

Research: Health Economics

Cost-effectiveness analysis of empagliflozin treatment in people with Type 2 diabetes and established cardiovascular disease in the EMPA-REG OUTCOME trial*

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Abstract

Aim In the EMPA-REG OUTCOME trial, empagliflozin therapy reduced cardiovascular death by 38% compared with placebo when added to standard of care. Using the trial results, we created a discrete-event simulation model to assess lifetime health economic outcomes in people with Type 2 diabetes and established cardiovascular disease.

Methods Time-dependent survival regression analysis was performed on data from EMPA-REG OUTCOME for 10 cardiovascular and renal events (e.g. stroke, heart failure hospitalization, macroalbuminuria, cardiovascular mortality) to capture event rates over time, and interaction between events. Model performance was assessed by comparing predicted and observed outcomes at 3 years. Costs in the United Kingdom (UK) and health utilities were obtained from published literature. Outcomes included cumulative event rates, life-years, costs and quality-adjusted life-years (QALYs).

Results The model predicted an 18% relative increase (by 2.1 life-years) in survival for empagliflozin (14.0 life-years) vs. standard of care (11.9 life-years), attributable to direct treatment effect on cardiovascular mortality, and to indirect effect via reductions in other events. Participants treated with empagliflozin may experience improved quality of life (1.0 QALY) and higher costs (£3737/participant), yielding an incremental cost-effectiveness ratio (ICER) of £4083/QALY. Sensitivity analyses confirmed the robustness of these results to changes in input parameters.

Conclusions Based on extrapolation of EMPA-REG OUTCOME trial data using a participant-level simulation model, empagliflozin in addition to standard of care is projected to be highly cost-effective using UK healthcare costs. The impact in other countries will vary due to differences in drug pricing and accrual of other costs. (Clinical Trial Registry No: NCT01131676)

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Introduction

Most of the Type 2 diabetes economic burden pertains to the diagnosis and management of related complications, mainly macrovascular, e.g. myocardial infarction (MI) and stroke, but also includes indirect costs of disease related to productivity loss and reduced life expectancy. The ultimate goal of

anti-glycaemic therapy in people with Type 2 diabetes is to prevent microvascular and macrovascular complications to increase life expectancy and quality of life (QoL) and to reduce costs [1–4]. However, demonstrating improvements in cardiovascular outcomes with anti-hyperglycaemic therapies has been challenging. Major studies, including UKPDS, ACCORD, ADVANCE and VADT [5], performed to assess the impact of glycaemic control, have been unable to demonstrate unequivocal improvements in the occurrence of complications or mortality [5].

The EMPA-REG OUTCOME study (Clinical Trial Registry No: NCT01131676) evaluated the effect of adding empagliflozin (10 or 25 mg once-daily) to the standard of care on cardiovascular events and mortality in people with diabetes with established cardiovascular disease. Trial

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What's new?

- The sodium–glucose co-transporter 2 inhibitor empagliflozin has been shown to mitigate cardiovascular risk and cardiovascular death in people with Type 2 diabetes with established cardiovascular disease.
- An economic model was developed to extrapolate the outcomes of empagliflozin plus standard of care compared with standard of care alone over peoples' remaining lifetime in the United Kingdom.
- Patient-level data from EMPA-REG OUTCOME were analysed to generate time-to-event distributions for 10 cardiovascular and renal outcomes, including myocardial infarction, stroke, heart failure hospitalization, development of chronic kidney disease and cardiovascular mortality.
- Empagliflozin may have a positive benefit for people at costs acceptable to payers.

participants were taking a mix of background medications (metformin, dipeptidyl peptidase-4 inhibitors, sulfonylureas, thiazolidinedione, glucagon-like peptide-1 agonists and insulin) alone or in combination for glycaemic control, and were receiving therapies to manage cardiovascular risk (lipid-lowering therapy, anti-hypertensive therapy and anti-coagulants). EMPA-REG-OUTCOME was the first placebo-controlled, randomized controlled trial of a glucose-lowering therapy in Type 2 diabetes to demonstrate a significant reduction in cardiovascular outcomes, with a 38% reduction in cardiovascular mortality [hazard ratio (HR) 0.62; 95% confidence interval (CI) 0.49–0.77] [6]. These results led to European Union and United States approval of empagliflozin to prevent cardiovascular death in people with Type 2 diabetes and established cardiovascular disease – the first glucose-lowering drug to be granted a mortality indication.

We developed an economic model to extrapolate the clinical and cost outcomes of people with Type 2 diabetes and established cardiovascular disease who were recruited to the EMPA-REG OUTCOME trial. The availability of quantitative outcome data allows this model to rely exclusively on observed event rates, rather than estimating event rates from extrapolated changes in biomarker values (e.g. HbA_{1c}).

Participants and methods

Model approach and description

The discrete-event simulation approach was used to simulate the rates of relevant clinical events in people with Type 2 diabetes with established cardiovascular disease from EMPA-REG OUTCOME and to assign associated lifetime costs and

QoL consequences. The number of complications and deaths that occur during the lifetime of a group of individuals with different characteristics are estimated based on event-free survival curves from analyses of the trial data. As events accumulate, they can alter the risk of future events and management costs, and QoL of the simulated participant. This approach was selected based on a systematic literature review of approaches for modelling event-driven clinical trial data [7]. It permits modelling of multiple events for each participant, with the probability of events contingent on the type of events the participant has already experienced and their clinical characteristics (e.g. age, HbA_{1c}).

At model initiation, a cohort of people with Type 2 diabetes and established cardiovascular disease is generated based on EMPA-REG OUTCOME data (Fig. 1). Identical participants are assigned to treatment with standard of care with empagliflozin (empagliflozin regimen) or standard of care with no additional active treatment (placebo regimen). Predicted time to events is assigned based on the relationship of clinical prognostic factors (e.g. prior MI) to event rates from EMPA-REG OUTCOME data. The model compares the event times to determine which event happens first. Following the event, two options are possible: (i) the participant exits the model if a fatal event occurs or the time horizon ends; or (ii) the participant remains in the model and treatment history, risk of future events and time to next event are updated. Once all participants have been simulated on both treatments, individual participant outcomes are aggregated to compute the mean population outcomes.

Participant population

The simulated population was created by randomly sampling complete individual profiles with replacement from the observed subject-level data describing characteristics of participants collected at baseline in the EMPA-REG OUTCOME trial ($N = 7020$), which considers natural correlations among risk factors and medical histories. Each participant record included demographic attributes such as age, sex, health condition (BMI and HbA_{1c}), history of cardiovascular and renal events, and region (Table 1). All participants with Type 2 diabetes had established cardiovascular disease. Assessment of effect modification suggested that treatment effect was homogeneous in patients of different region, ethnicity and race (P -values for interaction did not meet a significance level of 0.05), thus the overall trial population was used to evaluate the impact of treatment on costs and QoL [6].

We used deidentified data from a clinical trial involving human participants, but did not deal with or report on any specific participants, so we did not seek ethics committee approval. However, the EMPA-REG OUTCOME trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on

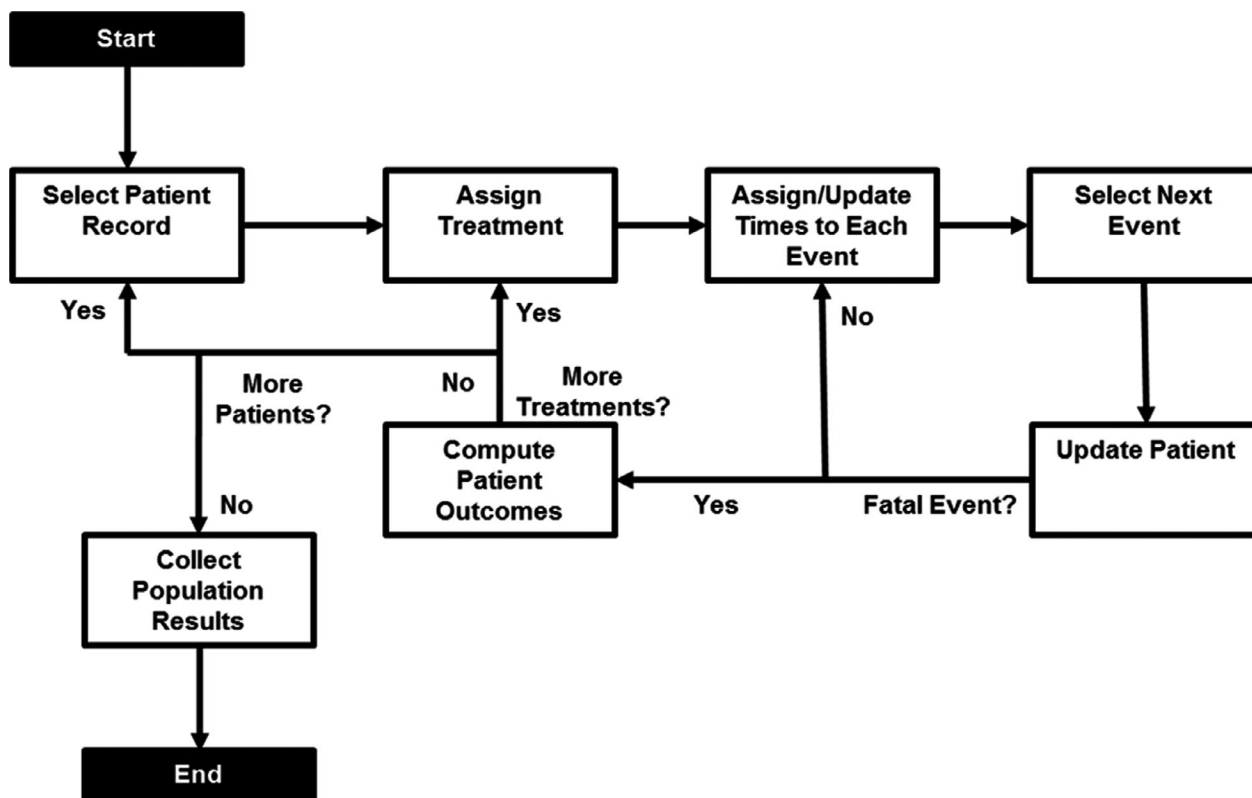


FIGURE 1 Schematic of the simulation flow.

Harmonization Good Clinical Practice guidelines and was approved by local authorities. An independent ethics committee or institutional review board approved the clinical protocol for each participating centre. Participants provided written informed consent before entering the trial.

Clinical and treatment inputs

The model captured treatment effectiveness by tracking 10 clinical events specified in EMPA-REG OUTCOME: cardiovascular death, non-fatal MI, non-fatal stroke, unstable angina hospitalization, heart failure hospitalization, transient ischaemic attack, revascularization, new onset of macroalbuminuria, renal injury (doubling of serum creatinine, with $eGFR < 45 \text{ ml/min/1.73 m}^2$), and renal failure (initiation of continuous renal replacement therapy). The model captures death through non-cardiovascular causes using United Kingdom (UK) mortality data [18]. Non-fatal cardiovascular events were permitted to recur; renal events were considered non-recurring. Rare complications of diabetes (e.g. blindness) were not included in the model because the occurrence rates were low. Similarly, adverse events (e.g. genital infection) were not included, because these are usually transient events not associated with hospitalization or inpatient costs.

Occurrence of cardiovascular and renal events was obtained from statistical analysis of EMPA-REG

OUTCOME data. Parametric models were used to extrapolate the observed trends in the hazard of each event to allow prediction of individual participant histories in the simulation model over a lifetime horizon. This is a conventional approach to long-term estimation of outcomes in cost-effectiveness modelling, when only short-term clinical trial evidence is available.

For modelled events, a two-stage analysis was performed. First, a population-level, event-free survival function was fit to the trial data using candidate parametric distributions. Second, Cox regression analysis was used to generate individual-level risk estimates based on participant characteristics and event history. The population-level occurrence of each diabetes-related complication in EMPA-REG OUTCOME was captured as an event-free survival curve. Individual-level data from EMPA-REG OUTCOME was fit using parametric survival models (Weibull, exponential, log-normal and Gompertz were tested) to describe the distribution of time to each first event in the clinical trial. The best-fit survival model was chosen based on numerical fit (Akaike's Information Criterion and Bayesian Information Criterion), realistic extrapolation beyond the trial time horizon and parsimony (preferring the simplest functional form) [19]. Survival analyses were performed in Statistical Analysis System version 9.4.

The individual-level risk equations were developed by testing baseline and time-dependent characteristics as

Table 1 Baseline characteristics and model inputs for the cost-effectiveness model

Parameters	Base-case value (95% CI)	Distribution	Data source [Ref.]
Baseline population characteristics			
Demographic characteristics			
Mean age, years	63		EMPA-REG OUTCOME [6]
Women, %	29		EMPA-REG OUTCOME [6]
BMI \geq 30, %	52		EMPA-REG OUTCOME [6]
HbA _{1c} \geq 69 mmol/mol (8.5%)	31		EMPA-REG OUTCOME [6]
CV history, %			
Non-fatal stroke	23		EMPA-REG OUTCOME [6]
Non-fatal MI	47		EMPA-REG OUTCOME [6]
CABG	25		EMPA-REG OUTCOME [6]
MCAD	47		EMPA-REG OUTCOME [6]
SVCAD	10		EMPA-REG OUTCOME [6]
PAD	21		EMPA-REG OUTCOME [6]
eGFR, %			
\geq 90 ml/min/1.73 m ²	22		EMPA-REG OUTCOME [6]
60 to < 90 ml/min/1.73 m ²	52		EMPA-REG OUTCOME [6]
<60 ml/min/1.73 m ²	26		EMPA-REG OUTCOME [6]
Geographical region, %			
Africa	4		EMPA-REG OUTCOME[6]
Asia	19		EMPA-REG OUTCOME[6]
Europe	41		EMPA-REG OUTCOME[6]
Latin America	15		EMPA-REG OUTCOME[6]
North America	20		EMPA-REG OUTCOME[6]
Empagliflozin daily drug cost, £	1.31		MIMS Drug Database[8]
Cost per episode of clinical events, £			
Non-fatal MI	8120	Gamma	Alva <i>et al.</i> , 2015[9]
Non-fatal stroke	11 921	Gamma	Alva <i>et al.</i> , 2015[9]
Unstable angina	5186	Gamma	Clarke <i>et al.</i> , 2003[10]
Heart failure	5001	Gamma	Alva <i>et al.</i> , 2015[9]
Transient ischemic attack	5654	Gamma	Ward <i>et al.</i> , 2012[11]
Revascularization	6192	Gamma	Cassar, 2006[12]
CV death	3684	Gamma	Alva <i>et al.</i> , 2015[9]
Macro-albuminuria	8896	Gamma	Gordios <i>et al.</i> , 2004[13]
Renal injury	676	Gamma	Kent <i>et al.</i> , 2015[14]
Renal failure	44,876	Gamma	NICE technology appraisal 336[15]
Baseline utility value	0.785	Beta	Sullivan <i>et al.</i> , 2015 [16]
Utility decrements for clinical events			
Non-fatal MI	-0.047 (-0.057, -0.036)	Beta	Sullivan <i>et al.</i> , 2015 [16]
Non-fatal stroke	-0.060 (-0.074, -0.046)	Beta	Sullivan <i>et al.</i> , 2015 [16]
Unstable angina	-0.047 (-0.057, -0.036)	Beta	Sullivan <i>et al.</i> , 2015 [16]
Heart failure	-0.050 (-0.064, -0.036)	Beta	Sullivan <i>et al.</i> , 2015 [16]
Transient ischemic attack	-0.070 (-0.131, -0.008)	Beta	Sullivan <i>et al.</i> , 2015 [16]
Revascularization	-0.030 (-0.036, -0.024)	Beta	Lindgren <i>et al.</i> , 2007[17]
Macro-albuminuria	-0.038 (-0.059, -0.016)	Beta	Sullivan <i>et al.</i> , 2015 [16]
Renal injury	-0.038 (-0.059, -0.016)	Beta	Sullivan <i>et al.</i> , 2015 [16]
Renal failure	-0.038 (-0.059, -0.016)	Beta	Sullivan <i>et al.</i> , 2015 [16]
Utility effect of multiple events (additive to utility)			
2 events	0.017		Sullivan <i>et al.</i> , 2015 [16]
3 events	0.042		Sullivan <i>et al.</i> , 2015 [16]
4 events	0.070		Sullivan <i>et al.</i> , 2015 [16]
\geq 5 events	0.087		Sullivan <i>et al.</i> , 2015 [16]

CABG, coronary artery bypass grafting; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MCAD, multivessel coronary artery disease; MI, myocardial infarction; NICE, National Institute for Health and Care Excellence; PAD, peripheral artery disease; SVCAD, single vessel coronary artery disease

potential predictors of the outcomes in Cox regression analyses. Candidate characteristics for predictors were selected based on clinical relevance, and included basic demographic information (age, sex, geographic region), baseline biomarkers (HbA_{1c}, BMI, eGFR), baseline event history (cardiovascular, cerebrovascular or peripheral arterial disease), and cardiovascular and renal events experienced during trial follow-up, along with treatment arm. Candidate

predictors were included in time-dependent multivariate parametric equations (using R, version 3.2.2). [20] The multivariate equations were developed by first considering all candidate predictors that trended towards significance in univariate analyses ($P < 0.20$). The final multivariate equations were then reduced by eliminating terms in order of highest P -value until all terms had $P < 0.20$ level. Treatment effect was assumed to apply across all participants and to be

constant over time. The assumption of common treatment effect was supported by subgroup analyses of trial data in which only baseline age and HbA_{1c} indicated significant interactions ($P \leq 0.05$) with treatment effect for the primary outcome, but not for cardiovascular mortality; meanwhile only BMI indicated an interaction with treatment for cardiovascular mortality, but not for the primary outcome. The assumption of constant treatment effect over time was justified by proportional hazards testing.

Based on the clinical relationships, renal events were permitted as predictors of the risk of future cardiovascular events and mortality, but cardiovascular events were not predictors of renal events.

Costs and perspective

A UK National Health Service (NHS) third-party healthcare payer perspective was taken; thus, only direct costs were included in the model (Table 1). All costs are expressed in UK pounds (£), with inflation to 2019 values using the health component of the UK Harmonized Index of Consumer Prices [21]. The model captures costs associated with empagliflozin drug use and the acute costs of managing each analysed clinical event. Events indirectly imposed long-term costs by increasing the risk of future costly events. Thus, to avoid any double counting, the model did not include any long-term costs associated with each clinical event. This approach captured most relevant inpatient costs, but excludes long-term outpatient costs.

Daily drug acquisition cost of empagliflozin (£1.31) was extracted from the MIMS Drug Database [22]. Because EMPA-REG OUTCOME compared empagliflozin plus standard of care, no other pharmacy costs were considered [23].

All other regular disease management and monitoring costs were assumed to be the same for both the empagliflozin and placebo regimens, and were therefore not included in the model.

Quality of life

Health outcomes were expressed in quality-adjusted life-years (QALYs) to measure the length of life adjusted for QoL (Table 1). QALYs were calculated using a baseline value and a permanent decrement associated with history of each event from published literature [16,17,23]. As participants accumulate multiple diabetes-related conditions, utility decrements from each event were summed and adjusted using an additive utility effect based on the number of events.

Model analyses

In the base-case, a lifetime horizon was chosen to fully capture costs and QoL benefits of empagliflozin. The same cohort (5000 participants) was used for all analyses to ensure comparability. Model outputs include cumulative events per

100 patient-years, life expectancy, QALYs, costs and incremental cost-effectiveness ratios (ICERs). Costs and utilities were discounted at 3.5% annually [24].

Univariate sensitivity analyses were carried out to assess: (i) what components of the treatment effect are most influential, (ii) how predictions vary over time, (iii) participant population histories and (iv) the impact of uncertainty in cost and utility inputs. Specifically, the impact of no treatment effect on cardiovascular mortality, heart failure hospitalization, non-fatal MI, and non-fatal stroke was assessed. The baseline risk of clinical events was varied by applying a hazard ratio (ranging from 0.90 to 1.10) to the survival function of each cardiovascular and renal outcome. The model was run using a reduced 10-year time horizon. Analyses in people with history of MI, stroke and peripheral artery disease at baseline was conducted. Discount rates on costs and QALYs ranging from 0% to 5% were applied. Higher (+20%) and lower (−20%) costs (drug acquisition and event management) and utilities (no event history and decrements) were used. Probabilistic sensitivity analysis was performed using distributions (beta distributions for probabilities and utilities and gamma distributions for costs) reflecting parameter uncertainties, producing 1000 pairs of incremental effectiveness and cost estimates.

Results

Table S1 shows the parameters included in the final risk equations that trended towards a significant effect (at $P < 0.20$) or are important prognostic factors that show a non-negligible effect size. The regression coefficients can be interpreted as the log of the HRs, with a negative value indicating that a characteristic is associated with lower risk and a positive value indicating association with higher risk. As expected, several linkages between events were observed. For example, a history of MI increases the risk of a stroke, i.e. experiencing an MI during follow-up has a positive coefficient in the stroke risk equation.

Validation of the derived equations reproduced the overall event rates in EMPA-REG OUTCOME when treated as competing events. A large number of participants (10 000) were simulated for the 3-year mean trial follow-up duration for the validation, because the short time horizon and relatively low rate of events make the validation results sensitive to random variation. The largest deviations are in rates of revascularization (model HR 0.92) and cardiovascular death (model HR 0.70), both of which show rate ratios that are slightly less favourable to empagliflozin than the trial data (HR 0.86 and 0.62, respectively).

The composite of cardiovascular mortality, non-fatal MI, and non-fatal stroke rates were 7.0 events/100 patient-years with empagliflozin vs. 8.6 events/100 patient-years with standard of care only (Table 2). This translated to improvements in survival, because participants who received empagliflozin plus standard of care lived on average 2 years

Table 2 Simulation model results comparing treatment with empagliflozin to standard of care

Results	Base-case*			Probabilistic sensitivity analysis†	
	Standard of care plus empagliflozin	Standard of care alone	Incremental	Standard of care plus empagliflozin	Standard of care alone
Non-fatal MI	2.0	2.2	−0.2	2.0 (1.7, 2.5)	2.4 (1.9, 3.0)
Non-fatal stroke	1.4	1.1	0.3	1.3 (1.0, 1.8)	1.1 (0.8, 1.5)
Unstable angina	1.3	1.2	0.1	1.4 (1.1, 1.9)	1.4 (0.9, 1.9)
Heart failure	2.0	3.0	−1.0	2.1 (1.6, 2.8)	3.1 (2.2, 4.2)
Transient ischemic attack	0.3	0.3	0.0	0.2 (0.2, 0.4)	0.3 (0.2, 0.4)
Revascularization	2.7	2.9	−0.2	2.6 (2.4, 2.8)	2.8 (2.5, 3.1)
Macro-albuminuria	5.4	6.5	−1.1	5.6 (5.1, 6.1)	6.7 (6.1, 7.3)
Renal injury	1.0	1.6	−0.6	0.9 (0.7, 1.3)	1.5 (1.1, 2.1)
Renal failure	0.3	0.6	−0.3	0.3 (0.1, 0.5)	0.5 (0.2, 0.8)
CV death	3.9	5.6	−1.7	4.2 (3.6, 5.0)	5.9 (5.1, 6.8)
Non-CV death	3.2	2.8	0.4	3.3 (3.1, 3.5)	2.9 (2.7, 3.1)
Undiscounted life expectancy (years)	14.0	11.9	2.1		
Discounted QALYs	7.8	6.8	1.0		
Discounted costs over participant lifetimes					
Total costs (£)	19 776	16 040	3737		
Drug acquisition cost (£)	4914	0	4914		
Event management cost (£)	14 862	16 040	−1177		
ICER (£/QALY)	–	–	4083		

*Cumulative events per 100 patient-years.

†Event rates per patient-years (95% confidence intervals).

CV, cardiovascular; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; QALY, quality-adjusted life years.

longer than participants treated with standard of care alone. Modelled participants receiving empagliflozin plus standard of care were estimated to have a higher rate of non-cardiovascular-related mortality than those on standard of care alone, although participants receiving empagliflozin in the trial had a lower rate of death from any cause. In the model, every participant dies, because we are running lifetime analyses. Given the magnitude of reductions in cardiovascular death, the population receiving empagliflozin survives longer and their increased age results in an increase in the predicted non-cardiovascular death rate. In net, longer overall survival and reduced rates of clinical events translate to an incremental 1.0 QALY. Clinical event costs were reduced by £1177/participant despite the longer survival, partially off-setting the total lifetime costs of empagliflozin (£4914/participant) to yield an incremental cost of £3737/participant. This results in an ICER of £4083/QALY, well below the commonly accepted £30 000/QALY UK cost-effectiveness threshold.

Results of one-way sensitivity analyses are largely stable relative to variation in most model parameters (Fig. 2). The ICER ranges from £1755 to £10 531/QALY, with all scenarios yielding ICERs below the £30 000/QALY UK threshold for cost-effectiveness. The predicted benefits of empagliflozin accumulate steadily over time, with the ICER dropping as the time horizon increased from 5 years (£10 531/QALY) to 10 years (£5618/QALY) to the base-case lifetime horizon (£4083/QALY). Varying the discount rate on QALYs (£1755 to £5052/QALY) and costs (£3418 to £6508/QALY) has an impact on cost-effectiveness results, as

does varying the acquisition cost of empagliflozin (£3020 to £5173/QALY). A key driver of cost-effectiveness results was empagliflozin's effect on cardiovascular mortality (ICER of £5978/QALY). Variation in the utility parameter with no event history results in ICERs from £3378/QALY to £5160/QALY. Discount rate on both costs and QALYs (£2796 to £4229/QALY), changes in event rates (except cardiovascular mortality; £3663 to £5320/QALY), baseline disease history (£3104 to £4556/QALY), baseline risk of events (£3895 to £4372/QALY), event management costs (£3826 to £4341/QALY) and utility decrements (£4035 to £4132/QALY), had smaller effects on the ICER.

Probabilistic sensitivity analyses found relatively broad 95% CIs around mean event rates for both the empagliflozin and placebo regimens (Table 2). Given that event rates in both treatment arms tended to vary together by similar magnitude as reflected in the covariance results from the statistical analysis, the resulting range of ICERs was relatively narrow, from £2497 to £7228/QALY (mean £4404/QALY). In all instances, empagliflozin plus standard of care provides a QALY benefit over standard of care alone, and the values simulated fall well below the UK's £30 000/QALY cost-effectiveness threshold (see Fig. S1), showing that empagliflozin is consistently cost-effective.

Discussion

Results of this cost-effectiveness model, based on EMPAREG OUTCOME, suggest that empagliflozin is highly cost-effective in the UK for treatment of people with diabetes and

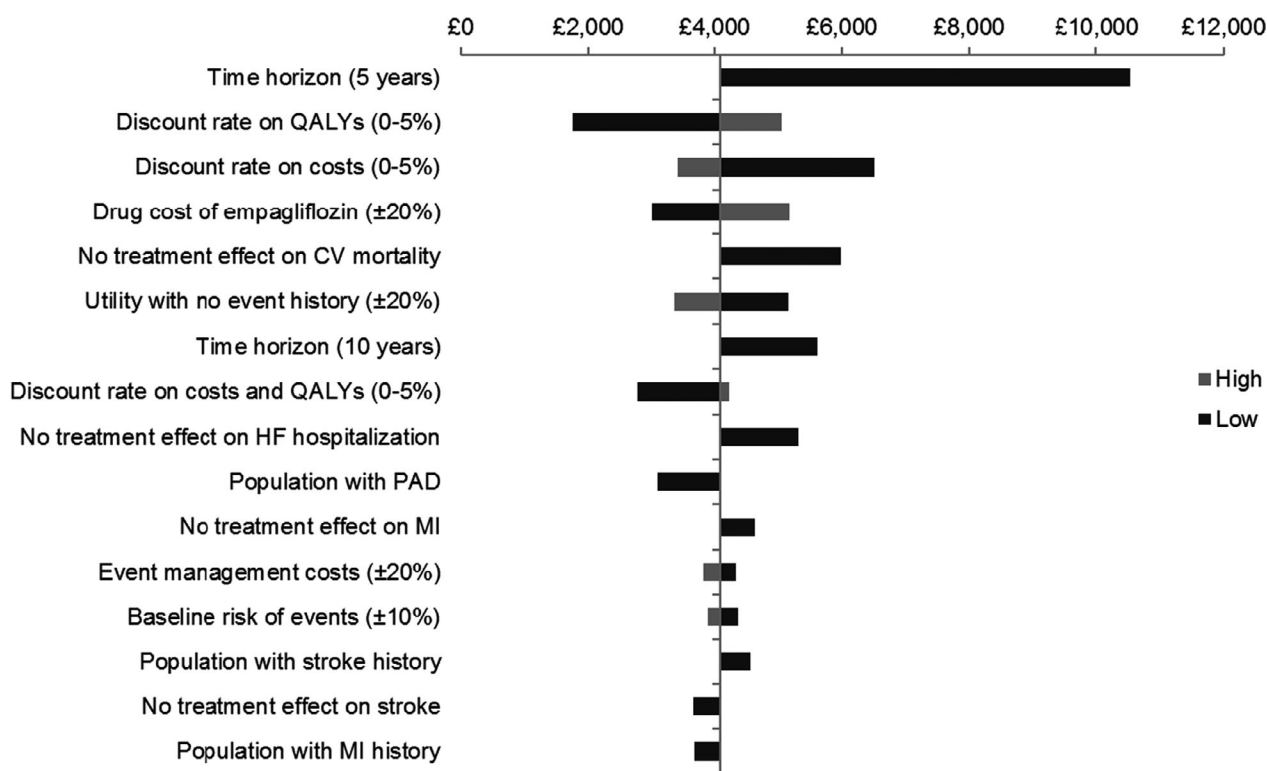


FIGURE 2 Tornado diagram. CV, cardiovascular; HF, heart failure; MI, myocardial infarction; PAD, peripheral artery disease; QALY, quality-adjusted life years.

high cardiovascular risk. The model closely reproduces the 3-year, within-trial outcomes and was used to extrapolate those results beyond the trial follow-up period to a lifetime horizon. Improvements in cardiovascular outcomes from the trial translated to long-term clinical benefits at acceptable costs. Model analyses showed that empagliflozin use in people with diabetes and high cardiovascular risk reduces cardiovascular mortality, events and their associated costs. These savings from management of fewer clinical events partially offset the additional cost of empagliflozin, resulting in a highly cost-effective use of NHS resources (£4083/QALY, well below the UK threshold of £30 000/QALY). The benefit was relatively, broadly distributed among the clinical endpoints (cardiovascular mortality, vascular outcomes), where no single endpoint dominated, as shown by the stability of the ICER in both deterministic and probabilistic sensitivity analyses.

This study uses only hard endpoint data from a cardiovascular outcomes trial to estimate the cost-effectiveness of a treatment for Type 2 diabetes. More commonly, diabetes models assume a cluster of major cardiovascular risk factors (e.g. high HbA_{1c}, elevated blood pressure) and predisposing determinants (e.g. obesity, sex) to predict cardiovascular risk in Type 2 diabetes. Treatment effects are then represented as changes in these surrogate markers with a set of risk equations, as in the UKPDS model [23,25], that is then used to predict treatment effect on cardiovascular events. This

approach, however, is not adequate for an analysis of cardiovascular event risk based on EMPA-REG OUTCOME. Specifically, an approach based on surrogate markers and UKPDS equations will not be able to capture the change in cardiovascular event rates observed in EMPA-REG OUTCOME and thus would yield model outcomes that could not be validated against the observed data.

The ICER for empagliflozin plus standard of care vs. standard of care alone may be influenced by modelling assumptions. First, we assume that clinical event rates observed in clinical practice will mirror those observed in EMPA-REG OUTCOME. This assumption is a typical limitation of interpreting any trial outcomes. However, the EMPA-REG OUTCOME trial design calls for usual standards of care in controlling HbA_{1c} – improving the likelihood of direct relevance to clinical practice. Additionally, risk factors, including HbA_{1c}, were similar between the arms in the trial, limiting the impact on net treatment effect of any potential deviation in control from clinical practice. Second, changes in risk due to changes in treatment are implicitly captured in event rate trajectories, and regardless of changes in event or treatment history, a constant treatment effect for the same event type is assumed. Third, there may be unmodelled comorbidities that would influence the shapes of the statistical extrapolations or the role of specific risk predictors. The role of any baseline confounders not influenced by empagliflozin is minimized by the randomization

process in the trial, which insures balance between treatment arms. Fourth, heterogeneity of event rates over time is assumed to be adequately captured by event history. Other evolving risk factors, such as the ongoing progression of diabetes pathophysiology, were assumed to be implicitly captured in the shape of the parametric survival functions.

The greatest strength of this study is that the model directly predicts lifetime clinical event rates in a high-risk population using data exclusively from EMPA-REG OUTCOME, requiring no extrapolated changes in surrogate biomarkers. Additionally, the model was conservative in modelling treatment, assuming no difference in the treatment costs between arms other than the presence of empagliflozin, and participants were assumed to remain on the same treatment regimen for the duration of the simulation. We know that ~ 16% more study participants in the placebo group (39.9%) had intensification of background glucose-lowering therapy compared with those in the empagliflozin groups (23.7% and 22.9% in the empagliflozin 10 and 25 mg arms, respectively) [26].

There are limitations of this study to acknowledge. First, analyses are based on data from the EMPA-REG OUTCOME trial that involve a selected patient population (inclusion/exclusion criteria were previously published [6]) treated in a specific practice environment, and may not be applicable to all people with cardiovascular disease or clinical practice settings. Second, the trial data and the modelling approach are not easily used to capture evolving treatment sequencing over time, as this cannot be simply extrapolated from the trial period; thus, conservative treatment assumptions are used. Third, the model does not capture some rare, but severe, diabetes-related complications, such as blindness and amputation, which were not observed in sufficient numbers in the trial data. Fourth, model outcomes are sensitive to the impact of subsequent events on future event rates (e.g. survivors of acute MI are at an elevated risk of a recurrent MI and other cardiovascular events), but there are relatively few data from the trial to estimate the change in risk associated with recurrent events. Nor did we incorporate the costs of well-recognized but relatively mild adverse events associated with sodium-glucose co-transporter 2 (SGLT-2) inhibitor therapy (e.g. genital infections, polyuria). These would have only minimal impacts on modelled overall healthcare costs, so would not materially affect the model findings. Fifth, we did not account for diabetic ketoacidosis episodes, an increasingly recognized rare complication of SGLT-2 inhibition, because in EMPA-REG OUTCOME there were few cases and no imbalance between the groups.

As is typically done in cost-effectiveness analyses, short-term clinical trial data with follow-up of ~ 3 years was used to make long-term predictions, assuming the risks of clinical events remain constant beyond the trial length. For example, as duration of diabetes lengthens, incidence of hypertension and development of renal dysfunction increases. However, in the absence of long-term clinical follow-up data, simulation

modelling is an efficient tool to integrate and synthesize short-term trial results with data from multiple sources to forecast long-term clinical outcomes and costs of healthcare strategies.

Overall, extrapolation of EMPA-REG OUTCOME trial data using an individual-level simulation model suggests that empagliflozin is highly cost-effective, contributing to QoL improvement at a reasonable increase in costs and thus has the potential to have a positive benefit for both payers and people with diabetes.

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Competing interests

A.K., O.S.R. and I.P. are current employees, and at the time of this project and manuscript development, Y.Z. was an employee, of Evidera, a research and consulting firm for the biopharmaceutical industry. As salaried employees, they do not accept remuneration of any kind directly from clients of Evidera for their services. E.P., J.T.G., P.K. and A.R. are employees of Boehringer Ingelheim.

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Author contributions

A.K. and O.S.R. wrote the manuscript and contributed to the model development. E.P. and J.T.G. researched data and reviewed/edited the manuscript. I.P. performed statistical analyses, and reviewed/edited the manuscript. Y.Z. contributed to the model development. P.K. and A.R. contributed to the model concept and reviewed/edited the manuscript.

Ethical approval

The study was approved by the Medical Ethics Committee of [INSTITUTION], and informed consent was obtained from all participants. This research study was conducted in accordance with the guidelines of the Declaration of Helsinki.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Scatterplot of incremental loss vs. incremental QALYs.

Table S1. Parameters included in risk equations.