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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Rationale & Objective: Benefits of sodium-glucose cotransporter 2 inhibitors on kidney outcomes have been demonstrated in clinical trials. Among patients with type 2 diabetes and established cardiovascular (CV) disease enrolled in the EMPA-REG OUTCOME study (ClinicalTrials.gov identifier NCT01131676), empagliflozin added to standard of care (SOC) reduced the risk of incident or worsening nephropathy compared with SOC alone. This analysis evaluated the cost-effectiveness of empagliflozin versus SOC alone in the subgroup with diabetic kidney disease (DKD) from the perspective of US commercial insurers and Medicare.

Study Design: Discrete event simulation model.

Setting & Population: Patients with DKD in a US health care 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 (2020 US dollars per quality-adjusted life-year [QALY] gained). Costs and QALYs were discounted 3.0% per year.

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

Results: The incremental cost-effectiveness ratio of empagliflozin with SOC versus SOC alone was $25,974 per QALY. Empagliflozin added 0.67 QALYs and $17,322 per patient over a lifetime horizon. Results were driven by fewer clinical events (including CV death, heart failure hospitalization, albuminuria progression, and a composite kidney outcome) experienced by patients receiving empagliflozin with SOC versus SOC alone. Results were sensitive to rates of CV death, nonfatal myocardial infarction, and heart failure hospitalization, as well as to drug costs and time horizon. Probabilistic sensitivity analyses indicated 91% of simulations at <$50,000 per 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/1.73 m².

Conclusions: Based on the 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.

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

Originally developed as a glucose-lowering therapy for type 2 diabetes, sodium-glucose cotransporter 2 (SGLT2) inhibitors have demonstrated beneficial effects in kidney disease. Clinical trials of SGLT2 inhibitors including type 2 diabetes patients with relatively preserved kidney function (EMPA-REG OUTCOME [ClinicalTrials.gov identifier NCT01131676], CANVAS Program [CANVAS and CANVAS-R ClinicalTrials.gov identifier NCT01032629 and NCT01989754, respectively], and DECLARE-TIMI 58 [ClinicalTrials.gov identifier NCT01730534])10), individuals with overt DKD (CREDEENCE [ClinicalTrials.gov identifier NCT 02065791]),11 and chronic kidney disease (CKD) with or without type 2 diabetes (DAPA-CKD12 [ClinicalTrials.gov identifier NCT03036150] have demonstrated risk reductions for incident and progressive kidney and CV endpoints. The ongoing EMPA-KIDNEY trial (ClinicalTrials.gov identifier NCT03594110) will provide further evidence in patients with CKD, including those with and without type 2 diabetes.

The effects of empagliflozin (10 or 25 mg; Boehringer Ingelheim) in patients with type 2 diabetes, established CV disease (CVD), and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m² who were receiving standard of care (SOC) were demonstrated in EMPA-REG OUTCOME (N = 7,020).8 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, 0.61; 95% confidence interval [CI],...
Kidney injury is a common complication of type 2 diabetes that is 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 of 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 (DKD) at baseline in the EMPA-REG OUTCOME trial. Treatment with empagliflozin combined with standard of care for US patients with DKD may lead to health benefits and be cost-effective versus standard of care alone for commercial insurers and Medicare. These results will help guide patients, clinicians, and decision-makers in selecting a regimen for management of DKD.

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 health care 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 type 2 diabetes and CVD in the United Kingdom based on the EMPA-REG OUTCOME intent-to-treat population data. This model incorporates new risk equations and population characteristics from a subanalysis of patients with baseline DKD in EMPA-REG OUTCOME and US-specific costs and utilities.

**Methods**

**Model Overview**

A discrete-event simulation approach was used to predict CV and kidney events associated with type 2 diabetes progression and estimate the cost-effectiveness of empagliflozin with SOC versus SOC alone for the management of patients with DKD in the United States. Discrete-event simulation is less restrictive than Markovian approaches because it can track change in characteristics and patients’

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**Figure 1.** Simulation model process. Abbreviations: CV, cardiovascular; DKD, diabetic kidney disease; LY, life-year; QALY, quality-adjusted life year; SoC, standard of care.
CV/kidney history, captures interdependencies between multiple events as patients evolve with no a priori restrictions (ie, future event times depend on patient history), and uses the trial data more directly. Discrete-event simulation was used previously for cost-effectiveness analyses in type 2 diabetes and CVD.18-21

At start of the simulation (Fig 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 was 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. When 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, mean life-years, QALYs, costs, and the incremental cost-effectiveness ratio (ICER) per QALY. Analyses discounted future costs and QALYs at 3.0% annual rate.22

Baseline Patient Characteristics
The modeled population was specified using demographic characteristics, physiologic parameters (eg, baseline metabolic risk factors), and clinical event history of EMPA-REG OUTCOME participants with DKD at baseline.17 Based on EMPA-REG OUTCOME’s inclusion criteria, all patients had type 2 diabetes and atherosclerotic CVD.8 Individuals with DKD at baseline exhibited eGFR (calculated using the Modification of Diet in Renal Disease [MDRD] Study equation) <60 mL/min/1.73 m² (80.8% of patients with baseline DKD), UACR >300 mg/g (34.2% of patients), or both (15.0% of patients). The subgroup had a mean age of 66.2 ± 8.2 (standard deviation) years, body mass index of 30.8 ± 5.4 kg/m², glycated hemoglobin (hemoglobin A1c) of 8.10 ± 0.87%, and eGFR of 54.4 ± 20.4 mL/min/1.73 m², and 31% were female. Compared with patients without DKD, those with baseline DKD tended to be older and had type 2 diabetes for a longer time; they were also more likely to have multivessel coronary artery disease, a coronary artery bypass graft, or cardiac failure.

Patient characteristics were generated by sampling with replacement of 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, nonfatal myocardial infarction (MI), nonfatal stroke, hospitalization for heart failure (HF), hospitalization for unstable angina, transient ischemic attack, and revascularization. Simulated patients could also experience non-CV death. Definitions of CV events in EMPA-REG OUTCOME have been published.8 Albuminuria was measured using UACR. Participants in EMPA-REG OUTCOME were categorized as having normoalbuminuria (UACR <30 mg/g), moderate albuminuria (UACR 30-≤300 mg/g), or severe albuminuria (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 (1) from baseline normoalbuminuria to moderate or severe albuminuria or (2) from baseline moderate albuminuria to severe albuminuria. Progression of albuminuria was evaluated in 1,481 participants with normoalbuminuria or moderate albuminuria at baseline. The composite kidney outcome was a sustained ≥40% eGFR reduction, development of kidney failure with replacement therapy, or kidney death. A sustained 40% decrease in eGFR from baseline was defined as being present on at least 2 consecutive assessments more than 30 days apart. Kidney failure with replacement therapy was based on initiation of dialysis treatment for at least 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. Because 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. Nonfatal CV events were permitted to occur repeatedly, but kidney events were nonrecurrent. 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 3-year mean trial duration and validated by estimating event rates and hazard ratios 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 1 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 type 2 diabetes in the US SHIELD study. Because no US-specific utility weight for revascularization was available, non-US utility reduction data were 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 (nongovernmental agencies who provide health insurance) and Medicare. All costs are expressed in 2020 US dollars adjusted for inflation by applying the medical care 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, which was regarded as an add-on to SOC because participants in both treatment groups of EMPA-REG OUTCOME used SOC. The wholesale acquisition cost (WAC) of empagliflozin ($529.68 per month for 10 or 25mg tablets) from RED BOOK, the manufacturer’s list price to wholesalers or direct purchasers in the United States, represented the drug cost parameter following principles for economic evaluations published by the Institute for Clinical and Economic Review. 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 resells them to pharmacies for approximately the same price (based on WAC). The pharmacy sells to their customers at that price plus a markup. However, pharmacies are reimbursed differently based on the plan and rates negotiated with a payer, which are 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 copayment (based on median $10, $35, and $55 copayments for 3-tier plans) 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

### Table 1. Utility Weight Summary

| Event                        | Deterministic Value (95% CI) | Probabilistic Distribution | Source                        |
|------------------------------|-----------------------------|----------------------------|--------------------------------|
| Baseline utility             | 0.792 (0.790 to 0.794)      | Beta: $\alpha = 281,013; \beta = 73,802$ | Sullivan and Ghushchyan27     |
| Nonfatal MI                  | ~0.029 (~0.036 to ~0.023)   | Gamma: $\alpha = 76; \beta = 0.0004$ | Sullivan and Ghushchyan27     |
| Nonfatal stroke              | ~0.037 (~0.048 to ~0.026)   | Gamma: $\alpha = 43; \beta = 0.0009$ | Sullivan and Ghushchyan27     |
| Hospitalization for unstable angina | ~0.029 (~0.036 to ~0.023)  | Gamma: $\alpha = 76; \beta = 0.0004$ | Sullivan and Ghushchyan27     |
| Hospitalization for HF       | ~0.036 (~0.047 to ~0.024)   | Gamma: $\alpha = 38; \beta = 0.0010$ | Sullivan and Ghushchyan27     |
| Transient ischemic attack   | ~0.049 (~0.088 to ~0.011)   | Gamma: $\alpha = 6; \beta = 0.0079$ | Sullivan and Ghushchyan27     |
| Revascularization            | ~0.030 (~0.036 to ~0.024)   | Gamma: $\alpha = 96; \beta = 0.0003$ | Lindgren et al19              |
| Progression of albuminuria  | ~0.024 (~0.040 to ~0.008)   | Gamma: $\alpha = 9; \beta = 0.0028$ | Sullivan and Ghushchyan27     |
| Composite kidney outcome     | ~0.047 (~0.089 to ~0.005)   | Gamma: $\alpha = 5; \beta = 0.0099$ | Grandy et al19               |
| Utility adjustment for multiple events (additive to utility) |                          |                               |                                |
| 2 events                     | 0.010 (0.002 to 0.018)       | Beta: $\alpha = 6; \beta = 599$ | Sullivan and Ghushchyan27     |
| 3 events                     | 0.023 (0.009 to 0.038)       | Beta: $\alpha = 10; \beta = 419$ | Sullivan and Ghushchyan27     |
| 4 events                     | 0.037 (0.016 to 0.058)       | Beta: $\alpha = 12; \beta = 321$ | Sullivan and Ghushchyan27     |
| ≥5 events                    | 0.041 (0.013 to 0.069)       | Beta: $\alpha = 9; \beta = 200$ | Sullivan and Ghushchyan27     |

Abbreviations: HF, heart failure; MI, myocardial infarction.

aUtility decrement assumed to be equal to that of MI.

bUtility decrement assumed to be equal to that of congestive heart failure.

cThe 95% CI was assumed to be ±20% of the base-case utility value.

dUtility decrement assumed to be equal to that of nephropathy.

Composite kidney outcome is defined as 40% reduction in estimated glomerular filtration rate, kidney replacement therapy initiation, or kidney death.

Decline in utility for nephropathy (diagnosis of chronic kidney disease, kidney failure, dialysis, kidney transplant, or protein in the urine) in adults with type 2 diabetes was applied. The 95% CI was calculated from the 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.
Healthcare Cost and Utilization Project’s National Inpatient Sample (N = 35,675,421) using the International Classification of Diseases, Tenth Revision, diagnostic codes on inpatient discharges. Published literature furnished clinical event costs not available from the Healthcare Cost and Utilization Project. Because 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 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 was performed with random sampling from distributions assigned to input parameters, and risk equation coefficients varied using Cholesky decomposition (item S7).

### Table 2. Event Cost Summary

| Events                              | ICD-10 Code          | Medicare Cost  | Commercial Cost | Base Case* Cost (SE) | Probabilistic Distribution, Gamma | Source                  |
|-------------------------------------|----------------------|----------------|----------------|----------------------|-----------------------------------|-------------------------|
| Nonfatal MI                          | I21.xx               | $22,542        | $24,191        | $23,215 ($46)        | $253,334; β = 0.0916              | HCUP23                  |
| Nonfatal stroke                      | I63.30, I63.40, I63.50, I66.09, I66.19, I66.29, I66.9 | $13,082        | $14,954        | $13,846 ($147)       | $8,830; β = 1.5682                | HCUP23                  |
| Hospitalization for unstable angina  | I20.0                | $8,522         | $8,167         | $8,377 ($134)        | 3,901; β = 2.1476                 | HCUP23                  |
| Hospitalization for HF               | I50.xx               | $9,187         | $12,229        | $10,429 ($79)        | 17,475; β = 0.5968                | HCUP23                  |
| Transient ischemic attack            | G45.9                | $7,675         | $7,570         | $7,632 ($39)         | 37,819; β = 0.2018                | HCUP23                  |
| Revascularization                    | 021.0.xxx            | $49,454        | $45,104        | $47,677 ($182)       | 68,467; β = 0.6964                | HCUP23                  |
| Progression of albuminuria<sup>a</sup> | R80.9               | $4,648         | $4,553         | $4,609 ($404)        | 130; β = 35,4563                  | HCUP23                  |
| Composite kidney outcome<sup>b,c</sup> | R94.4, N17.9         | $7,840         | $7,815         | $7,830 ($655)        | 143; β = 54,7526                  | HCUP23, Saran et al<sup>36</sup> |
| CV death<sup>b</sup>                | NA                   | $40,703        | $40,703        | $40,703 ($465)       | 7,648; β = 5,3221                 | Shetty et al<sup>35</sup> |

Costs expressed in 2020 US dollars. Abbreviations: CV, cardiovascular; HCUP, Healthcare Cost and Utilization Project; HF, heart failure; ICD-10, International Classification of Diseases, Tenth Revision; MI, myocardial infarction; NA, not applicable; SE, standard error.

<sup>a</sup>Consists of a weighted average of inpatient Medicare and commercial costs; the weights are based on the proportion of the diabetic kidney disease subpopulation of the EMPA-REG OUTCOME trial that were aged ≥65 years (59.2%) or <65 years (40.8%) at baseline.

<sup>b</sup>Medicare cost assumed similar to commercial cost.

<sup>c</sup>Consists of a weighted average cost of 40% reduction in estimated glomerular filtration rate (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).

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**Figure 2.** Simulated event rates for cardiovascular (CV)/kidney events per 100 patient-years. Abbreviations: HF, heart failure; Hosp., hospitalization; MI, myocardial infarction; Prog., progression; SoC, standard of care. Composite kidney outcome is defined as 40% reduction in estimated glomerular filtration rate (using the Modification of Diet in Renal Disease Study equation), kidney replacement therapy, or kidney death.
Table 3. Cost-Effectiveness Analysis Results

| Outcome                          | Empagliflozin With SOC | SOC Alone | Incremental |
|----------------------------------|------------------------|-----------|-------------|
| Life expectancy (undiscounted), y| 11.77                  | 10.50     | 1.27        |
| Lifetime QALYs (discounted)      | 7.07                   | 6.41      | 0.67        |
| Lifetime patient costs (discounted) | $66,274             | $48,953   | $17,322     |
| Drug acquisition cost            | $26,506                | $0        | $26,506     |
| Clinical event management cost   | $39,768                | $48,953   | $-9,184     |
| ICER/QALY*                       | –                      | –         | $25,974     |

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%.

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, nonfatal MI, nonfatal stroke, and transient ischemic attack, but a similar rate of hospitalization for unstable angina (Fig 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. Because 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 as a result of 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 life-years 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 per patient in additional average lifetime discounted costs for US commercial insurers and Medicare. The resultant ICER was $25,974 per QALY.

Sensitivity Analyses

Results of the deterministic sensitivity analysis top 10 drivers are presented in Table 4. The strongest drivers were the highest net empagliflozin price in the Federal Supply Schedule, short time horizons (3, 5, and 10 years), CV death, nonfatal 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 to $143,333 per QALY. Results were relatively insensitive to changes in other parameters (Item S6). Varying model parameters through deterministic sensitivity analysis did not affect conclusions about the cost-effectiveness of empagliflozin with SOC versus SOC alone, considering a $150,000-per-QALY cost-effectiveness threshold.

Results of the probabilistic sensitivity analysis generated a mean ICER of $29,750 (95% CI, $13,410-$88,301) per QALY. The probabilistic sensitivity analysis produced relatively broad 95% CIs around mean event rates for empagliflozin with SOC and SOC alone, which was expected given that the EMPA-REG OUTCOME trial (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 ICERS that do not exceed $50,000 per QALY and $150,000 per QALY were 90.9% and 99.8%, respectively. These results (Fig 3) indicate that QALYs and costs are typically higher with empagliflozin with SOC than with SOC alone (reflecting 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 patients with type 2 diabetes concurrently managing CVD and DKD. Although one cost model in patients with type 2 diabetes 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, to our knowledge, 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 life-years (1.27) and discounted QALYs (0.67) and accrued greater average discounted costs.
Table 4. Deterministic Sensitivity Analyses Results: Top 10 Scenarios

| Scenario| Rank | Base Case Input | Alternative Input | Description | ICER/QALY |
|---------|------|-----------------|-------------------|-------------|------------|
| Base case | -    | -               | -                 | -           | $25,974     |
| Time horizon |      |                 |                   |             |            |
| 3 y Lifetime | 2    | 3 y             | Applies model horizon of 3 y | $113,234    |
| 5 y Lifetime | 4    | 5 y             | Applies model horizon of 5 y | $68,807     |
| 10 y Lifetime | 9    | 10 y            | Applies model horizon of 10 y | $38,769     |
| No treatment effect on risk of CV death | 6    | Risk of CV death using risk equation with treatment effect applied | No treatment effect | $49,993     |
| Adjust treatment effect on CV death | 3    | Point estimate of treatment effect, –0.2261 | Lower 95% CI, –0.5514 | Apply lower 95% CI of point estimate of treatment effect for CV death | $16,926     |
|                 |      |                 | Upper 95% CI, 0.0993 | Apply upper 95% CI of point estimate of treatment effect for CV death | $91,704     |
| Adjust treatment effect on nonfatal MI | 7    | Point estimate of treatment effect, –0.1695 | Lower 95% CI, –0.5125 | Apply lower 95% CI of point estimate of treatment effect for nonfatal MI | $18,998     |
|                 |      |                 | Upper 95% CI, 0.1735 | Apply upper 95% CI of point estimate of treatment effect for nonfatal MI | $38,864     |
| Adjust treatment effect on hospitalization for HF | 10   | Point estimate of treatment effect, –0.3727 | Lower 95% CI, –0.7451 | Apply lower 95% CI of point estimate of treatment effect for hospitalization for HF | $21,614     |
|                 |      |                 | Upper 95% CI, –0.0003 | Apply upper 95% CI of point estimate of treatment effect for hospitalization for HF | $34,332     |
| Inclusion of manufacturer rebate | 5    | 52%             | 0%                | Assume no manufacturer rebate for empagliflozin | $68,645     |
| % Rebate: empagliflozin | 8    | 52%             | 41%               | Assume reduced (~20%) manufacturer rebate for empagliflozin | $34,508     |
|                 |      |                 | 62%               | Assume increased (+20%) manufacturer rebate for empagliflozin | $17,440     |
| Monthly cost to payer: empagliflozin | 1    | Adjusted WAC: $239 | FSS highest net price: $978 | Increase monthly cost of empagliflozin using highest price reported in FSS | $143,333   |

Abbreviations: AWP, average wholesale price; CV, cardiovascular; FSS, Federal Supply Schedule; HF, heart failure; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; QALY, quality-adjusted life-year; WAC, wholesale acquisition cost.

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

*WAC was adjusted for a $35 patient copayment and 52% manufacturer rebate.
The ICER was $25,974 per QALY, which is far below the lower range of cost-effectiveness thresholds ($50,000–$150,000 per 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 health care sector (scenario) perspectives. The payer perspective included medical costs incurred by the payer related to inpatient management of clinical events and pharmacies, whereas the health care sector perspective also included copayments paid as out-of-pocket expenses by patients. From the perspective of health care 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 patients with DKD, using empagliflozin with SOC showed benefits in terms of reduced risks of CV and kidney events.

The model offers several advantages. First, the model used hard CV and kidney end point data from EMPA-REG OUTCOME, sidestepping methodologic issues that result from relying on surrogate measures to estimate mediated treatment effects. Second, model-generated simulation results align closely with event rates and hazard ratios observed for this subgroup in EMPA-REG OUTCOME. Third, non-CV death rates were taken from US life tables and are therefore specific to the US population.

However, the model did not account for costs or utility losses attributable to adverse events associated with empagliflozin with SOC. Clinical trials have demonstrated an overall favorable safety profile for empagliflozin, although genital mycotic infection occurred more frequently in the empagliflozin group than in the control group. Unnikrishnan et al, who reviewed management strategies for genital mycotic infection in patients with type 2 diabetes using SGLT2 inhibitor therapies, found that episodes of genital mycotic infection with empagliflozin were mild to moderate and infrequent (typically 1 episode) and that many patients were self-treated. Adverse events 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, that is, 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 nonsignificant differences for some events, including those with large point estimates, and variability in probabilistic sensitivity analysis–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 per QALY).

The model does not include costs of SOC or allow treatment intensification over time, conservatively assuming that empagliflozin does not impact SOC use. More EMPA-REG OUTCOME trial participants (16%) in the placebo group versus the 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 durations receiving SOC. Furthermore, US pharmaceutical agents have a wide range of prices, which are 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 Federal Supply Schedule price, AWP, no rebate percentage, +20% change in rebate, varying the copayment), yielding ICERS from $17,440 to $143,333 per 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 per QALY) remained sufficiently lower than a $150,000-per-QALY threshold. Implications of other parameters explored in sensitivity analyses did not change the overall conclusions of the base case analysis.

In addition, participants in EMPA-REG OUTCOME were at relatively low risk for progression to kidney failure, suggesting that the 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 type 2 diabetes treatment options available in the United States have demonstrated renoprotective qualities. Findings from the 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 SGLT2 inhibitors in DKD, contributing to the American Diabetes Association’s recommendation that physicians prescribe SGLT2 inhibitors to reduce risk of kidney disease progression and/or CV events in patients with type 2 diabetes with decreased kidney function. Findings from SGLT2 inhibitor clinical trials designed to evaluate outcomes in large CKD populations focusing on cardiac and kidney outcomes in high-risk patient subgroups with or without type 2 diabetes have shown positive results or are still pending. The DAPA-CKD trial was stopped early after producing compelling evidence of efficacy in patients with CKD stages 2–4 with increased urinary albumin excretion with and without type 2 diabetes.

The DAPA-CKD and CREDENCE trials investigated a small proportion of the overall CKD population as a result of the trials’ inclusion criteria. The EMPA-KIDNEY trial will extend current knowledge by providing data of unstudied patients with low to no albuminuria. The EMPA-KIDNEY trial remains under way 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 (eg, dapagliflozin with SOC based on the DAPA-CKD trial) among patients with or without type 2 diabetes at varying levels of risk for CKD progression.

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

Supplementary Material

Supplementary File (PDF).

Item S1: Statistical analyses.

Item S2: Estimated risk equations.

Item S3: Time to event estimation.

Item S4: Validation of the risk equations.

Item S5: Utility approach.

Item S6: Deterministic sensitivity analyses.

Item S7: Probabilistic sensitivity analyses.

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