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Cost-effectiveness of empagliflozin versus canagliflozin, dapagliflozin, or standard of care in patients with type 2 diabetes and established cardiovascular disease

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ABSTRACT

Introduction Empagliflozin, a sodium-glucose co-transporter-2 (SGLT-2) inhibitor, is approved in the USA to reduce risk of cardiovascular (CV) death in adults with type 2 diabetes mellitus (T2DM) and established CV disease, based on EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial results. Empagliflozin reduced major adverse CV event (MACE) by 14%, CV death by 38%, and hospitalization for heart failure (HHF) by 35% vs placebo, each on top of standard of care (SoC). SGLT-2 inhibitors canagliflozin and dapagliflozin have also been compared with placebo, all on top of SoC, in CV outcome trials. In the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program, canagliflozin reduced MACE by 14% and HHF by 33%. Dapagliflozin reduced HHF by 27% in the DECLARE-TIMI 58 trial (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events). This analysis estimated the cost-effectiveness of empagliflozin versus canagliflozin, dapagliflozin, or SoC, in US adults with T2DM and established CV disease.

Research design and methods Individual patient-level discrete-event simulation was conducted to predict time-to-event for CV and renal outcomes, and specific adverse events over patients' lifetimes. Occurrence of events in EMPA-REG OUTCOME was estimated based on event-free survival curves with time-dependent covariates. An HR for canagliflozin or dapagliflozin versus empagliflozin on each clinical event was estimated from published CANVAS, DECLARE-TIMI 58, and EMPA-REG OUTCOME data using indirect treatment comparison. Public sources provided US costs and utilities.

Results The model predicted longer survival for empagliflozin versus canagliflozin, dapagliflozin, and SoC mainly due to direct reduction in CV death. Empagliflozin dominated canagliflozin, yielding more quality-adjusted life years (QALYs; 0.38) at a lower cost (–US$306). Compared with dapagliflozin and SoC, empagliflozin yielded 0.50 and 0.84 incremental QALYs at US$1517 and US$27 539 incremental costs, yielding incremental cost-effectiveness ratios of US$3054/QALY and US$32 848/QALY, respectively.

Conclusions Empagliflozin was projected to dominate canagliflozin and be highly cost-effective compared with dapagliflozin and SoC using US healthcare costs.

Significance of this study

What is already known about this subject?

- The sodium glucose co-transporter-2 inhibitor (SGLT-2) empagliflozin is Food and Drug Administration (FDA) approved to reduce the risk of cardiovascular (CV) death in adults with type 2 diabetes mellitus (T2DM) and established CV disease (CVD) based on the EMPA-REG OUTCOME trial, which showed a significant reduction in the major adverse CV event (3-point MACE: a composite of CV death, non-fatal myocardial infarction, non-fatal stroke), CV death, and hospitalization for heart failure (HHF) for empagliflozin versus placebo, each in addition to standard of care (SoC).
- SGLT-2 therapies canagliflozin and dapagliflozin have FDA approval for different CV indications—canagliflozin to reduce the risk of MACE in patients with T2DM and established CVD based on results from the CANVAS Program, and dapagliflozin to reduce the risk of HHF in patients with T2DM and established CVD or multiple CV risk factors based on results from the DECLARE-TIMI 58 trial.

What are the new findings?

- Based on a lifetime cost-effectiveness analysis of empagliflozin plus SoC compared with canagliflozin plus SoC, dapagliflozin plus SoC, or SoC alone, in adults with T2DM and established CVD, empagliflozin plus SoC was projected to dominate canagliflozin plus SoC (ie, cost less and have greater quality-adjusted life years) and be a highly cost-effective therapy compared with dapagliflozin plus SoC and SoC alone.
- Results were driven by the reduction in CV death with empagliflozin and were robust to variation in most parameters in sensitivity analyses.

INTRODUCTION

The high costs of type 2 diabetes mellitus (T2DM) in the USA are exacerbated by elevated risks of vascular complications in

Significance of this study

How might these results change the focus of research or clinical practice?

- The potential of empagliflozin to have a positive health benefit for patients at cost savings to third-party payers in the US healthcare system should be considered by decision makers who determine whether interventions are implemented in clinical practice.

patients with T2DM, such as myocardial infarction (MI) and hospitalization for heart failure (HHF). One US study attributed between 48% and 64% of the lifetime direct medical cost of T2DM to complications, primarily cardiovascular (CV) disease and nephropathy.[1] Another study estimated a national cost of T2DM of US$327 billion, including US$69 billion in increased use of inpatient services and US$71 billion in medication excluding therapies for T2DM.[2] Accordingly, T2DM management focuses on reducing complication risks to increase patients' life expectancy and improve quality of life.[3] Although excess risks of complications and premature death in patients with versus without diabetes has been known for years,[4] until recently there have been gaps in our understanding of the CV impact of glucose-lowering therapies.[5]

Several randomised controlled cardiovascular outcome trials (CVOTs) of glucose-lowering drugs have been completed recently. CVOTs that evaluated dipeptidyl peptidase-4 inhibitors,[6–9] alpha-glucosidase inhibitors,[10] and insulin analogues[11] yielded neutral findings. In CVOTs of glucagon-like peptide-1 receptor agonists, liraglutide[12] and semaglutide[13] showed improvements versus placebo in a composite major adverse CV event (MACE) outcome. Two sodium-glucose co-transporter-2 (SGLT-2) inhibitors, empagliflozin[14] and canagliflozin,[15] demonstrated an improvement in both MACE and HHF versus placebo in CVOTs. Another SGLT-2 inhibitor, dapagliflozin, demonstrated a reduction in HHF versus placebo.[16] Among adults with T2DM and chronic kidney disease, canagliflozin showed CV and renal benefits compared with placebo.[17]

Empagliflozin (10 or 25 mg once daily) was the first glucose-lowering therapy indicated to reduce the risk of CV death in adults with T2DM and established CV disease (CVD) to be approved by the US Food and Drug Administration (FDA), based on significant reduction in CV outcomes in EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients).[18] In this CVOT, patients received empagliflozin or placebo in addition to standard of care (SoC) therapy according to local treatment guidelines.[14] The SoC in patients with T2DM and established CVD includes multiple drugs for glycemic control and CV risk management taken alone or in combination. Empagliflozin plus SoC significantly reduced the composite outcome of 3-point MACE (CV death, non-fatal MI, and non-fatal stroke; HR 0.86, 95% CI 0.74 to 0.99), with a 38% reduction in CV death (HR 0.62, 95% CI 0.49 to 0.77) versus placebo plus SoC in the EMPA-REG OUTCOME trial.[14] Moreover, a risk reduction in HHF of 35% (HR 0.65, 95% CI 0.50 to 0.85) for patients receiving empagliflozin versus placebo was also reported.[14] The overall benefit-risk profile of empagliflozin in patients with T2DM and established CVD is favourable, although there is a somewhat higher incidence of genital mycotic infection (GMI) in the empagliflozin group (6.4%) compared with the placebo group (1.8%). Canagliflozin (100 or 300 mg once daily) is FDA-approved to reduce the risk of MACE in adults with T2DM and established CVD.[19] The CANVAS (Canagliflozin Cardiovascular Assessment Study) trial of canagliflozin plus SoC[15] has shown a 14% reduction in composite 3-point MACE (HR 0.86, 95% CI 0.75 to 0.97) and a 33% reduction in HHF (HR 0.67, 95% CI 0.52 to 0.87) compared with placebo plus SoC, although no significant reduction was seen in CV death (HR 0.87, 95% CI 0.72 to 1.06) and results showed an increased risk of bone fracture (HR 1.26, 95% CI 1.04 to 1.52) and lower-limb amputation (LLA; HR 1.97, 95% CI 1.41 to 2.75). Dapagliflozin (10 mg once daily) is FDA-approved to reduce the risk of HHF in adults with T2DM and either established CVD or multiple CV risk factors.[20] The DECLARE-TIMI 58 trial (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events) of dapagliflozin plus SoC[16] showed a 27% reduction in HHF (HR 0.73, 95% CI 0.61 to 0.88) compared with placebo plus SoC, but no significant reduction in MACE (HR 0.93, 95% CI 0.84 to 1.03) or CV death (HR 0.98, 95% CI 0.82 to 1.17). Results of safety analyses showed lower risk versus placebo plus SoC in major hypoglycemic event (HR 0.68, 95% CI 0.49 to 0.95) and acute kidney injury (AKI; HR 0.69, 95% CI 0.55 to 0.87), but an increase in risk of GMI (HR 8.36, 95% CI 4.19 to 16.68).

Quantifying health benefits and net costs is important in understanding the full economic impact of a therapy, which can inform medical decision making and healthcare policy. Differences in clinical outcomes with empagliflozin 10 or 25 mg once daily plus SoC (empagliflozin), canagliflozin 100 or 300 mg once daily plus SoC (canagliflozin), dapagliflozin 10 mg once daily plus SoC (dapagliflozin), or SoC alone (SoC) may impact patients' life expectancy, quality of life (QoL), and medical costs; thus, comparative analyses are important. The purpose of this study was to compare the cost-effectiveness of empagliflozin versus canagliflozin, versus dapagliflozin, or versus SoC for the treatment of patients with T2DM and established CVD from the perspective of the third-party payer in the US healthcare system.

METHODS

Model approach and description

An individual patient-level discrete-event simulation model was developed in Microsoft Excel to track patients' risk of CV and renal events and adverse events (AEs) over

their lifetimes when treated with empagliflozin, canagliflozin, dapagliflozin or SoC (figure 1). This approach was chosen based on a systematic literature review of approaches in modelling hard end points from clinical trials.[21] Multiple events for each patient can be captured, with the risk of events changing over time dependent on the type of events previously experienced by the patient and their clinical characteristics (eg, age, hemoglobin A1c (HbA1c)).

The simulation began by generating a cohort of patients with T2DM and established CVD. Patients were duplicated and assigned to each therapy arm. Based on patients' CV risk profiles, the model simulated nine possible CV or renal events that corresponded to end points in EMPA-REG OUTCOME and published data from CANVAS and DECLARE-TIMI 58: CV death, non-fatal MI, non-fatal stroke (the primary outcome in EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58 was a composite of these three events), HHF, progression of albuminuria (a primary outcome in CANVAS-R), a composite renal outcome (defined as a 40% reduction in estimated glomerular filtration rate, renal replacement therapy, or renal death), hospitalization for unstable angina (UA), transient ischemic attack (TIA), and revascularization (online supplemental table OS1).[14 15] Recurrent non-fatal CV events were permitted in the model (eg, a simulated patient may experience more than one non-fatal MI), but renal events were considered non-recurring. Selected AEs in the model were GMI, AKI, LLA, bone fracture, and major hypoglycemic event.

For each simulated patient, the time-to-event for CV, renal events, and AEs were estimated. Then the model compared the timing of all events, and the earliest time determined which event happened first. When any non-fatal event occurred, the patient remained in the model and their treatment history, risk of future events, and time to next event were updated. The model process repeated to identify the next event. Non-fatal events could recur and influence the patient's risk (or experience) of future events. If a fatal event occurred or the end of the time horizon was reached, the simulation of the patient ended, and the model moved to the next patient. For each patient, cumulative events per 100 patients-years (PYs), cumulative costs of management, life years, and quality-adjusted life years (QALYs) were tracked. Once all patients had been simulated on all treatments, the individual patient outcomes were aggregated to compute the mean population outcomes.

Population baseline characteristics

Individual patient profiles were created (see online supplemental file 1) based on the EMPA-REG OUTCOME trial population baseline characteristics previously published.[14] Each sampled profile was duplicated, and identical copies were simulated for empagliflozin and each comparator (canagliflozin, dapagliflozin, and SoC) so that treatment comparisons captured observed incremental treatment effects, and were not influenced by differences in patient characteristics.

Risk equations

Time-dependent parametric survival analyses of the EMPA-REG OUTCOME trial data were conducted to characterise CV and renal event rates over time under SoC and empagliflozin. An individual patient-level risk equation was developed for each CV and renal event in the model using a systematic two-stage analysis. First, event-free survival (EFS) curves were fit to the trial data to describe the population-level occurrence of each CV and renal event. Second, individual patient-level estimates of risk were generated by testing baseline and time-dependent patient characteristics as potential predictors of the outcomes in parametric proportional-hazards regression analyses. Details on statistical analyses and risk

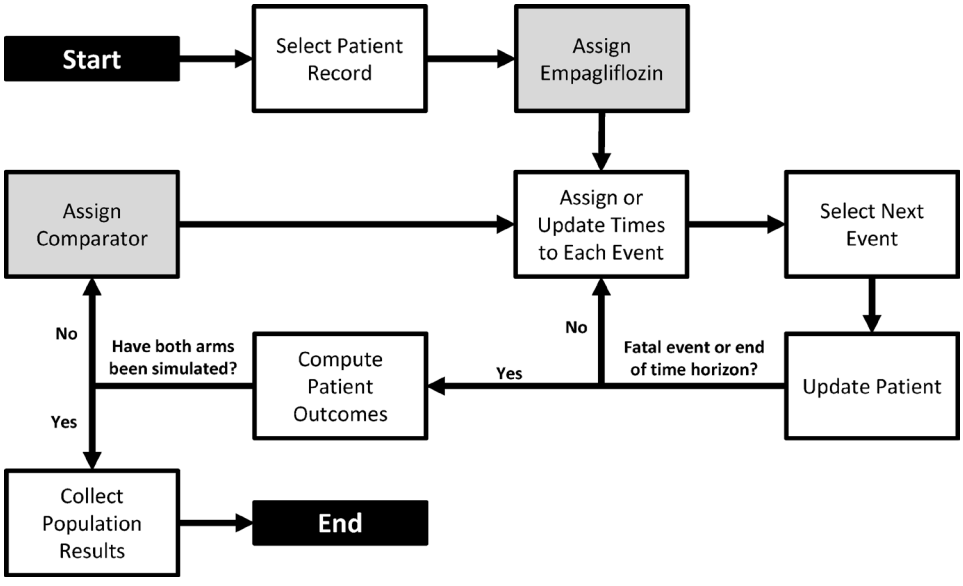

Figure 1 Diagram of the simulation model process.

equations included in the economic model are provided in online supplemental table OS2. To validate that the derived risk equations reproduced the overall event rates in the EMPA-REG OUTCOME trial when treated as competing events, the model was run for a 3-year time horizon to match the mean trial follow-up duration. Predicted 3-year HRs for empagliflozin versus SoC were congruent with the trial data (online supplemental table OS3).

US life table data were used to predict risk of non-cardiac death in simulated patients. An exponential-shaped EFS curve was assumed to estimate risk of AEs from published data.

Relative treatment effects

Head-to-head trial data were not available, thus treatment effects of SGLT2 inhibitors against the common placebo comparator were used to derive indirect estimates of the relative effect of canagliflozin versus empagliflozin and dapagliflozin versus empagliflozin using the indirect treatment comparison (ITC) method previously described by Bucher *et al*.[22]

The publications for EMPA-REG OUTCOME,[14] CANVAS Program,[15] and DECLARE-TIMI 58[16] were used for the ITC. Outcomes from the CREDENCE trial (canagliflozin) were not used for comparison due to population differences.[17] A standard process was followed to assess whether an ITC was feasible in terms of CV and renal outcomes (details in online supplemental file 1).

The feasibility analysis concluded the control arms could serve as the common comparator. In all CVOTs, use of SoC therapies was encouraged in line with local treatment guidelines, and not restricted to a specific type of SoC. Some differences were identified across the CVOTs with regard to inclusion criteria, baseline demographic and clinical characteristics, concomitant CV medications, history of CVD and outcome definitions (online supplemental table OS4 and table OS5). Mean age, percentage female, and most clinical characteristics (eg, HbA1c, BMI, SBP) were homogeneous across the CVOTs. There was heterogeneity across the CVOTs with respect to renal function, particularly between the EMPA-REG OUTCOME and DECLARE-TIMI 58 trials. Clinical history (prior PAD, MI, stroke, HF) was not consistently reported and showed some heterogeneity across the trials. Concomitant CV medications were generally similar between EMPA-REG OUTCOME and the CANVAS Program; some differences between EMPA-REG OUTCOME and DECLARE-TIMI 58 were observed in baseline treatment with beta-blockers and lipid-lowering therapy. The proportion of patients with established CVD at baseline varied from 100% in EMPA-REG OUTCOME, 65.6% in the CANVAS Program, and 40.6% in DECLARE-TIMI 58. Published subpopulation data were available from the CANVAS Program[23] and DECLARE-TIMI 58 trial[16] for patients with established CVD at baseline. Thus, it was possible to reduce the heterogeneity between the EMPA-REG OUTCOME trial and the CANVAS Program and DECLARE-TIMI 58 trial populations by using this subpopulation data for patients with baseline CVD to inform the ITC. Intent-to-treat (ITT) population data were used to derive relative efficacy parameters for scenario analyses. The definitions of clinical events were not identical, but the differences were modest and considered not to preclude the feasibility of an ITC.

HRs with 95% CIs for canagliflozin versus empagliflozin and dapagliflozin versus empagliflozin are shown in figure 2A,B, respectively. The survival functions for each of the CV and renal events were used to estimate risk of clinical events for empagliflozin, and this risk was adjusted for canagliflozin and dapagliflozin using the HRs. The AE rates for empagliflozin were similarly adjusted.

Quality of life

Published health utility scores were obtained from studies of patients with T2DM.[24–26] Health-related utilities were computed by applying permanent event disutilities to a baseline utility value (online supplemental table OS6). As patients accumulated multiple clinical events, the total combined utility decrement was adjusted based on the number of events experienced to account for overlapping effects.[26] QALYs consisted of the number of life years (ie, length of survival from model initiation to death or until the time horizon expires) weighted by the utility score associated with each of those years.

Costs and perspective

Direct costs were accrued in 2020 US$ (online supplemental table OS7). The model simulated commercially insured and Medicare populations separately and overall.

Treatment costs were based on published[27] wholesale acquisition costs (WAC) of empagliflozin, canagliflozin, and dapagliflozin. Costs to the health plan were computed net of a US$35 patient co-pay[28] and rebate (assumed to be 50% in commercially insured patients, 53% in Medicare patients, or 51% overall weighted based on patients in EMPA-REG OUTCOME). Pharmacy costs for SoC therapies and all other regular disease management and monitoring costs were assumed to be the same across regimens and were therefore not included in the model.

Acute costs of care for each clinical event were identified for commercial[29–32] and Medicare[31–33] payers and inflated to 2020 prices using the medical component of the US consumer price index.[29 31 32 34] For each event, the model used an average of the commercial and Medicare costs, weighted by the per cent of patients below age 65 years at baseline. Non-CV death events were assumed to incur no costs.

Model assumptions

A few key additional modeling assumptions were made. First, changes in the risk of clinical events due to changes in treatment were implicitly captured in event

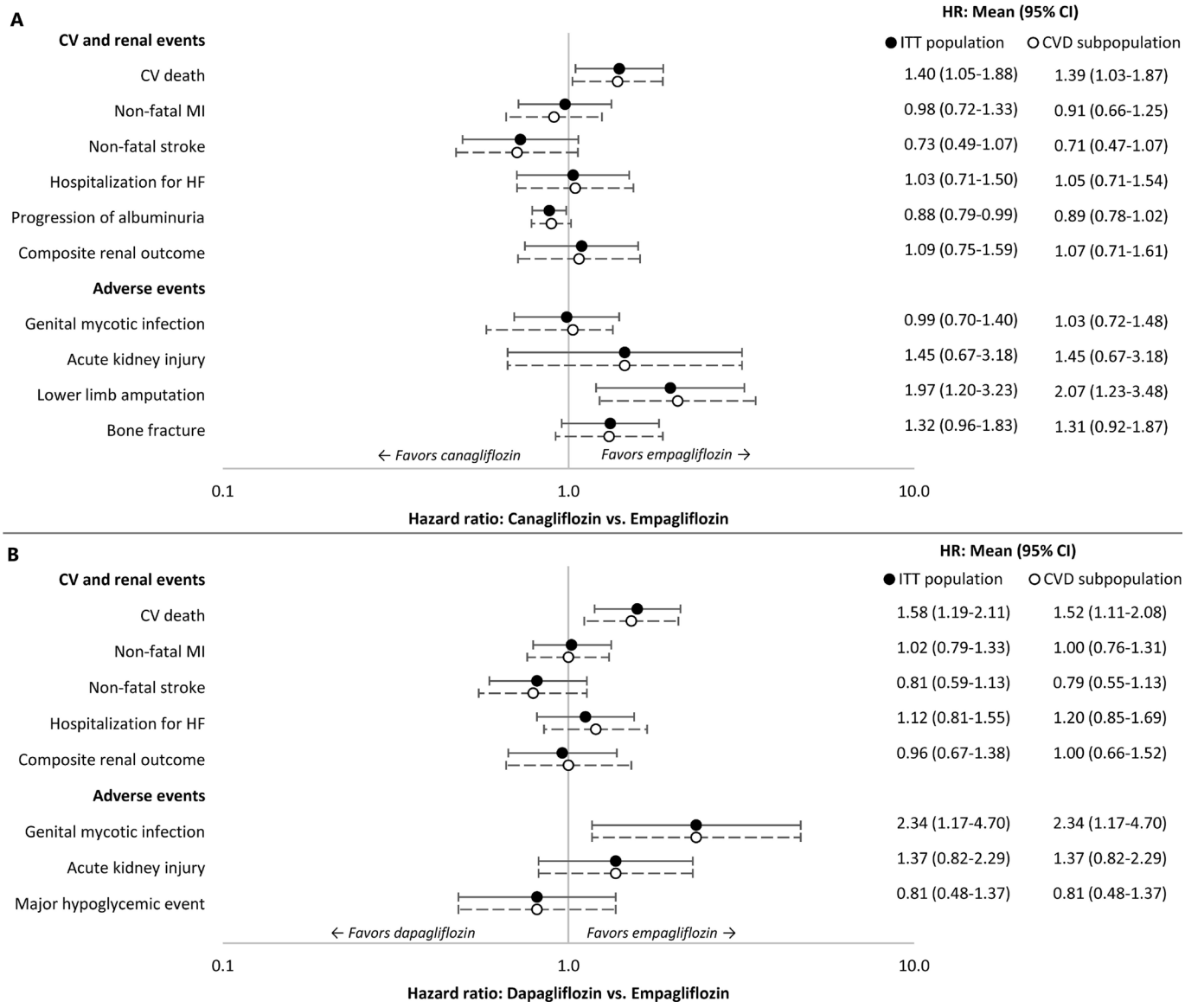

Figure 2 HRs of event rates for sodium-glucose co-transporter-2 therapies versus empagliflozin. (A) canagliflozin versus empagliflozin, (B) dapagliflozin versus empagliflozin. Studies included in the indirect treatment comparison: EMPA-REG OUTCOME, CANVAS Program, and DECLARE-TIMI 58. CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; ITT, intent-to-treat; MI, myocardial infarction.

rate trajectories. The statistical analyses of EMPA-REG OUTCOME data quantified associations among time-dependent risk factors. Event histories were predictors across other events, creating coupled, time-dependent risk equations (ie, as events accumulate, they can alter the risk of future events). Second, regardless of changes in event or treatment history, a constant treatment effect was assumed for each event. Proportional-hazards models assumed that the effect of the covariates on the hazard rate was the same at all times. Third, unmodeled comorbidities were assumed to not significantly influence the shapes of the statistical extrapolations or the role of specific risk predictors. The role of any baseline confounders not influenced by empagliflozin was minimized by the trial randomization process, which insured balance between treatment arms.

Model analyses

In the base case, a lifetime horizon was selected to fully capture costs and QoL associated with each treatment. Future costs and QALYs were discounted at a 3.0% annual rate. Relative clinical effects of canagliflozin and dapagliflozin versus empagliflozin for patients with baseline CVD in the CANVAS Program and DECLARE-TIMI 58 trial, respectively, were used. The analysis for empagliflozin versus canagliflozin excluded hospitalization for UA, TIA, and revascularization, because these were not published outcomes of the CANVAS Program, but included GMI, AKI, LLA, and bone fracture AEs. For empagliflozin versus dapagliflozin, the analysis excluded hospitalization for UA, TIA, revascularization, and progression of albuminuria, as these were not published outcomes in DECLARE-TIMI 58, but included GMI, AKI,

and major hypoglycemic event AEs. All nine CV and renal events from EMPA-REG OUTCOME were included in the empagliflozin versus SoC analysis, plus GMI and AKI AEs. EMPA-REG OUTCOME data indicated that GMI and AKI occurred at significantly different rates (p<0.05) between treatment arms.

Deterministic sensitivity analyses were conducted to evaluate the robustness of the model inputs and assumptions. The model varied discount rates, empagliflozin treatment effect, and relative efficacy of comparators (notably, comparator HRs vs empagliflozin using their 95% CIs and ITT population data), utilities, and costs. A probabilistic sensitivity analysis was performed using distributions reflecting parameter uncertainties (online supplemental table OS8).[35] Risk equation coefficients derived from EMPA-REG OUTCOME were varied using Cholesky decomposition, and the comparator HRs versus empagliflozin derived from ITCs were varied over their 95% CIs using a lognormal distribution. The model produced 1000 pairs of incremental effectiveness and cost estimates. Scenario analyses assessed the impact of shorter time horizons (1, 3, 5, and 10 years).

RESULTS

Base-case analysis

Patients receiving empagliflozin were predicted to survive longer due to lower rates of CV death versus canagliflozin (incremental −0.56 events/100 PY), dapagliflozin (incremental −0.58 events/100 PY), and SoC (incremental −1.29 events/100 PY) (table 1; see additional details in online supplemental table OS9). When compared with canagliflozin, empagliflozin had lower rates of progression of albuminuria, LLA, AKI, and bone fracture; similar rates of HHF, composite renal outcome, and GMI but higher rates of non-fatal MI and non-fatal stroke. When compared with dapagliflozin, empagliflozin had lower rates of GMI and AKI; similar rates of non-fatal MI, HHF, and composite renal outcome but higher rates of non-fatal stroke. Relative to SoC, empagliflozin had lower

Table 1 Simulation model base case incremental results over a lifetime horizon

	Empagliflozin versus canagliflozin	Empagliflozin versus dapagliflozin	Empagliflozin versus SoC
CV and renal event rates per 100 PYs			
CV death	−0.56	−0.58	−1.29
Non-fatal MI	0.21	0.03	−0.33
Non-fatal stroke	0.38	0.24	0.24
Hospitalization for HF	0.05	−0.08	−1.02
Progression of albuminuria	−0.16	–	−0.86
Composite renal outcome	−0.02	0.02	−0.64
Hospitalization for UA	–	–	0.04
Transient ischemic attack	–	–	−0.04
Revascularization	–	–	−0.20
Non-CV death	0.14	0.18	0.32
AE rates per 100 PYs			
Genital mycotic infection	−0.06	−1.47	1.16
Acute kidney injury	−0.14	−0.11	−0.23
Lower limb amputation	−0.55	–	–
Bone fracture	−0.29	–	–
Major hypoglycemic event	–	0.08	–
Undiscounted life expectancy (years)	0.80	1.09	1.77
Discounted QALY	0.38	0.50	0.84
Discounted costs over patients' lifetime			
Drug acquisition cost, US$	1675	2917	31 539
CV/renal event management cost, US$	13	−1558	−4.070
AE management cost, US$	−1994	157	70
Total cost, US$	−306	1517	27 539
ICER, US$/LY	Dominates	1398	15 524
ICER, US$/QALY	Dominates	3054	32 848

AE, adverse event; CV, cardiovascular; HF, heart failure; ICER, incremental cost-effectiveness ratio; LY, life year; MI, myocardial infarction; PY, patient-year; QALY, quality-adjusted life year; SoC, standard of care; UA, unstable angina.

Table 2 Sensitivity analyses results

	ICER-QALY for low and high scenario values (US$)					
	Empagliflozin versus canagliflozin		Empagliflozin versus dapagliflozin		Empagliflozin versus SoC	
	Low	High	Low	High	Low	High
Perspective, Medicare	*	NA	787	NA	23 255	NA
Perspective, commercial	*	NA	4174	NA	52 666	NA
Discount rate, cost: 0%–5%	1372	*	6044	1964	44 899	27 497
Discount rate, health: 0%–5%	*	*	1827	4136	20 438	43 673
Baseline CV/renal event rates HR:±10%	*	*	2984	3116	22 803	51 384
HRs versus empagliflozin: 95% CI	†	*	†	*	NA	NA
HRs versus empagliflozin: ITT population	*	NA	2665	NA	NA	NA
Drug cost, empagliflozin: ±20%	*	16 738	*	18 360	24 792	40 904
Rebate percentage, empagliflozin:±20%	8530	*	11 199	*	37 135	28 561
Rebate percentage, comparator:±20%	*	8026	*	10 529	NA	NA
CV/renal event management cost:±20%	*	*	3681	2427	33 819	31 877
AE management cost: ±20%	246	*	2991	3117	32 831	32 865
Baseline utility: 95% CI	*	*	3070	3039	33 017	32 681
Utility decrements, CV/renal events: 95% CI	*	*	3104	3007	33 100	32 624
Utility decrements, AEs: 95% CI	*	*	2970	3083	33 218	32 713

*Empagliflozin is less costly and more effective than the comparator.
†The comparator is less costly and more effective than empagliflozin.
AE, adverse event; CV, cardiovascular; ICER, incremental cost-effectiveness ratio; ITT, intent-to-treat; NA, not applicable; QALY, quality-adjusted life year; SoC, standard of care.

rates of non-fatal MI, HHF, revascularization, progression of albuminuria, composite renal outcome, and AKI; similar rates of hospitalization for UA and TIA but higher rates of non-fatal stroke and GMI.

Simulated patients receiving empagliflozin were estimated to have a higher rate of non-CV-related mortality than those on comparator treatments. Since a lifetime time horizon was applied, every patient in the model experienced a terminal death event. Given the reductions in CV death for patients receiving empagliflozin, these patients survived longer, and their increased age led to an increase in the estimated non-CV death rates.

Longer overall survival and reduced rates of clinical events translated to incremental QALYs gained for empagliflozin versus canagliflozin (0.38), dapagliflozin (0.50), and SoC (0.84). The total net cost per patient was –US$306 vs canagliflozin, US$1517 vs dapagliflozin, and US$27 539 vs SoC. Savings from management of fewer clinical events with empagliflozin offset (for canagliflozin) or partially offset (for dapagliflozin and SoC) the additional drug cost due to extended survival. Empagliflozin showed dominance[36] (cost less and had higher QALYs) over canagliflozin and yielded ICERs of US$3054/QALY and US$32 848/QALY versus dapagliflozin and SoC, respectively.

Sensitivity analyses

Empagliflozin remained dominant over canagliflozin in the majority of deterministic sensitivity analyses (table 2), and ICERs ranged from US$246/QALY to US$16 738/QALY in the remaining analyses. Empagliflozin was dominant over dapagliflozin in several pricing scenarios and when the treatment effect of dapagliflozin was worsened (applying the dapagliflozin vs empagliflozin HR 95% CI upper limit). Reducing HRs for the comparator SGLT-2 treatment versus empagliflozin (favouring the comparators) had the largest impact on cost-effectiveness results. Empagliflozin remained cost-effective compared with SoC, with ICERs ranging from US$20 438/QALY (no discount rate on health outcomes) to US$52 666/QALY (commercial perspective). All ICERs fell below the US$100 000/QALY US cost-effectiveness threshold.[37]

In probabilistic sensitivity analyses, the ICER (US$/QALY) scatter plot demonstrated that empagliflozin always yielded more QALYs than canagliflozin, and empagliflozin was less expensive compared with canagliflozin in the majority of model iterations. In 88% of cases, empagliflozin dominated canagliflozin (ie, points fall in the southeast quadrant of the scatter plot; online supplemental figure OS1). The iterations for empagliflozin versus dapagliflozin yielded a mean ICER of US$2811/QALY (95% CI US$1597/QALY–US$3918/QALY), with all iterations below a stringent US$50 000/QALY cost-effectiveness threshold.[37] Empagliflozin was more expensive and more effective in terms of QALYs gained compared with SoC (99.8% of iterations were below US$150 000/QALY). The mean (95% CI) ICER for empagliflozin versus SoC was US$36 387/QALY (US$21 724/QALY–US$62 859/QALY). These results are based on

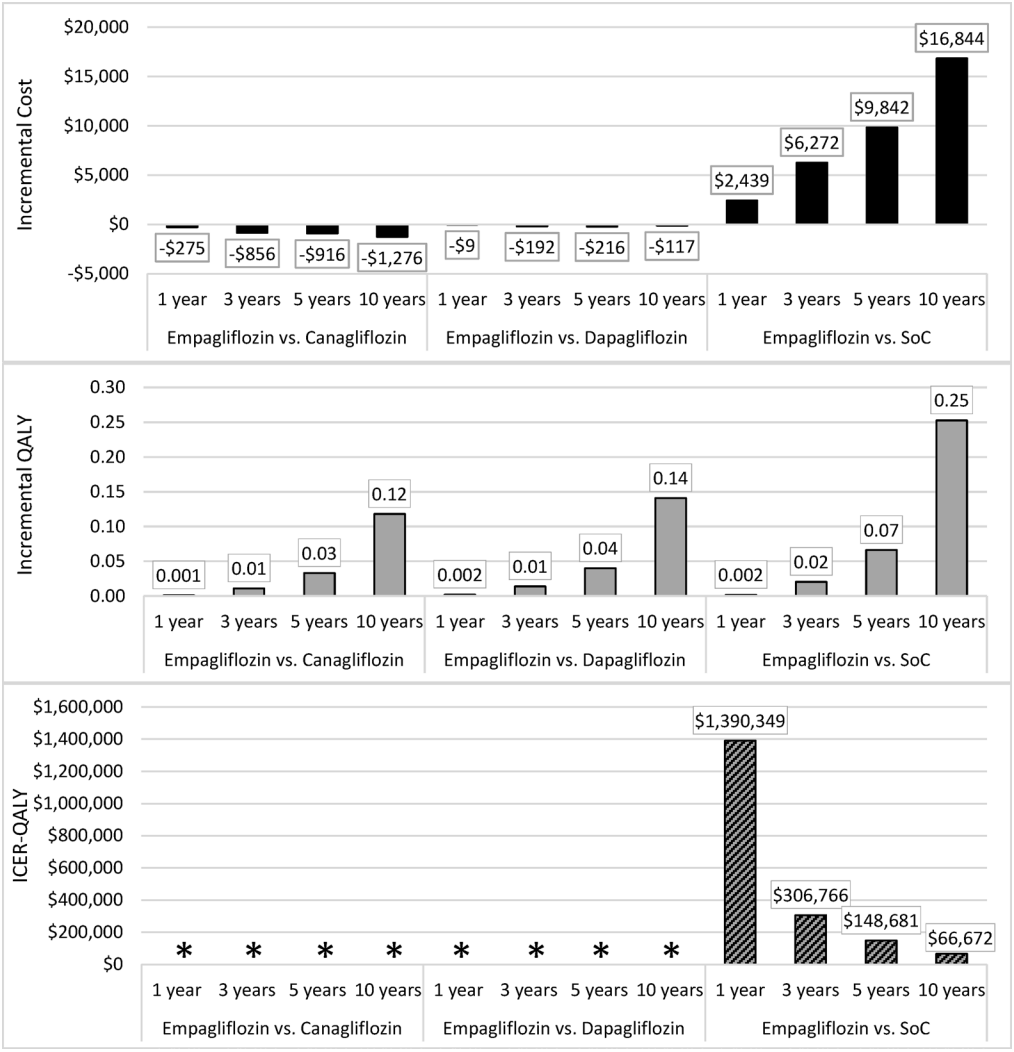

Figure 3 Short-term analyses with different time horizons. *Empagliflozin is less costly and more effective than the comparator. ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

the clinical event rates shown in online supplemental table OS10.

Scenario analyses

Changing the time horizon (1–10 years) did not have an effect on the direction of results (figure 3). Empagliflozin was dominant (less costly, more effective) over both canagliflozin and dapagliflozin over the shorter durations. Empagliflozin remained cost-effective relative to SoC over 10 years (US$66 672/QALY) and 5 years (US$148 681/QALY) at US$100 000/QALY and US$150 000/QALY thresholds,[37] respectively.

DISCUSSION

Patients with T2DM have increased risks of microvascular/macrovascular complications and premature death, with increased medical expenditures. Emerging evidence from CVOTs suggests a CV protective role for newer medications in people with T2DM and established CVD. Pharmacoeconomic evaluation can translate observed reductions in CV events to savings in healthcare expenditure and quantify the value of glucose-lowering drugs. This health economic evaluation demonstrated the benefits of empagliflozin compared with canagliflozin or dapagliflozin as an addition to SoC or SoC alone in the USA from a payer perspective, suggesting that empagliflozin economically dominates canagliflozin (ie, provides greater health benefits at a lower cost) and is highly cost-effective compared with dapagliflozin and SoC. The findings showed some sensitivity of results to drug rebates and parameters that affect clinical event risks; however, empagliflozin was consistently the dominant or cost-effective treatment.

Existing studies have performed similar analyses for empagliflozin versus SoC in various settings based on patient-level data from EMPA-REG OUTCOME, drawing consistent conclusions with our analysis about cost-effectiveness.[38–42] Differences in model design, inputs, and assumptions, make it difficult to compare our model with other published cost-effectiveness analysis for empagliflozin versus comparators in patients with T2DM and established CVD. However, a targeted literature search identified one key US payer-perspective cost-effectiveness study with a treatment comparison included in

our model. A study that used a Markov model to estimate the lifetime cost-effectiveness of empagliflozin versus SoC in the USA based on EMPA-REG OUTCOME trial data found that empagliflozin was associated with higher costs (US$98 484 per patient) and more QALYs (1.29) compared with SoC, yielding an ICER of US$76 167/QALY, still below the US cost-effectiveness threshold (US$100 000/QALY).[43] Although not a cost-effectiveness analysis, another published study evaluated costs avoided (in 2016 US$) for patients treated with canagliflozin and empagliflozin in a US commercially insured population aged <65 years.[44] That study found a positive cost avoidance for each treatment, based on unadjusted clinical event rates and assuming independent non-recurrent events, for each treatment versus placebo from CANVAS and EMPA-REG OUTCOME. Only CV event costs were captured; no costs associated with drug utilization, renal events, or AEs were included in their analysis. No studies including empagliflozin and dapagliflozin were identified.

This model directly predicted clinical event rates exclusively using data from the EMPA-REG OUTCOME trial, CANVAS Program, and DECLARE-TIMI 58, requiring no extrapolated changes in surrogate biomarkers. Drug pricing was conservative, assuming no difference in the costs of treatment between arms other than the presence of SGLT-2 treatment, and that treatment was never discontinued. Empagliflozin's survival benefit and thus longer treatment duration contribute to the higher pharmacy cost of empagliflozin versus comparator treatments, and discontinuation would help reduce this cost. Three-year overall outcomes from the EMPA-REG OUTCOME trial were closely reproducible by the model.

Limitations of this model should be considered when interpreting the results. First, the clinical event rates observed in EMPA-REG OUTCOME were based on controlled trial settings and may not be reproduced in clinical practice. This is a typical limitation of interpreting any trial outcomes. However, the CVOT designs were not prescriptive to the type of SoC, instead calling for the usual SoC in controlling HbA1c and CV risk factors according to local treatment guidelines, thus improving the likelihood of direct relevance to clinical practice. Next, the relative effects of canagliflozin or dapagliflozin versus empagliflozin on each modeled clinical event were estimated based on ITC rather than direct trial comparisons. The ITC was informed by data from CVOTs for empagliflozin (EMPA-REG OUTCOME),[14] canagliflozin (CANVAS Program; integrated analysis of CANVAS and CANVAS-R),[15] and dapagliflozin (DECLARE-TIMI 58),[16] with efficacy parameters stratified by baseline presence of CVD. We acknowledge the possibility of misclassification in the trial data, in that baseline presence of established CVD was investigator-reported and some participants could have had undiagnosed CVD. Sensitivity analyses using treatment effect in the ITT population for canagliflozin (empagliflozin was dominant) and dapagliflozin (US$2665/QALY) showed little variation in the results. In addition, treatment intensification beyond the trial duration cannot be easily captured in the model; thus, conservative treatment assumptions were used. Downstream treatment may affect clinical and cost outcomes observed in real-world practice. Model outcomes were sensitive to the impact of subsequent events of the same type on future event rates (eg, survivors of acute MI are at elevated risk of recurrent MI and other CV events, such as stroke), but there were relatively few data from the trials to estimate the change in risk associated with recurrent events. The model does not capture recognized but relatively mild AEs (eg, polyuria, episodes of dehydration) or rare complications (ie, diabetic ketoacidosis) of SGLT-2 inhibitors; these were not observed in sufficient numbers in the trials.

CONCLUSIONS

This research evaluated the lifetime cost-effectiveness of empagliflozin versus canagliflozin, dapagliflozin, and SoC in patients with T2DM and established CVD in the USA, by implementing an economic model that draws on the results of the EMPA-REG OUTCOME trial (all patients had CVD), CANVAS Program CVD subpopulation and DECLARE-TIMI 58 trial CVD subpopulation. Findings suggest that prescribing empagliflozin in addition to SoC for the treatment of patients with T2DM and CVD leads to substantial health benefits and is a dominant (vs canagliflozin plus SoC) or cost-effective (vs dapagliflozin plus SoC or SoC) treatment option from the perspective of US payers, and may assist patients, clinicians, and decision makers in the selection of a regimen for the management of T2DM and CVD.

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Contributors All authors contributed to the interpretation of data and results and drafting the manuscript. Additionally, OSR, ARK, LC, and SBB contributed to the model development, identification of data sources, conduct of analyses, and implementation of the design. KF performed the indirect treatment comparison. PKG, EP, and AU reviewed the final model design, data sources, and results.

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Competing interests OSR, SBB, and KF are employees of Evidera, which provides consulting and other research services to the biopharmaceutical industry. ARK and LC were employees of Evidera during the conduct of this study and development of this article, but are now employed elsewhere. In their salaried positions, Evidera employees work with a variety of companies and organizations, and are precluded from receiving any payment or honoraria directly from these organisations for services rendered. Evidera received funding from Boehringer Ingelheim Pharma GmbH & Co KG. EP and AU are current employees of Boehringer Ingelheim Pharma GmbH & Co. KG of Ingelheim am Rhein, Germany. PKG was an employee of Boehringer Ingelheim Pharmaceuticals, Inc. in Ridgefield, Connecticut, USA during the conduct of this study and development of this article, but he is now employed elsewhere.

Patient consent for publication Not required.

Ethics approval We used de-identified data from a clinical trial involving human participants, but we did not deal with or report on any specific participants, so we did not seek ethics committee approval.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Our study data (which is based on de-identified data from a clinical trial) is not in a repository,

but is available on reasonable request from the corresponding author (ORCiD 0000-0003-0714-5619).

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Cost-effectiveness of empagliflozin versus canagliflozin, dapagliflozin, or standard of care in patients with type 2 diabetes and established cardiovascular disease

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ONLINE SUPPLEMENT

Table of Contents

1. POPULATION

The model randomly sampled complete individual patient profiles one at a time with replacement from the observed EMPA-REG OUTCOME data describing characteristics of the 7,020 patients at baseline in EMPA-REG OUTCOME. A cohort size of 5,000 patients was sufficient to obtain stable results (assessed by variation in the incremental cost-effectiveness ratio [ICER] over multiple runs) for lifetime simulations. The profile for each simulated patient included demographics and medical history.

2. CLINICAL EVENTS

Table OS1. Clinical events in CVOTs

EMPA-REG OUTCOME	CANVAS Program	DECLARE-TIMI 58
CV and renal events		
CV death (primary outcome*)	CV death (primary outcome*, CANVAS)	CV death (primary outcome†)
Non-fatal MI (primary outcome*)	Non-fatal MI (primary outcome*, CANVAS)	Non-fatal/fatal MI (primary outcome†)
Non-fatal stroke (primary outcome*)	Non-fatal stroke (primary outcome*, CANVAS)	Non-fatal/fatal stroke (primary outcome†)
Hospitalization for HF	Hospitalization for HF	Hospitalization for HF
Progression of albuminuria‡	Progression of albuminuria (primary outcome, CANVAS-R)	Composite renal outcome
Composite renal outcome	Composite renal outcome	
Hospitalization for UA§		
Transient ischemic attack§		
Revascularization§		
Adverse events		
Genital mycotic infection	Genital mycotic infection	Genital mycotic infection
Acute kidney injury	Acute kidney injury	Acute kidney injury
Lower limb amputation‖	Lower limb amputation‖	Major hypoglycaemic event¶
Bone fracture‖	Bone fracture‖	
Major hypoglycaemic event¶		

CANVAS, Canagliflozin Cardiovascular Assessment Study, CV cardiovascular; CVOTs, cardiovascular outcome trials; EMPA-REG OUTCOME Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HF, heart failure; MI, myocardial infarction; SoC, standard of care; UA, unstable angina.

* Primary outcome was a composite of death from CV causes, non-fatal myocardial infarction, or non-fatal stroke

† Primary outcome was a composite of death from CV causes, non-fatal/fatal myocardial infarction, or non-fatal/fatal stroke

‡ Relevant for the empagliflozin versus SoC and empagliflozin versus canagliflozin comparisons. Progression of albuminuria from DECLARE-TIMI 58 was not published; therefore, this event cannot be included in the model comparison of empagliflozin versus dapagliflozin.

§ Relevant for the empagliflozin versus SoC comparison. Hospitalization for unstable angina, transient ischemic attack, and revascularization outcomes from CANVAS and DECLARE-TIMI 58 are not published; therefore, these events cannot be included in the model comparison of empagliflozin versus canagliflozin or empagliflozin versus dapagliflozin.

| Relevant for the empagliflozin versus canagliflozin comparison. Lower limb amputation was neutral and bone fracture was not statistically significant between treatment arms in EMPA-REG OUTCOME; therefore, these adverse events are not included in the comparison of empagliflozin versus SoC or empagliflozin versus dapagliflozin.

¶ Relevant for the empagliflozin versus dapagliflozin comparison.

3. STATISTICAL ANALYSIS APPROACH

A two-stage analysis was conducted to estimate individual patient-level risk equations for each cardiovascular (CV) and renal event in the model.

First, event-free survival (EFS) curves were fit to EMPA-REG OUTCOME trial patient-level data to describe the population-level occurrence of each CV and renal event. The best-fit parametric distribution was identified for each CV and renal outcome following the approach by Ishak and colleagues.[1] Common parametric survival models (Weibull, exponential, log-normal, and Gompertz) were fit to the Kaplan-Meier (KM) data for each CV and renal outcome and evaluated based on statistical goodness of fit (Akaike Information Criterion and Bayesian Information Criterion). The statistical fits described the distribution of times until that event was observed in the clinical trial. Parameterization models were visually inspected to evaluate clinical plausibility of the projections over the trial duration and extrapolation beyond the trial time horizon. The shape of each survival curve was selected based on numerical fit, realistic extrapolation beyond the trial time horizon, and parsimony (simplicity of the functional form). Survival analyses were performed in Statistical Analysis System (SAS Institute, Cary, NC) version 9.4.

Second, individual patient-level estimates of risk were generated by testing baseline and time-dependent patient characteristics as potential predictors of the outcomes in parametric proportional hazards regression analyses. Candidate characteristics for predictors in the risk equations were selected based on clinical relevance, and included basic demographic information (age, sex, geographic region), baseline biomarkers (haemoglobin A1c [HbA1c], body mass index, eGFR), baseline event history (of CV, cerebrovascular, or peripheral arterial disease), and CV and renal events experienced during the trial, along with treatment arm. Based on the clinical relationships, renal events could be included as predictors of the risk of future CV events and mortality, but CV

events were not used as predictors of renal events. Potential predictors affecting the time of event outcomes were investigated in univariate models, and predictors that were associated with the outcome (p <0.2) were combined in a multivariate model using R, version 3.2.2. The final multivariate equations were then reduced by eliminating terms in order of highest p-value until all terms had p <0.2 level.

4. RISK EQUATIONS

The derived risk equation covariates estimated (significant at p <0.2 or important prognostic factors that show a non-negligible effect size) for CV and renal event rates are provided in Table OS2. The covariates may be interpreted as the log of the hazard ratios (HRs), with a value <1 suggesting that a variable will result in lower probability of experiencing an event and a value ≥1 adjusting risk to a higher probability.

Reifsnider OS, *et al. BMJ Open Diab Res Care* 2021; 9:e001313. doi: 10.1136/bmjdrc-2020-001313

Table OS2. Parameters in the final risk equations

Clinical Events	CV death	Non-fatal MI	Non-fatal stroke	Hospitalisation for HF	Progression of albuminuria	Composite renal outcome	Hospitalisation for UA	Transient ischaemic attack	Revascularisation
Distribution	Weibull	Exponential	Weibull	Weibull	Weibull	Exponential	Exponential	Exponential	Exponential
Shape	1.033	1.000	0.901	0.914	1.103	1.000	1.000	1.000	1.000
Scale	5.219	4.696	5.200	6.403	1.573	5.574	5.149	5.635	3.915
Coefficients									
Age (years)	0.159	0.104	0.062	0.262	0.100	-0.101	-0.321	0.719	-0.123
Female					0.196				-0.239
BMI ≥30 kg/m^2			-0.264	0.438					0.223
HbA1c ≥8.5%									0.354
Stroke history	0.515		0.736			0.298	-0.300	0.548	-0.590
MI history	0.584	0.663		0.469			0.257		
CABG						-0.272		0.431	-0.365
MCAD		0.578		0.240			0.747		0.522
SVCAD					-0.111	-0.456			
PAD	0.273	0.429		0.534	0.072	0.818	-0.285		
eGFR mod–severe <60 ml/min/1.73m^2	0.429	0.160		0.700	0.230	0.674	0.318		
eGFR mild 60–90 ml/min/1.73m^2	0.118	-0.233		0.350	-0.041	-0.142	0.386		
Region: Africa		0.201	-0.687	0.396	0.070	0.924	0.108	-0.266	-0.424
Region: Asia		-0.563	-0.209	-0.325	0.163	0.459	-0.340	-1.495	-0.582
Region: Europe		-0.143	-0.181	-0.155	0.008	0.047	-0.206	-0.775	-0.265
Region: Latin America		-0.326	-1.012	-0.673	0.156	0.755	0.097	-2.203	-0.248
Empagliflozin treatment	-0.369	-0.125	0.253	-0.363	-0.188	-0.538	0.011	-0.157	-0.057
Non-fatal MI	1.552		1.090	1.347			0.736		3.122

Clinical Events	**CV death**	**Non-fatal MI**	**Non-fatal stroke**	**Hospitalisation for HF**	**Progression of albuminuria**	**Composite renal outcome**	**Hospitalisation for UA**	**Transient ischaemic attack**	**Revascularisation**
Non-fatal stroke	0.782							0.881	
Hospitalisation for HF	1.514	1.061	0.647						
Progression of albuminuria	0.921	0.241	0.352	0.972		1.248	-0.221		
Composite renal outcome				1.660	0.519				
Hospitalisation for UA		0.650		0.670					2.768
Transient ischaemic attack	1.053		1.700						
Revascularisation	-0.527						0.871		

BMI, body mass index; CABG, coronary artery bypass graft; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HF, heart failure; MCAD, multi-vessel coronary artery disease; MI, myocardial infarction; PAD, peripheral artery disease; SVCAD, single vessel coronary artery disease; UA, unstable angina

5. VALIDATION OF RISK EQUATIONS IN THE MODEL

Overall, the absolute clinical event rates per 100 person-years and the HRs for empagliflozin versus standard of care estimated by the model are consistent with EMPA-REG OUTCOME trial results (i.e., predicted HRs fall within the 95% confidence intervals (CIs) for corresponding trial data; see Table OS3). The largest deviation was in the rate of revascularization, which showed a mean rate ratio that is slightly less favourable (but not statistically significant) to empagliflozin than the trial data; this implied that the model results were conservative in capturing the benefit of empagliflozin.

Table OS3. Validation of 3-year overall hazard ratios

	EMPA–REG OUTCOME	Model*
	Hazard ratio (95% CI)	**Hazard ratio**
Cardiovascular and renal events		
Cardiovascular death	0.62 (0.49–0.77)	0.65
Non-fatal myocardial infarction	0.87 (0.70–1.09)	0.88
Non-fatal stroke	1.24 (0.92–1.67)	1.38
Hospitalisation for heart failure	0.65 (0.50–0.85)	0.66
Progression of albuminuria	0.83 (0.76–0.90)	0.88
Composite renal outcome	0.55 (0.41–0.73)	0.56
Hospitalisation for unstable angina	0.99 (0.74–1.34)	1.01
Transient ischemic attack	0.85 (0.51–1.42)	0.83
Revascularisation	0.86 (0.72–1.04)	0.95
Adverse events		
Genital mycotic infection	3.56 (NR–NR)	3.60
Acute kidney injury	0.50 (0.32–0.80)	0.56

CI, confidence interval; NR, not reported.

*A large number of patients (10,000) were simulated for the validation to obtain stable results over the short time horizon and given the relatively low rate of events.

6. FEASIBILITY ASSESSMENT FOR INDIRECT TREATMENT COMPARISON

The initial step for an indirect treatment comparison (ITC) is assessing the feasibility of quantitative synthesis. The feasibility assessment considers the available studies (in our case, EMPA-REG OUTCOME,[2] CANVAS,[3] and DECLARE-TIMI 58[4]) and study characteristics that permit quantitative synthesis. Aspects of the study that require evaluation include, but are not limited to, the following elements.

- Confounding factors in relation to patient populations/effect modifiers

- Differences in the measurement and reporting of outcomes.

Then, recommendations are made regarding outcomes and whether stratification by populations or other variables is recommended.

Population

Study characteristics for the three CV outcome trials (CVOTs) are summarized in Table OS4. The EMPA-REG OUTCOME trial included adult patients with type 2 diabetes mellitus (T2DM) and established atherosclerotic CV disease (CVD). The CANVAS Program and DECLARE-TIMI 58 trial included adult patients with T2DM and either (a) established atherosclerotic CVD, or (b) no known CVD and CV risk factors. Definitions of established atherosclerotic CVD were similar across CVOTs. DECLARE-TIMI 58 considered history of only ischemic stroke, whereas EMPA-REG OUTCOME and the CANVAS Program considered ischemic and haemorrhagic stroke in its definition of pre-existing CVD. Some differences were identified with regard to how each study defined the at-risk CV populations. All CVOTs included patients ≥18 years of age, while CANVAS was restricted to patients ≥30 years with a history of symptomatic atherosclerotic CVD or patients ≥50 years with more than two known risk factors for CVD, and DECLARE-TIMI 58 was restricted to patients ≥40 years with a history of symptomatic atherosclerotic CVD or patients ≥55 (men) and ≥60 (women) years with multiple risk factors for CVD. A minimum HbA1c of 6.5% was required for entry in all CVOTs. The EMPA-REG OUTCOME and CANAS Program permitted patients with a minimum HbA1c of 7%, with upper limit restrictions of 10% and 10.5%, respectively. DECLARE-TIMI 58 permitted patients with HbA1c values up to 12%. All CVOTs specified eGFR values as exclusion criteria. EMPA-REG OUTCOME and CANVAS excluded patients with eGFR <30 ml/min/1.73m^2 and DECLARE-TIMI 58 excluded patients with eGFR <60 ml/min/1.73m^2.

Table OS5 summarizes demographic and CV risk factors at baseline among patients in the included CVOTs. A lower proportion of patients in the CANVAS Program had a history of atherosclerotic CVD (65.6%) compared to EMPA-REG OUTCOME (100%). Otherwise, patient characteristics were well-balanced and comparable across these CVOTs. Overall, DECLARE-TIMI 58 enrolled a broader and healthier population than EMPA-REG OUTCOME, with 59.4% of patients with T2DM who were at risk but did not already have atherosclerotic CVD. Notably, baseline renal function was much worse in the EMPA-REG OUTCOME trial population versus the DECLARE-TIMI 58 trial subpopulation with baseline CVD (25.9% versus 9.2% eGFR < 60 ml/min/1.73 m^2). This is in part a result of the DECLARE-TIMI 58 trial design in which patients with creatinine clearance <60 ml/min/1.73m^2 were excluded. Baseline history of stroke was higher in the EMPA-REG OUTCOME trial population versus the DECLARE-TIMI 58 trial baseline CVD subpopulation (23.3% versus 16.0%; history of stroke was not reported for the overall DECLARE-TIMI 58 trial population). This may be in part to the fact that the EMPA-REG OUTCOME trial considered ischemic and

haemorrhagic stroke whereas the DECLARE-TIMI 58 trial considered only ischemic stroke. Additional differences were noted in the baseline history of MI (46.4% versus 51.4%), congestive heart failure (10.1% versus 16.6%), PAD (20.8% versus 14.7%), and baseline treatment with beta-blockers (64.9% versus 72.7%) and lipid-lowering therapy (81.0% versus 86.9%).

To reduce the heterogeneity between the EMPA-REG OUTCOME trial and the CANVAS Program and DECLARE-TIMI 58 trial populations, subpopulation data for patients with established atherosclerotic CVD at baseline was used to inform the ITC.

Outcomes

CV and renal events included in this analysis were generally defined in a similar way across the CVOTs, with a few exceptions. However, these differences were not considered to preclude the feasibility of an ITC.

- CV death was reported for all three CVOTs, and the definitions were generally consistent.
- Hospitalization for heart failure (HF) was reported for all three CVOTs, and the definitions were generally consistent. EMPA-REG OUTCOME had more permissive criteria (ER visits with ≥12-hour length of stay) than DECLARE-TIMI 58 (hospital admissions with ≥24-hour length of stay).
- Non-fatal MI was reported similarly in the EMPA-REG OUTCOME trial and CANVAS Program. The MI outcome in DECLARE-TIMI 58 included fatal or non-fatal MI including silent MI. To best align MI outcomes, data for fatal or non-fatal MI excluding silent MI was used for empagliflozin in the ITC. We assumed that silent MI does not impact costs or quality of life as it is detected through biochemical analyses. The contribution of fatal MI events in DECLARE-TIMI 58 to the HR was assumed to be small, based on data from EMPA-REG OUTCOME which showed that 96% of MI events were non-fatal.
- Non-fatal stroke in the EMPA-REG OUTCOME trial and CANVAS Program were similar. The stroke outcome in DECLARE-TIMI 58 included fatal or non-fatal stroke. To match definitions, the ITC for dapagliflozin versus empagliflozin was based on fatal or non-fatal stroke in the absence of non-fatal data. The contribution of fatal stroke events in DECLARE-TIMI 58 to the HR was assumed to be small, based on data from EMPA-REG OUTCOME which showed that 87% of stroke events were non-fatal.
- The composite renal outcome was reported in the EMPA-REG OUTCOME trial (defined as the doubling of serum creatinine accompanied by eGFR ≤45 ml/min/1.73m^2, initiation of renal replacement therapy, or death from renal cause), CANVAS Program (defined as a sustained doubling in serum creatinine, end-stage kidney disease, or death from renal causes),

and the DECLARE-TIMI 58 trial (defined as a ≥40% decrease in eGFR to <60 ml/min/1.73m^2, end-stage renal disease, or death from renal cause).

- Progression of albuminuria estimated from EMPA-REG OUTCOME trial data and reported in the CANVAS Program were defined consistently. Published data on albuminuria progression from the DECLARE-TIMI 58 trial was not available.

Differences across the CVOTs with regards to inclusion criteria, baseline demographic and clinical characteristics, concomitant CV medications, history of CVD, and outcome definitions have been clearly presented to ensure that interpretation of the ITC findings is done so taking into consideration these differences. From a clinical and methodological perspective, ITC analyses were deemed feasible for all outcomes of interest for which data were reported by the trials.

Table OS4. Criteria in trials assessed for inclusion in the ITC

Trial Name	EMPA-REG OUTCOME	CANVAS Program	DECLARE-TIMI 58
Definition of CVD	• Presence of ≥1 of the following: history of MI*; evidence of MCAD (50% stenosis in ≥2 major coronary arteries or the left main artery), SVCAD (50% stenosis in ≥1 main coronary artery and a positive stress test, or hospitalization for UA**), or UA* with evidence of SVCAD/MCAD; history of stroke; PAD (limb angioplasty, stenting, or bypass surgery; limb/foot amputation from circulatory insufficiency; evidence of peripheral artery stenosis in one limb; ABI <0.9 in ≥1 ankle)	• Presence of ≥1 of the following: history of MI, stroke, hospitalization for UA, coronary revascularization (CABG or PCI), peripheral revascularization (angioplasty or surgery), symptomatic with document haemodynamically-significant carotid or PAD, amputation secondary to vascular disease	• Presence of ≥1 of the following: ischemic heart disease (MI, PCI, CABG, ≥50% stenosis in ≥2 coronary artery territories including the main vessel, a major branch, or a bypass graft); cerebrovascular disease (history of stroke, carotid stenting or endarterectomy); PAD (peripheral arterial intervention, stenting, or surgical revascularization; lower limb amputation resulting from peripheral arterial obstructive disease; current symptoms of intermittent claudication and ABI <0.9 within 12 months)
Age and CV Risk	• ≥18 years old	• ≥30 years old with a history of symptomatic atherosclerotic CVD • ≥50 years old with ≥2 of the following risk factors for CVD: diabetes duration ≥10 years; SBP >140 mm Hg while receiving one or more antihypertensive agents; current smoking; microalbuminuria or	• ≥40 years old for baseline CVD subpopulation • ≥55 years old in men and ≥60 years old in women for baseline multiple risk factor subpopulation

Trial Name	EMPA-REG OUTCOME	CANVAS Program	DECLARE-TIMI 58
		macroalbuminuria; or HDL-C level of <1 mmol per litre	
HbA1c Level	• Had not received glucose-lowering agents for at least 12 weeks: ≥7.0% and ≤9.0% • Had received glucose-lowering therapy for at least 12 weeks: ≥7.0% and ≤10.0%.	• ≥7.0% and ≤10.5%	• ≥6.5% and <12.0%, 6.5% to < 7.0% capped at ~5% of study population
eGFR	• At entry: more than 30 ml per minute per 1.73 m2 of body surface area	• At entry: >30 ml per minute per 1.73 m2 of body surface area	• Excluded patients with creatinine clearance < 60 ml per minute per 1.73 m2 of body surface area

ABI, ankle brachial index; CABG, coronary artery bypass graft; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; MCAD, multi-vessel coronary artery disease; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SVCAD, single vessel coronary artery disease; UA, unstable angina.

* ≥2 months prior to informed consent

** ≤12 months prior to informed consent

Table OS5. Baseline patient characteristics in trials assessed for inclusion in the ITC

Trial Name	**EMPA-REG OUTCOME, ITT Population**	**CANVAS Program, ITT Population**	**CANVAS Program, CVD Subpopulation**	**DECLARE-TIMI 58, ITT Population**	**DECLARE-TIMI 58, CVD subpopulation**
Treatment	Empagliflozin	Canagliflozin	Canagliflozin	Dapagliflozin	Dapagliflozin
Dose, once daily	10mg, 25 mg	100 mg, 300 mg	100 mg, 300 mg	10 mg	10 mg
Trial participants (N)	7,020	10,142	6,656	17,160	6,974
Established CVD (%)	100	65.6	100	40.6	100
Age, years, mean	63.1	63.3	63.6	64	62.6
Female sex (%)	28.5	35.8	30.9	37.4	27.9
HbA1c, %, mean	8.1	8.2	8.2	8.3	8.4
Body mass index, kg/m^2, mean	30.6	32	31.8	32.1	NR
Systolic blood pressure, mmHg, mean	135.5	136.6	135	135	134.1
eGFR, mL/min per 1.73m^2, mean	74.1	76.5	75.5	85.3	84.7
eGFR <60 mL/min per 1.73m^2 (%)	25.9	20.1	NR	7.4	9.2
History of PAD (%)	20.8	NR	NR	6.0	14.7
History of MI (%)	46.4	NR	44.1	NR	51.4
History of stroke (%)	23.3	NR	19.2	NR	16.0
History of HF (%)	10.1	14.4	17.6	10.0	16.6

Trial Name	**EMPA-REG OUTCOME, ITT Population**	**CANVAS Program, ITT Population**	**CANVAS Program, CVD Subpopulation**	**DECLARE-TIMI 58, ITT Population**	**DECLARE-TIMI 58, CVD subpopulation**
Antiplatelet or Anticoagulant Therapy (%)	89.9	73.6	86.6	61.1	91.1
Diuretics (%)	43.2	44.3	44.2	40.6	40.7
Beta-Blockers (%)	64.9	53.5	64.2	52.6	72.7
ACE-inhibitors or ARBs (%)	80.7	80.0	79.8	81.3	82.2
Lipid-Lowering Therapy (%)	81.0	74.9	81.1	75.0	86.9

CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; ITC, indirect treatment comparison; NR, not reported; SD, standard deviation

7. MODEL INPUTS

Table OS6. Utility inputs

Event	Utility Mean (95% CI)	Source
Baseline Utility*	0.792 (SE: 0.002)	Sullivan and Ghushchyan, 2016[5]
CV and Renal Event Decrements (Duration: Permanent)		
Non-fatal MI	-0.029 (-0.036, -0.023)	Sullivan and Ghushchyan, 2016[5]
Non-fatal stroke	-0.037 (-0.048, -0.026)	Sullivan and Ghushchyan, 2016[5]
Hospitalization for UA	-0.029 (-0.036, -0.023)	Assumption: equivalent to non-fatal MI
Hospitalization for HF	-0.036 (-0.047, -0.024)	Sullivan and Ghushchyan, 2016[5]
Progression of albuminuria	-0.024 (-0.040, -0.008)	Sullivan and Ghushchyan, 2016[5]
Composite renal outcome	-0.047 (-0.089, -0.005)	Grandy et al., 2012[6]**
Transient ischemic attack	-0.049 (-0.088, -0.011)	Sullivan and Ghushchyan, 2016[5]
Revascularization	-0.030 (-0.036, -0.024)	Lindgren et al., 2007[7]^
AE Decrements (Duration: 1 year)		
Genital mycotic infection	-0.024 (-0.034, -0.014)	Sullivan and Ghushchyan, 2016[5]
Acute kidney injury	-0.024 (-0.040, -0.008)	Sullivan and Ghushchyan, 2016[5]
Lower limb amputation	-0.051 (-0.108, 0.005)	Sullivan and Ghushchyan, 2016[5]
Bone fracture	-0.039 (-0.050, -0.029)	Sullivan and Ghushchyan, 2016[5]
Major hypoglycaemic event	-0.005 (-0.006, -0.004)	NICE 2011[8]^
Adjustment for Overlapping Utility Impacts of Multiple Events (Added to Utility Score as Applicable)		
2 concurrent events	0.010 (0.002, 0.018)	Sullivan and Ghushchyan, 2016[5]
3 concurrent events	0.023 (0.009, 0.038)	Sullivan and Ghushchyan, 2016[5]
4 concurrent events	0.037 (0.016, 0.058)	Sullivan and Ghushchyan, 2016[5]
5 or more concurrent events	0.041 (0.013, 0.069)	Sullivan and Ghushchyan, 2016[5]

AE, adverse event; CI, confidence interval; CV, cardiovascular; HF, heart failure; MI, myocardial infarction; N, number; SD, standard deviation; SE, standard error; UA, unstable angina.

* The baseline utility value is based on analyses of 20,705 patients with diabetes and valid EQ-5D scores in the 2000-2011 Medical Expenditure Panel Survey data; about 56% had at least one diabetes-related chronic condition.

** 95% CI derived from reported SD = 0.164 and N = 58.

^ 95% CI assumed to be +/-20% of the mean.

^^ Based on MedDRA preferred terms.

Inpatient costs for CV and renal events were retrieved from the Healthcare Cost and Utilization Project (HCUP) where possible,[9] using relevant Internal Classification of Disease, Tenth Revision (ICD-10) diagnostic codes for each event; other costs were retrieved from published literature.[10, 11] CV and renal events indirectly imposed long-term costs by increasing the risk of future costly events. For example, while patients who have experienced a non-fatal MI have higher lifetime healthcare costs, some of that cost represented the increased rate of CV events in these patients. Because the model explicitly accounted for the event cost of those future CV events, an accurate computation of the increase in cost of care must exclude costs directly associated with future events. Because empagliflozin reduced the total rate of most events, excluding long-term costs was a conservative approach (e.g., underestimating the cost benefit of empagliflozin).

All patients treated for LLA, bone fracture, and major hypoglycaemic event were assumed to receive inpatient care. The percentage of patients treated for GMI and AKI in an outpatient (17%) or inpatient hospitalisation (3%) setting was obtained from published data [12]; other patients were managed by self-treatment (80%) and were assumed to incur no costs.

Table OS7. Cost inputs (2020 USD)

	Medicare	Commercial	Overall population^	Sources and medical codes
Drug acquisition: monthly cost to payer				
Rebate (all SGLT-2 inhibitors)	53%	50%	51%	Assumption
Co-pay (all SGLT-2 inhibitors)	$35	$35	$35	UBA 2016[13]
Empagliflozin 10 or 25 mg: monthly WAC	$529.68	$529.68	$529.68	*REDBOOK 2020*[14]^^
Canagliflozin 100 or 300 mg: monthly WAC	$525.73	$525.73	$525.73	*REDBOOK 2020*[14]^^
Dapagliflozin 10 mg: monthly WAC	$514.22	$514.22	$514.22	*REDBOOK 2020*[14]^^
CV or renal events: cost per episode for inpatient treatment[†]				
CV death	$40,703	$40,703	$40,703	Shetty et al., 2016[10]
Non-fatal MI	$22,542	$24,191	$23,456	HCUPnet 2016,[9] ICD-10: I21.xx
Non-fatal stroke	$13,082	$14,954	$14,120	HCUPnet 2016,[9] ICD-10: I63.30, I63.40 , I63.50, I66.09, I66.19, I66.29, I66.9
Hospitalisation for HF	$9,187	$12,229	$10,874	HCUPnet 2016,[9] ICD-10: I50.9
Progression of albuminuria	$4,648	$4,553	$4,595	HCUPnet 2016,[9] ICD-10: R80.9
Composite renal outcome*	$7,840	$7,815	$7,826	Calculated; weights: EMPA-REG OUTCOME
40% reduction in eGFR (85%)	$7,306	$7,306	$7,306	*HCUPnet 2016,*[9] *ICD-10: R94.4*
RRT (14%)	$9,497	$9,317	$9,397	*HCUPnet 2016,*[9] *ICD-10: N17.9*
Renal death (2%)	$22,265	$22,265	$22,265	*USRDS 2018* [11]
Hospitalisation for UA	$8,522	$8,167	$8,325	HCUPnet 2016,[9] ICD-10: I20.0
Transient ischemic attack	$7,675	$7,570	$7,617	HCUPnet 2016,[9] ICD-10: G45.9
Revascularization	$49,454	$45,104	$47,042	HCUPnet 2016,[9] ICD-10: 021.0xxx

	Medicare	Commercial	Overall population^	Sources and medical codes
Non-CV death	$0	$0	$0	Assumption
Adverse events: cost per episode				
Genital mycotic infection*	$558	$520	$537	Calculated; weights: Li, et al., 2013[12]
Treated outpatient (17%)	$76	$138	$111	*CMS 2020,[15] CPT: 99213; InHealth 2020[16]*
Treated inpatient (3%)	$18,158	$16,544	$17,263	*HCUPnet 2016,[9] ICD-10: N48.29, N49.8, N77.1*
Self-treated (80%)	$0	$0	$0	*Assumption*
Acute kidney injury*ǂ	$232	$243	$238	Calculated; weights: assumption
Treated outpatient (17%)	$76	$138	$111	*CMS 2020[15], CPT: 99213, InHealth 2020[16]*
Treated inpatient (3%)	$7,306	$7,306	$7,306	*HCUPnet 2016,[9] ICD-10: R94.4*
Self-treated (80%)	$0	$0	$0	*Assumption*
Lower limb amputation**	$23,779	$22,659	$23,158	ICD-10: 0Y6.xxxx
Bone fracture**	$23,885	$31,112	$27,893	ICD-10: M84.5xx
Major hypoglycaemic event**	$15,502	$26,369	$21,529	ICD-10: E11.641

CV, cardiovascular; HF, heart failure; MI, myocardial infarction; PSA, probabilistic sensitivity analyses; RRT, renal replacement therapy; SGLT-2, sodium-glucose co-transporter-2; T2DM, type 2 diabetes mellitus; UA, unstable angina; USD, United States dollar.

* Cost input is calculated as an average of multiple components, weighted by the specified percentage for each.

** Assumption: 100% of events are treated in the inpatient setting.

^ Calculated as the weighted cost of Medicare and Commercial costs, with weights based on the proportion of the EMPA-REG OUTCOME population that were aged 65 years and older (45%) or aged less than 65 years (55%) at baseline in the trial.

^^ Daily costs are the same across package sizes and tablet strengths. Monthly cost assumes (365/12) = 30.4 days per month.

ǂ Management of CV and renal events was assumed to occur in an inpatient setting.

ǂ Based on MedDRA preferred terms.

Costs were inflated from prior years, where applicable, using the medical component of the US consumer price index.

Table OS8. PSA distributions

Parameter	PSA Inputs	Distribution	Source
Clinical			
Empagliflozin and SoC			
CV and renal event rates per 100 PY	Variance-covariance matrices	Cholesky	EMPA-REG OUTCOME
Percent experiencing AEs	Sample size in trial	Beta	EMPA-REG OUTCOME
Canagliflozin and dapagliflozin			
CV and renal events: HRs vs. empagliflozin	95% CI	Lognormal	ITC**
AEs: HRs vs. empagliflozin*	95% CI	Lognormal	ITC**
Costs			
Drug acquisition costs	Not varied	-	
Copays and rebates	Not varied	-	
All event management costs	SE	Gamma	Assumption: SE = 10%^
Utilities			
Utility at baseline	SE	Beta	Sullivan and Ghushchyan, 2016[5]^^
All event decrements	95% CI	Gamma	Sullivan and Ghushchyan, 2016[5]^^
Adjustments for multiple concurrent events	95% CI	Beta	Sullivan and Ghushchyan, 2016[5]^^

AE, adverse event; CI, confidence interval; CV, cardiovascular; ITC, indirect treatment comparison; SE, standard error.

*Applied to calculated rates per 100 PY for empagliflozin.

** Refer to Figure 2 in the main article for 95% CIs.

^ Refer to Table OS6 for mean values used to estimate the SE.

^^ Refer to Table OS7 for 95% CIs

8. DETAILED BASE CASE RESULTS

Table OS9. Detailed base case results over a lifetime horizon

	Empagliflozin vs. Canagliflozin		**Empagliflozin vs. Dapagliflozin**		**Empagliflozin vs. SoC**	
	Empagliflozin	Canagliflozin	Empagliflozin	Dapagliflozin	Empagliflozin	SoC
CV and renal event rates per 100 PY						
CV death	3.35	3.91	1.62	2.21	3.15	4.43
Non-fatal MI	1.95	1.74	1.66	1.63	2.02	2.36
Non-fatal stroke	1.20	0.82	0.99	0.75	1.26	1.02
Hospitalisation for HF	1.74	1.69	0.78	0.86	1.84	2.85
Progression of albuminuria	6.03	6.18	-	-	5.91	6.77
Composite renal outcome	1.18	1.20	0.51	0.49	1.16	1.80
Hospitalisation for UA	-	-	-	-	1.17	1.13
Transient ischemic attack	-	-	-	-	0.25	0.30
Revascularization	-	-	-	-	2.52	2.72
Non-CV death	3.72	3.59	4.31	4.14	3.78	3.46
AE rates per 100 PY						
Genital mycotic infection	1.73	1.80	1.68	3.14	1.71	0.55
Acute kidney injury	0.32	0.46	0.32	0.43	0.31	0.54
Lower limb amputation	0.61	1.16	-	-	-	-
Bone fracture	1.19	1.48	-	-	-	-
Major hypoglycaemic event	-	-	0.40	0.32	-	-
Undiscounted life expectancy (years)	14.14	13.34	16.85	15.77	14.44	12.67

	Empagliflozin vs. Canagliflozin		**Empagliflozin vs. Dapagliflozin**		**Empagliflozin vs. SoC**	
	Empagliflozin	Canagliflozin	Empagliflozin	Dapagliflozin	Empagliflozin	SoC
Discounted QALY*	8.23	7.85	9.62	9.12	8.30	7.47
Discounted costs*						
Drug acquisition cost, $	$31,047	$29,371	$35,494	$32,577	$31,539	$0
CV/renal event management cost, $	$26,722	$26,710	$15,663	$17,221	$41,372	$45,442
AE management costs, $	$5,350	$7,343	$1,178	$1,021	$112	$42
Total cost, $	$63,118	$63,424	$52,336	$50,819	$73,023	$45,484

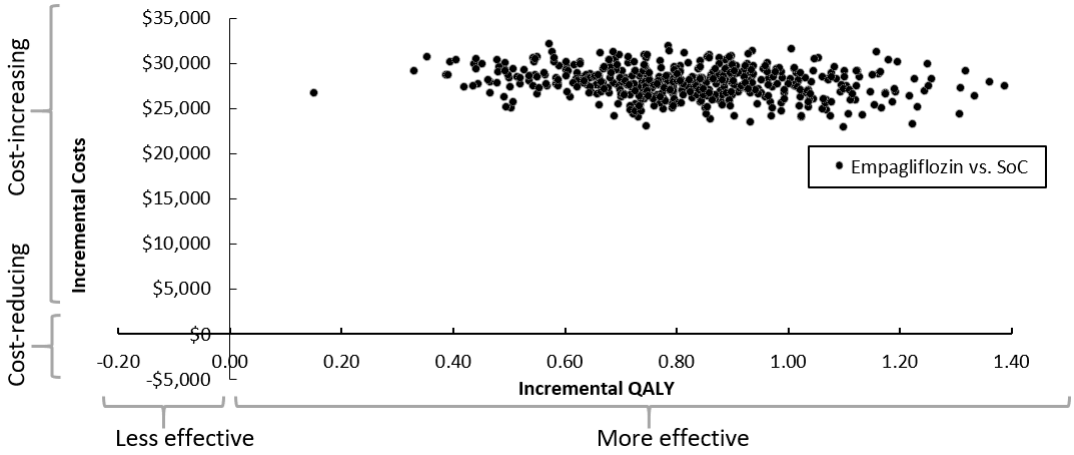
AE, adverse event; CV, cardiovascular; HF, heart failure; ICER, incremental cost-effectiveness ratio; LY, life year; MI, myocardial infarction; PY, patient-year; QALY, quality-adjusted life year.

* Incremental costs and QALYs are displayed versus empagliflozin.

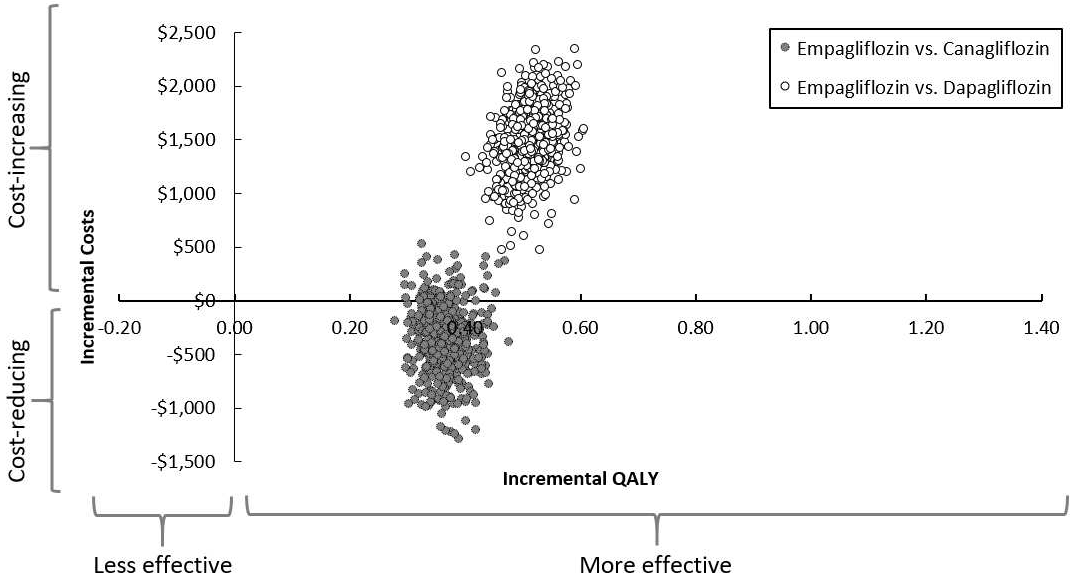
9. PROBABILISTIC SENSITIVITY ANALYSIS RESULTS

Figure OS1. Scatterplots of incremental QALY versus incremental cost

A. Incremental QALY versus incremental cost: Empagliflozin versus SoC



B. Incremental QALY versus incremental cost: Empagliflozin versus SGLT-2 therapies



QALY, quality-adjusted life year; SoC, standard of care; SGLT-2, sodium-glucose co-transporter-2.

Table OS10. Event rates estimated in PSA

Empagliflozin vs.	Canagliflozin		Dapagliflozin		SoC	
	Empagliflozin	Canagliflozin	Empagliflozin	Dapagliflozin	Empagliflozin	SoC
CV and renal event rates per 100 PYs (95% CI)						
CV death	3.21 (2.65-3.98)	3.73 (3.07-4.59)	1.65 (1.21-2.14)	2.22 (1.73-2.78)	3.03 (2.47-3.72)	4.29 (3.54-5.37)
Non-fatal MI	1.87 (1.59-2.17)	1.66 (1.39-1.93)	1.56 (1.30-1.87)	1.56 (1.28-1.83)	2.02 (1.67-2.44)	2.30 (1.82-2.86)
Non-fatal stroke	1.14 (0.83-1.54)	0.73 (0.52-1.02)	0.88 (0.63-1.29)	0.66 (0.48-0.96)	1.18 (0.86-1.60)	0.93 (0.60-1.38)
Hospitalisation for HF	1.67 (1.18-2.33)	1.61 (1.14-2.24)	0.71 (0.49-1.06)	0.80 (0.57-1.20)	1.80 (1.32-2.37)	2.90 (2.14-4.13)
Progression of albuminuria	6.00 (5.66-6.41)	6.11 (5.75-6.59)	-	-	5.87 (5.57-6.22)	6.66 (6.23-7.28)
Composite renal outcome	1.12 (0.92-1.35)	1.15 (0.95-1.39)	0.43 (0.30-0.58)	0.42 (0.30-0.59)	1.11 (0.90-1.34)	1.76 (1.47-2.09)
Hospitalisation for UA	-	-	-	-	1.36 (1.02-1.83)	1.32 (0.93-1.80)
Transient ischemic attack	-	-	-	-	0.23 (0.13-0.36)	0.28 (0.15-0.48)
Revascularization	-	-	-	-	2.51 (2.29-2.73)	2.67 (2.42-2.96)
Non-CV death	3.79 (3.54-3.96)	3.67 (3.40-3.88)	4.29 (4.11-4.45)	4.13 (3.99-4.29)	3.82 (3.57-4.01)	3.50 (3.17-3.77)
AE rates per 100 PYs (95% CI)						
Genital mycotic infection	1.85 (1.81-1.88)	1.92 (1.88-1.96)	1.79 (1.76-1.82)	3.20 (3.12-3.28)	1.83 (1.78-1.87)	0.61 (0.58-0.64)
Acute kidney injury	0.26 (0.24-0.27)	0.41 (0.40-0.43)	0.26 (0.25-0.28)	0.38 (0.37-0.40)	0.24 (0.22-0.26)	0.48 (0.45-0.50)
Lower limb amputation	0.69 (0.67-0.72)	1.19 (1.15-1.24)	-	-	-	-
Bone fracture	1.22 (1.19-1.25)	1.58 (1.54-1.62)	-	-	-	-
Major hypoglycaemic event	-	-	0.40 (0.39-0.42)	0.30 (0.29-0.31)	-	-

AE, adverse event; CI, confidence interval; CV, cardiovascular; HF, heart failure; MI, myocardial infarction; PY, patient-year; SoC, standard of care.

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