

Cost of Glycemic Target Achievement with Sodium Glucose Co-transporter 2 Inhibitors in Patients with Type 2 Diabetes in the UK

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ABSTRACT

Introduction: Diabetes-related costs make up a large portion of healthcare expenditures in the UK. Many of these costs are related to treatment of diabetes-related complications. Reducing HbA1c to <7.0% (53 mmol/mol) reduces the incidence of complications and comorbidities. Metformin plus sulfonylurea is the most common dual oral combination therapy in the UK. The costs of achieving HbA1c <7.0% in patients inadequately controlled on metformin plus sulfonylurea were analyzed for the sodium glucose co-transporter 2 (SGLT2) inhibitors canagliflozin, dapagliflozin, and empagliflozin from the perspective of the UK National Health System.

Methods: A Bayesian network meta-analysis (NMA) was used to compare the proportion of patients with type 2 diabetes mellitus inadequately controlled on metformin plus

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sulfonylurea that achieved HbA1c <7.0% after 26 weeks with canagliflozin 100 and 300 mg, dapagliflozin 10 mg, and empagliflozin 10 and 25 mg; odds ratios (ORs) and pairwise probabilities (*P*) for canagliflozin versus dapagliflozin and empagliflozin were calculated. The costs associated with achieving HbA1c <7.0% were estimated on the basis of medication costs and the proportion of patients achieving the HbA1c goal.

Results: NMA results showed that a higher proportion of patients treated with canagliflozin 300 mg achieved HbA1c <7.0% (41%) compared with those treated with dapagliflozin 10 mg (25%), empagliflozin 10 mg (23%), empagliflozin 25 mg (28%), or canagliflozin 100 mg (27%). The odds of achieving HbA1c <7.0% were greater with canagliflozin 300 mg than with dapagliflozin 10 mg (OR 2.03 [*P* = 94%]), empagliflozin 10 mg (OR 2.29 [*P* = 99%]), or empagliflozin 25 mg (OR 1.71 [*P* = 93%]). The per patient costs of achieving HbA1c <7.0% at 26 weeks were £881, £580, £951, £1034, and £849 with canagliflozin 100 and 300 mg, dapagliflozin 10 mg, and empagliflozin 10 and 25 mg.

Conclusions: This analysis suggests that, in the UK, canagliflozin 300 mg provides the best value for money among all SGLT2 inhibitors in terms of achieving HbA1c <7.0% when used as part of triple therapy with metformin plus sulfonylurea.

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INTRODUCTION

Approximately 3.5 million people living in the UK have been diagnosed with diabetes. Currently, annual indirect and direct costs associated with diabetes are estimated to be £23.7 billion, which constitutes around 10% of the National Health Service (NHS) budget [1, 2]. As the prevalence of type 2 diabetes mellitus (T2DM) is projected to increase in the coming years, the disease will pose an even greater economic and healthcare burden. By 2035/2036, the total cost associated with diabetes in the UK is projected to rise to £39.8 billion [1].

Currently, the cost of prescription medication makes up only a small proportion of total spending on diabetes, about £803 million, with the majority of T2DM costs ($\geq 80\%$) attributable to the management of diabetes-related micro- and macrovascular complications [1, 3]. If funding and efficiency rates remain the same, the overall increased demand for healthcare will create a £30 billion shortfall in the NHS budget by 2020/2021 [4]. Prevention of diabetes-related complications is essential to controlling healthcare costs and helping to close this budget gap.

The NHS plan for the future, the Five Year Forward View (FYFV), is based on achieving the triple aim of improving the health of the entire population and providing better-quality patient care, while at the same time providing better value for taxpayers within a financially sustainable healthcare system [4, 5]. Through the NHS Right Care program, the FYFV also aims to reduce the variation in quality, safety, and health outcomes while optimizing the allocation of resources across the healthcare system [6]. As part of achieving these aims, the FYFV emphasizes the need for preventative care. For patients with T2DM, serious complications can be postponed or even avoided completely with

relatively small investments in preventative care, providing a huge payback to the individual, their family, the community, and the NHS.

An important component of preventative care for patients with T2DM is achieving and maintaining glycemic control. Glycemic control is the cornerstone of T2DM management, with a target of HbA1c $\leq 7.0\%$ (53 mmol/mol) recommended for most patients by the National Institute for Health and Care Excellence (NICE) in the UK [7]. Maintaining HbA1c $< 7.0\%$ has been shown to reduce the risk of T2DM-related complications and may lead to significant cost savings [8, 9]. Although metformin is the standard first-line therapy, many patients with T2DM require combination therapy with multiple antihyperglycemic agents (AHAs) to achieve glycemic control. Metformin plus sulfonylurea is the most common oral dual-therapy combination in the UK. However, many patients fail to achieve glycemic targets on existing treatments, including metformin plus sulfonylurea [10].

Sodium glucose co-transporter 2 (SGLT2) inhibitors lower blood glucose by increasing urinary glucose excretion, which leads to a mild osmotic diuresis and a net caloric loss [11, 12]. Three SGLT2 inhibitors are approved for the treatment of T2DM in the UK—canagliflozin, dapagliflozin, and empagliflozin. In clinical trials, canagliflozin 100 and 300 mg, dapagliflozin 10 mg, and empagliflozin 10 and 25 mg improved glycemic control, reduced body weight, and reduced blood pressure in patients with T2DM in a range of studies, including as add-on to metformin plus sulfonylurea [13–18].

While there have not been any head-to-head clinical trials of SGLT2 inhibitors in patients with T2DM, indirect comparisons suggest that canagliflozin 300 mg has the greatest HbA1c-lowering efficacy [19, 20], which may impact long-term health outcomes and costs. NICE guidelines specify an HbA1c goal of $\leq 7.0\%$ for most patients [7]. The purpose of this study was to compare the cost of achieving HbA1c $< 7.0\%$ with canagliflozin, dapagliflozin, and empagliflozin in patients with T2DM inadequately controlled with metformin plus sulfonylurea from the perspective of the NHS using a network meta-analysis (NMA).

METHODS

Network Meta-Analysis

Relative effects between SGLT2 inhibitors for the proportion of patients achieving HbA1c <7.0% were estimated by performing a Bayesian NMA on a study population consisting of patients who participated in placebo- or active-controlled clinical trials reporting data

greater with canagliflozin 100 or 300 mg versus the alternative.

Cost Analysis

The per patient cost associated with achieving HbA1c <7.0% at 26 weeks was calculated in Microsoft Excel using the following equation:

$$\text{Cost of achieving HbA1c} < 7.0\% = \frac{\text{Drug cost for 26 weeks of treatment}}{\text{Proportion of patients achieving HbA1c} < 7.0\% \text{ at 26 weeks}}$$

for triple therapy with metformin plus sulfonylurea in adults with inadequately controlled T2DM [21]. Achievement of HbA1c <7.0% was chosen for this analysis because it was the most commonly reported target in the publications of clinical trials included in the network of evidence. This target has been used in other Bayesian NMAs evaluating the relative efficacy of SGLT2 inhibitors [20, 21].

The NMA was based on a systematic literature review (SLR) at 26 ± 4 weeks and was conducted in line with NICE guidelines [22, 23]. The outcome of interest was the proportion of patients reaching the target of HbA1c <7.0%. The selection of fixed versus random effects was based on the deviance information criterion (DIC), which measures the relative goodness of fit between models [24]. Networks had treatment- and dose-specific nodes for all AHA classes, but only results for SGLT2 inhibitors were used in this analysis. Odds ratios (ORs) for comparisons of canagliflozin 100 and 300 mg versus empagliflozin 10 and 25 mg and dapagliflozin 10 mg were estimated. Additionally, Bayesian pairwise probabilities (*P*) of canagliflozin 100 and 300 mg versus empagliflozin 10 and 25 mg and dapagliflozin 10 mg were calculated, reflecting the likelihood that canagliflozin performed better than the comparator. *P* > 50% indicates an increased likelihood that the proportion achieving HbA1c <7.0% is

The total drug acquisition cost for each SGLT2 inhibitor was calculated as the list price per unit dose (the daily cost of all three SGLT2 inhibitors marketed in the UK is the same, ~£1.31) multiplied by the number of doses received over 26 weeks (182 doses; total of £238 each, since each agent is a once-daily drug). The costs of background treatments were not considered and were assumed to be the same for all analyzed treatments given the similarity among the trial designs. The proportion of patients achieving HbA1c <7.0% at 26 weeks with each treatment was reported in the primary publications [13–16].

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

NMA Results

The SLR identified 16 trials that reported the proportion of patients who reached the HbA1c target of <7.0% at 26 ± 4 weeks of treatment as add-on to metformin plus sulfonylurea (Fig. 1). Only studies of SGLT2 inhibitors were included

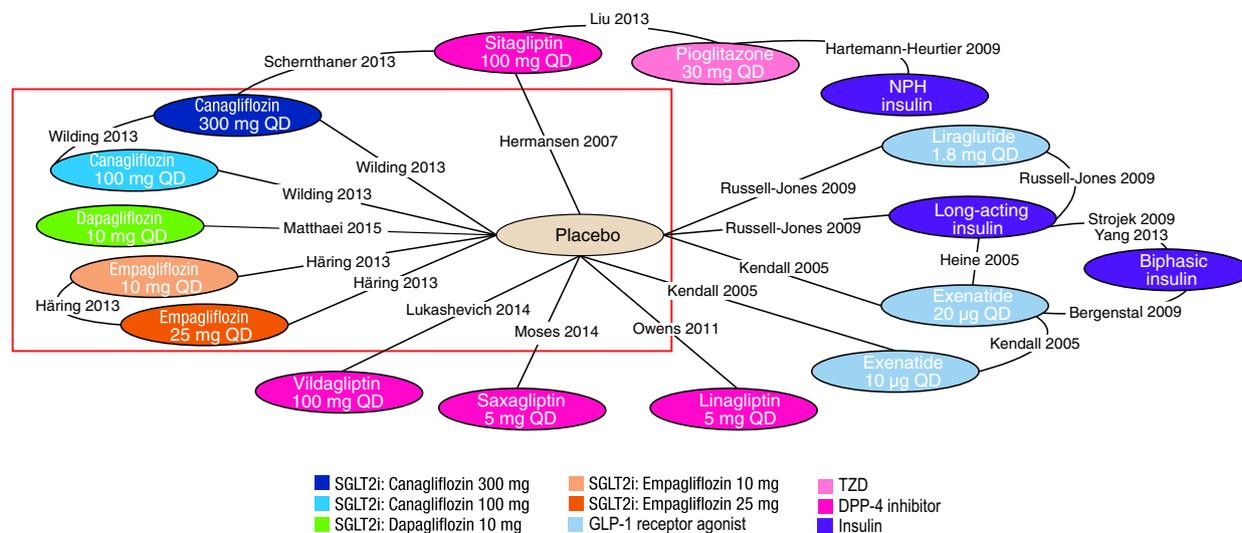


Fig. 1 Network of evidence included in this analysis [13–16, 45–55]. SGLT2i sodium glucose co-transporter 2 inhibitor, TZD thiazolidinedione, DPP-4 dipeptidyl

peptidase-4, GLP-1 glucagon-like peptide-1, QD once daily, NPH neutral protamine Hagedorn. The studies of SGLT2 inhibitors included in this analysis are surrounded by a box

in this analysis. Two trials assessed canagliflozin 100 and 300 mg (one trial was placebo controlled and one was versus sitagliptin 100 mg) [13, 14]. One trial assessed dapagliflozin 10 mg versus placebo [15], and one trial assessed empagliflozin 10 and 25 mg versus placebo [16].

Baseline demographics were generally similar across the studies (Table 1). Mean baseline HbA1c was 8.1% (65 mmol/mol) in the canagliflozin studies, 8.1–8.2% (65–66 mmol/mol) in the dapagliflozin study, and 8.1–8.2% (65–66 mmol/mol) in the empagliflozin study [13–16]. NMA results showed that 41% of patients achieved HbA1c <7.0% over 26 weeks with canagliflozin 300 mg as add-on to metformin plus sulfonylurea compared with 27%, 25%, 23%, and 28% with canagliflozin 100 mg, dapagliflozin 10 mg, and empagliflozin 10 and 25 mg, respectively (Fig. 2). Patients treated with canagliflozin 300 mg had higher odds of achieving HbA1c <7.0% compared with dapagliflozin 10 mg (OR 2.03 [$P = 94\%$]), empagliflozin 10 mg (OR 2.29 [$P = 99\%$]), and empagliflozin 25 mg (OR 1.71 [$P = 93\%$]; Fig. 3). Patients treated with canagliflozin 100 mg had fairly similar odds of achieving HbA1c <7.0% compared with dapagliflozin 10 mg (OR 1.12 [$P = 60\%$]) and empagliflozin 25 mg (OR 0.94

[$P = 44\%$]) and higher odds versus empagliflozin 10 mg (OR 1.26 [$P = 73\%$]).

Cost of Achieving Glycemic Control

The costs of achieving HbA1c <7.0% were £881, £580, £951, £1034, and £849 with canagliflozin 100 and 300 mg, dapagliflozin 10 mg, and empagliflozin 10 and 25 mg, respectively, as add-on to metformin plus sulfonylurea (Fig. 4). The cost was lowest with canagliflozin 300 mg owing to the larger percentage of patients achieving HbA1c <7.0%.

DISCUSSION

The results from a Bayesian NMA of trials of SGLT2 inhibitors as add-on to metformin plus sulfonylurea for patients with T2DM inadequately controlled with metformin plus sulfonylurea showed that canagliflozin 300 mg was more likely to provide HbA1c <7.0% compared with other SGLT2 inhibitors. These results are consistent with other indirect comparisons of SGLT2 inhibitors from Bayesian and frequentist NMAs, which found that canagliflozin 300 mg provides greater reductions in HbA1c compared

Table 1 Baseline characteristics across studies of SGLT2 inhibitors

Parameter	Canagliflozin		Dapagliflozin	Empagliflozin
	Wilding et al. [13]	Scherthaner et al. [14]	Matthaei et al. [15]	Häring et al. [16]
Patients, <i>n</i>	469	755	216	666
Age ^a , years	56.1–57.4	56.6–56.7	60.9–61.1	56.9–57.4
HbA1c inclusion criteria, % (mmol/mol)	7.0–10.5 (53–91)	7.0–10.5 (53–91)	7.0–10.5 (53–91)	7.0–10.0 (53–86)
HbA1c ^a , % (mmol/mol)	8.1 (65)	8.1 (65)	8.1–8.2 (65–66)	8.1–8.2 (65–66)
Body weight ^a , kg	91.2–93.8	87.4–89.1	88.6–90.1	76.2–77.5
BMI ^a , kg/m ²	32.7–33.3	31.5–31.7	31.9–32.0	27.9–28.3
Duration of T2DM ^a , years	9.0–10.3	9.4–9.7	9.3–9.6	NR
Metformin inclusion criteria	≥2000 or ≥1500 mg/day if unable to tolerate a higher dose	≥2000 or ≥1500 mg/day if unable to tolerate a higher dose	≥1500 mg/day	≥1500 mg/day or maximum tolerated or maximum according to local label
Sulfonylurea inclusion criteria	≥Half maximal labeled dose	≥Half maximal labeled dose	Maximum tolerated dose (≥half maximal labeled dose)	≥Half of the maximum recommended dose, or maximum tolerated dose, or maximum according to local label
Stable dose of metformin and sulfonylurea inclusion criteria	≥8 weeks	≥8 weeks	≥8 weeks	≥12 weeks

SGLT2 sodium glucose co-transporter 2, BMI body mass index, T2DM type 2 diabetes mellitus, NR not reported

^a Data are mean baseline values across treatment arms for each study

with dapagliflozin 10 mg and empagliflozin 25 mg and helps a greater proportion of patients achieve HbA1c <7.0% compared with dapagliflozin 10 mg [19, 20]. These previous studies also showed that canagliflozin 300 mg as monotherapy or in combination with metformin reduced fasting plasma glucose and systolic blood pressure to a greater extent than other SGLT2 inhibitors [19, 20]. Taken together, these results suggest that canagliflozin 300 mg

may have greater glycemic efficacy than other SGLT2 inhibitors.

In the current analysis of patients with T2DM and suboptimal glycemic control on metformin plus sulfonylurea, initiation of canagliflozin at the recommended starting dose of 100 mg provides a lower cost of achieving HbA1c <7.0% than initiation of dapagliflozin 10 mg or empagliflozin 10 mg (recommended starting dose). For patients who do not achieve

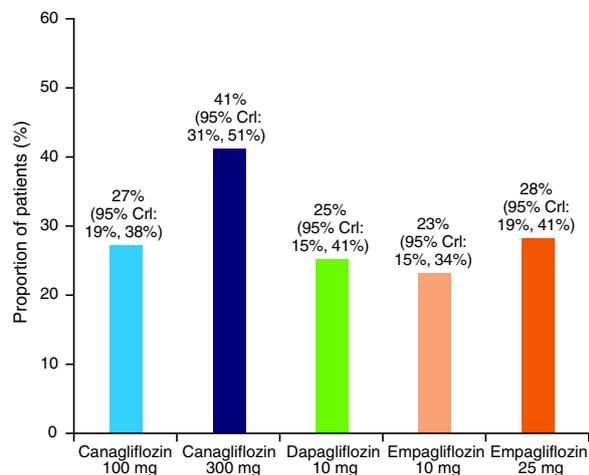


Fig. 2 Proportion of patients achieving HbA1c <7.0% at 26 weeks. CrI credible interval

adequate glycemic control with lower doses of SGLT2 inhibitors and can tolerate the increase, the dose of SGLT2 inhibitor will be increased to 300 mg for canagliflozin or 25 mg for empagliflozin. Of all the doses of SGLT2 inhibitors compared in this study, the cost of achieving HbA1c <7.0% over 26 weeks was lowest for canagliflozin 300 mg.

Analysis of cost per response is a simple and transparent way to compare the actual versus

daily acquisition drug costs per patient [25]. This straightforward analysis may be easier to understand and more meaningful to physicians and payers than conventional cost-effectiveness analyses that report quality-adjusted life years (QALYs). An analysis similar to the current study was performed on the basis of the outcome of cost per 1% reduction in HbA1c for canagliflozin, dapagliflozin, and empagliflozin, which was intended to serve as a preliminary report demonstrating to US formulary committees that cost per response may be a valuable measure to include in decision-making related to inclusion of SGLT2 inhibitors [25]. Notably, that study used data from the studies reported in each drug's US Food and Drug Administration (FDA)-approved prescribing information and did not allow for statistical comparisons between the different SGLT2 inhibitors, which were possible in the current study owing to the use of the NMA as the data source.

This kind of cost per response analysis can also help guide policies aimed at reducing variation in quality of care and be used to inform local and national guideline development. Across the UK, the percentage of patients achieving glycemic control (HbA1c \leq 7.5% [59 mmol/mol]) varies from 65.4% in Northern

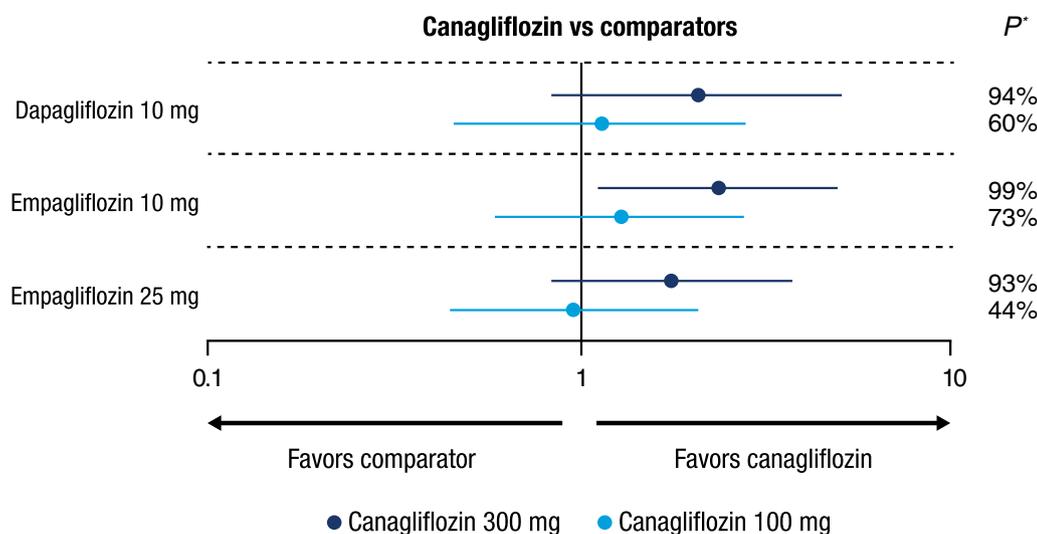


Fig. 3 OR (95% CrI) for achieving HbA1c <7.0% with canagliflozin 100 and 300 mg versus comparators. CANA canagliflozin, DAPA dapagliflozin, EMPA empagliflozin,

OR odds ratio, CrI credible interval. **P* = Bayesian probability for CANA to be more effective versus comparator

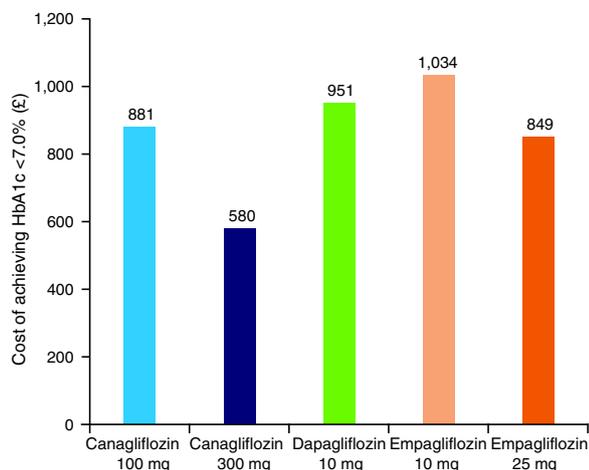


Fig. 4 Cost per patient of achieving HbA1c <7.0% at 26 weeks

Ireland to 71.5% in Wales [26]. Additionally, there is a large degree of variation in both spending on diabetes and diabetes-related outcomes among Clinical Commissioning Groups, NHS bodies responsible for local planning and commissioning of healthcare services, within England [27]. Estimating the costs per response allows healthcare providers to make informed recommendations about treatment options that balance efficacy and cost and can reduce variations in care.

The recent Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) of empagliflozin and The Comparative Effectiveness of Cardiovascular Outcomes (CVD-REAL) real-world study of SGLT2 inhibitors found that SGLT2 inhibitor treatment provided cardiovascular (CV) benefits in patients with T2DM and a history of CV disease [28, 29]. Similarly, the CANagliflozin cardioVascular Assessment Study (CANVAS) Program of canagliflozin in a broad population of patients with T2DM and a history or high risk of CV disease found a reduced risk of the primary composite major adverse CV events endpoint with canagliflozin compared with placebo (hazard ratio [95% confidence interval]: 0.86 [0.75, 0.97]) [30]. Thus, the emerging evidence suggests that CV benefits are likely to be a class effect of SGLT2 inhibitors and these potential benefits will be important to consider in future cost-effectiveness analyses.

Results from the ongoing Dapagliflozin Effect on Cardiovascular Events (DECLARE; NCT01730534) trial of dapagliflozin will provide further information on the CV benefits of SGLT2 inhibitors.

In addition to the potential benefits of SGLT2 inhibitor treatment, the safety profiles of these agents may impact their cost-effectiveness. Commonly reported adverse events include genital mycotic infections, transient polyuria with mild dehydration, and lower urinary tract infections [31]. Furthermore, a few safety signals have recently emerged that may also negatively impact the cost-effectiveness of SGLT2 inhibitors versus other AHAs. Rare cases of diabetic ketoacidosis (DKA), including life-threatening ones, have been reported in patients with T2DM treated with SGLT2 inhibitors [32]. In the clinical trials of canagliflozin, 12 patients experienced DKA, including 4 (0.07%), 6 (0.11%), and 2 (0.03%) treated with canagliflozin 100 and 300 mg and comparator, respectively; the majority of these patients were being treated with insulin, and six of the patients treated with canagliflozin had evidence of latent autoimmune diabetes or type 1 diabetes [33]. Rates of DKA were also low in the clinical trials of empagliflozin; a total of 11 patients experienced DKA, including 5 (0.1%), 1 (<0.1%), and 5 (0.1%) treated with empagliflozin 10 and 25 mg and placebo, respectively [34]. Of note, no increase in the risk of DKA was observed in the CANVAS Program or EMPA-REG OUTCOME [28, 30].

Post-marketing data from the FDA Adverse Events Reporting System (FAERS) through the end of 2015 identified a potential safety signal for acute kidney injury with all three SGLT2 inhibitors [35]. Canagliflozin, dapagliflozin, and empagliflozin all carry warnings from the FDA about increased risk of acute kidney injury [36, 37]. In contrast, no evidence of an increased risk of acute kidney injury was observed in the CANVAS Program or EMPA-REG OUTCOME [28, 30].

Emerging evidence suggests that SGLT2 inhibitors may be associated with an increased risk of lower-extremity amputation, the mechanism for which is unknown, but under investigation [38]. In the high CV risk population that

comprised the CANVAS Program, an increased risk of amputation, mainly of the toe, was observed. Over the course of the CANVAS Program, amputation was uncommon, occurring at a rate of 6.3 and 3.4 per 1000 patient-years for patients treated with canagliflozin and placebo, respectively, which constitutes an increased risk of 1.97-fold; patients with a history of prior amputation, peripheral vascular disease, and neuropathy were at the highest risk [30]. To date, limited additional data are available on the risk of amputation with empagliflozin and dapagliflozin, so it is currently not possible to establish whether or not the increased risk of amputation is an SGLT2 inhibitor class effect [39]. To further evaluate this risk, the European Medicines Agency (EMA) has now mandated that lower-extremity amputations be systematically captured in studies of SGLT2 inhibitors [40]. Information on the risk of lower-limb amputation has been added to the canagliflozin EMA summary of product characteristics; however, risk factors, other than general risk factors for amputation, are not known since the underlying mechanism has not been identified [41]. As a precaution, it is recommended that patients at high risk for amputation events should be carefully monitored and counseled about the importance of routine preventative foot care and maintaining adequate hydration, and that consideration should be given to stopping treatment in patients who develop amputation-preceding events including lower-extremity skin ulcer, infection, osteomyelitis, and gangrene [41].

Across phase 3 trials, canagliflozin treatment was associated with an increased risk of adverse events related to the mechanism of SGLT2 inhibition (i.e., genital mycotic infections, osmotic diuresis-related adverse events), but was generally well tolerated with a low rate of discontinuation due to adverse events [42]. As with all therapies, it will be important from both a clinical and economic perspective to balance these potential risks with the possible benefits for patients.

This study was limited by the simplistic nature of the analysis. Simple cost per HbA1c response analyses do not factor in the impact of potential differences in side effects or other benefits (i.e.,

avoidance of hypoglycemia, improvements in weight and blood pressure, and the potential cardioprotective effects of SGLT2 inhibition). Future studies evaluating cost per patient achieving relevant composite endpoints could also provide potentially valuable economic data. Two recent studies took this approach and showed cost advantages with liraglutide compared with lixisenatide and older therapies for T2DM [43, 44]. Additionally, this type of analysis does not include a willingness-to-pay threshold per patient achieving their glycemic target, and comparisons across therapeutic areas are not possible, unlike conventional cost per QALY modeling. However, estimating the cost of achieving HbA1c targets remains valuable given the known impact of good glycemic control on reducing the risk of complications in patients with T2DM [9].

CONCLUSION

Overall, this analysis suggests that canagliflozin 300 mg provides the best value for money among all SGLT2 inhibitors available in the UK in terms of achieving HbA1c <7.0%. The addition of canagliflozin to the treatment regimen of patients with T2DM who have inadequate glycemic control with metformin and sulfonylurea may provide significant cost savings by reducing diabetes-related complications.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Data Availability. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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