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.

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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

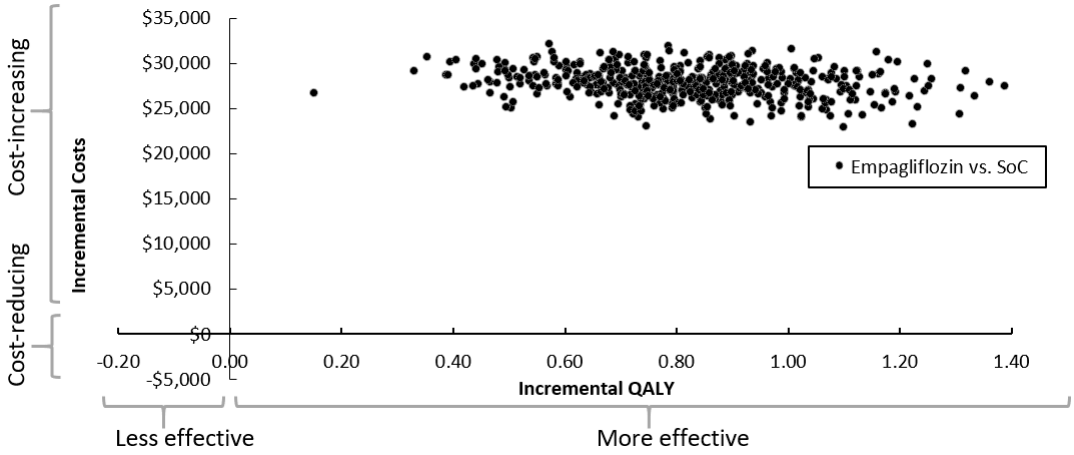
AE, adverse event; CV, cardiovascular; HF, heart failure; ICER, incremental cost-effectiveness ratio; LY, life year; MI, myocardial infarction; PY, patient-year; QALY, quality-adjusted life year.

* Incremental costs and QALYs are displayed versus empagliflozin.

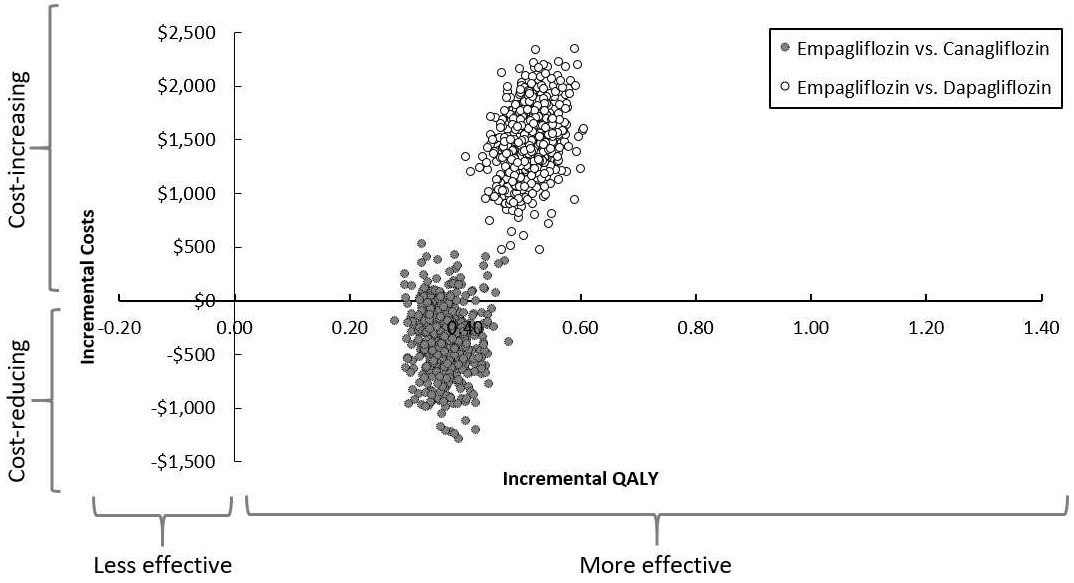
9. PROBABILISTIC SENSITIVITY ANALYSIS RESULTS

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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