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ORIGINAL RESEARCH

The Cost-Effectiveness of Empagliflozin Versus Liraglutide Treatment in People with Type 2 Diabetes and Established Cardiovascular Disease

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ABSTRACT

Introduction: The increasing financial burden associated with diabetes treatment presents a challenge to healthcare systems worldwide. Recently, clinical guidelines have focussed on patients with type 2 diabetes (T2D) and established cardiovascular disease (CVD) and recommend a sodium-glucose co-transporter 2 (SGLT2) inhibitor or a glucagon-like peptide 1 (GLP-1) receptor agonist as second-line treatment after metformin or independently of baseline glycated haemoglobin A1c (HbA1c). In Danish clinical guidelines, empagliflozin and liraglutide are highlighted owing to their positive impact on mortality. Thus, this study aimed to assess the cost-effectiveness of empagliflozin plus standard of care (SoC) versus liraglutide plus SoC in Danish patients with T2D and established CVD using a lifetime and 5-year horizon.

Methods: The IQVIA Core Diabetes Model (CDM) was calibrated to reproduce the clinical event rates observed in the cardiovascular outcome trial EMPA-REG OUTCOME. Network meta-analysis provided the relative risks for cardiovascular outcomes with empagliflozin versus liraglutide. Microvascular outcomes were predicted by standard CDM risk equations. The relative treatment effect was assumed for 9 years after which treatment was switched to basal-bolus therapy. The CDM was populated with Danish costs of events and drug costs at price-level 2019. Discounting of 4% was applied.

Results: Over a lifetime horizon, CDM projected 9.858 and 9.667 life years, 6.162 and 5.976 quality-adjusted life years (QALY) and DKK 478,026 (€64,079) and DKK 500,025 (€67,027) in total costs for empagliflozin plus SoC and liraglutide plus SoC, respectively. For a 5-year horizon, the results were 4.189 and 4.140 life years, 2.746 and 2.655 QALY, as well as DKK 123,413 (€16,543) and DKK 161,783 (€21,687), respectively. Empagliflozin was the

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dominant treatment alternative. Sensitivity analyses showed the robustness of these results. ***Conclusion***: The cost-effectiveness analysis suggests that empagliflozin plus SoC is dominant compared to liraglutide plus SoC in Denmark over both lifetime and 5-year horizons.

Keywords: Cardiovascular outcomes; Cost-effectiveness; Diabetes type 2; Empagliflozin; Liraglutide

Key Summary Points

Why carry out this study?

International clinical guidelines recommend an SGLT2 inhibitor or a GLP-1 receptor agonist as second-line treatment after metformin or independently of baseline HbA1c in people with type 2 diabetes and established cardiovascular disease. In Danish clinical guidelines, empagliflozin and liraglutide are highlighted owing to their positive impact on mortality.

Clinical guidelines, however, do not consider costs. Thus, this study aimed to assess the cost-effectiveness of empagliflozin versus liraglutide.

What was learned from the study?

This study showed that empagliflozin was cost effective compared to liraglutide in a Danish healthcare setting in the management of patients with type 2 diabetes and established cardiovascular disease.

Considerable cost savings were associated with the use of empagliflozin, as well as a small QALY gain mainly driven by a small estimated gain in survival.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14077133.

INTRODUCTION

The global economic burden of diabetes is staggering [1]. In the USA alone, the American Diabetes Association estimated the total costs associated with patients diagnosed with type 2 diabetes mellitus (T2D) to be $327 billion in 2017 and care for people with diabetes now accounts for one in four healthcare dollars in the USA [2]. In Denmark, these costs are currently estimated to be €4.27 billion and expected to rise because of a number of factors including a rapidly increasing population with T2D [3, 4]. The cost of diabetes medication is now the largest item on the primary care drug budget in Denmark [5]. T2D is a progressive and chronic disease requiring treatment intensification over time focussed on maintaining an adequate glycaemic control while avoiding hypoglycaemia [6–9]. The ultimate treatment goals for T2D are to prevent or delay costly complications as well as maintaining quality of life [6]. Modern care for T2D entails a multifactorial approach comprising the minimization of additional risk factors for both micro- and macrovascular diabetes-related complications. Therefore, the impact of interventions reducing cardiovascular (CV) risk is an increasingly important consideration when choosing therapies.

Because patients with diabetes have an increased risk of cardiovascular disease (CVD), as well as safety signals seen with some previous diabetes medications, in 2008 the US Food and Drug Administration (FDA) determined that concerns about CV risk should be more thoroughly addressed during diabetes drug development [10]. This decision was followed by the European Medicines Agency (EMA) in 2012 [11]. Consequently, these agencies required the industry to conduct post-marketing

cardiovascular outcome trials (CVOT) to document the safety of all novel diabetes therapies [10, 11]. The first CVOTs completed after 2008 on new glucose-lowering agents, such as the dipeptidyl peptidase 4 (DPP4) inhibitors saxagliptin, alogliptin and sitagliptin as well as the glucagon-like peptide 1 (GLP-1) receptor agonist lixisenatide, were all shown to be safe with respect to CV outcomes in high CV risk populations [12, 13]. The EMPA-REG OUTCOME trial with the sodium-glucose co-transporter 2 (SGLT2) inhibitor empagliflozin was the first CVOT to not only show non-inferiority but also to significantly reduce CV risk compared to placebo, as shown by the composite primary and secondary outcomes, as well as a composite outcome of hospitalization due to heart failure (HF) and CV death [14, 15]. Moreover, the LEADER trial showed that liraglutide was not only safe but also capable of reducing CV risk and the incidence of CV death [16, 17].

In people with T2D and established CVD, clinical guidelines now recommend an SGLT2 inhibitor or GLP-1 receptor agonist as second-line treatment after metformin [7, 8] independently of baseline glycated haemoglobin A1c (HbA1c) [6, 9]. These clinical guidelines, however, do not consider cost. The treatment recommendations are based on systematic literature reviews of clinical evidence only, and do not include economic evidence based on costs and cost-effectiveness.

Health economic evaluations should be considered as valuable information for decision-makers in healthcare because they provide data on the opportunity costs of alternative treatment strategies [18]. Resources in healthcare are limited, and every decision about using scarce resources on a specific treatment is associated with an opportunity cost which reflects the health benefit foregone (i.e. the health benefit that could have been obtained if the resources were used otherwise). Internationally, there is no consensus on how to incorporate economic considerations pertaining to the cost of diabetes into clinical recommendations regarding treatment strategy. The cost of diabetes has been described as the elephant in the room, "impossible to miss, but frequently ignored" [19].

In Danish clinical guidelines, empagliflozin and liraglutide are highlighted owing to their positive impact on mortality. The aim of the present analyses was to assess the cost-effectiveness of empagliflozin versus liraglutide in adult patients with T2D and established CVD in Denmark.

METHODS

Decision Analytic Model

The IQVIA Core Diabetes Model (CDM) CVO version 9.0 was used to estimate the cost and quality-adjusted life years (QALYs) with respect to empagliflozin plus standard of care (SoC) versus liraglutide plus SoC in patients with T2D and established CVD. The primary outcome of the model was the incremental cost-effectiveness ratio (ICER). A Danish health sector perspective was used for a long-term (50 years) and short-term (5 years) time horizon. Future costs and QALYs were discounted with a rate of 4% as recommended by the Danish guidelines for health economic evaluation of pharmaceuticals [20]. All prices are stated in Danish krone (DKK) price-level 2019 excluding value added tax (VAT). Main results are also presented in euros (DKK 746 = €100).

The CDM is a web-based simulation model that determines the long-term health outcomes and economic consequences associated with different interventions in patients with diabetes. It has been used in more than 100 peer-reviewed publications and a significant number of reimbursement submissions worldwide. The structure of the CDM and the most recent validation are described in detail elsewhere [21, 22]. More information on CDM version 9.0 is available online (http://www.core-diabetes.com/). The CDM is a non-product-specific microsimulation tool that models the effect of glucose monitoring, diabetes therapies and treatment strategies on disease progression and outcomes. Disease progression is based on a series of interdependent Markov submodels that simulate progression of disease-related complications (angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular

disease, diabetic retinopathy, macular oedema, cataract, hypoglycaemia, ketoacidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer, amputation) and non-specific mortality. Each submodel uses time-, state- and diabetes type-dependent probabilities derived from published sources. The use of tracker variables bypasses the memoryless properties of standard Markov models. The model facilitates interconnectivity and interaction between the modelled complications, representing the complex and varied sequelae of the disease.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Clinical Data

The model calculations assume a cohort of individuals with T2D and baseline characteristics replicating the patients in the EMPA-REG OUTCOME trial (Table 1).

Data on treatment effects of empagliflozin and liraglutide on risk factors for CVD (i.e. annual progression of risk factors HbA1c, body mass index (BMI), blood pressure, lipids) were taken directly from the EMPA-REG OUTCOME [14, 15] and LEADER trials [16, 17].

Data on 3-year event rates for empagliflozin plus SoC were taken directly from the EMPA-REG OUTCOME trial. Event rates for liraglutide were calculated using the relative risks (RR) from an indirect treatment comparison (network meta-analysis) (Table 2) [23].

The CDM calibration process ensures that the CDM can replicate the trials' outcomes accurately at 3 years, which is a joint time point shared by the clinical trials, and has been described before [24]. In the CDM, different risk equations were tested and the United Kingdom Prospective Diabetes Study (UKPDS) 82 was found to be the best fit to predict the 3-year clinical outcomes. The outcomes used to calibrate the predictions were primary and secondary myocardial infarction (MI), primary and secondary stroke, hospitalization for angina, hospitalization for heart failure, CV death, non-CV death, microalbuminuria and end-stage renal disease. During this calibration, RR adjustments for outcomes were estimated by successively running the model until the CDM-predicted outcomes matched the observed ones closely. The 3-year observed CV events for empagliflozin plus SoC versus liraglutide plus SoC are presented in Table 3.

The UKPDS 82 combined mortality approach was also chosen for the calculation of mortality and thus country-specific life tables were not needed.

Treatment Intensification and Long-Term Risks

Since empagliflozin and liraglutide are both relatively new therapies, data on the long-term duration of treatment effect is currently lacking, and therefore assumptions were necessary. The drug-specific treatment effects on hard outcomes were assumed for 9 years (corresponding to the point at which HbA1c reached 8.5% in the empagliflozin arm and treatment was escalated). After this period, all patients were assumed to switch therapy and receive basal-bolus insulin as next line of therapy. The UKPDS 82 risk equations were applied to predict future CV events based on co-existing risk factors.

Costs and Management

Unit costs for treatment, including empagliflozin and liraglutide, were obtained from Medicinpriser.dk in November 2019 and corresponded to the average of the lowest unit cost for each drug during six price periods from 9 September 2019 to 18 November 2019. Pharmacy purchase price excluding VAT and pharmacy fee (In Danish: Apotekets Indkøbspriser, AIP) were used. For empagliflozin, the price per day was DKK 11.49 corresponding to an annual cost per patient of DKK 4195.38. For liraglutide, aligned with the LEADER study [17], the daily dose was 1.8 mg corresponding to a daily price of DKK 34.29 per day and an annual cost of DKK 12,526.10.

Table 1 Baseline characteristics of the EMPA-REG OUTCOME study

Patient characteristics	Value
Age; mean (SD)	63.1 (8.6)
% male; *n* (%)	72%
Currently smoking	13%
Ex-smoker	46%
Time since diagnosis of diabetes	
$\leq$ 5 years	18%
$>$ 5 years to $\leq$ 10 years	25%
$>$ 10 years	57%
History of MI	47%
Single-vessel CAD	11%
Multi-vessel CAD	47%
CABG	25%
History of stroke	23%
Peripheral occlusive arterial disease	21%
Key baseline laboratory test	
HbA1c (%), mean (SD)	8.1 (0.8)
Fasting plasma glucose (mmol/L), mean (SD)	8.5 (2.4)
Body mass index (BMI) (kg/m^2), mean (SD)	30.6 (5.3)
Weight (kg), mean (SD)	86.4 (18.9)
Waist circumference (cm), mean (SD)	105 (14)
Systolic blood pressure (SBP) (mmHg), mean (SD)	135 (17)
Diastolic blood pressure (DBP) (mmHg), mean (SD)	77 (10)
TC (mmol/L; mg/dl); mean (SD)	4.2 (1.1); 162.4 (42.5)
LDL (mmol/L; mg/dl); mean (SD)	2.2 (0.9); 85.1 (34.8) mg/dl
HDL (mmol/L; mg/dl); mean (SD)	1.2 (1.4); 46.4 (54.14) mg/dl
Triglycerides (mmol/L; mg/dl); mean (SD)	1.9 (1.4); 168.3 (124) mg/dl

SD standard deviation, *nF* nonfatal, *MI* myocardial infarction, *CAD* coronary artery disease, *HbA1c* glycated haemoglobin, *CABG* coronary artery bypass graft surgery, *eGFR* estimated glomerular filtration rate, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index, *LDL* low-density lipoprotein cholesterol, *HDL* high-density lipoprotein cholesterol

Source: Table 1 in Zinman et al. 2014 [14]

Costs of CV complications were obtained from a report prepared by the Danish national institute VIVE [25]. This report used the unique Danish registries based on personal identification numbers (CPR) to identify the average real-world cost of patients with a specific CV event

Table 2 Indirect comparison of empagliflozin versus liraglutide (relative risk, 95% CI)

Comparison	CV-related mortality	All-cause mortality	Composite endpoint	Hospitalization due to HF	Non-fatal stroke	Non-fatal MI
Empagliflozin vs. liraglutide	0.80 (0.60, 1.06)	0.80 (0.64, 1.00)	0.99 (0.82, 1.18)	0.75 (0.54, 1.03)	1.39 (0.97, 2.01)	0.99 (0.76, 1.30)

MI myocardial infarction, *HF* heart failure
Source: Balijepalli et al. 2018 [23]

Table 3 CDM predicted 3-year cumulative incidence (%) outcomes for empagliflozin and liraglutide compared to EMPA-REG OUTCOME trial and indirect comparison results

	Empagliflozin		Liraglutide	
	EMPA-REG observed	Model predicted	Estimated by IDC	Model predicted
Death from any cause	5.82	5.78	7.28	7.24
Death from cardiovascular causes	3.72	3.68	4.65	4.63
MI	5.04	5.05	5.09	5.08
Angina	3.00	3.01	3.00	3.06
Stroke	3.69	3.70	2.72	2.71
HF	2.82	2.83	3.76	3.79
MAU	75.75	75.86	75.75	76.76
GRP	12.54	12.34	12.54	9.17
ESRD	0.3	0.3	0.3	0.28

MI myocardial infarction, *HF* heart failure, *MAU* microalbuminuria, *GRP* gross proteinuria, *ESRD* end-stage renal disease, *IDC* indirect comparison (network meta-analysis)

compared to a matched control group with no such event.

The costs of treating other diabetes-related complications (in the year of the event) and the annual follow-up costs (applied in each year of the simulation subsequent to the first event) were identified through literature reviews and inflated using the consumer price index published by Statistics Denmark. More information on the applied unit costs for clinical management and complications is available in the supplementary material.

Utilities

To estimate the expected QALY gain of each treatment pathway, the CDM uses a comprehensive set of utility weights for each model state [26]. Utilities are assessed on a scale from 0 to 1, where 0 represents death (no quality of life) and 1 indicates a healthy person without complications. Disutilities due to illness are values in the range − 1 to 0, and therefore cause the quality of life utility to either decrease or remain constant. Following an event, patients change state and the new state is associated with different state utilities. Quality of life values are then estimated for every hypothetical patient in each year of the simulation and used to estimate the average quality-adjusted life expectancy. For all simulations, the minimum approach method was applied to calculate the quality-adjusted life utility. The values used for this analysis and

references are available in the supplementary material.

Sensitivity Analyses

The CDM uses Monte Carlo simulations together with a non-parametric bootstrapping approach to capture parameter uncertainty throughout the model, so that the imprecision of cost-effectiveness results can be assessed. Furthermore, several one-way and scenario analyses were conducted including the exclusion of insulin costs from treatment costs and changes in the number of years people with T2D receive empagliflozin or liraglutide after which point patients switch to basal-bolus therapy.

RESULTS

Empagliflozin provides additional life years and QALYs compared to liraglutide both in a lifetime and 5-year horizon (Table 4). In terms of total costs, liraglutide is more expensive compared to empagliflozin. No incremental cost-effectiveness ratios (ICERs) were calculated as empagliflozin is a dominant treatment alternative (both lower cost and higher QALYs).

Treatment costs were higher for liraglutide than for empagliflozin. Part of this was offset over time by higher complication costs in patients receiving empagliflozin compared to liraglutide (Fig. 1). Thus, the estimated savings from empagliflozin were higher in the 5-year than lifetime horizon. As a result of the longer survival with empagliflozin and consequent prolonged exposure to diabetes complications, complication costs were higher in the empagliflozin plus SoC arm than in the liraglutide plus SoC arm. The probabilistic sensitivity analysis (lifelong time horizon) showed that empagliflozin is cost-effective in comparison to liraglutide in more than 78% of the simulations for a willingness to pay threshold of DKK 357,100 per QALY (1 time Gross Domestic Product (GDP) per capita) (Figs. 2 and 3). Dominance was observed in 59% of the simulations. All one-way and scenario analyses confirmed the robustness of the results (Supplementary material Appendix 1 table 10).

Total costs for the 50-year period were DKK 478,026 for empagliflozin plus SoC and DKK 500,025 for liraglutide plus SoC per patient. For the 5-year period, total costs were DKK 123,413 for empagliflozin plus SoC and DKK 161,783 for liraglutide plus SoC per patient (Fig. 1).

DISCUSSION

Overall, this study demonstrates the cost-effectiveness of empagliflozin compared to liraglutide in the management of patients with T2D and established CVD for both a lifetime and 5-year horizon. Results show considerable cost savings associated with the use of empagliflozin, as well as a small QALY gain mainly driven by a small estimated gain in survival.

Modelling cost-effectiveness using CVOTs is the most widely used approach for incorporating evidence of drug-mediated cardioprotection

Table 4 Cost-effectiveness results

	Lifetime horizon		5-year horizon	
	Empagliflozin	**Liraglutide**	**Empagliflozin**	**Liraglutide**
LY	9.858	9.667	4.189	4.067
QALY	6.162	5.976	2.746	2.655
Total cost	478,026	500,025	123,413	161,783
ICER (DKK/QALY)	Dominant	Dominated	Dominant	Dominated

LY life years, *QALY* quality-adjusted life years, *ICER* incremental cost-effectiveness ratio

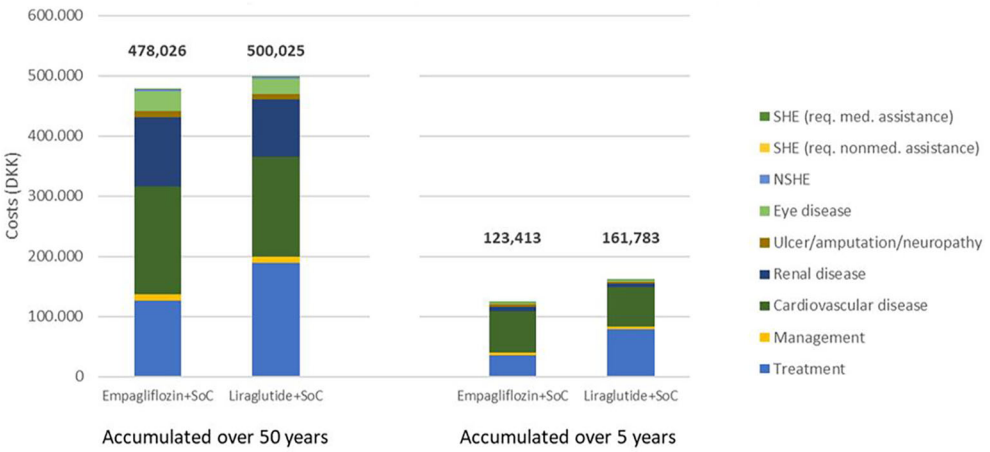

Fig. 1 Total costs per individual (DKK)*. T2D type 2 diabetes, CVD cardiovascular disease, SoC standard of care, NSHE nonsevere hypoglycemic events, SHE severe hypoglycemic events. *Total cost per individual (DKK) is available in Table 9 in the supplementary material

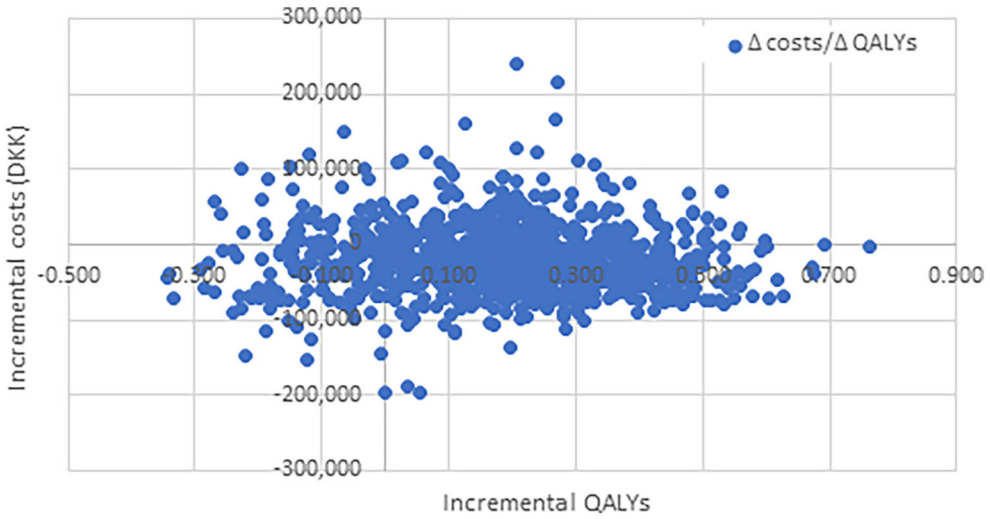

Fig. 2 ICER scatter plot, empagliflozin vs. liraglutide

in people with T2D [27]. This approach generally has advantages compared to other modelling approaches; however, there are also several limitations.

The clinical data considered in the current analyses do not come from head-to-head comparisons, but from an indirect comparison between the LEADER and the EMPA-REG OUTCOME trials [23]. Indirect comparison for relative risks is limited by substantial heterogeneity. In particular, because the trials differ by study population and differences in SoC.

Another limitation is that the current analysis uses the UKPDS 82 risk equations to predict lifetime health outcomes after treatment switch. The UKPDS 82 was applied because the calibration exercise showed that this option provided the best prediction of the EMPAREG-OUTCOME trial outcomes. Treatment switch was assumed to happen after 9 years in the model. Sensitivity analysis up to 13 years for liraglutide did not alter the results.

Furthermore, the CDM calculations are based on assumptions on utilities and costs.

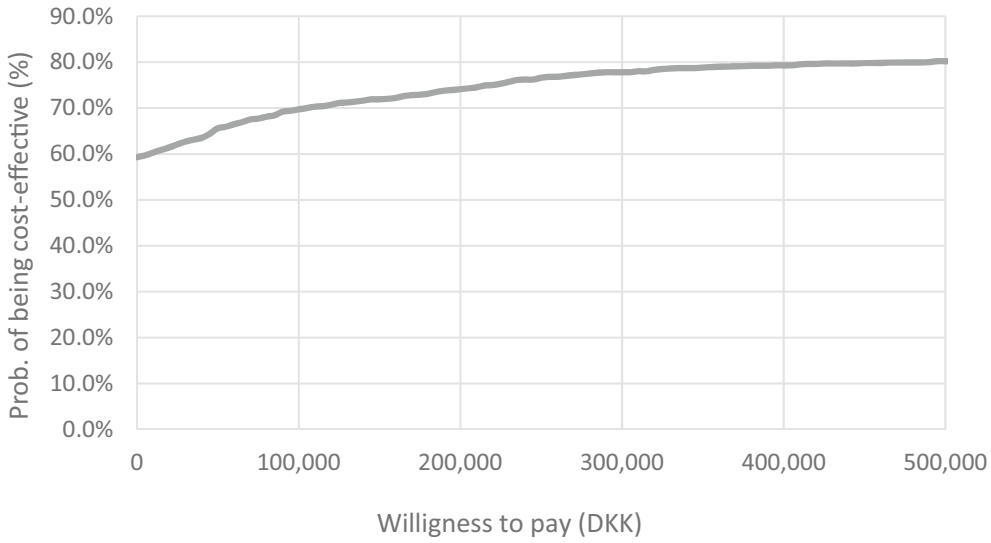

Fig. 3 Cost-effectiveness acceptability curve of empagliflozin versus liraglutide

Utility data were not trial specific, but instead taken from published literature for a general T2D population. Therefore, utility data specific to patients with T2D and established CVD were not available. However, this utility data set has previously been established as a good reference set of utility values in accordance with health economic guidelines [26]. Cost data on comorbidity were similar to those assumptions used in economic evaluations of orally administered semaglutide [28] except for CVD costs, where new evidence has been published [25].

Our results generally align with other findings in the literature; however, only a few health economic studies have so far compared empagliflozin with liraglutide in people with T2D and established CVD. A US study on the economic aspects of empagliflozin versus liraglutide for prevention of CV mortality concludes that empagliflozin prescribed for preventing CV death in patients with T2D and high CV risk seems to be a major cost-saving strategy compared with liraglutide [29]. A UK study on the cost-effectiveness of empagliflozin versus liraglutide based on CVOT finds empagliflozin plus SoC to be dominant compared to liraglutide plus SoC from the UK NHS perspective [24]. The current study was an adaptation of this UK study to a Danish setting. More details on the methodology can be found in this publication. A systematic review on the pharmacoeconomic evaluation of SGLT2 inhibitors for the treatment of T2D finds that, in studies based on data from EMPA-REG OUTCOME, treatment with empagliflozin generally appears to be especially cost-effective in those with the pre-existing CVD. This review, however, does not include GLP-1 receptor agonists or DPP4 inhibitors [30].

The Danish payer requests information on total cost differences at 5 years [31]. Total costs for the 5-year period showed a difference of DKK 38,370 (€5143) per patient or − 24% with empagliflozin plus SoC versus liraglutide plus SoC (Fig. 3). Even taking a life-long perspective (50 years) where the higher life expectancy with empagliflozin plus SoC resulted in a higher number of complications, empagliflozin plus SoC still had lower total costs than liraglutide plus SoC.

According to a recent registry study, 24.4% of Danes with T2D have established CVD [32], which corresponds to roughly 60,000 people [33]. Of these, 75% are currently estimated to not be treated with either an SGLT2 inhibitor or a GLP-1 receptor agonist despite the recommendation in Danish clinical guidelines (Data on file 2020). This study indicates that the

future treatment strategy may have significant impact on the regional budgets, and that further budget impact analysis is warranted.

Health economic evaluations provide important input for decision-makers in healthcare as they yield information on the opportunity costs of alternative treatment strategies. Since 2017, the Danish Medicines Council has published recommendations for hospital drug use based on both clinical and economic evidence of the costs and consequences with respect to alternative treatments [34]. For primary care prescription medicine, however, the Danish reimbursement system still does not require pharmaceutical companies to submit economic evaluations. Besides voluntary price-cap agreements, there is free pricing on primary care prescriptions drugs in Denmark. Nonetheless, the recent years' development in the market for hospital drugs shows an increasing focus among Danish decision-makers on pharmaceutical prices and consumption. It seems likely that this focus will eventually also be directed towards the market for primary care prescription medicine. The market for primary care prescription medicine constitutes approximately 40% of the annual costs of medicine in Denmark, with patients paying approximately 30% of the bill [34].

Further real-life studies focussing on the costs and consequences of treatment of patients with T2D and established CVD should be conducted.

Limitations of the Current Study

These main limitations in the study are (1) the lack of a head-to-head comparison between the two drugs, (2) the use of published risk equations to predict long-term costs and health outcomes and (3) the use of assumptions taken from published literature regarding unit costs and utility values for different health states.

CONCLUSION

This study demonstrates that empagliflozin is a dominant treatment compared to liraglutide in the management of T2D patients with established CVD in a Danish setting.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. All data generated or analysed during this study are included in this published article/as supplementary information files.

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