin with SoC regimen (highest FSS price, AWP, no rebate percentage, ±20% change in the rebate, varying the co-pay), yielding ICERs from $17,440–$143,333/QALY.

Choice of model parameters in extrapolating long-term costs and QALYs past the trial follow-up may impact the cost-effectiveness of empagliflozin with SoC. To minimize uncertainty of assumptions on long-term risk estimates, the time horizon was reduced to the period covered by the clinical data (3 years) and shortly thereafter (5 and 10 years) in sensitivity analyses and the ICERs ($38,769–$113,234/QALY) remained sufficiently lower than a $150,000/QALY threshold. Implications of other parameters explored in sensitivity analyses did not change the overall conclusions of the base case analysis.

Participants in EMPA-REG OUTCOME were at relatively low risk for progression to kidney failure, suggesting results may not generalize to higher-risk patient populations.
Finally, cost-effectiveness from the commercial insurer and Medicare perspective is not the same as affordability for patients, particularly uninsured patients.

Historically, few T2D treatment options available in the US have demonstrated renoprotective qualities.\textsuperscript{45} Findings from EMPA-REG OUTCOME trial for empagliflozin, CANVAS Program and CREDENCE trial for canagliflozin, and DECLARE-TIMI 58 trial for dapagliflozin have provided consistent signals on the renoprotective properties of these SGLT2i in DKD, contributing to the American Diabetes Association’s recommendation that physicians prescribe SGLT2i to reduce risk of kidney disease progression and/or CV events in T2D patients with impaired renal functioning.\textsuperscript{46} Findings from SGLT2i clinical trials designed to evaluate outcomes in large CKD populations, focusing on cardiokidney outcomes in high-risk patient subgroups with or without T2D, have shown positive results or are still pending. The DAPA-CKD trial was stopped early after compelling evidence of efficacy in patients with CKD stages 2–4 with elevated urinary albumin excretion, with and without T2D.\textsuperscript{47} The DAPA-CKD and CREDENCE\textsuperscript{11} trials investigated a small proportion of the overall CKD population due to the trials’ inclusion criteria. The EMPA-KIDNEY trial\textsuperscript{14} will extend current knowledge by providing data of unstudied patients with low to no albuminuria. The EMPA-KIDNEY trial\textsuperscript{14} remains underway as of the time of writing, but results from this and other ongoing or planned clinical studies will inform future analyses comparing the cost-effectiveness of empagliflozin with SoC relative to SoC alone and other comparators (e.g., dapagliflozin with SoC based on the DAPA-CKD trial), among patients with or without T2D at varying levels of risk for CKD progression.

In summary, results of the health economic analyses suggest that, from the perspective of US commercial insurers and Medicare, prescribing empagliflozin with SoC to patients with DKD
rather than SoC alone may improve clinical outcomes and patient quality of life at an acceptable willingness-to-pay threshold for the healthcare system.

SUPPLEMENTARY MATERIAL

Item S1. Statistical Analyses

Table S1. Comparison of fitted models using Akaike & Bayesian Information Criteria

Figure S1. Comparison of statistical fits vs. observed data – CV death

Figure S2. Comparison of statistical fits vs. observed data – non-fatal MI

Figure S3. Comparison of statistical fits vs. observed data – non-fatal stroke

Figure S4. Comparison of statistical fits vs. observed data – hospitalization for HF

Figure S5. Comparison of statistical fits vs. observed data – hospitalization for UA

Figure S6. Comparison of statistical fits vs. observed data – revascularization

Figure S7. Comparison of statistical fits vs. observed data – transient ischemic attack

Figure S8. Comparison of statistical fits vs. observed data – progression of albuminuria

Figure S9. Comparison of statistical fits vs. observed data – composite kidney outcome

Item S2. Estimated Risk Equations

Table S2. Risk equations for cardiovascular and kidney events

Table S3. Parameters of risk equations for non-cardiovascular death

Item S3. Time to Event Estimation

Item S4. Validation of the Risk Equations

Table S4. Validation of 3-year hazard ratios for empagliflozin with SoC vs. SoC alone

Item S5. Utility Approach

Item S6. Deterministic Sensitivity Analyses (DSA)

Table S5. Deterministic sensitivity analysis results
Item S7. Probabilistic Sensitivity Analyses (PSA)

Table S6. Event rates per PY estimated in PSA

ARTICLE INFORMATION

Authors’ Contributions

Interpretation of data and results: all authors; model development, conduct of analyses, implementation of the design: OSR, ARK, SBB, MS; reviewed the final model design, data sources, and results: AU. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual’s own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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and from other companies. A.R. Kansal was employed by Evidera during the conduct of this study and creation of this article. E. Pfarr and A. Ustyugova are employed by Boehringer Ingelheim International GmbH; C. Wang and E. Kuti are employed by Boehringer Ingelheim Pharmaceuticals, Inc. A. Koitka-Weber was employed by Boehringer Ingelheim International GmbH at the time of submitting the manuscript, but she is now employed by AstraZeneca. C. Wanner has received honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly and MSD.

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Table 1. Utility Weight Summary

<table>
<thead>
<tr>
<th>Event</th>
<th>Deterministic Value (95% CI)</th>
<th>Probabilistic Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline utility</td>
<td>0.792 (0.790, 0.794)</td>
<td>Beta: $\alpha = 281,013$; $\beta = 73,802$</td>
<td>27</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>-0.029 (-0.036, -0.023)</td>
<td>Gamma: $\alpha = 76$; $\beta = 0.0004$</td>
<td>27</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>-0.037 (-0.048, -0.026)</td>
<td>Gamma: $\alpha = 43$; $\beta = 0.0009$</td>
<td>27</td>
</tr>
<tr>
<td>Hospitalization for UA</td>
<td>-0.029 (-0.036, -0.023)$^a$</td>
<td>Gamma: $\alpha = 76$; $\beta = 0.0004$</td>
<td>27</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>-0.036 (-0.047, -0.024)$^b$</td>
<td>Gamma: $\alpha = 38$; $\beta = 0.0010$</td>
<td>27</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>-0.049 (-0.088, -0.011)</td>
<td>Gamma: $\alpha = 6$; $\beta = 0.0079$</td>
<td>27</td>
</tr>
<tr>
<td>Revascularization</td>
<td>-0.030 (-0.036, -0.024)$^c$</td>
<td>Gamma: $\alpha = 96$; $\beta = 0.0003$</td>
<td>29</td>
</tr>
<tr>
<td>Progression of albuminuria</td>
<td>-0.024 (-0.040, -0.008)$^d$</td>
<td>Gamma: $\alpha = 9$; $\beta = 0.0028$</td>
<td>27</td>
</tr>
<tr>
<td>Composite kidney outcome$^e$</td>
<td>-0.047 (-0.089, -0.005)$^f$</td>
<td>Gamma: $\alpha = 5$; $\beta = 0.0099$</td>
<td>28</td>
</tr>
</tbody>
</table>

Utility adjustment for multiple events (additive to utility)

<table>
<thead>
<tr>
<th></th>
<th>Deterministic Value (95% CI)</th>
<th>Probabilistic Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 events</td>
<td>0.010 (0.002, 0.018)</td>
<td>Beta: $\alpha = 6$; $\beta = 599$</td>
<td>27</td>
</tr>
<tr>
<td>3 events</td>
<td>0.023 (0.009, 0.038)</td>
<td>Beta: $\alpha = 10$; $\beta = 419$</td>
<td>27</td>
</tr>
<tr>
<td>4 events</td>
<td>0.037 (0.016, 0.058)</td>
<td>Beta: $\alpha = 12$; $\beta = 321$</td>
<td>27</td>
</tr>
<tr>
<td>≥ 5 events</td>
<td>0.041 (0.013, 0.069)</td>
<td>Beta: $\alpha = 9$; $\beta = 200$</td>
<td>27</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HF, heart failure; MI, myocardial infarction; UA, unstable angina.

$^a$ Utility decrement assumed to be equal to that of MI.

$^b$ Utility decrement assumed to be equal to that of congestive heart failure.

$^c$ The 95% CI was assumed to be +/-20% of the base-case utility value.

$^d$ Utility decrement assumed to be equal to that of nephropathy.

$^e$ Composite kidney outcome is defined as 40% reduction in eGFR, kidney replacement therapy, or kidney death.

$^f$ Decline in utility for nephropathy (diagnosis of chronic kidney disease, dialysis, end-stage kidney disease, kidney transplant, or protein in the urine) in adults with T2D was applied. The 95% CI was calculated from reported standard deviation (0.164) and sample size (N = 58). The utility loss for the composite kidney outcome was assumed to be more than that of progression of albuminuria.
Table 2. Event Cost Summary (Expressed in 2020 USD)

<table>
<thead>
<tr>
<th>Events</th>
<th>ICD-10 Code</th>
<th>Medicare Cost</th>
<th>Commercial Cost</th>
<th>Base Case&lt;sup&gt;b&lt;/sup&gt; Cost (SE)</th>
<th>Probabilistic Distribution (Gamma)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal MI</td>
<td>I21.xx</td>
<td>$22,542</td>
<td>$24,191</td>
<td>$23,215 ($46)</td>
<td>$\alpha = 253,334; \beta = 0.0916$</td>
<td>34</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>I63.30, I63.40, I63.50, I66.09, I66.19, I66.29, I66.9</td>
<td>$13,082</td>
<td>$14,954</td>
<td>$13,846 ($147)</td>
<td>$\alpha = 8,830; \beta = 1.5682$</td>
<td>34</td>
</tr>
<tr>
<td>Hospitalization for UA</td>
<td>I20.0</td>
<td>$8,522</td>
<td>$8,167</td>
<td>$8,377 ($134)</td>
<td>$\alpha = 3,901; \beta = 2.1476$</td>
<td>34</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>I50.xx</td>
<td>$9,187</td>
<td>$12,229</td>
<td>$10,429 ($79)</td>
<td>$\alpha = 17,475; \beta = 0.5968$</td>
<td>34</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>G45.9</td>
<td>$7,675</td>
<td>$7,570</td>
<td>$7,632 ($39)</td>
<td>$\alpha = 37,819; \beta = 0.2018$</td>
<td>34</td>
</tr>
<tr>
<td>Revascularization</td>
<td>021.0xxx</td>
<td>$49,454</td>
<td>$45,104</td>
<td>$47,677 ($182)</td>
<td>$\alpha = 68,467; \beta = 0.6964$</td>
<td>34</td>
</tr>
<tr>
<td>Progression of albuminuria*</td>
<td>R80.9</td>
<td>$4,648</td>
<td>$4,553</td>
<td>$4,609 ($404)</td>
<td>$\alpha = 130; \beta = 35.4563$</td>
<td>34</td>
</tr>
<tr>
<td>Composite kidney outcome*</td>
<td>R94.4, N17.9</td>
<td>$7,840</td>
<td>$7,815</td>
<td>$7,830 ($655)</td>
<td>$\alpha = 143; \beta = 54.7526$</td>
<td>34, 36</td>
</tr>
<tr>
<td>CV death*</td>
<td>N/A</td>
<td>$40,703</td>
<td>$40,703</td>
<td>$40,703 ($465)</td>
<td>$\alpha = 7,648; \beta = 5.3221$</td>
<td>35</td>
</tr>
</tbody>
</table>

Abbreviations: CV, cardiovascular; HF, heart failure; ICD-10, International Classification of Diseases-Tenth Revision; MI, myocardial infarction; NA, not applicable; SE, standard error; UA, unstable angina; USD, United States dollars.

* Medicare cost assumed similar to commercial cost.
a Consists of a weighted average cost of 40% reduction in eGFR (85%; $7,306, assumed same for all payers), kidney replacement therapy (14%; Medicare=$9,497, commercial=$9,317, overall=$9,424), and kidney death (2%; $22,265, assumed same for all payers).

b Consists of a weighted average of inpatient Medicare and commercial costs; the weights are based on the proportion of the DKD subpopulation of the EMPA-REG OUTCOME trial that were 65 years of age and older (59.2%) or younger than 65 years (40.8%) at baseline.

Composite kidney outcome is defined as 40% reduction in eGFR, kidney replacement therapy, or kidney death.
Table 3. Cost-effectiveness Analysis Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Empagliflozin with SoC</th>
<th>SoC Alone</th>
<th>Incremental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life expectancy (undiscounted, years)</td>
<td>11.77</td>
<td>10.50</td>
<td>1.27</td>
</tr>
<tr>
<td>Lifetime QALYs (discounted)</td>
<td>7.07</td>
<td>6.41</td>
<td>0.67</td>
</tr>
<tr>
<td>Lifetime patient costs (discounted)</td>
<td>$66,274</td>
<td>$48,953</td>
<td>$17,322</td>
</tr>
<tr>
<td>Drug acquisition cost</td>
<td>$26,506</td>
<td>$0</td>
<td>$26,506</td>
</tr>
<tr>
<td>Clinical event management cost</td>
<td>$39,768</td>
<td>$48,953</td>
<td>-$9,184</td>
</tr>
<tr>
<td>ICER/QALY*</td>
<td>—</td>
<td>—</td>
<td>$25,974</td>
</tr>
</tbody>
</table>

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

* Costs and QALYs are discounted at an annual rate of 3.0%.
Table 4. Deterministic Sensitivity Analyses Results: Top 10 Scenarios

<table>
<thead>
<tr>
<th>Scenario*</th>
<th>Rank</th>
<th>Base Case Input</th>
<th>Alternative Input</th>
<th>Description</th>
<th>ICER ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>$25,974</td>
</tr>
<tr>
<td>Time Horizon: 3 Years</td>
<td>2</td>
<td>Lifetime</td>
<td>3 years</td>
<td>Applies model horizon of 3 years</td>
<td>$113,234</td>
</tr>
<tr>
<td>Time Horizon: 5 Years</td>
<td>4</td>
<td>Lifetime</td>
<td>5 years</td>
<td>Applies model horizon of 5 years</td>
<td>$68,807</td>
</tr>
<tr>
<td>Time Horizon: 10 Years</td>
<td>9</td>
<td>Lifetime</td>
<td>10 years</td>
<td>Applies model horizon of 10 years</td>
<td>$38,769</td>
</tr>
<tr>
<td>No Treatment Effect on Risk of CV Death</td>
<td>6</td>
<td>Risk of CV death using the risk equation with treatment effect applied</td>
<td>No treatment effect</td>
<td>Assume no empagliflozin treatment benefit on risk of CV death</td>
<td>$49,993</td>
</tr>
<tr>
<td>Adjust Treatment Effect on CV Death</td>
<td>3</td>
<td>Point estimate of treatment effect: -0.2261</td>
<td>Lower 95% CI: -0.5514</td>
<td>Apply the lower 95% CI of the point estimate of the treatment effect for CV death</td>
<td>$16,926</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Upper 95% CI: 0.0993</td>
<td>Apply the upper 95% CI of the point estimate of the treatment effect for CV death</td>
<td>$91,704</td>
</tr>
<tr>
<td>Scenario*</td>
<td>Rank</td>
<td>Base Case Input</td>
<td>Alternative Input</td>
<td>Description</td>
<td>ICER ($/QALY)</td>
</tr>
<tr>
<td>-------------------</td>
<td>------</td>
<td>-----------------------</td>
<td>----------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Adjust Treatment Effect on Non-fatal MI</td>
<td>7</td>
<td>Point estimate of treatment effect: -0.1695</td>
<td>Lower 95% CI: -0.5125</td>
<td>Apply the lower 95% CI of the point estimate of the treatment effect for non-fatal MI</td>
<td>$18,998</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Upper 95% CI: 0.1735</td>
<td>Apply the upper 95% CI of the point estimate of the treatment effect for non-fatal MI</td>
<td>$38,864</td>
</tr>
<tr>
<td>Adjust Treatment Effect on Hospitalization for HF</td>
<td>10</td>
<td>Point estimate of treatment effect: -0.3727</td>
<td>Lower 95% CI: -0.7451</td>
<td>Apply the lower 95% CI of the point estimate of the treatment effect for HHF</td>
<td>$21,614</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Upper 95% CI: 0.0003</td>
<td>Apply the upper 95% CI of the point estimate of the treatment effect for HHF</td>
<td>$34,332</td>
</tr>
<tr>
<td>Inclusion of manufacturer rebate</td>
<td>5</td>
<td>52%</td>
<td>0%</td>
<td>Assume no manufacturer rebate for empagliflozin</td>
<td>$68,645</td>
</tr>
<tr>
<td>% Rebate: Empagliflozin</td>
<td>8</td>
<td>52%</td>
<td>41%</td>
<td>Assume reduced (-20%) manufacturer rebate for empagliflozin</td>
<td>$34,508</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>62%</td>
<td>Assume increased (+20%) manufacturer rebate for empagliflozin</td>
<td>$17,440</td>
</tr>
<tr>
<td>Scenario*</td>
<td>Rank</td>
<td>Base Case Input</td>
<td>Alternative Input</td>
<td>Description</td>
<td>ICER ($/QALY)</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
<td>-----------------</td>
<td>-------------------</td>
<td>-------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Monthly cost to payer: Empagliflozin</td>
<td>1</td>
<td>Adjusted WAC: $239**</td>
<td>FSS Highest Net Price: $978</td>
<td>Increase monthly cost of empagliflozin using the highest price reported in the FSS</td>
<td>$143,333</td>
</tr>
</tbody>
</table>

Abbreviations: AWP, average wholesale price; CI, confidence interval; CV, cardiovascular; DKD, diabetic kidney disease; FSS, Federal Supply Schedule; HF, heart failure; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; QALY, quality-adjusted life year; SoC, standard of care; WAC, wholesale acquisition cost

* In all scenarios, both health outcomes and costs were estimated over consistent time horizons.

** The WAC was adjusted for a $35 patient copayment and 52% manufacturer rebate.
FIGURE LEGENDS

Figure 1. Diagrammatic representation of the simulation model process

Abbreviations: CV, cardiovascular; DKD, diabetic kidney disease; LY, life year; QALY, quality-adjusted life year; SoC, standard of care.

Figure 2. Simulated event rates for CV/kidney events, per 100 patient-years

Abbreviations: CV, cardiovascular; HF, heart failure; Hosp., hospitalization; MI, myocardial infarction; Prog., progression; SoC, standard of care.

Composite kidney outcome is defined as 40% reduction in eGFR (MDRD), kidney replacement therapy, or kidney death.

Figure 3. Cost-effectiveness plane scatterplot

Abbreviation: QALY, quality-adjusted life year.
Event rate per 100 Patient-Years

<table>
<thead>
<tr>
<th>CV/Kidney event</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>Empagliflozin + SoC</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>SoC</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>Empagliflozin + SoC</td>
</tr>
<tr>
<td>Hosp. for HF</td>
<td>SoC</td>
</tr>
<tr>
<td>Hosp. for UA</td>
<td>Empagliflozin + SoC</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>SoC</td>
</tr>
<tr>
<td>Revasc.</td>
<td>Empagliflozin + SoC</td>
</tr>
<tr>
<td>Prog. of albuminuria</td>
<td>SoC</td>
</tr>
<tr>
<td>Composite kidney outcome</td>
<td>Empagliflozin + SoC</td>
</tr>
<tr>
<td>Non-CV death</td>
<td>SoC</td>
</tr>
</tbody>
</table>
Generate individual simulated patients with DKD

Clone profiles and assign treatment: empagliflozin with SoC or SoC alone

Estimate time to CV/kidney events

Determine CV/kidney event experienced by simulated patient

Update clinical event history of simulated patient

Aggregate outcomes for the DKD subpopulation and compare treatments

Simulate another patient?

Yes

Update clinical event history of simulated patient

Yes

Fatal event or time horizon exhausted?

No

Simulate another patient?

No

Record cumulative clinical events, LYs, QALYs, and costs for simulated patient

Yes
Incremental Costs vs. Incremental QALY

- Not cost-effective at $150,000/QALY
- Cost-effective at $150,000/QALY