**Assessing the cost-effectiveness of SGLT2i in type 2 diabetes mellitus: a comprehensive economic evaluation using clinical trial and real-world evidence**

**Running title:** Cost-effectiveness of SGLT2i for T2DM

Phil McEwan1, Hayley Bennett1, Kamlesh Khunti2, John Wilding3, Christopher Edmonds4, Marcus Thuresson5, Eric Wittbrodt4, Peter Fenici6, Mikhail Kosiborod7,8

1Health Economics & Outcomes Research Ltd, Cardiff, UK

2Diabetes Research Centre, University of Leicester, Leicester General Hospital, Leicester, UK

3Clinical Sciences Centre, University Hospital Aintree, Liverpool, UK

4AstraZeneca, Gaithersburg, USA

5Statisticon AB, Sweden

6AstraZeneca, Cambridge, UK

7Saint Luke's Mid America Heart Institute and University of Missouri-Kansas City, Kansas City*,* USA

8The George Institute for Global Health and University of New South Wales, Sydney, Australia

**Corresponding author:**

Phil McEwan

Health Economics & Outcomes Research Ltd

Rhymney House, Unit A Copse Walk, Cardiff Gate Business Park, CF23 8RB, UK

[phil.mcewan@heor.co.uk](mailto:phil.mcewan@heor.co.uk)

+44 (0)2920 399146

**Abstract**: 236 words; **Main body**: 3734 words; **References**: 43; **Tables**: 3; **Figures**: 3

# ABSTRACT

**Aims**: The economic burden of diabetes is driven by the management of vascular complications. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have demonstrated reductions in cardiovascular and renal complications, including hospitalisation for heart failure (HHF) and renal disease progression, in randomised clinical trials. The objective of this study was to evaluate the cost-effectiveness of the SGLT2i class versus standard of care in type 2 diabetes mellitus (T2DM), using evidence from both clinical trial and real-world studies.

**Methods**: An established T2DM model was adapted to use contemporary outcomes evidence from real-world studies and randomised controlled trial evaluations of SGLT2i and extrapolated over a lifetime for HHF, myocardial infarction, stroke, end-stage renal disease, and all-cause mortality. The economic analysis considered adults with T2DM, with and without established cardiovascular disease, and was conducted over a lifetime from the perspective of the healthcare payer in the UK, US, and China, discounted at country-specific rates.

**Results**: SGLT2i were consistently associated with increased treatment costs, reduced complication costs and gains in quality-adjusted life years driven by differences in projected life expectancy, cardiovascular and microvascular morbidity and weight loss. SGLT2i were estimated to be cost-saving or cost-effective at relevant thresholds for the overall population in the UK, US and China, with the cost-effectiveness being greatest in higher risk subgroups.

**Conclusions**: The findings highlight the need to take into account cost savings from reducing common, morbid and preventable T2DM complications when considering the cost of diabetes medications.

# INTRODUCTION

Global prevalence of type 2 diabetes mellitus (T2DM) continues to grow, driven by increased incidence, population growth, and ageing.1 The economic burden of diabetes is significant, accounting for 6-17% of total healthcare budgets globally.1 The most significant driver of diabetes-related healthcare expenditure is the management of vascular complications.2 Consequently, strategies to minimise complication rates have the potential to reduce healthcare costs2 alongside improving quality-adjusted life expectancy.3

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are the most recent treatment advance for the management of T2DM. Recent cardiovascular outcomes trials (CVOTs) of SGLT2i have demonstrated reductions in cardiovascular (CV) complications, including major adverse cardiovascular events and hospitalisation for heart failure (HHF). Consequently, American and European guidelines recommend SGLT2i in individuals with T2DM and established atherosclerotic cardiovascular disease (ASCVD) regardless of glucose lowering potential.4,5 Furthermore, the DAPA-HF trial recently demonstrated that dapagliflozin reduced CV death or worsening heart failure (HF) compared with placebo in individuals with HF with reduced ejection fraction, with and without T2DM.6 Secondary analysis of the CVOTs and a renal outcome trial of SGLT2i also showed a significant reduction in progression of diabetic kidney disease, with reduced requirements for dialysis and transplantation.7-10 Recent meta-analysis of three randomised, placebo-controlled CVOTs of SGLT2i in people with T2DM suggested that reductions in the risk of HHF and progression of diabetic kidney disease may be observed irrespective of kidney function or the presence of ASCVD or HF at baseline.11

A key economic challenge facing healthcare systems is reconciling additional disease management expenditure in the short term, in order to deliver long-term health outcome benefits. A recent systematic review identified 37 pharmacoeconomic studies (15 dapagliflozin; 10 canagliflozin; 12 empagliflozin) demonstrating the health benefits associated with the use of individual SGLT2i to justify their acquisition cost.12 Much of the health benefit reported in these studies was driven by improved health-related quality of life (HRQoL) related to weight loss and low rates of hypoglycaemia, with any estimates of long-term CV benefit being derived purely from changes in established risk factors utilising published risk equations.13,14 This introduces a degree of uncertainty as established risk equations neither adequately reflect the CV event-rates nor the relative risk reductions observed across the SGLT2i CVOTs (in which CV and kidney benefits appeared to be entirely unrelated to changes in glucose control or other risk factors).15

Cost-effectiveness evidence for SGLT2i that incorporates data from CVOTs is limited to two evaluations, both using EMPA-REG OUTCOME trial data (empagliflozin).16 Neither evaluation considered the full range of expected health outcomes and associated costs expected to accrue over the individual’s lifetime.17,18 Additionally, the EMPA-REG OUTCOME trial recruited people with established ASCVD only, thereby limiting the generalisability of any cost-effectiveness results to a lower CV risk population. Recent studies have indicated that the EMPA-REG population may represent only 4% and 21% of the general T2DM population in the US19 and Europe20, respectively. In contrast, the inclusion criteria were broader in the CANVAS Program (canagliflozin)21 and more so in the DECLARE-TIMI 58 trial (dapagliflozin),22 which was representative of 40% and 59% of the US and European populations, respectively.19,20 CV outcomes and mortality rates associated with SGLT2i in routine clinical practice have also been studied in the observational study of more than 400,000 people with T2DM newly initiated on SGLT2i as a class (dapagliflozin, canagliflozin, empagliflozin, and others). The Comparative Effectiveness of Cardiovascular Outcomes (CVD-REAL) studies reported a lower rate of HHF and all-cause mortality (ACM) in people receiving SGLT2i versus other oral glucose lowering drugs (oGLDs) over more than one year of follow-up.23-25

Despite the growing body of evidence for SGLT2i demonstrating favourable morbidity and mortality effects across a wide range of T2DM populations in both trial and routine clinical practice settings, no formal health economic analyses of SGLT2i have been conducted at the therapeutic class level that directly incorporate all clinical trial and real-world evidence data. Therefore, the objective of this study was to evaluate the cost effectiveness of SGLT2i as a class, compared to placebo in addition to current standard of care, or compared to oGLDs, in people with and without established ASCVD, using clinical trial and real-world evidence.

# METHODS

## Model structure

A hybrid model combining contemporary outcomes evidence with the Cardiff T2DM cost-effectiveness Model26 was used for this study. The Cardiff T2DM Model is a Microsoft Excel based patient-level fixed-time increment (6-monthly) Monte Carlo simulation employing evidence drawn predominantly from the United Kingdom Prospective Diabetes Study (UKPDS)13,14 to model disease progression. This model was adapted to incorporate survival curves derived from either real-world studies or trial evaluations of SGLT2i and extrapolated over a lifetime for the following observed hard endpoints: ACM, HHF, stroke, myocardial infarction (MI), and end-stage renal disease (ESRD). Incidence of blindness and lower limb ulceration due to diabetes were estimated via the UKPDS 82 risk equations.14 Due to the reliance of the UKPDS equations on surrogate risk factors (e.g. HbA1c, systolic blood pressure (SBP), weight, and cholesterol), the effects of treatment were applied to these modifiable risk factors in the first year and their progression tracked over the remaining horizon. Treatment-specific rates of decline in estimated glomerular filtration rate (eGFR) were also modelled and mapped to progression through chronic kidney disease (CKD) stages. The structure of the model is outlined in Figure 1, and equations used for each endpoint are summarised in Table S1.

Adherence to treatment and escalation of background T2DM therapies were implicitly assumed to be captured within the extrapolation of survival curves. Discontinuation of SGLT2i was modelled when eGFR declined below 45 mL/min/1.73m2 and according to an annual probability of discontinuation in line with trial-based observations. Following discontinuation of SGLT2i, patients were subject to complication risks associated with the control arm.

## Model inputs

The modelled impact of SGLT2i on the incidence of CV outcomes was informed by the most up-to-date results from the CVD-REAL observational study24 and a published meta-analysis11 of three CVOTs: CANVAS,21 EMPA-REG,16 and DECLARE-TIMI 58.22 Hazard ratios (HRs) quantifying the comparative effectiveness of SGLT2i versus oGLD for the overall population in CVD-REAL, and versus placebo for the overall population and patient subgroups of the CVOTs (established ASCVD versus multiple risk factors (MRF), and prior HF versus no prior HF), were used. Published Kaplan-Meier survival plots from CVOTs were digitised and parametric survival equations fitted to model event survival in the control arm, to which HRs were applied in the treatment arm where reported to be statistically significant (Table S2). As Kaplan-Meier survival plots have not been published for the pooled analysis of CVD-REAL 1 and 2, survival curves from CVD-REAL 124,27 were refitted to event rates reported from the pooled CVD-REAL 1 and 2 analysis at the mean reported follow-up. Survival curves were chosen based on best fit to CVD-REAL 1 data prior to adjustment (based on the Akaike Information Criterion (AIC)) and the feasibility of extrapolations inspected following adjustment to CVD-REAL 1 and 2 data. To account for long-term increases in mortality risk associated with ageing, country-specific life tables were applied if the age- and sex-specific probability of death in the general population exceeded the predicted probability of death from the survival curves.

Baseline patient characteristics, the effects of treatment on modifiable risk factors, and annual incidence of adverse events and SGLT2i discontinuation were sourced from the CVOT publications and weighted averages derived across the trials (Table 1 and Table S3). Following the application of treatment effects to modifiable risk factors in year 1 of the simulation, HbA1c, SBP, and cholesterol were assumed to progress in line with UKPDS data13 over the remaining time horizon. Following the application of an initial weight loss of −2.61 kg to the SGLT2i arm, weight was assumed to converge gradually with the control arm at an annual rate of +0.063 kg, based on observations from the CVOTs.

A constant ESRD rate was applied to the control arm, derived from clinical trials (CANVAS,7 EMPA-REG,9 DECLARE-TIMI 5810) and CVD-REAL,28 with corresponding HRs applied to the treatment arm. Treatment-specific linear declines in eGFR were modelled based on reported rates of change and digitised plots of eGFR from clinical trials (CANVAS,7 EMPA-REG,9 DECLARE-TIMI 5810), and from recent CVD-REAL analyses of eGFR over time.28

Utility decrements associated with T2DM complications, CKD health states, and weight changes were sourced from published literature and applied additively (Table S4). Published costs of T2DM complications and CKD health states were inflated to 2017 prices where necessary. The costs of SGLT2i were sourced from local price lists and applied to the treatment arm,29,30 in addition to published costs of T2DM management (Table S4).

## Cost-utility analysis

The economic analysis considered adults with T2DM at high CV risk as represented by the CVOTs or initiated on SGLT2i in real-world clinical practice as observed in the CVD-REAL studies. Total and incremental costs, life years and quality-adjusted life years (QALYs) associated with SGLT2i versus control (oGLD or placebo) were estimated over a lifetime for a cohort of 1,000 patients, simulated 1,000 times. Costs and health benefits were applied from the perspective of the healthcare payer in the UK, US, and China and discounted at country-specific rates (UK: 3.5%; US and China: 3%). Willingness-to-pay thresholds of £20,000, $100,000, and ¥179,490 (3 x GDP per capita) were applied in the derivation of net monetary benefit (i.e. the total monetary value of costs and QALYs) and to assess cost-effectiveness, for the UK, US, and China, respectively.

## Scenario analysis

A range of scenario analyses were undertaken to assess the impact of alternative input asumptions on modelled outcomes in real-world and overall CVOT analyses. In particular, there was uncertainty regarding costs associated with CKD health states. Medical costs directly attributable to CKD prior to the onset of ESRD were identified for the US, which had been adjusted for MI, stroke and HF. However, CKD stage costs sourced for the UK analysis are defined as CKD care costs, and include inpatient stays, nephrology outpatient vistis, antihypertensive drugs and GP visits. As such, there is potential in the UK analysis for double counting of complication-related costs. A scenario analysis was conducted whereby CKD costs were removed from the UK analysis, to measure the influence of these costs on modelled results. CKD costs prior to ESRD were not identified for China, with the exception of CKD stage 5.31 To assess the potential impact that further CKD costs could have on the Chinese analyses, a scenario was conducted whereby costs were assigned to CKD stages 3 - 4.

The following scenario analyses were assessed for the overall populations (real-world and CVOT): exclusion of CKD costs prior to ESRD in the UK analysis; inclusion of CKD costs prior to ESRD in the China analysis; no annual discontinuation of SGLT2i; inclusion of fracture and amputation adverse events (based on the CANVAS Program estimates); and baseline characteristics and survival curves derived from the CREDENCE study.8

# RESULTS

Figure 2 presents the predicted incidence of events in the CVD-REAL and the overall CVOT analysis for simulated cohorts over a lifetime. The predicted incidence of events for CVOT subgroups are presented in Table S5. Whether applying real-world or trial-based evidence, SGLT2i were associated with fewer HHF and ESRD events. With the exception of the MRF subgroup from the CVOTs, SGLT2i were also associated with fewer MI events per life year compared to the control arm. A greater number of complications were predicted in higher risk subgroups from the CVOTs (established ASCVD versus MRF; prior HF versus no prior HF) and consequently the estimated avoidance of future events with the use of SGLT2i was greater in these individuals.

Despite increased predicted life expectancy in the SGLT2i arm the reduced incidence of complications and progression of renal disease led to reduced time lived with comorbidities, with significant implications for long-term costs and HRQoL.

Figure 3 presents the breakdown of estimated costs by treatment and category of complications in the real-world analysis and CVOT overall population. In the UK, total estimated costs were driven by renal costs; decreases in renal and complication costs associated with SGLT2i offset the additional costs associated with treatment. Treatment costs accounted for a larger proportion of total costs in the US analysis, and consequently the complication-related cost savings were not sufficient to completely offset these costs. Costs associated with renal disease accounted for a smaller proportion of total costs in the China analysis, as only costs related to ESRD and CKD stage 5 were included. Table S6 summarises the breakdown of costs per CVOT subgroup; all of which follow similar patterns to the full population.

Table 2 summarises the lifetime discounted cost, QALY, life year, and cost-effectiveness estimates at the patient level (Table S7 provides results with all costs presented in 2017 US dollars for ease of comparison between results; conversion rates of 0.691089 and 3.549759 were used to convert UK and Chinese costs, respectively32). Larger QALY gains for patients treated with SGLT2i were estimated for the overall population when analyses were informed by real-world versus trial-based evidence, driven by the greater reduction in ACM risk with SGLT2i reported in CVD-REAL (HR: 0.52) compared to the CVOTs (0.85). For the overall population, most of the QALY gain estimated using CVOT evidence related to differences in ACM, CV, and microvascular complications (40%), however, a large proportion was attributable to differences in weight (39%), with the remainder relating to renal progression (21%); corresponding ratios estimated using CVD-REAL evidence were 54%, 32%, and 14%, respectively.

Patterns in estimated QALY gains and cost-effectiveness across CVOT population subgroups reflected the pattern in events avoided; consequently, SGLT2i were estimated to be most cost-effective in higher risk subgroups. In the UK analyses, SGLT2i were estimated to be cost-saving compared to the control arm across all scenarios informed by either real-world or trial evidence, driven by reduced costs associated with progression of renal disease. Similarly, scenarios informed by real-world evidence were cost-saving in China, as well as the analysis informed by trial evidence in the established ASCVD subgroup. All other subgroups in the China analysis were cost-effective. In contrast, SGLT2i were associated with increased cost estimates compared to the control arm in all US analyses, driven by the higher cost of SGLT2i in the US. Nevertheless, in the US, SGLT2i were estimated to be cost-effective at a willingness-to-pay threshold of $100,000 per QALY gained in both the real-world analysis and the overall CVOT populations, and across all subgroups except MRF.

In scenario analyses SGLT2i remained highly cost-effective in the overall population across all scenarios modelled in the UK and China, and in most cases in the US. Results of the scenario analyses are presented in Table S8.

In the UK analyses, excluding CKD costs was most influential; however, SGLT2i remained dominant in the real-world analysis and highly cost-effective in the overall CVOT analysis, with an ICER of £5,265. In China, including CKD costs resulted in greater estimated cost savings due to faster renal progression modelled in the control arm. Application of a faster rate of eGFR decline from the CREDENCE study increased estimated cost savings associated with SGLT2i in the UK and China, and improved cost-effectiveness in the US, due to the control arm spending longer in CKD stage 5, where high costs are applied. Excluding discontinuation of SGLT2i led to the application of high treatment costs over a lifetime and consequently SGLT2i no longer being cost-effective in the real-world and overall CVOT analyses for the US. The inclusion of additional adverse events made minimal differences to cost-effectiveness across countries.

The potential value associated with SGLT2i at the population level is considerable, due principally to the size of the relevant T2DM population. Table 3 presents results for the overall CVOT population scaled to a national level based on estimates of T2DM prevalence1,33 and the proportion of the general T2DM population represented by the CVOTs.19,20

# DISCUSSION

The analysis presented here demonstrates for the first time that SGLT2i as a class are cost-effective compared to oGLD or to placebo in addition to current standard of care. This statement holds for those with and without prior HF and for those with established ASCVD. SGLT2i are also cost-saving in the MRF subgroup in the UK, and cost-effective in this subgroup in China. Although still cost-effective across all subgroups other than the MRF subgroup, results from the US analyses were less favourable than those presented for the UK and China. This is largely driven by the high list price of SGLT2i therapy in the US compared to other countries.

Previous cost-effectiveness research of SGLT2i in the treatment of T2DM that incorporates data from CVOTs is limited to two evaluations both of which focussed on the cost effectiveness of a specific SGLT2i - empagliflozin. Gourzoulidis et al.17 evaluated the cost-effectiveness of empagliflozin to treat people with T2DM and high CV risk, in Greece, utilising a health economic model incorporating patient level data from the EMPA-REG OUTCOME trial. Although empagliflozin was more costly compared to standard of care, the results of the study demonstrated greater improvements in life expectancy and quality-adjusted life expectancy, as well as reduced incidence rates of CV complications, with empagliflozin which was concluded to be a cost-effective treatment for people with T2DM at increased CV risk. A similar study by Nguyen et al.18 investigated the cost-effectiveness of empagliflozin for the prevention of CV morbidity and mortality in patients with T2DM and also utilised data from the EMPA-REG OUTCOME trial alongside other published epidemiological studies. Treatment with empagliflozin resulted in higher total lifetime treatment costs but yielded greater QALYs compared to standard treatment, with the results suggesting that empagliflozin may be cost effective compared with standard treatment in patients with T2DM and high CV risk. In the study presented here we have expanded on the previous research by investigating SGLT2i as a class, including a wider patient population and considering the full range of expected health outcomes and associated costs expected to accrue over the individual’s lifetime.

Relatively few cost-effectiveness analyses have been undertaken in populations with T2DM using direct evidence of clinical event rate reductions. Typically, models extrapolate changes in short-term intermediate outcomes e.g. HbA1c to predict life expectancy and quality adjusted life expectancy.13,14 In this study a hybrid approach has been taken, whereby an established diabetes model that uses changes in surrogate risk markers has been supplemented with direct observed and extrapolated event rate reductions. This approach ensures that the widest range of factors known to influence cost-effectiveness evaluations in diabetes are captured in a broad population. In particular, the incorporation of a meaningful reduction in CV events in the short term (< five years) is both unusual and noteworthy. The health economic consequences typically captured within the short term commonly reflect differences in weight, hypoglycaemia and other treatment-related side-effects. Consequently, previous economic evaluations of SGLT2i are likely to be conservative. The analysis presented here suggests that cost offsets associated with reduced rates of HHF and renal disease progression in the short and longer term confer significant additional economic benefits.

The UKPDS equations13,14 form the basis of CV risk prediction in many diabetes models, yet concerns have been expressed as to their continued validity in contemporary diabetes populations; it has been reported that they may either underestimate risk, notably of hypoglycaemia, HF and ESRD,34 or over-estimate it.35 The development of risk equations capable of better capturing the expected effects of SGLT2i on T2DM outcomes is clearly warranted. Our approach provides a more effective way of capturing the economic effects of SGLT2i and may be adapted to other classes of agents with proven outcome benefits that may be independent of changes in HbA1c and other risk factors.

There are several potential limitations to this study. The approach to parametrically modelling CV outcomes, while following guidelines, did not explicitly capture disease progression mechanisms. This is not relevant for within-study modelling as the mechanisms are inherent to the data, but may represent a limitation when extrapolating over longer time horizons when clinical events become structurally dependent in nature (e.g. HF increases the risk of death); validation against UKPDS confirms that long-term event rates are realistic (Figures S1-S4).

Despite robust propensity-matching between study arms, observations from CVD-REAL may be subject to residual, unmeasured confounding.23 However, the inability to confirm comparative effectiveness using real-world evidence is not necessarily a limitation. The benefits observed in CVD-REAL reflect real-world clinical prescribing patterns and the estimated health economic benefit predicted in this study reflect this. Furthermore, despite significant differences in CVD history between study populations, the results of CVD-REAL were broadly consistent with the SGLT2i CVOTs for most of the outcomes assessed.23 Regardless, the cost-effectiveness of SGLT2i was confirmed using outcomes estimates from meta-analysis of the CVOTs, despite more modest ACM effects than in CVD-REAL.

Outcomes in clinical practice are a useful supplement to clinical trial data because the strict inclusion criteria typically applied to trial recruitment has implications for the generalisability of their results. The CV benefits of SGLT2i may be larger in terms of absolute event risk among individuals with established ASCVD, but the benefits of treatment for those without prior disease are important due to the greater numbers in this category and their remaining life expectancy. The availability of the dapagliflozin CVOT (DECLARE-TIMI 58),22 which included more people without established ASCVD compared to other CVOTs, also provides broader insight into the effect of an SGLT2i on a study population representing a larger proportion (40-59%)19,20 of the general T2DM population than considered in previous CVOTs.7,16,21

Evaluating SGLT2i compared to oGLD or to placebo in addition to current standard of care reflects the recommendations in American and European guidelines.5,36,37 Furthermore, this study builds upon previous SGLT2i health economic research by utilising data from both randomised, placebo-controlled trials and real-world studies, in an established T2DM model that considers a comprehensive range of health outcomes, their associated costs, and impact upon HRQoL. Additionally, the analysis considered multiple geographical regions. Consequently, results are derived from a broad evidence base, evaluating a comprehensive set of health outcomes of relevance to a wide geographical area where SGLT2i are used for T2DM management.

As the prevalence of T2DM continues to rise1 and survival improves despite presence of co-morbidities, the financial burden of managing complications and pressures upon service delivery will increase further. The avoidance of complications will become critical as healthcare systems are required to manage recurrent hospital admissions, and even modest event reductions in healthcare systems running at, or close to, capacity can have a meaningful impact on service delivery. Consequently, prioritising T2DM therapies that can effectively prevent costly CV events, including HHF, and kidney disease progression will become increasingly advantageous for healthcare systems worldwide.

**Acknowledgements**

This work was supported by AstraZeneca. Medical writing and editorial support were provided by Kerrie Ford of Health Economics and Outcomes Research Ltd. Funding for this support was provided by AstraZeneca. KK acknowledges support from National Institute for Health Research (NIHR) Applied Research Collaboration (ARC) East Midlands and the NIHR Leicester BRC.

**Author contributions**

PM, HB, KK, JW, CE, and MK conceptualised and designed the study. PM and HB were responsible for data analysis. All authors contributed to interpretation of the results, preparation and review of the manuscript, approved the final manuscript for publication, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy of integrity of any part of the work are appropriately investigated and resolved.

**Declaration of interests**

# KK has received honoraria from Abbot, AstraZeneca, Berlin-Chemie AG / Menarini Group, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche, and Sanofi, and research support from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche, and Sanofi.

MK has received research grants from AstraZeneca and Boehringer Ingelheim, and served as a consultant and/or on advisory board forAmarin, Applied Therapeutics, AstraZeneca, Amgen, Bayer, Boehringer-Ingelheim, Glytec, GSK, Janssen, Merck (Diabetes), Novartis, Novo Nordisk, Sanofi and Vifor**.**

JW has received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Mundipharma, Napp, Novo Nordisk, Sanofi and Takeda, and research support from AstraZeneca and Novo Nordisk.

CE, EW and PF are employees of AstraZeneca.

PM is an employee of Health Economics and Outcomes Research Ltd and HB was an employee of Health Economics and Outcomes Research Ltd at the time of conducting the study. Health Economics and Outcomes Research Ltd received fees from AstraZeneca in relation to this study.

MT has no conflicts of interest.

# REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas - 8th Edition. 2017. Available from: <https://diabetesatlas.org/resources/2017-atlas.html>.

2. Baxter M, Hudson R, Mahon J, et al. Estimating the impact of better management of glycaemic control in adults with Type 1 and Type 2 diabetes on the number of clinical complications and the associated financial benefit. Diabet Med. 2016;33(11):1575–81.

3. McEwan P, Evans M, Kan H, et al. Understanding the inter-relationship between improved glycaemic control, hypoglycaemia and weight change within a long-term economic model. Diabetes Obes Metab. 2010;12(5):431–6.

4. American Diabetes Association. 8. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Supplement 1):S73–S85.

5. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). European Heart Journal. 2019.

6. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. New England Journal of Medicine. 2019.

7. Perkovic V, de Zeeuw D, Mahaffey KW, et al. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. Lancet Diabetes Endocrinol. 2018;6(9):691–704.

8. Perkovic V, Jardine M, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. New England Journal of Medicine. 2019;380(24):2295–306.

9. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. New England Journal of Medicine. 2016;375(4):323–34.

10. Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. The Lancet Diabetes & Endocrinology. 2019;7(8):606–17.

11. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. The Lancet. 2019;393(10166):31–9.

12. Rahman W, Solinsky PJ, Munir KM, et al. Pharmacoeconomic evaluation of sodium-glucose transporter-2 (SGLT2) inhibitors for the treatment of type 2 diabetes. Expert Opinion on Pharmacotherapy. 2019;20(2):151–61.

13. Clarke PM, Gray AM, Briggs A, et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia. 2004;47(10):1747–59.

14. Hayes AJ, Leal J, Gray AM, et al. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia. 2013;56(9):1925–33.

15. McEwan P, Foos V, Bennett H, et al. 1213-P: Assessing the Performance of Cardiovascular Risk Equations in the DECLARE-TIMI 58 Population. Diabetes. 2019;68(Supplement 1):1213–P.

16. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. New England Journal of Medicine. 2015;373(22):2117–28.

17. Gourzoulidis G, Tzanetakos C, Ioannidis I, et al. Cost-Effectiveness of Empagliflozin for the Treatment of Patients with Type 2 Diabetes Mellitus at Increased Cardiovascular Risk in Greece. Clin Drug Investig. 2018;38(5):417–26.

18. Nguyen E, Coleman CI, Nair S, et al. Cost-utility of empagliflozin in patients with type 2 diabetes at high cardiovascular risk. J Diabetes Complications. 2018;32(2):210–5.

19. Wittbrodt ET, Eudicone JM, Bell KF, et al. Eligibility varies among the 4 sodium-glucose cotransporter-2 inhibitor cardiovascular outcomes trials: implications for the general type 2 diabetes US population. Am J Manag Care. 2018;24(8 Suppl):S138–S45.

20. Birkeland KI, Bodegard J, Norhammar A, et al. How representative of a general type 2 diabetes population are patients included in cardiovascular outcome trials with SGLT2 inhibitors? A large European observational study. Diabetes Obes Metab. 2018:968–74.

21. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. New England Journal of Medicine. 2017;377(7):644–57.

22. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. New England Journal of Medicine. 2019;380(4):347–57.

23. Kosiborod M, Cavender MA, Fu AZ, et al. Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors). Circulation. 2017;136(3):249–59.

24. Kosiborod M, Thuresson M, Tangri N, et al. Lower cardiovascular risk with SGLT-2 inhibitors versus other glucose-lowering drugs – real world data from Asia Pacific, North America, Europe and Middle East: The CVD-REAL study [Abstract 635]. In: European Association for the Study of Diabetes, Berlin. 2018.

25. Heerspink HJ, Karasik A, Thuresson M, et al. Kidney outcomes associated with initiation of sodium–glucose cotransporter-2 inhibition versus other glucose lowering drugs – an analysis from the CVD-REAL study [Abstract MON-299] In: the ISN World Congress of Nephrology (WCN); 12-15 April 2019, Melbourne, Australia. 2019.

26. McEwan P, Ward T, Bennett H, et al. Validation of the UKPDS 82 risk equations within the Cardiff Diabetes Model. Cost effectiveness and resource allocation : C/E. 2015;13:12.

27. Persson F, Nystrom T, Jorgensen ME, et al. Dapagliflozin is associated with lower risk of cardiovascular events and all-cause mortality in people with type 2 diabetes (CVD-REAL Nordic) when compared with dipeptidyl peptidase-4 inhibitor therapy: A multinational observational study. Diabetes Obes Metab. 2018;20(2):344-51.

28. Heerspink HJL, Karasik A, Thuresson M, et al. Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study. Lancet Diabetes Endocrinol. 2020;8(1):27-35.

29. IBM Micromedex RED BOOK (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: <https://www.micromedexsolutions.com/> (accessed: 04/02/2020).

30. Haymarket Media Group Ltd. Monthly Index of Medical Specialities. Available from: <https://www.mims.co.uk/> [accessed 23/01/2020]. 2019.

31. Lin M-Y, Cheng L-J, Chiu Y-W, et al. Effect of national pre-ESRD care program on expenditures and mortality in incident dialysis patients: A population-based study. PLOS ONE. 2018;13(6):e0198387.

32. Organisation for Economic Co-operation and Development. Purchasing power parities. Available from: <https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm#indicator-chart> [accessed 26.07.2019].

33. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nature Reviews Endocrinology. 2017;14:88.

34. McEwan P, Bennett H, Ward T, et al. Refitting of the UKPDS 68 risk equations to contemporary routine clinical practice data in the UK. Pharmacoeconomics. 2015;33(2):149–61.

35. Kengne AP, Patel A, Colagiuri S, et al. The Framingham and UK Prospective Diabetes Study (UKPDS) risk equations do not reliably estimate the probability of cardiovascular events in a large ethnically diverse sample of patients with diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) Study. Diabetologia. 2010;53(5):821–31.

36. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes—2019. Diabetes Care. 2019;42(Supplement 1):S103.

37. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018;41(12):2669-701.

38. Fitchett D, Butler J, van de Borne P, et al. Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME(R) trial. Eur Heart J. 2018;39(5):363–70.

39. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention &amp; Rehabilitation (EACPR). European Heart Journal. 2016;37(29):2315–81.

40. Kato Eri T, Silverman Michael G, Mosenzon O, et al. Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus. Circulation. 2019;139(22):2528–36.

41. Radholm K, Figtree G, Perkovic V, et al. Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus. Circulation. 2018;138(5):458–68.

42. Raz I, Mosenzon O, Bonaca MP, et al. DECLARE-TIMI 58: Participants’ baseline characteristics. Diabetes, Obesity and Metabolism. 2018;20(5):1102–10.

43. Mahaffey KW, Neal B, Perkovic V, et al. Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). Circulation. 2018;137(4):323–34.

**LEGENDS TO FIGURES**

**Figure 1.** Schematic of the model**.**

**Figure 2.** Lifetime incidence of events (%) predicted for the overall population informed by real-world (CVD-REAL) or CVOT evidence.

**Figure 3.** Lifetime breakdown of costs predicted for the overall population informed by real-world (CVD-REAL) or CVOT evidence, by country.

# TABLES

Table 1. Mean baseline characteristics for the overall population and by subgroup in the CVOTs

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **Overall (real-world)** | **Overall (CVOTs)** | **eCVD** | **MRF** | **Prior HF** | **No prior HF** | **Source** |
| Age (years) | 57·80 | 63·51 | 63·06 | 64·19 | 64·17 | 63·57 | 16,21,24,38-43 |
| Proportion female | 0·44 | 0·35 | 0·29 | 0·44 | 0·37 | 0·35 | 16,21,22,24,38,40-43 |
| Duration diabetes (years) | 12·43 | 12·43 | 13·2 | 14·3 | 10·85 | 12·02 | 21,22,40,41,43 |
| Height (m) | 1·68 | 1·68 | 1·68 | 1·68 | 1·69 | 1·68 | 16,21,22,38 |
| HbA1c (%) | 8·23 | 8·23 | 8·23 | 8·3 | 8·23 | 8·07 | 16,21,22,38,40-43 |
| SBP (mmHg) | 135·47 | 135·47 | 134·66 | 136·67 | 135·84 | 136·16 | 16,21,22,38,41-43 |
| Weight (kg) | 89·66 | 89·66 | 86·4 | 90·53 | 92·47 | 87·93 | 16,21,22,38,40-43 |
| eGFR (ml/min/1·73m2) | 80·79 | 80·79 | 78·09 | 83·74 | 78 | 82·57 | 16,21,22,38,40-43 |
| Heart rate | 73 | 73 | 71·5 | 74·1 | 73\* | 73\* | 22,42 |

CVOT: cardiovascular outcome trial; eCVD: established cardiovascular disease; eGFR: estimated glomerular filtration rate; HF: heart failure; MI: myocardial infarction; MRF: multiple risk factors; SBP: systolic blood pressure

\* Not reported for subgroup, assumed equal to overall population

Where data required by the UKPDS 82 risk equations was unavailable, UKPDS values were applied

Table 2. Lifetime discounted cost-effectiveness results, by evidence source and population subgroup

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Scenario** | **Outcome** | **UK** | | | **US** | | | **China** | | |
| **Control** | **Treatment** | **Difference** | **Control** | **Treatment** | **Difference** | **Control** | **Treatment** | **Difference** |
| **Overall  (real-world)** | Life years | 15.72 | 16.09 | 0.37 | 16.82 | 17.10 | 0.27 | 15.05 | 15.20 | 0.16 |
| QALYs | 11.83 | 12.43 | 0.59 | 12.63 | 13.18 | 0.55 | 11.36 | 11.77 | 0.41 |
| Costs | £39,247 | £31,490 | -£7,757 | $157,890 | $188,478 | $30,588 | ¥153,294 | ¥149,846 | -¥3,448 |
| NMB | £197,411 | £217,065 | £19,655 | $1,105,086 | $1,129,455 | $24,370 | ¥1,886,177 | ¥1,962,425 | ¥76,249 |
| ICER |  |  | Dominant |  |  | $55,658 |  |  | Dominant |
| **Overall  (CVOT)** | Life years | 13.38 | 13.57 | 0.19 | 14.39 | 14.61 | 0.22 | 12.52 | 12.54 | 0.02 |
| QALYs | 9.99 | 10.40 | 0.41 | 10.71 | 11.16 | 0.46 | 9.38 | 9.64 | 0.26 |
| Costs | £38,890 | £31,734 | -£7,155 | $131,105 | $165,096 | $33,990 | ¥123,746 | ¥125,746 | ¥2,000 |
| NMB | £161,009 | £176,354 | £15,345 | $939,757 | $951,396 | $11,639 | ¥1,560,460 | ¥1,604,657 | ¥44,197 |
| ICER |  |  | Dominant |  |  | $74,493 |  |  | ¥7,772 |
| **MRF**  **(CVOT)** | Life years | 13.56 | 13.56 | 0.00 | 14.16 | 14.16 | 0.00 | 13.19 | 13.19 | 0.00 |
| QALYs | 10.31 | 10.55 | 0.24 | 10.75 | 11.00 | 0.25 | 10.03 | 10.26 | 0.23 |
| Costs | £31,746 | £25,742 | -£6,004 | $108,487 | $143,738 | $35,251 | ¥111,050 | ¥116,411 | ¥5,361 |
| NMB | £174,405 | £185,219 | £10,814 | $966,056 | $956,174 | -$9,882 | ¥1,688,865 | ¥1,725,502 | ¥36,636 |
| ICER |  |  | Dominant |  |  | $138,955 |  |  | ¥22,912 |
| **eCVD**  **(CVOT)** | Life years | 12.74 | 13.06 | 0.32 | 13.65 | 14.02 | 0.37 | 12.43 | 12.56 | 0.13 |
| QALYs | 9.40 | 9.91 | 0.51 | 10.03 | 10.60 | 0.57 | 9.19 | 9.55 | 0.36 |
| Costs | £42,472 | £34,837 | -£7,635 | $139,213 | $172,258 | $33,045 | ¥138,885 | ¥138,736 | -¥149 |
| NMB | £145,573 | £163,407 | £17,834 | $863,414 | $887,365 | $23,951 | ¥1,510,914 | ¥1,575,762 | ¥64,849 |
| ICER |  |  | Dominant |  |  | $57,978 |  |  | Dominant |
| **No prior HF**  **(CVOT)** | Life years | 13.30 | 13.46 | 0.16 | 14.28 | 14.47 | 0.19 | 12.49 | 12.51 | 0.02 |
| QALYs | 9.98 | 10.35 | 0.37 | 10.68 | 11.09 | 0.41 | 9.40 | 9.64 | 0.24 |
| Costs | £35,834 | £29,731 | -£6,103 | $125,483 | $160,929 | $35,446 | ¥119,737 | ¥123,375 | ¥3,638 |
| NMB | £163,841 | £177,289 | £13,449 | $942,173 | $947,980 | $5,806 | ¥1,567,880 | ¥1,607,503 | ¥39,623 |
| ICER |  |  | Dominant |  |  | $85,925 |  |  | ¥15,094 |
| **Prior HF**  **(CVOT)** | Life years | 10.43 | 10.99 | 0.56 | 10.94 | 11.56 | 0.62 | 10.77 | 11.28 | 0.50 |
| QALYs | 7.67 | 8.31 | 0.64 | 8.02 | 8.71 | 0.69 | 7.90 | 8.51 | 0.61 |
| Costs | £33,513 | £28,915 | -£4,598 | $104,593 | $140,007 | $35,414 | ¥124,058 | ¥128,413 | ¥4,355 |
| NMB | £119,792 | £137,232 | £17,440 | $697,097 | $731,176 | $34,079 | ¥1,294,190 | ¥1,399,341 | ¥105,152 |
| ICER |  |  | Dominant |  |  | $50,960 |  |  | ¥7,139 |

CVOT: cardiovascular outcome trial; eCVD: established cardiovascular disease; HF: heart failure; ICER: incremental cost-effectiveness ratio; MRF: multiple risk factors; NMB: net monetary benefit; QALYs: quality-adjusted life years

Table 3. National level estimates based on overall CVOT population; number of individuals and health economic estimates reported in millions

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | | **UK** | **US** | **China** |
| Number of people: | (millions) |  |  |  |
| with diabetes |  | 2.7 | 30.2 | 114.4 |
| with T2DM (90%) |  | 2.5 | 27.2 | 103.0 |
| represented by CVOTs | percentage | 21–59%20 | 4.1–39.8%19 | Assumed 4.1–59% |
| represented by CVOTs | number of people | 0.5 to 1.5 | 1.1 to 10.8 | 4.2 to 60.7 |
| Health economic impact of SGLT2i: | (millions) |  |  |  |
| Total cost difference |  | –£3,716 to –£10,440 | $37,862 to $367,543 | ¥8,444 to ¥121,512 |
| Total life years gained |  | 0.1 to 0.3 | 0.2 to 2.4 | 0.1 to 1.4 |
| Total QALYs gained |  | 0.2 to 0.6 | 0.5 to 4.9 | 1.1 to 15.6 |
| Incremental NMB | | £7,969 to £22,389 | $12,965 to $125,852 | ¥186,562 to ¥2,684,678 |

CVOT: cardiovascular outcome trial; NMB: net monetary benefit; QALYs: quality-adjusted life years; SGLT2i: sodium–glucose cotransporter-2 inhibitor; T2DM: type 2 diabetes mellitus