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ORIGINAL RESEARCH

CELESTIA: Cost-Effectiveness Analysis of Empagliflozin Versus Sitagliptin in Patients with Type 2 Diabetes in Greece

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Purpose: Globally, the prevalence of diabetes is on the rise, with the number of affected individuals predicted to cross 700 million by 2045. In Greece, in 2015, almost 700,000 people received prescribed medication for type 2 diabetes. The CELESTIA study aims to assess the cost-effectiveness of empagliflozin compared to branded sitagliptin in type 2 diabetes patients both with and without established cardiovascular disease in Greece from a third payer perspective.

Methods: The IQVIA Core Diabetes Model was used and analyses were conducted from the Greek healthcare payer perspective. Patients received either empagliflozin or sitagliptin until HbA1c threshold of 8.5% (69 mmol/mol) was exceeded. Subsequently, patients were assumed to intensify to insulin therapy. Baseline cohort characteristics and treatment effects were derived from clinical trial data. Literature data were used for input (utilities, treatment costs and costs of diabetes-related complications costs). A lifetime time horizon (50 years) was applied, and costs and benefits were discounted at an annual rate of 3.5%.

Results: Over a lifetime horizon, for empagliflozin, the estimated ICER was of €6,587 and €966 per quality-adjusted life years gained versus sitagliptin, in patients without established cardiovascular disease and in patients with established cardiovascular disease, respectively. Probabilistic sensitivity analysis confirmed the robustness of the analysis.

Conclusion: The analysis demonstrated that for type 2 diabetes patients, empagliflozin is a cost-effective treatment option versus branded sitagliptin in Greece.

Keywords: cost-effectiveness, empagliflozin, Greece, IQVIA core diabetes model, sitagliptin, type 2 diabetes

Introduction

Diabetes and its complications are a significant cause of mortality and disability worldwide. In 2017, an estimated 6.28% (462 million) people worldwide were reported to be suffering from the disease. Diabetes is one of the top 10 leading causes of mortality, with more than 1 million deaths per year that can be attributed to the disease alone.[1] Globally, the number of affected individuals is predicted to cross 700 million by 2045.[2]

In 2015, in Greece, an estimated 6.8% of the population (almost 700,000 people) received prescribed medication for type 2 diabetes.[3] The annual economic burden associated with diabetes patients was estimated to be around €7,000 in a 2014 study. In this study, it emerged that the economic burden was significantly higher in patients with poor glycemic control (glycosylated hemoglobin >7%). Furthermore, most of the economic burden was due to diabetes-related complications and comorbidities.[4]

Many landmark studies have shown that maintaining good glycemic control can reduce the incidence of diabetes-related complications over the long term[5–9] and thus improving glycemic control remains one more focus of care in combination with the reduction of cardio-renal risk for patients with type 2 diabetes. Based on this, treatment intensification is recommended when glycated hemoglobin (HbA1c) exceeds the 7.5% (58 mmol/mol).[10] In addition to this, also multifactorial care, targeting not only glycemic control but also blood pressure, serum lipids, body weight and

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hypoglycemia risk, is associated with a reduced risk of complications.[11–14] Indeed, the latest consensus report by the European Association for the Study of Diabetes and the American Diabetes Association recommends a more holistic approach to diabetes treatment, with additional focus on the treatment effects on cardiovascular disease, body weight and hypoglycemia risk, rather than a sole focus on glycemic control.[15]

The aim of the Cost-Effectiveness anaLysis of Empagliflozin versus Sitagliptin in patients with Type 2 dIAbetes (CELESTIA) study was to assess the cost-effectiveness of empagliflozin 10 mg, a sodium-glucose cotransporter-2 (SGLT-2) inhibitor, compared to branded sitagliptin 100 mg, a dipeptidyl peptidase-4 (DPP-4) inhibitor, in Greece. The analysis considered both type 2 diabetes patients without established cardiovascular disease (CVD) and type 2 diabetes patients with established CVD.

Materials and Methods

Modelling Approach

The IQVIA CORE Diabetes Model (CDM) was used to perform the analyses. IQVIA CDM is an online simulation tool that estimates both clinical and economic results for cohorts of patients with diabetes. In particular, it performs real-time simulations, of patient receiving intensive or conventional insulin therapy, oral antidiabetic drugs, screening and treatment strategies for microvascular complications, treatment strategies for end-stage complications and multifactorial interventions. Disease progression is based on a series of inter-dependent Markov sub-models that simulate progression of disease-related complications and other cause mortality. Each sub-model uses time-state- and diabetes type-dependent probabilities derived from published sources, utilizing tracker variables to overcome 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. Clinical and economic outcomes are calculated within the model using a non-parametric bootstrapping approach. The reliability of simulated outcomes has been tested, with results validated against those reported by clinical trials and epidemiological studies. The interested reader should refer to previously published articles describing this tool[16–18] and to the information that are available online (http://www.core-diabetes.com/).

The outputs of the model include amongst other outcomes: life years (LY), quality-adjusted life-years (QALY), direct healthcare costs and incidence of complications. A lifetime horizon was considered in the analyses (50 years), as recommended in American Diabetes Association guidelines.[19] Both costs and benefits were discounted by an annual 3.5% rate, in line with previous cost-effectiveness studies in type 2 diabetes in Greece.[20,21]

Clinical Data: Patients without Established CVD

The IQVIA CDM version 9.5 was used to estimate the long-term cost-effectiveness of empagliflozin versus branded sitagliptin in adult patients without established CVD whose HbA1c level is inadequately controlled on metformin alone in Greece.

EMPA-REG MET trial data[22] were used for baseline cohort characteristics. Baseline values required by the IQVIA CDM that were not reported in the publication were based on cohort data from another study that enrolled a similar patient population and other published data. Table S1 summarizes patients baseline characteristics used in the analysis.

The treatment benefits on physiological parameters and adverse event rates were sourced from a network-meta-analysis (NMA) [data on file] and from the publication of Häring et al[22] (Table 1).

Clinical Data: Patients with Established CVD

The IQVIA CDM version 9.0 was used to estimate the long-term cost-effectiveness of empagliflozin versus branded sitagliptin in adult patients with established CVD in Greece.

The model was calibrated to align the three-year event rates predicted by the IQVIA CDM with the results of the EMPA-REG OUTCOME trial for empagliflozin.[23] For sitagliptin efficacy was estimated using the results from an indirect treatment comparison (ITC) of empagliflozin to sitagliptin[24] (Table 2). Table S2 summarizes the assumptions considered to match the endpoints in the EMPA-REG OUTCOME trial and those reported by the ITC with the

Table 1 Treatment Effects and Adverse Event Rates Applied in the Analyses for Patients without Established CVD

	Empagliflozin	Sitagliptin
Physiological parameters (applied in the first year of the analysis), mean		
HbA1c (change from baseline)	−0.685†	−0.45†
BMI (change from baseline)	−0.80	0.10
SBP (change from baseline)	−3.95†	−1.39†
Adverse event rates (applied while patients received treatment)		
NSHE rate (per 100 patient-years)	3.53	4.02†
GUI (per 100 patient-years)	19.00	10.00

Note: †Data on file (not previously published).
Abbreviations: BMI, body mass index; GUI, genital and urinary infection; HbA1c, glycated hemoglobin; NSHE, non-severe hypoglycemic event; SBP, systolic blood pressure.

Table 2 Comparison of Expected vs Projected 3-Year Cumulative Incidence (%) Outcomes for Empagliflozin and Sitagliptin Post CDM Outcome Calibration

Event	Empagliflozin		Sitagliptin	
	From EMPA-REG OUTCOME	Calibrated	Estimated by ITC	Calibrated
Death from any cause	5.82	5.78	8.69	8.67
Death from CV causes	3.72	3.68	6.20	6.13
MI	5.04	5.05	5.04	5.00
Angina	3.00	3.01	3.00	3.01
Stroke	3.69	3.70	3.69	3.69
HF	2.82	2.83	4.34	4.36
MA	75.75	75.86	79.8	79.1
GRP	12.54	12.34	19.47	14.89
ESRD	0.3	0.3	0.63	0.54

Abbreviations: CV, cardiovascular; ESRD, end-stage renal disease; GRP, gross proteinuria; HF, heart failure; ITC, indirect treatment comparison; MA, microalbuminuria; MI, myocardial infarction.

IQVIA CDM endpoints. The calibration process, with all the conducted steps, have been already described in previous published analysis.[25–27]

EMPA-REG OUTCOME trial data[23] were used for baseline cohort characteristics. Baseline values required by the IQVIA CDM that were not reported in the publication were taken from clinical study report data and other published articles. Table S3 summarizes patients baseline characteristics used in the analysis.

The treatment benefit on physiological parameters and adverse event rates in the first year were aligned with each trial[23,28,29] (Table 3). For second and third years, the treatment effect followed the progression over time available in each trial. From the fourth year onwards, the two treatments were assumed equally effective and, thus, HbA1c progression from the EMPA-REG OUTCOME trial was applied to both.

Table 3 Treatment Effects and Adverse Event Rates Applied in the Analyses for Patients with Established CVD

Variable	Empagliflozin	Sitagliptin‡
Physiological parameters (applied in the first year of the analysis), mean		
HbA1c†	−0.58	−0.328
SBP†	−3.9	−0.62
DBP†	−1.72	−0.78
T-Chol†	7.81	3.56
HDL†	1.81	−0.09
LDL†	4.79	1.42
TRIG†	0	0
BMI†	−0.64	−0.04
eGFR†	−0.16	0.18
Adverse event rates (applied while patients received treatment)		
NSHE rate (per 100 patient-years)	13.62	13.98
SHE1 rate (per 100 patient-years)	0.44	0.64
SHE2 rate (per 100 patient-years)	0.06	0.14
GUI rate (per 100 patient-years)	10.53	8.95

Notes: †Effect on the surrogate endpoints is applied on the first year of treatment. ‡Aside HbA1c effect, all other endpoints were assumed to be equal to placebo described in the EMPA-REG OUTCOME trial.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GUI, genital and urinary infection; HbA1c, glycosylated hemoglobin; HDL, high density lipoprotein; NSHE, non-severe hypoglycemic event; SBP, systolic blood pressure; SHE1, Severe hypoglycemic event (not requiring medical assistance); SHE2, Severe hypoglycemic event (requiring medical assistance); T-Chol, total cholesterol; TRIG, triglycerides.

Treatment Intensification and Long-Term Disease Progression: Patients without Established CVD

The patient cohort was assumed to receive a first-line treatment of empagliflozin or sitagliptin, plus metformin as background therapy. An HbA1c threshold of 8.5% (69 mmol/mol) was defined which triggered the patients to receive an escalation therapy. Patients were switched to basal insulin therapy, as assumed in other recent analyses.[30,31] In particular, an escalation therapy of insulin glargine 42 units per day with metformin as background therapy was considered in the analysis. Both treatment effect and adverse event rates of insulin glargine were derived from published literature data[32] (Table 4). The United Kingdom Prospective Diabetes Study (UKPDS) 82 risk equation[33] was used to model HbA1c after the first year for the remainder of the analysis. Similarly, also the evolution of blood pressure and serum lipids were predicted by applying the progression factors available in the IQVIA CDM (UKPDS 82 and Framingham). Regarding body mass index (BMI), as long as patients stayed on empagliflozin or sitagliptin, the impact on BMI was maintained.

Treatment Intensification and Long-Term Disease Progression: Patients with Established CVD

The patient cohort was assumed to receive a first-line treatment of empagliflozin or sitagliptin. An HbA1c threshold of 8.5% (69 mmol/mol) was defined which triggered the patients to receive an escalation therapy. Patients were switched to basal-bolus insulin therapy, as assumed in other recent analyses.[25–27] In particular, a basal insulin dose of 94 units per day and bolus insulin of 59 units per day were considered, as reported by Riddle et al.[34] Based on a Greek cross-sectional disease registry, basal insulin regimens

Table 4 Treatment Effects and Adverse Event Rates Applied in the Analyses for Patients without Established CVD (Second-Line Treatment)

	Insulin
Physiological parameters (applied in the first year of the analysis), mean	
HbA1c (change from baseline)	−1.7
BMI (change from baseline)	0.818
Adverse event rates (applied while patients received treatment)	
NSHE rate (per 100 patient-years)	486
SHE1 rate (per 100 patient-years)	1.76
SHE2 rate (per 100 patient-years)	0.24

Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin; NSHE, non-severe hypoglycemia rate; SBP, systolic blood pressure; SHE1, Severe hypoglycemic event (not requiring medical assistance); SHE2, Severe hypoglycemic event (requiring medical assistance).

were prescribed for 80% of the patients.[35] Both treatment effect and adverse event rates of basal-bolus insulin were taken from published data[34] (Table 5). In the analysis, CVO outcomes were extended until treatment escalation. Therefore, before treatment switch, HbA1c progression, mortality, and cardiovascular and renal outcomes followed CVO trials results. After treatment switch, the UKPDS 82 risk equations[33] were applied to predict all outcomes.

Table 5 Treatment Effects and Adverse Event Rates Applied in the Analyses for Patients with Established CVD (Second-Line Treatment)

Variable	**Basal-Bolus Therapy**
Physiological parameters (applied in the first year of the analysis), mean	
HbA1c*	−0.828
SBP*	0
DBP*	0
T-Chol*	0
HDL*	0
LDL*	0
TRIG*	0
BMI*	0.32
eGFR*	0
Adverse event rates (applied while patients received treatment)	
NSHE rate (per 100 patient-years)	2566.83
SHE1 rate (per 100 patient-years)	23.81
SHE2 rate (per 100 patient-years)	3.19
GUI rate (per 100 patient-years)	–

Note: *Effect on the surrogate endpoints was applied on the first year of treatment.
Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GUI, genital and urinary infection; HbA1c, glycosylated hemoglobin; HDL, high density lipoprotein; NSHE, non-severe hypoglycemic event; SBP, systolic blood pressure; SHE1, severe hypoglycemic event (not requiring medical assistance); SHE2, severe hypoglycemic event (requiring medical assistance); T-Chol, total cholesterol; TRIG, triglycerides.

Patient Management

Input data regarding the clinical management of patients were derived from published literature. These data included the proportion of patients on preventive medications, undergoing routine screening for diabetic complications, and the sensitivity and specificity of the screening tests performed.

Utility Data

Table S4 summarizes the data used in the analysis and the related sources. In the analysis, a minimum approach was applied to estimation of utilities, so that in the case of multiple events, the lower utility was applied. For BMI, in line with published results,[36] a disutility of – 0.0061 per unit gain in BMI for over 25 kg/m^2 was considered in the analysis.

Costs

The analysis was conducted from a third-party payer perspective (National Organization for Healthcare Services Provision [EOPYY]) and, therefore, only direct healthcare costs were included. The analysis aimed at comparing the lifetime costs and effects of empagliflozin versus branded sitagliptin. All prices used were euros (€).

Treatment costs considered in the analysis included drug cost, and needle and the costs associated with self-monitoring of blood glucose for patients receiving insulin (Table S5). Unit costs were sourced from the most recent price bulletin issued by the Greek Ministry of Health.[37] For patients with established CVD, aside the main therapy (either empagliflozin or sitagliptin), also insulin as concomitant therapy was considered. The proportion of patients receiving insulin at baseline was considered in the calculation of first-year cost (48% for empagliflozin and 24% for sitagliptin). To estimate the cost of the following-up years, the proportion of patients receiving insulin at the end of trial was used (51% for empagliflozin and 33% for sitagliptin).

Other captured direct healthcare costs were diabetes-related complications (cardiovascular disease, renal, acute events, eye disease, neuropathy, foot ulcer and amputation), costs and patient management costs. Annual costs were obtained from published literature,[20,38] and all costs were inflated to 2021 using the National Statistical Service.[39] Table S6 summarized all the input costs used in the analysis.

Results

Base Case Analysis

Over a lifetime horizon, empagliflozin provided additional life years (+0.026 LY and +0.492 LY) and quality-adjusted life years (+0.132 QALY and +0.333 QALY) at an additional cost of €868 and €321 compared to sitagliptin, respectively, in patients without established CVD and in patients with established CVD. The ICER estimated for empagliflozin compared to sitagliptin was €6,587/QALY gained and €966/QALY gained, respectively (Table 6).

Compared to sitagliptin, the use of empagliflozin implies an increase in the treatment cost of 11.2% and 19.0%, respectively, for patients without established CVD and patients with established CVD (Table 7). This increase is partially offset by a saving of resources in other cost categories. Overall, the increase in total costs with empagliflozin is estimated in 2.2% and 0.4%, respectively, for patients without established CVD and patients with established CVD (Table 7).

Regarding clinical results, empagliflozin was associated with a lower cumulative incidence of events per 1,000 patient-years for almost every event considered in the analysis in both patients without and with established CVD (Table 8).

Probabilistic Sensitivity Analysis

Results of the probabilistic sensitivity analysis were presented on an incremental cost-effectiveness plane and as a cost-effectiveness acceptability curve.

For patients without established CVD, most of the simulations (75.4%) lie in the south-east and north-east quadrants (Figure 1A). Empagliflozin was dominant (less costly and more effective) in 23.1% of the simulations, and the

Table 6 Long-Term Cost-Effectiveness Outcomes in the Base Case Analyses

Health Outcomes	Empagliflozin	Sitagliptin	Difference
Patients without established cardiovascular disease			
Discounted LY	15.28	15.26	0.026
Discounted QALY	10.58	10.45	0.132
Discounted total costs (€)	40,331	39,464	868
ICER (€/QALY gained)	6,587		
Patients with established cardiovascular disease			
Discounted LY	11.50	11.01	0.492
Discounted QALY	7.10	6.77	0.333
Discounted total costs (€)	83,162	82,840	321
ICER (€/QALY gained)	966		

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life years; QALY, quality-adjusted life years.

Table 7 Breakdown of Costs

Cost Category	Empagliflozin	Sitagliptin	Difference
Patients without established cardiovascular disease			
Total cost (€)	40,331	39,464	868
Treatment (€)	10,505	9,444	1,061
Management (€)	2,803	2,794	9
CVD (€)	5,536	5,583	−47
Renal (€)	246	227	20
Ulcer/Amputation/Neuropathy (€)	8,406	8,528	−121
Eye (€)	12,677	12,720	−43
NSHE (€)	0	0	0
SHE1 (€)	142	152	−10
SHE2 (€)	16	17	−1
Patients with established cardiovascular disease			
Total cost (€)	83,162	82,840	321
Treatment (€)	17,007	14,294	2,713
Management (€)	2,398	2,287	111
CVD (€)	31,367	30,343	1,024
Renal (€)	18,482	22,083	−3,601
Ulcer/Amputation/Neuropathy (€)	7,384	7,233	151

(*Continued*)

Table 7 (Continued).

Cost Category	Empagliflozin	Sitagliptin	Difference
Eye (€)	5,447	5,587	−140
NSHE (€)	0	0	0
SHE1 (€)	990	928	62
SHE2 (€)	87	86	1

Abbreviations: CVD, cardiovascular disease; NSHE, non-severe hypoglycemic event; SHE1, severe hypoglycemic event (not requiring medical assistance); SHE2, severe hypoglycemic event (requiring medical assistance).

Table 8 Cumulative Incidence of Events per 1,000 Patient-Years

Events	Empagliflozin	Sitagliptin	Difference
Patients without established cardiovascular disease			
Renal disease			
Microalbuminuria	10.25	10.46	−0.22
Gross renal proteinuria	1.35	1.35	0.00
End-stage renal disease	0.16	0.17	0.00
Cardiovascular disease			
Peripheral vascular disease	5.98	5.98	−0.01
Heart failure	3.29	3.49	−0.20
Angina	6.58	6.62	−0.04
Stroke	4.17	4.20	−0.02
Myocardial infarction	8.82	8.87	−0.05
Eye disease			
Background diabetic retinopathy	11.97	12.14	−0.17
Proliferative diabetic retinopathy	1.13	1.16	−0.03
Macular oedema	10.93	11.12	−0.18
Severe vision loss	5.49	5.62	−0.13
Cataract	5.80	5.83	−0.03
Ulcer/Amputation/Neuropathy			
Ulcer	1.55	1.62	−0.07
Recurrent ulcer	1.67	1.74	−0.07
1st amputation	0.42	0.44	−0.02
2nd amputation	0.13	0.14	−0.01
Neuropathy	30.69	30.94	−0.25
Hypoglycemia (event/patient)			
Non-Severe hypoglycemia	85.46	89.71	−4.25
Severe hypoglycemia (requiring non-medical assistance)	0.39	0.41	−0.02
Severe hypoglycemia (requiring medical assistance)	0.04	0.05	0.00

(*Continued*)

Table 8 (Continued).

Events	Empagliflozin	Sitagliptin	Difference
Patients with established cardiovascular disease			
Renal disease			
Microalbuminuria	60.58	63.43	−2.85
Gross renal proteinuria	28.02	29.99	−1.97
End-stage renal disease	11.09	12.55	−1.46
Cardiovascular disease			
Peripheral vascular disease	13.48	13.71	−0.23
Heart failure	12.38	15.50	−3.12
Angina	14.26	15.05	−0.79
Stroke	11.19	11.29	−0.10
Myocardial infarction	21.19	22.68	−1.49
Eye disease			
Background diabetic retinopathy	12.58	13.32	−0.74
Proliferative diabetic retinopathy	1.22	1.37	−0.15
Macular oedema	11.74	12.37	−0.63
Severe vision loss	6.46	6.82	−0.36
Cataract	6.00	6.20	−0.20
Ulcer/Amputation/Neuropathy			
Ulcer	2.35	2.43	−0.09
Recurrent ulcer	4.48	4.59	−0.10
1st amputation	1.03	1.07	−0.05
2nd amputation	0.38	0.38	−0.01
Neuropathy	37.99	39.66	−1.67
Hypoglycemia (event/patient)			
Non-Severe hypoglycemia	248.06	231.68	16.38
Severe hypoglycemia (requiring non-medical assistance)	2.43	2.28	0.16
Severe hypoglycemia (requiring medical assistance)	0.22	0.21	0.01

probability of being cost-effective compared with sitagliptin for a WTP threshold of €30,000/QALY gained was 72.2% (Figure 1B).

For patients with established CVD, in almost all simulations (98.8%) empagliflozin was more effective (Figure 1C). Empagliflozin was dominant in 40.4% of the simulations, and the probability of being cost-effective compared with sitagliptin for a WTP threshold of €30,000/QALY gained was 98.4% (Figure 1D).

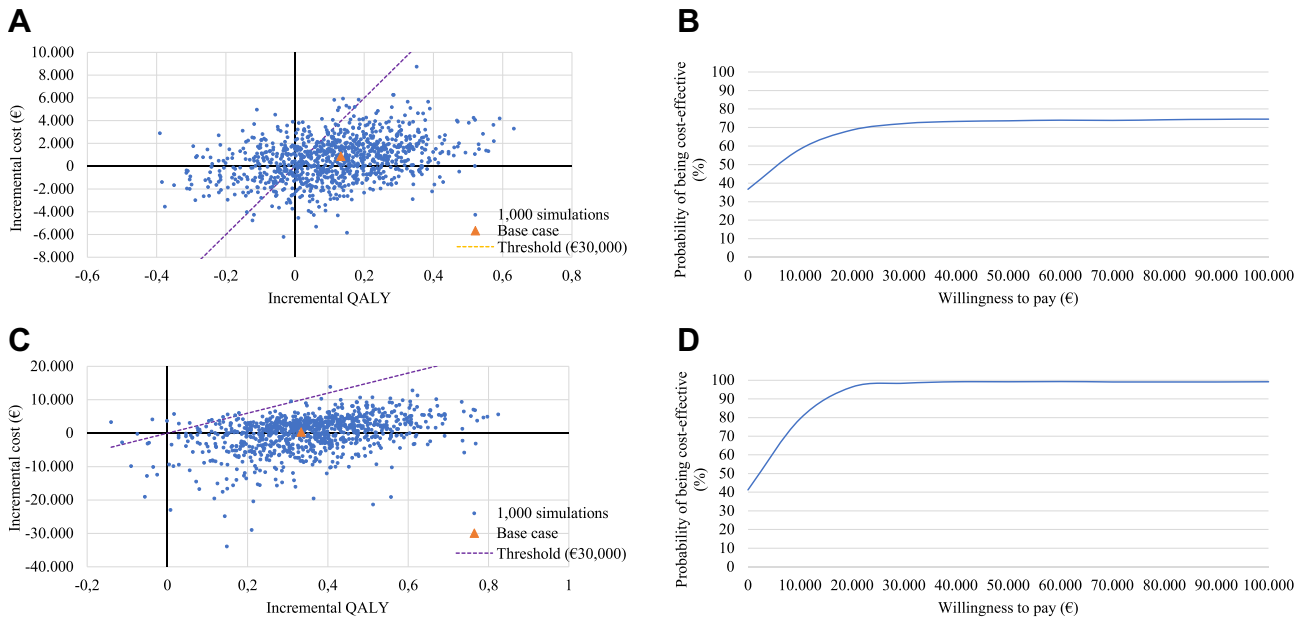

Figure 1 Incremental cost-effectiveness plane and cost-effectiveness acceptability curves. (**A**) Incremental cost-effectiveness plane for patients without established cardiovascular disease. (**B**) Cost-effectiveness acceptability curve for patients without established cardiovascular disease. (**C**) Incremental cost-effectiveness plane for patients with established cardiovascular disease. (**D**) Cost-effectiveness acceptability curve for patients with established cardiovascular disease.

Discussion

The CELESTIA study was conducted from a payer perspective to estimate the long-term cost-effectiveness of empagliflozin 10 mg versus branded sitagliptin 100 mg in both type 2 diabetes patients without established CVD and type 2 diabetes patients with established CVD in Greece.

Sitagliptin was chosen as a comparator in the analysis because it was the first DPP-4 inhibitor that received the marketing authorization and the first launched into the Greek market. Therefore, healthcare professionals clinical experience with this drug could be considered longer in time.

Empagliflozin resulted as a cost-effective treatment option versus sitagliptin for type 2 diabetes, and it was also associated with less diabetes-related complications. This implied cost savings that partially offset the higher treatment costs versus branded sitagliptin. The estimated ICER for empagliflozin versus branded sitagliptin was €6,587 and €966/QALY gained, respectively, in patients without established CVD and in patients with established CVD. The results suggested that empagliflozin was cost-effective as the ICER was well below the median willingness to pay (WTP) threshold of €34,000/QALY gained identified for non-oncology studies in Greece.[40] The probabilistic sensitivity analysis confirmed the robustness of base case results.

According to the results of a Greek cross-sectional study,[41] the prevalence of heart disease in patients with diabetes mellitus is 24.0%. Thus, we obtained that, on average, treatment with empagliflozin resulted in both additional LYs (+0.138) and additional QALYs (+0.180) compared to sitagliptin. In terms of direct healthcare costs, empagliflozin was associated on average with a direct healthcare cost of €50,610 versus €49,874 for branded sitagliptin. These results led to an ICER of €4,092/QALY gained for empagliflozin compared to branded sitagliptin.

This study reports novel cost-effectiveness results of empagliflozin versus sitagliptin, taking into account both type 2 diabetes patients without established CVD and type 2 diabetes patients with established CVD. Previous cost-effectiveness analyses for empagliflozin versus sitagliptin, using the IQVIA CDM, in type 2 diabetes patients have been reported, although only patients with established CVD were modelled.[25,27] Similar trends were observed in both studies, as empagliflozin was found to be cost-effective compared with sitagliptin. In another study, the objective was to estimate the long-term cost-effectiveness of sequential therapy of empagliflozin versus sitagliptin for treatment in patients with type 2 diabetes with or without CVD from the perspective of the US payer.[42] Although different treatment pathways were considered, the results of this analysis are consistent with our findings. Indeed, the analysis showed that for US

payers, second-line empagliflozin followed by addition of sitagliptin is a highly cost-effective treatment compared with second-line sitagliptin then empagliflozin in patients with or without CVD on metformin monotherapy.

Limitations to this study should be considered. Regarding input data, it was assumed that published utility data were applicable to the Greek patients and healthcare setting. In the absence of local data, this choice was deemed appropriate. Literature data were used to estimate diabetes-related complications costs, and these inputs were validated by expert opinion. Regarding methodology, in our analysis we considered only intensification to insulin therapy and discontinuation of initial therapy when HbA1c threshold of 8.5% (69 mmol/mol) was exceeded. We used UKPDS 82 risk equations to estimate physiological parameters progression. Even if based on old data, these have been extensively used in the literature and their use permit detailed and reliable lifetime simulations of key health outcomes in people with type 2 diabetes. As a lifetime simulation, our analysis relies on extrapolation of short-term outcomes over a lifetime horizon. To minimize the risk connected to this approach, we used the IQVIA CDM, that has been widely published and validated as simulation model for type 2 diabetes analysis.

Another item of discussion can arise looking at the results of the EMPagliflozin compaRative effectIveness and SafEty (EMPRISE) study. The EMPA-REG OUTCOME study showed that empagliflozin has an impact on the number of hospitalizations due to heart failure as well as on cardiovascular and non-cardiovascular mortality in type 2 diabetes patients with established CVD. However, these beneficial effects were not evaluated in patients without clinical evidence of CVD. The EMPRISE study aimed to assess comparative effectiveness, safety, and health care utilization of empagliflozin in type 2 diabetes patients, using real-world data from three databases in the US. An interim analysis from the EMPRISE study, based on data from August 2014 through September 2017, was recently published.[43] The aim of this analysis was to evaluate the association between empagliflozin and several cardiovascular and safety outcomes compared to DPP-4 inhibitor. After propensity-score matching, the use of empagliflozin resulted in a 37–52% decreased risk of hospitalization for heart failure (HHF) compared with DPP-4 inhibitor and a similar risk of myocardial infarction or stroke. In our analysis, we did not consider any beneficial effect of empagliflozin on heart failure for patients without established cardiovascular disease, therefore the results for these patients can be considered conservative.

Conclusion

The CELESTIA study highlights that, in Greece, empagliflozin can be considered a cost-effective treatment option for both type 2 diabetes patients without established CVD and type 2 diabetes patients with established CVD in Greece.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article/as Supplementary Information Files.

Ethics Approval

This article is based on the IQVIA CDM, which was used to simulate the long-term clinical and economic results of empagliflozin and sitagliptin based on existing literature findings and completed clinical trials. Moreover, it does not involve any studies on human participants and animals directly performed by any of the authors.

Code Availability

Access to the IQVIA CDM is available upon payment. For more information visit http://www.core-diabetes.com/.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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