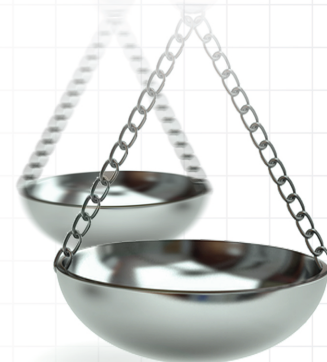




Cost-effectiveness of empagliflozin compared with liraglutide based on cardiovascular outcome trials in Type II diabetes

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Aim: Cost-effectiveness (CE) analysis of empagliflozin+standard of care (SoC) compared with SoC and liraglutide+SoC, in patients with Type II diabetes and established cardiovascular disease, was conducted using evidence from cardiovascular outcomes trials. **Methods:** The IQVIA Core Diabetes Model was calibrated to predict same outcomes observed in EMPA-REG OUTCOME and LEADER trials. Three-year observed cardiovascular events of SoC, empagliflozin+SoC and liraglutide+SoC were derived from EMPA-REG OUTCOME trial and an indirect comparison. Time horizon was 50 years and the UK payer perspective was taken. **Results:** Empagliflozin+SoC dominated liraglutide+SoC with greater quality-adjusted life years and reduced costs. Base-case incremental CE ratio of 6428 GBP/QALY was observed for empagliflozin+SoC versus SoC. **Conclusion:** Results suggest that empagliflozin+SoC is cost effective versus SoC and liraglutide+SoC.

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Keywords: cardiovascular outcomes • cost-effectiveness • empagliflozin • liraglutide • type II diabetes mellitus

Diabetes is a major global health issue with a prevalence of 463 million at present and is projected to reach 700 million by 2045 [1]. Patients with diabetes have an increased risk of developing macrovascular complications (cardiovascular disease [CVD], ischemic heart disease, peripheral vascular disease and cerebrovascular disease) and microvascular complications (retinopathy, nephropathy and neuropathy), among which cardiovascular (CV) conditions are considered to be the leading cause of both morbidity and mortality for patients with Type II diabetes (T2D) [1–3].

Several trials have demonstrated that there is a potential risk of heart failure (HF) associated with certain anti-diabetic medications such as thiazolidinediones [4].

In 2008, the US FDA released guidance on glucose-lowering treatments stating that, in addition to assessing their impact on HbA1c, long-term cardiovascular outcome (CVO) effects should also be studied and reported [5]. The European Medicines Agency also revised their guidelines in 2012, wherein new glucose-reducing therapies are required to provide CV safety evidence through large-scale cardiovascular outcome trials (CVOT) [6].

Subsequently, several CVOTs were conducted on glucose-reducing drugs like DPP-4 inhibitors [7–9], GLP-1 receptor agonists [10–13] and SGLT2 inhibitors [14,15]. The evidence generated by these CVOTs has confirmed that it is not only relevant to achieve and maintain target glycemic control (HbA1c) to avoid or delay the progression of diabetes [16], but also to reduce the risks of CV complications and CV death [17]. Empagliflozin, a selective inhibitor of SGLT2 and liraglutide, a GLP-1 analog, have been assessed in randomized, double-blind placebo-controlled trials assessing the CV risk in T2D patients.

The effect of empagliflozin on CVOs was assessed in the EMPA-REG OUTCOME trial [14] in patients with T2D and established CV disease. Patients were treated with 10 or 25 mg of empagliflozin or placebo, on top of SoC, over a median observation time of 3.1 years. The primary end points, in other words, death from CV causes,

nonfatal myocardial infarction (MI), or nonfatal stroke, occurred in significantly fewer patients in the empagliflozin group than in the placebo group (hazard ratio [HR] = 0.86; $p = 0.038$). Empagliflozin resulted in a significantly lower risk of death from CV causes (HR: 0.62; $p < 0.001$), death from all causes (HR: 0.68; $p < 0.001$) and hospitalization for heart failure (HR: 0.65; $p = 0.002$) as compared with placebo [18–20].

The CV safety profile of liraglutide has been assessed in the LEADER trial in which T2D patients with high CV risk (vast majority with established CV disease) were randomly assigned to receive liraglutide or placebo as an add-on to SoC [11]. The primary outcomes, in other words, death from CV causes, nonfatal MI or nonfatal stroke occurred in significantly fewer patients in the liraglutide group than in the placebo group (HR: 0.87; $p < 0.001$ for noninferiority; $p = 0.01$ for superiority). Significantly fewer deaths from CV causes were reported in the liraglutide group than in the placebo group (HR: 0.78; $p = 0.007$). The risk of death from any cause was lower in the liraglutide group than in the placebo group (HR: 0.85; $p = 0.02$). The rates of nonfatal MI, nonfatal stroke and hospitalization due to HF were similar in the two arms of the study.

As healthcare resources are scarce, clinical and economic benefits need to be assessed before making any treatment recommendation. This study aimed to evaluate the cost–effectiveness (CE) of empagliflozin+SoC versus SoC alone and liraglutide+SoC in T2D patients with established CVD using the IQVIA Core Diabetes model (CDM).

Methods

IQVIA core diabetes model calibrated for cardiovascular outcomes trials

The IQVIA CDM is a web-based computer simulation model used to project long-term health economic outcomes of therapies commonly considered in the management of diabetes, for a range of economic analyses (CE, cost-utility, cost-benefit or cost of disease). Drug therapies, lifestyle interventions, public health programs, medical devices and surgical interventions can be modeled using the CDM. The basic structure of the CDM has been described by Palmer and colleagues in 2004 [21], and has been extensively validated against results from clinical and epidemiological studies [22]. The outcomes of analyses consist of life years (LYs), quality-adjusted life years (QALYs), cumulative incidence of diabetes-related complications, progression of physiologic parameters, direct medical costs and indirect costs.

For the current analysis, the standard version of CDM 9.0 was used and calibrated to reflect the outcomes observed in both EMPA-REG OUTCOME and LEADER trials. The data input structure and model codes were modified to calibrate the model for CVOTs [23]. First, the annual progression of risk factors for each treatment arm were programmed in the CDM for the initial cycles, according to the follow-up period and end points available in each trial. These risk factors included HbA1c, systolic blood pressure (SBP), diastolic blood pressure (DBP), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), hypoglycemia rates, body mass index (BMI) change and heart rate that were reported in both EMPA-REG OUTCOME and LEADER trials. The risk equations (REs) available in the CDM v9.0 predict diabetes complications and are dependent on the progression of these risk factors. The REs used in the model have been derived from UKPDS 68 [24], UKPDS 82 [25], Advance [26], Swedish national Diabetes Register [27,28], ARIC study [29], Fremantle [30] and PROCAM [31]. To identify which CDM RE was the best fit to predict the macrovascular complications reported in the EMPA-REG OUTCOME trial, a pre-analysis was conducted. The CDM analyses with a time horizon restricted to 3 years were run, to match the trial follow-up period. By comparing the predicted outcomes of CDM and the observed outcomes reported in the EMPA-REG OUTCOME trial, UKPDS 82 RE [25] was found to be the best fit.

The second step of the calibration was an iterative process to identify the best set of relative risk (RR) adjustments required to align the UKPDS 82 RE predictions to match the observed 3-year clinical outcomes. The selected outcomes for this analysis were primary and secondary MI, primary and secondary stroke, angina, HF, CV death, non-CV death, microalbuminuria and end stage renal disease (ESRD).

The observed outcomes from empagliflozin+SoC and SoC arms were taken from the EMPA-REG OUTCOME trial. Using the RR adjustments described in the indirect treatment comparison (ITC) [32], the corresponding outcomes for liraglutide+SoC were estimated (Table 1).

Since there was inconsistency in reporting certain end points in the CDM and the ITC, a number of assumptions were made (Supplementary Table 1); for example, renal outcomes were not reported in the ITC, so similar effects were assumed.

Table 1. Indirect comparison of empagliflozin versus other glucose-lowering drugs.

Comparison empagliflozin+SoC vs		Cardiovascular-related mortality	All-cause mortality	Composite end point	Hospitalization due to heart failure	Nonfatal stroke	Nonfatal myocardial infarction
Liraglutide+SoC	HR (95% CrI)	0.80 (0.60, 1.06)	0.80 (0.64, 1.00)	0.99 (0.82, 1.18)	0.75 (0.54, 1.03)	1.39 (0.97, 2.01)	0.99 (0.76, 1.30)

Data published from [32].
HR: Hazard ratio.

Table 2 First year treatment effects of first and second line treatments.

Treatment effects	Empagliflozin+SoC [14]	SoC [14]	Liraglutide+SoC [11]	Basal bolus [23,36]
HbA1c [†]	-0.58	-0.1	-1.37	-0.828
SBP [†]	-3.9	-0.62	-1.82	0
DBP [†]	-1.72	-0.78	0.17	0
T-Chol [†]	7.81	3.56	0	0
HDL [†]	1.81	-0.09	0	0
LDL [†]	4.79	1.42	0	0
TRIG [†]	0	0	0	0
BMI [†]	-0.64	-0.04	-0.88	0.32
eGFR [†]	-0.16	0.18	0	0
NSHE rate [‡]	13.62	13.98	289.12	2566.83
SHE1 rate [‡]	0.44	0.56	8.24	23.81
SHE2 rate [‡]	0.06	0.07	1.10	3.19
GUI [§]	10.53	8.95	8.95 [§]	–

[†] Effect on the surrogate end points is applied on the first year of treatment.

[‡] Rate per 100 patient-year.

[§] Aside HbA1c effect, all other end points are assumed to be equal to placebo described in the EMPA-REG OUTCOME trial.

BMI: Body mass index; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; GUI: Genital and urinary tract infection; HbA1c: Glycated hemoglobin; HDL: High-density lipoprotein cholesterol; LDL: Low-density lipoprotein cholesterol; NSHE: Nonsevere hypoglycemic event; SBP: Systolic blood pressure; SHE: Severe hypoglycemic event; SoC: Standard of care; TChol: Total cholesterol; TRIG: Triglyceride.

Patient data

Baseline characteristics of T2D patients with established CV disease were used in the model which were derived from the patients of the EMPA-REG OUTCOME trial at study onset [14] (Supplementary Table 2).

Clinical data

Treatment effects

The EMPA-REG OUTCOME and LEADER trials were designed to assess the effect of the investigational drug versus placebo as an add-on to background therapy on CV complications. The progression of risk factors over time (first year till the end of the trial period) were populated in the CDM as annual increments and aligned with each trial. The associated adverse event rates per treatment were taken from the respective trials (Table 2) [11,14,33]. It is important to note that the treatment effects described in each trial reflected the impact of both main therapy and the intensification of SoC, as specified in the study protocols.

In both EMPA-REG OUTCOME and LEADER trials, patients received high doses of combined glucose-lowering drugs. Background treatment intensification, considered in both trials, was performed at the discretion of the physicians according to patients' needs, with the purpose to have glycemia controlled to the same extent in the two arms. Thus, different combinations of glucose-lowering drugs such as sulphonylureas, metformin, glitazone, glinide and insulin were either administered at study initiation, or added, or escalated over the study duration. This was reflected in the treatment effect measured at the completion of both the CVOTs. In particular, background insulin was given to 50, 58 and 73% of patients receiving empagliflozin+SoC, SoC and liraglutide+SoC, respectively, at the end of the trial period. However, over the course of the studies, there was a relatively greater increase in the proportion of patients in the liraglutide+SoC arm (29%) as compared with the empagliflozin+SoC arm (3%).

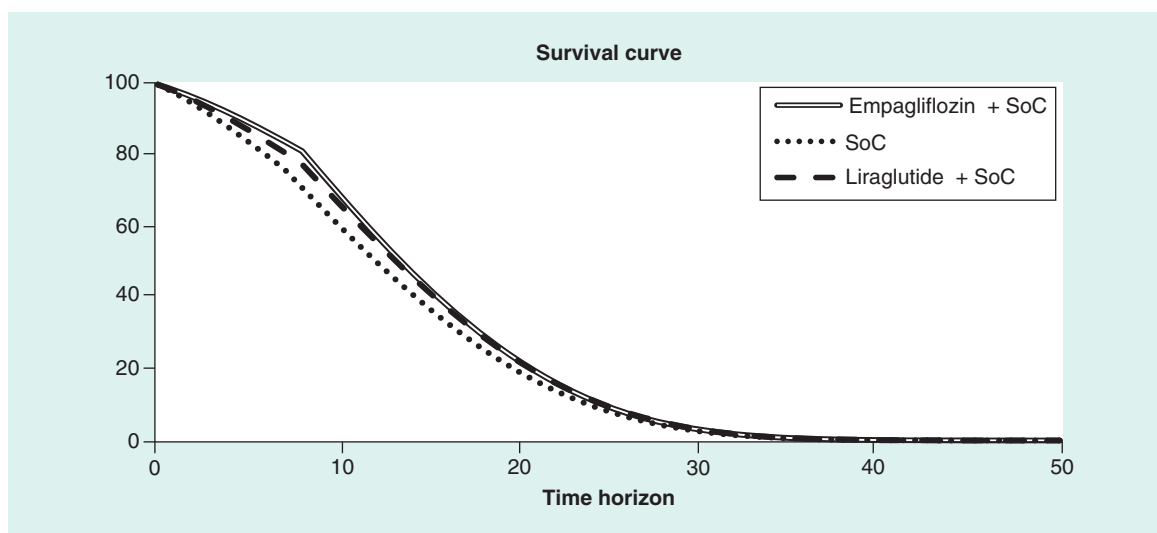


Figure 1. Lifetime survival of all therapies.
SoC: Standard of care.

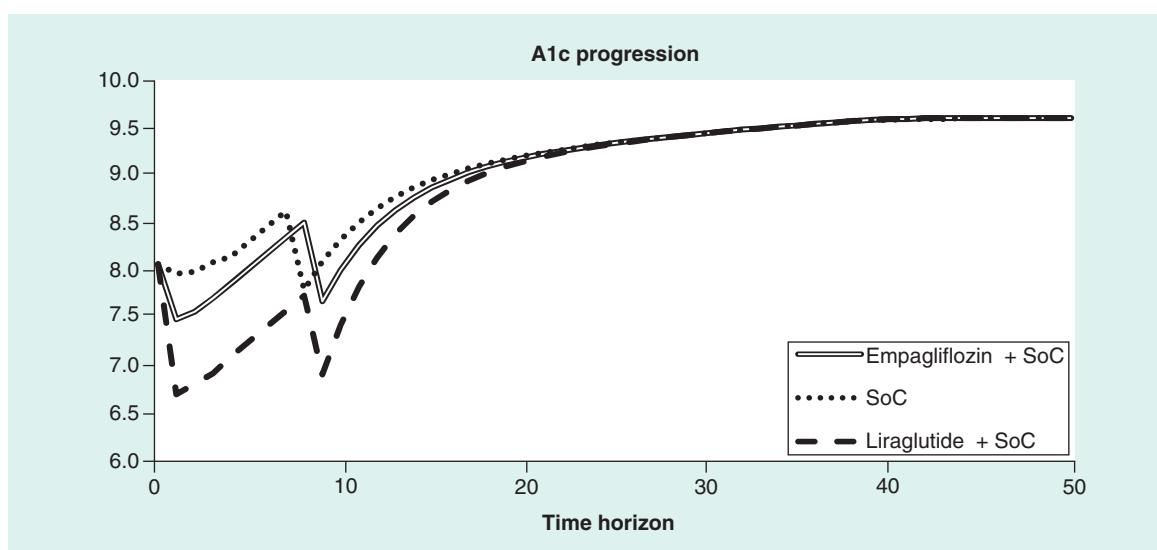


Figure 2. Progression of HbA1c over time.
SoC: Standard of care.

Treatment duration/switch to second line

As CE analyses are lifelong and treatment strategies for T2D may change, it would not be suitable to apply the same reported combined therapies throughout the time horizon of 50 years. Therefore, treatment switch to next line of therapy was defined when HbA1c level reached 8.5%. Following the progression of HbA1c over time, treatment switch happened after 8 years for empagliflozin+SoC, and after 7 years for SoC alone. For liraglutide+SoC, treatment switch would occur after 13 years due to the steep initial decrease in HbA1c levels as reported in the LEADER trial (Figure 2). Due to differences in the background therapy pattern between EMPAREG OUTCOME and LEADER trials (much more use of insulin in the latter), progression of HbA1c could be considered an unreliable predictor for the time of treatment escalation. Thus, it was assumed that treatment intensification with discontinuation of study drug after 8 years of treatment was also applicable to liraglutide.

Given the duration of diabetes and the proportion of patients receiving background insulin at the end of both trials, a high dose of basal bolus insulin regimen, described by Riddle *et al.* 2014 was applied as the next line of

Table 3. First year and following up year treatment costs of each alternative including insulin (GBP).

Treatment	1st year	Subsequent years
Empagliflozin+SoC	816.65	833.97
SoC	343.60	406.11
Liraglutide+SoC	1741.88	1945.29
Basal bolus	1718.91	1718.91

SoC: Standard of care.

treatment [36]. It consists of a high dose mealtime insulin (57 international unit [IU]) combined with high dose glargine (94 IU).

Up to treatment switch, the RRs described in the calibration section, were applied. After treatment switch, the treatment effects observed in the CVOTs were no longer considered, and the standard UKPDS 82 RE [25] without the calibrated RRs, was applied to predict all CV outcomes.

Sensitivity analysis was performed to further explore the implications of these assumptions in the study outcomes.

Disease management

Clinical management information included costs associated with preventive medications such as aspirin, statins and angiotensin blocking agents, undergoing routine screening for diabetic complications and the sensitivity and specificity of the screening tests performed. Data on disease management costs were sourced from the published literature (Supplementary Table 4).

Cost data

The study considered UK healthcare payer perspective and only direct costs were included. The key cost inputs comprised cost of drugs, needles and the associated self-monitoring blood glucose (SMBG) strips, as applicable. Unit costs were extracted from the British National Formulary (BNF) and Monthly Index of Medical Specialities (MIMS) [34,37]. Cost of background insulin therapy was considered as an additive cost to the treatment alternatives under assessment. Since the proportion of patients receiving this additional medication varied from the start to the end of the trials, distinct annual treatment costs of each therapy was included for first year and subsequent years (Table 3). The impact of this cost on the results was explored in sensitivity analysis. Cost of diabetes-related complications was also considered as direct costs and were deduced from the published literature (Supplementary Table 4). Costs associated with all other concomitant medications were excluded from the analysis. All costs were inflated to 2018 using the Hospital & Community Health Service (HCHS) Index from Personal Social Services Research Unit (PSSRU 2017) [35].

Utility data

The default CDM utility data were taken from Beaudet *et al.* 2014 [38]. A minimum approach was applied to estimate utilities, meaning that for a patient with a history of MI and stroke, the lowest utility value (i.e., associated to stroke event) was used. In addition, the impact of change in BMI on utility was estimated through the inclusion of a disutility of -0.0061 per unit gain in BMI for over 25 kg/m², based on Bagust *et al.* 2005 [39]. It was assumed that BMI remained constant over time in all trial arms after treatment switch.

Analysis plan

Base case

A time horizon of 50 years was applied to estimate lifetime clinical and economic outcomes using nonparametric bootstrapping. Base-case analyses were run with 1000 hypothetical patients (generated randomly according to the baseline characteristics) for 1000 iterations. Costs and effects were discounted at an annual rate of 3.5%, as per the recommendations by the National Institute for Health and Care Excellence (NICE) [40].

Scenario analyses and probabilistic sensitivity analyses (PSA) were also conducted.

Scenarios

Key inputs and assumptions were varied to assess their impact on clinical and economic outcomes. These included scenarios where insulin cost from treatment costs were excluded, direct CVOT outcomes for 3 years followed by

Table 4. Comparison of observed versus expected outcomes - 3-year cumulative incidence (%) outcomes for empagliflozin and comparators post-CDM CVO calibration.

Observed outcomes	From EMPA-REG OUTCOME trial		ITC
	Empagliflozin+SoC	SoC	Liraglutide+SoC
Death from any cause	5.82	8.58	7.28
Death from cardiovascular causes	3.72	6.06	4.65
Myocardial infarction	5.04	5.79	5.09
Angina	3.00	3.00	3.00
Stroke	3.69	3.15	2.72
Heart failure	2.82	4.35	3.76
Microalbuminuria	75.75	79.8	75.75
Gross renal proteinuria	12.54	19.47	12.54
End-stage renal disease	0.3	0.63	0.3
Predicted outcomes	Empagliflozin+SoC	SoC	Liraglutide+SoC
Death from any cause	5.78	8.74	7.24
Death from CV causes	3.68	6.10	4.63
Myocardial Infarction	5.05	5.81	5.08
Angina	3.01	3.00	3.06
Stroke	3.70	3.18	2.71
Heart failure	2.83	4.34	3.79
Microalbuminuria	75.86	80.2	76.76
Gross renal proteinuria	12.34	15.9	9.17
End-stage renal disease	0.3	0.63	0.28

CV: Cardiovascular; ITC: Indirect treatment comparison; SoC: Standard of care.

the standard UKPDS82 RE to predict events was applied, and time horizon of 5 years with CVOT outcomes. Furthermore, HbA1c threshold was altered from 8.5 to 9% for treatment switch, and the treatment duration of liraglutide was varied.

Probabilistic sensitivity analysis

The CDM uses Monte Carlo simulations with a nonparametric bootstrapping approach to capture parameter uncertainty. This process involves sampling of input parameters by distribution in each bootstrap iteration of the analysis. Cohort baseline values (age, duration of diabetes and baseline physiological parameter levels), treatment effects on physiological parameter levels, transition probabilities for events, health state utilities and event disutilities, as well as direct costs were subjected to random sampling. The outcomes were represented in the form of a CE scatter plot and the CE acceptability curve.

Results

Calibration

The observed and CDM projected outcomes are displayed in Table 4. Differences between the observed and projected outcomes were considered acceptable when below 5%, implying that the model has been calibrated to an acceptable degree of accuracy.

Base-case analysis

When compared with SoC alone, empagliflozin+SoC was associated with an increase in LYs (0.85) and QALYs (0.57), and higher direct lifetime costs (GPB 50,801 vs GPB 47,137; Δ GPB 3664), which resulted in an incremental cost-effectiveness ratio (ICER) of GPB 6428 per QALY gained. As ICER remained below the willingness-to-pay (WTP) threshold of GBP 20,000 per QALY as recommended by NICE, empagliflozin+SoC was deemed cost effective in comparison to SoC alone [40]. When compared with liraglutide+SoC, empagliflozin+SoC was associated with an increase in LYs (0.23) and QALYs (0.22), but lower direct lifetime costs (GPB 50,801 vs GPB 54,185; Δ GPB 3384) (Table 5), which led to empagliflozin+SoC being dominant over liraglutide+SoC.

Table 5. Cost-effectiveness results when cardiovascular outcomes are extended till treatment switch (per average patient).

Cost-effectiveness results per arm	Empagliflozin+SoC	SoC	Liraglutide+SoC
LY	10.259	9.406	10.029
QALY	6.408	5.838	6.190
Total costs	50,801	47,137	54,185
Incremental cost-effectiveness results empagliflozin+SoC versus	SoC	Liraglutide+SoC	
Incremental LY	0.853	0.230	
Incremental QALY	0.570	0.218	
Incremental total cost (GBP)	3664	-3384	
ICER (GBP/QALY)	6428	Dominant	

Cardiovascular outcomes till treatment switch.
ICER: Incremental cost-effectiveness ratio; ICUR: Incremental cost-utility ratio; LY: Life year; QALY: Quality-adjusted life year; SoC: Standard of care.

Table 6. Cumulative incidence of events at 5 years.

Clinical outcomes	Empagliflozin+SoC	SoC	Liraglutide+SoC
Cardiovascular disease			
Peripheral vascular disease	3.67	3.76	2.91
Heart failure	5.79	8.7	7.77
Angina	7.11	7.1	4.46
Stroke	3.41	2.99	2.43
Myocardial infarction	6.1	7.47	6.07
Renal disease			
Microalbuminuria	91.41	92.58	91.65
Gross proteinuria	16.07	20.04	11.86
End-stage renal disease	1.08	2.1	1.09
Eye disease			
Background diabetic retinopathy	4.55	5.49	3.27
Proliferative diabetic retinopathy	0.43	0.54	0.3
Macular edema	3.96	4.75	2.82
Severe vision loss	1.63	1.91	1.15
Cataract	2.52	2.65	2.13
Ulcer/amputation/neuropathy			
Ulcer	0.9	0.99	0.82
Recurrent ulcer	0.81	0.84	0.8
Amputation ulcer	0.27	0.29	0.25
Amputation rec ulcer	0.04	0.04	0.04
Neuropathy	20.59	24.05	15.06
Hypoglycemia (event/patient)			
Non-severe hypoglycemia	0.69	0.68	13.829
Severe hypoglycemia (type 1)	0.05	0.05	0.424
Severe hypoglycemia (Type II)	0.00	0.00	0.053

SoC: Standard of care.

For the long-term outcomes, patients treated with empagliflozin+SoC were projected to have better survival compared with liraglutide+SoC and SoC alone (Figure 1). It should be noted that by having a better survival than liraglutide+SoC and SoC alone, more events are expected to happen (survival paradox) and, therefore, the cumulative incidence of events were reported over a shorter time period so that this effect is less evident.

For the short-term outcomes, patients receiving empagliflozin+SoC reported a lower incidence of HF but a higher incidence of stroke compared with liraglutide+SoC (Table 6). Compared with SoC alone, patients receiving empagliflozin+SoC had a lower incidence of CV and renal disease (Table 6). Overall, patients receiving

Table 7. Breakdown of costs (per average patient).

Breakdown of costs	Empagliflozin+SoC	SoC	Liraglutide+SoC
Total	50,801	47,137	54,185
Treatment	13,017	9898	19,542
Management	581	532	568
Cardiovascular disease	24,097	21,926	22,853
Renal disease	10,517	12,245	8507
Ulcer/amputation/neuropathy	430	395	383
Eye disease	1025	1013	848
NSHE	479	478	537
SHE (req. nonmed. assistance)	504	500	702
SHE (req. med. assistance)	151	150	244

NSHE: Nonsevere hypoglycemic event; SHE: Severe hypoglycemic event; SoC: Standard of care.

Table 8. Cost-effectiveness results of scenarios.

Cost-effectiveness results	Empagliflozin+SoC	SoC	Liraglutide+SoC
Insulin costs are excluded			
LY	10.259	9.406	10.029
QALY	6.408	5.838	6.190
Total cost	48,541	44,937	51,159
ICER (GBP/QALY)		6322	Dominant
Time horizon up to 5 years			
LY	4.254	4.118	4.201
QALY	2.789	2.688	2.685
Total cost	13,973	12,255	18,432
ICER (GBP/QALY)		17,007	Dominant
Mortality			
CV-related	6.70	11.18	7.87
Non-CV related	3.82	4.79	4.8
All mortality	10.52	15.97	12.67
CVO up to 3 years			
LY	9.614	9.215	9.573
QALY	6.036	5.734	5.923
Total cost	44,592	43,392	48,846
ICER (GBP/QALY)		3972	Dominant
HbA1c threshold at 9%			
LY	10.742	9.539	10.354
QALY	6.776	5.984	6.428
Total cost	44,592	43,392	48,846
ICER (GBP/QALY)		8720	Dominant

ICER provides data of empagliflozin+SoC vs SoC or Liraglutide+SoC.

CV: Cardiovascular; CVO: Cardiovascular outcome; ICER: Incremental cost-effectiveness ratio; LY: Life year; QALY: Quality-adjusted life year; SoC: Standard of care.

empagliflozin+SoC had the lowest CV-related or non-CV-related mortality compared with liraglutide+SoC and SoC alone (Table 8).

In terms of costs, treatment with empagliflozin+SoC was associated with higher CVD costs compared with liraglutide+SoC and SoC alone. Treatment costs with liraglutide+SoC were higher than those with empagliflozin+SoC and SoC alone. As empagliflozin+SoC slowed down the progression of renal disease, the costs of treating these complications declined compared with SoC alone. Management costs were also higher compared with liraglutide+SoC and SoC alone due to longer survival in the empagliflozin+SoC arm (Table 7).

Scenario analyses

When the time horizon was limited to 5 years, empagliflozin+SoC led to additional LYs (0.136), QALYs (0.101) and total cost (GBP 1718) in comparison to SoC alone, thus resulting in an ICER of GBP 17,007 per QALY gained. Compared with liraglutide+SoC, empagliflozin+SoC led to additional LYs (0.053) and QALYs (0.104), but at a lower cost (GBP 4459), and thus continued to be dominant over liraglutide+SoC (Table 8). After applying the direct CVOT outcomes up to 3 years (time horizon of the EMPA-REG OUTCOME trial) [14], the ICER comparing empagliflozin+SoC versus SoC alone was GBP 3972 per QALY gained, based on an incremental cost of GBP 1200 and incremental LY and QALY of 0.399 and 0.302, respectively. Compared with liraglutide+SoC, empagliflozin+SoC remained dominant as a result of additional LYs and QALYs (0.041 and 0.113) and lower total cost attributed to empagliflozin+SoC (incremental cost: - GBP 4254) (Table 8). Similar results were observed after varying the treatment switch threshold from HbA1c 8.5 to 9% and excluding the cost of insulin therapy (Table 8). Overall, all ICERs remained under the threshold of 20,000GBP per QALY.

To assess the impact of treatment duration of liraglutide, an additional scenario analysis was conducted, with treatment switch occurring at 13 years (i.e., an additional 5 years of therapy, when liraglutide reaches the HbA1c threshold of 8.5%). In addition, CVOT outcome benefits were applied across the full treatment duration. This resulted in negative incremental LYs and QALYs (-0.102 and -0.038, respectively) but higher cost savings of GBP 9877 for empagliflozin+SoC as compared with liraglutide+SoC, positioning it in the south-western quadrant on the CE plane. The resulting ICER was above GBP 250,000 per QALY gain, thereby indicating empagliflozin+SoC as being cost effective compared with liraglutide+SoC (net monetary benefit >0).

Probabilistic sensitivity analyses

PSA showed that empagliflozin+SoC is a cost-effective therapy in 97% of the simulations versus SoC alone and in 91% of simulations versus liraglutide+SoC, for a WTP threshold of GBP 20,000 per QALY (Figures 3 & 4).

Discussion

This study projects the outcomes of the EMPA-REG OUTCOME trial [14,33] and ITC [32] in patients with established CVD. The CDM version 9.0 was calibrated to project CV and renal outcomes that matched the results of CVOTs.

The base-case analysis demonstrated that empagliflozin+SoC is associated with improved LYs and QALYs compared with liraglutide+SoC and SoC alone. Empagliflozin+SoC was considered more effective since it reported the lowest CV-related or non-CV-related mortality compared with both liraglutide+SoC and SoC alone. In terms of costs, empagliflozin+SoC was costlier than SoC alone, which can be attributed to higher CVD costs and management costs. In contrast, the treatment costs in the liraglutide+SoC arm was higher than that in the empagliflozin+SoC and SoC alone arms. The resulting ICER for empagliflozin+SoC versus SoC alone was GBP 6428 per QALY gained, meaning that at the WTP threshold of GBP 20,000 per QALY gained, empagliflozin+SoC is considered cost effective versus SoC alone. Compared with liraglutide+SoC, empagliflozin can be considered dominant.

The scenario analyses performed in this study reported similar findings, confirming the robustness and the validity of the base-case analysis. In all scenarios (except longer treatment duration of liraglutide), empagliflozin+SoC remained cost effective compared with SoC alone and dominant versus liraglutide+SoC at a WTP threshold of GBP 20,000 per QALY. In the scenario where treatment duration of liraglutide was extended to 13 years, empagliflozin+SoC, despite, being associated with lower incremental LYs and QALYs, it was still cost effective as compared with liraglutide+ SoC due to increased cost savings. It should be noted that this scenario was introduced primarily to assess the impact of treatment duration of administering liraglutide than to assess the value of the drug. This extended treatment duration for liraglutide+SoC was prolonged due to a strong immediate decrease in HbA1c, followed by continuous treatment escalation as reported in the LEADER trial (with insulin), thereby, delaying the progression of HbA1c over the study period.

Furthermore, when fixing the time horizon at 5 years, short-term clinical benefits of empagliflozin+SoC confirmed lower CV and non-CV events and HF events; however, lifetime analyses showed that these benefits were partly offset by the extended life expectancy and prolonged exposure to diabetes complications ('survival paradox'). As a result of higher survival, both complications and management costs were greater in the empagliflozin+SoC arm compared with both liraglutide+SoC and SoC alone.

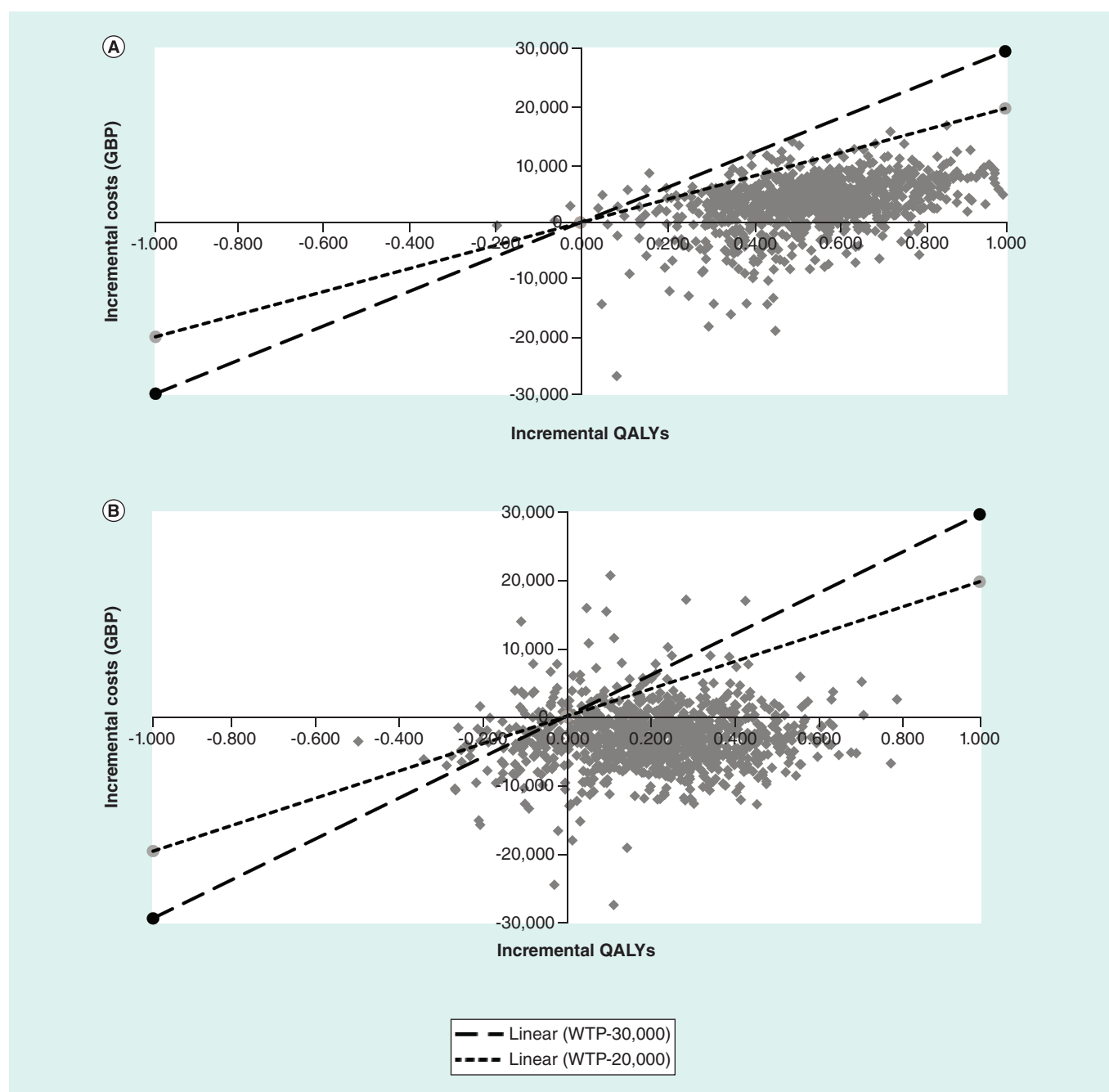


Figure 3. Cost-effectiveness scatter plot of empagliflozin+SoC versus SoC (A) and Liraglutide+SoC (B) (in terms of QALYs). QALY: Quality adjusted life-year; SoC: Standard of care; WTP: Willingness to pay.

The PSA findings also confirmed the robustness of the results. In most simulations (at least 90 and 83%), empagliflozin+SoC is a cost-effective therapy compared with both SoC alone and liraglutide+SoC respectively and dominant over liraglutide+SoC in 69% of simulations.

Recently, several health economic studies have been published based on the EMPA-REG OUTCOME trial [23,41–46] demonstrating that empagliflozin is a cost-effective therapy in patients with diabetes and established CVD. Another study also used the CDM 9.0 with calibration to study empagliflozin in patients with T2D, free of a history of CVD [47]. Similar to the current study, both studies also demonstrated that with the existing evidence on

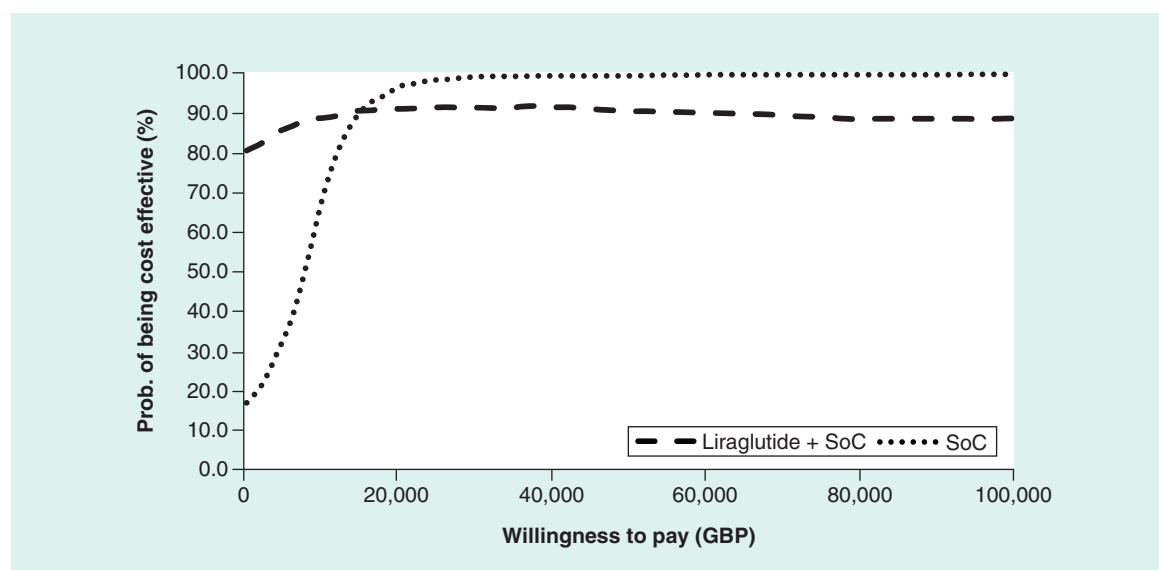


Figure 4. Cost-effectiveness acceptability curve of empagliflozin versus SoC and Liraglutide.
SoC: Standard of care.

the impact of drugs on CV and renal outcomes, calibration of the CDM is a valuable option to assess and compare the long-term and short-term clinical and economic benefits of medications.

Due to the absence of head-to-head clinical trials between empagliflozin and liraglutide, the present study inherited some limitations by obtaining relative efficacy of the comparators via ITC [32]. Authors described some drawbacks related to its methodology, as a consequence of the existing differences across CVOTs. The same limitations apply also to the current economic analyses [28,32,48].

Nevertheless, the present study used a customized version of the CDM, to project the outcomes of different CVO trials and the ITC in the analyses. The CDM calibration process included a validation step, to ensure that the methodology used would allow the CDM to predict the trials' outcomes accurately at 3 years.

Conclusion

This study demonstrates that empagliflozin+SoC is a cost-effective treatment compared with SoC alone and dominant versus liraglutide+SoC in the management of patients with T2D with established CVD from the UK healthcare payer perspective. Sensitivity and scenario analyses confirmed the robustness of the base-case findings.

Future perspective

Typical diabetes disease models using well-established risk equations (REs) to predict diabetes complications need to be calibrated to project the outcomes of CVO trials. Calibrating for one drug in a class does not mean the calibration is valid for another drug in the same class. The evidence generated by clinical trials should be analysed in detail to pinpoint relevant physiological parameters/risk factors that explain differences between these trials and REs predictions. Also, to identify which drug class effects impact the human body. The CVO trials have a limited time horizon (maximum up to 4–5 years but most trials much less), thus, real world effectiveness data and observational studies could be used to confirm and validate CVO trials findings.

Summary points

- EMPA-REG OUTCOME and LEADER trials provide relevant information about the safety profile of empagliflozin and liraglutide as add-on to standard of care (SoC), in patients with established cardiovascular disease. The main outcomes of the cardiovascular outcome trials (CVOT) point toward cardiovascular and renal complications.
- Using the treatment effects reported in these trials and the comparative evidence derived from an indirect treatment comparison, the Core Diabetes model was calibrated to be able to predict well the outcomes observed on the treatment alternatives (less than 5% variation).
- In the calibration process, the UKPDS 82 REs was found to be the best option to predict diabetes complications.
- The analysis assumed that CVOT benefits would apply while patients were on treatment. Several scenarios were added to assess the impact of this assumption.
- Considering the background insulin therapy given to patients in both trials, the next line therapy was defined with high dose of basal bolus insulin.
- In the short-term, empagliflozin+SoC was projected to reduce the risk of CV death, non-CV death and heart failure hospitalizations compared with SoC alone and liraglutide+SoC.
- Treatment with empagliflozin resulted in additional life years (0.853, 0.230) and quality-adjusted life years (QALY) (0.570, 0.218), for an incremental cost of GBP (+3664–3384) compared with SoC alone and liraglutide+SoC, respectively.
- The present analysis has demonstrated that empagliflozin+SoC is a cost-effective therapy compared with SoC alone and dominant compared with liraglutide+SoC from the UK healthcare payer perspective.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <https://www.futuremedicine.com/doi/suppl/10.2217/ce-2020-0071>

Author contributions

All authors are responsible for the content of the manuscript, including the data collection and analyses. M Ramos, M Lamotte, A Ustyugova and N Hau contributed to the conception and design of the study, acquisition and review of data, analyses and interpretation of results. M Ramos and M Lamotte drafted the manuscript. A Ustyugova and N Hau revised it critically for important intellectual content and final approval of the version to be submitted.

Financial & competing interests disclosure

This study was sponsored by Boehringer Ingelheim International GmbH. IQVIA, the employer of M Ramos and M Lamotte received consulting fees for the adaptation of the Core Diabetes model. A Ustyugova and N Hau were full-time employees of Boehringer Ingelheim at the time the study was conducted. Part of the content of this manuscript was presented as a poster at the 2018 European ISPOR, held in Barcelona. The current health economic analysis was conducted based on the results of published clinical trials. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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- **Sets the need to evaluate diabetes therapies not only from the point of view of controlling blood glucose level, but also demands that industry provides safety data in terms of cardiovascular outcomes (CVO) on drugs. Since then, CVO trials have been designed and run to respond to both needs, in some of them including also other outcomes (e.g., renal outcomes).**
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