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Cost-Effectiveness of Liraglutide Versus Dapagliflozin for the Treatment of Patients with Type 2 Diabetes Mellitus in the UK

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ABSTRACT

Introduction: To date there is a lack of economic analysis comparing glucagon-like peptide-1 receptor agonists (GLP-1RAs) to sodium-glucose co-transporter 2 inhibitors (SGLT-2i) for the treatment of type 2 diabetes mellitus (T2DM). Liraglutide and dapagliflozin are the most commonly prescribed GLP-1RA and SGLT-2i in the UK. This analysis investigated the cost-effectiveness of liraglutide 1.2 and 1.8 mg/day compared to dapagliflozin 10 mg/day for the treatment of T2DM in the UK in patients on dual and triple antidiabetic therapy.
Methods: Cost-effectiveness analysis was conducted in the QuintilesIMS CORE Diabetes Model (CDM). The model estimated expected costs and outcomes over a lifetime horizon using the UK national payer perspective. Liraglutide

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efficacy estimates and patient characteristics were sourced from a trial in patients on prior metformin monotherapy, and from a trial in patients on prior combination therapy. Comparative efficacy data for the other interventions were derived from a network meta-analysis. Utility inputs were extracted from a systematic literature review. Costs are presented in Great British Pound (GBP), 2016 values.
Results: In dual and triple therapy, liraglutide 1.2 mg was less costly and more effective compared with dapagliflozin 10 mg, providing a QALY gain of 0.04 and cost savings of GBP 11 per patient in dual therapy, and a QALY gain of 0.06 and cost savings of GBP 71 per patient in triple therapy. For liraglutide 1.8 mg, increased efficacy and costs compared with dapagliflozin 10 mg were observed in both dual and triple therapy. In dual therapy, a QALY gain of 0.07 and additional costs of GBP 888 per patient yielded an ICER of GBP 13,227, whereas in triple therapy a QALY gain of 0.07 and additional cost of GBP 791 per patient gave an ICER of 11,857.
Conclusion: This long-term modelling analysis found that both dosages of liraglutide may be cost-effective treatment alternatives as part of a dual or a triple antidiabetic therapy in patients for whom an SGLT-2i therapy is considered.
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Keywords: Cost-effectiveness analysis; Glucagon-like peptide 1; Sodium-glucose transporter 2; Type 2 diabetes mellitus

INTRODUCTION

Diabetes imposes a substantial societal and financial burden globally. In the UK, the prevalence of diabetes is 6% in people aged 20–79 years [1] and it accounts for 10% of the overall health expenditure [1]. The total economic cost of type 2 diabetes mellitus (T2DM) amounted to GBP 21.8 billion in 2010/11 [2], including both direct and indirect costs.

Glucagon-like peptide-1 receptor agonists (GLP-1RA) are a class of glucose-lowering drugs currently used in the UK for the treatment of T2DM. Guidelines for the treatment of T2DM by the National Institute for Health and Care Excellence (NICE) [3] recommend the use of GLP-1RAs in triple therapy when previous triple therapy with oral antidiabetes drugs (OADs) is not effective, not tolerated, or contraindicated [3].

Currently, there is evidence assessing the cost-effectiveness of the GLP1-RA liraglutide versus other GLP-1RAs [4, 5]. However, there is a lack of health economic analyses comparing liraglutide to SGLT-2is. The aim of this analysis was to assess the cost-effectiveness of liraglutide 1.2 and 1.8 mg/day, the most commonly used GLP-1RA in the UK, with dapagliflozin 10 mg, the most commonly used SGLT-2i in the UK, for the treatment of T2DM as part of a dual and a triple antidiabetic therapy.

This article does not contain any new studies with human or animal subjects performed by any of the authors.

METHODS

This study used the CORE Diabetes Model (CDM), a widely published and previously validated simulation model [6–11]. The CDM estimates long-term health and cost outcomes of interventions in diabetes taking into account population characteristics at baseline and accounting for evolution of a range of micro- and macrovascular complications over a set time horizon. Model outputs include economic consequences, incidence of complications, life years and quality-adjusted life years (QALYs)

gained, as well as incremental cost-effectiveness ratios (ICERs).

The interventions included in the study were the daily GLP-1RA liraglutide 1.2 mg daily and liraglutide 1.8 mg daily and the SGLT-2i dapagliflozin 10 mg daily. The current analyses assessed the interventions as dual or triple therapies in the management of patients with T2DM in the UK.

Patient baseline characteristics for the dual therapy analysis, including glycemia, cardiovascular risk factors, and the presence of existing diabetic complications, were taken from the NN2211-1860 study [12], Table 1. This was an international, open-label, randomized trial of patients with T2DM who had inadequate glycemic control on metformin and who were randomized to receive 1.2 or 1.8 mg liraglutide once daily, subcutaneously or 100 mg sitagliptin once daily, orally. Patient baseline characteristics for the triple therapy analysis were derived from the Liraglutide Effect and Action in Diabetes 4 (LEAD-4) study, a double-blind, randomized, placebo-controlled, parallel-group, multicenter trial [13] in which patients were randomized to receive 1.2 or 1.8 mg of once--daily liraglutide or liraglutide placebo injected subcutaneously in combination with metformin and rosiglitazone in all three treatment groups. The proportion of smokers and alcohol consumption data were not available from the trials and were obtained from the World Health Organization [14] and Health and Social Care Information Centre (HSCIC) statistics on smoking [15].

As a result of the lack of head-to-head clinical trials comparing the efficacy of liraglutide versus dapagliflozin, estimation of the relative treatment effects between the interventions was derived from a network meta-analysis (NMA) [16]. The NMA included 17 randomized controlled trials (RCTs) (8784 patients), which were broadly consistent with the NN2211-1860 and LEAD-4 trials in terms of key baseline characteristics such as age and BMI (Table A1 in the online supplementary material); baseline HbA1c in the NN2211-1860 and LEAD-4 studies was at the upper end of trials included in the NMA.

Table 1 Patient baseline characteristics

Parameter	Dual therapy		Triple therapy	
	Mean (SD) or %	References	Mean (SD) or %	References
Age	55.30 (9.2)	[12]	55.00 (10.34)	[13]
Duration of diabetes	6.20 (5.1)	[12]	9.00 (6.0)	[13]
Proportion male	52.9%	[12]	56.7%	[13]
Proportion white	71.4%[b]	[12]	70.8%[b]	[13]
Proportion black	8.3%[b]	[12]	12.2%[b]	[13]
Proportion Hispanic	17.3%[b]	[12]	12.9%[b]	[13]
Proportion Asian/Pacific Islander	3.0%[b]	[12]	1.5%[b]	[13]
HbA1c (%)	8.40 (0.80)	[12]	8.50 (1.20)	[13]
Systolic blood pressure (mmHg)	132.20 (14.50)	[12]	127.7 (14.56)	[13]
Diastolic blood pressure (mmHg)	81.20 (8.90)	[12]	75.7 (8.88)	[13]
Triglycerides (mg/dL)	210.80 (196.63)[c]	[11]	222.10 (206.20)	[34]
HDL-C (mg/dL)	44.86 (11.99)[c]	[11]	48.70 (11.70)	[34]
LDL-C (mg/dL)	102.48 (31.71)[c]	[11]	110.30 (38.50)	[34]
Total cholesterol (mg/dL)	185.23 (14.69)[c]	[11]	195.40 (52.80)	[34]
BMI (kg/m^2)	32.80 (5.20)	[12]	33.53 (5.24)	[34]
Proportion smoker	16.0%	[15]	16.0%	[15]
Cigarettes per day	12	[15]	12	[15]
Alcohol consumption (ml/week)	8.3	[14]	8.3	[14]
Proportion myocardial infarction	2.7%	[11]	5.8%	[34]
Proportion angina	1.8%	[11]	2.6%	[34]
Proportion peripheral vascular disease	0.9%	[11]	0.4%	[34]
Proportion stroke	0.8%	[11]	1.1%	[34]
Proportion heart failure	0.4%	[11]	0.8%	[34]
Proportion atrial fibrillation	1.5%	[11]	0.6%	[34]
Proportion left ventricular hypertrophy	0.2%	[11]	0.2%	[34]
Proportion microalbuminuria	1.1%	[11]	3.9%	[34]
Proportion gross proteinuria	0.2%	[11]	0.6%	[34]
Proportion end-stage renal disease	0.4%	[11]	0.2%	[34]
Proportion background diabetic retinopathy	2.7%	[11]	2.3%	[34]
Proportion proliferative diabetic retinopathy	0.2%	[11]	0.2%	[34]
Proportion severe vision loss	0.4%	[11]	0.2%	[34]
Proportion macular edema	1.1%	[11]	0.0%	[34]

Table 1 continued

Parameter	Dual therapy		Triple therapy	
	Mean (SD) or %	References	Mean (SD) or %	References
Proportion cataract	1.7%	[11]	5.8%	[34]
Proportion uninfected ulcer	0.6%	[11]	0.2%	[34]
Proportion infected ulcer	0.3%	[11]	0.0%[a]	N/A
Proportion healed ulcer	0.0%	[11]	0.0%[a]	N/A
Proportion history of amputation	0.0%	[11]	0.8%	[34]
Proportion neuropathy	11.6%	[11]	3.2%	[34]

BMI body mass index, *HDL* high density lipoprotein, *LDL* low density lipoprotein

[a] Not reported—assumed 0%

[b] Other ethnicity categories were evenly split among the categories reported in this table

[c] Values converted from mmol/L to mg/dL

NMA results indicated a greater percentage HbA1c reduction with liraglutide 1.2 mg (mean difference −0.64; 95% confidence interval [CI] −0.94, −0.34) and 1.8 mg (mean difference −0.81; 95% CI −1.11, −0.51) versus dapagliflozin 10 mg. Efficacy and safety parameters included in the model but not reported in the NMA were assumed equivalent in all arms.

The relative treatment effects reported in the NMA were then applied to the estimates for liraglutide on HbA1c, systolic blood pressure, weight, and hypoglycemic events (severe and mild) as reported in the NN2211-1860 and LEAD-4 studies in order to obtain estimates for dapagliflozin.

In the base case, all treatment arms assumed that patients remained on active treatment for a period of 3 years, followed by a switch to insulin glargine at a dose of 40 international units (IU) daily [17].

Long-term progressions of HbA1c, blood pressure, and lipids were estimated using UKPDS 68 risk equations [18]. BMI differences between the interventions were applied during the time on treatment only; patients were assumed to rebound to baseline values after treatment is changed to insulin at 3 years.

The model estimated expected costs and outcomes over a lifetime horizon adopting a UK national payer perspective (National Health Service). Only direct costs were considered.

Annual therapy costs were calculated using daily doses of the interventions within the scope of the analysis. Unit costs of drugs, injection needles, and the self-monitoring of blood glucose were derived from the British National Formulary (BNF) and the Monthly Index of Medical Specialities (MIMS) [19, 20]. Underlying assumptions of drug management costs, derived from the BNF [19], were 20 mg statins (atorvastatin) daily, 2.5 mg angiotensin-converting enzyme (ACE) inhibitors (ramipril) twice-daily, and additionally 75 mg aspirin daily for patients with cardiovascular disease only. Costs associated with screening tests for eye disease, proteinuria, depression, and foot screening programs were taken from the Personal Social Services Research Unit (PSSRU) [21]. The cost of diabetes-related complications was obtained from published literature, inflated to 2015 values using the PSSRU Pay & Price index [21] wherever necessary. Costs of background OAD therapy were not included as these were expected to be equal in both treatment arms. In the base case, a discount rate of 3.5% was applied to future costs and outcomes, as per NICE guidelines [22]. Unit costs used in this study are presented in Table 2.

Health state utilities were derived from a published systematic literature review of utility values associated with T2DM [23] and are presented in Table 3. The disutility associated with

Table 2 Unit costs of diabetes management and complications

Cost category	Cost (GBP)	References
Management costs		
Liraglutide 1.2 mg (annual)	955.49	[19]
Liraglutide 1.8 mg daily (annual)	1433.24	[19]
Dapagliflozin 10 mg daily (annual)	445.48	[19]
Insulin glargine 40 IU daily (annual)	404.21	[19]
Statins (annual)	18.00	[19]
Aspirin (annual)	10.56	[19]
ACEs (annual)	14.61	[19]
Eye screening	33.98	[35]
Microalbuminuria screening	14.55	[19, 21]
Gross proteinuria screening	14.53	[19, 21]
Foot screening program	130.00	[21]
Direct costs of cardiovascular complications		
Myocardial infarction 1st year	5647.76	[36]
Myocardial infarction subsequent years	634.56	[36]
Angina 1st year	2908.55	[37, 38]
Angina subsequent years	1947.54	[37, 38]
Congestive heart failure 1st year	2718.80	[36]
Congestive heart failure subsequent years	590.69	[36]
Stroke 1st year	9499.99	[36]
Stroke subsequent years	2553.53	[36]
Stroke death within 30 days	10,178.42	[39]
Peripheral vascular disease	1708.28	[35]
Direct costs of renal complications		
Hemodialysis 1st year	41,436.97	[40]
Hemodialysis subsequent years	41,436.97	[40]
Peritoneal dialysis 1st year	22,787.93	[40]
Peritoneal dialysis subsequent years	22,787.93	[40]
Renal transplant 1st year	24,486.55	[40]
Renal transplant subsequent years	7958.49	[40]
Direct costs of acute events		
Major hypoglycemia (per event)	384.61	[41]
Minor hypoglycemia (per event)	4.61	[42][a]

Table 2 continued

Cost category	Cost (GBP)	References
Direct costs of eye disease		
Laser treatment	119.28	[35]
Cataract operation	857.78	[35]
Cost following cataract operation	504.99	[43]
Blindness	5601.86	[44]
Direct costs of neuropathy, foot ulcer and amputation		
Neuropathy	968.49	[35]
Amputation	11,336.13	[35]
Amputation prosthesis	2064.86	[35]
Gangrene treatment (monthly)	41,679.78	[45]
After healed ulcer	263.20	[45]
Infected ulcer (monthly)	23,896.88	[45]
Uninfected ulcer (monthly)	23,428.62	[45]
Healed ulcer history of amputation	263.20	[45]

HCP health care professional

[a] Based on a HCP visit following a hypo episode and average number of self-monitoring of blood glucose (SMBG) tests

loss of health-related quality of life due to an increase in BMI was applied as per the CODE-2 study by Bagust and Beale [24]. A diminishing approach was used to estimate utility decrements associated with non-severe hypoglycemia, based on results of a study by Lauridsen et al. [25].

The primary analysis considered was the incremental cost per QALY gained with each daily dose of liraglutide compared to dapagliflozin 10 mg/day. A number of sensitivity analyses were conducted to assess the impact of parameters on the base case cost-effectiveness results. One-way sensitivity analyses included variations in the discount rate (between 0% and 6%), time horizon (20, 30, and 40 years), and alternative risk equations (UKPDS82). The impact of the cost of diabetes-related complications was tested by varying these costs on ±10% of the mean value. We also tested the impact of using alternative costs sourced from a recent UK study of immediate and long-term costs of T2DM-related complications [26].

Management costs were varied by ±20% of their mean values. For the efficacy parameters, the effect of abolishing BMI and systolic blood pressure treatment differences was investigated.

Four scenario analyses were tested. The first scenario explored the impact of simulating more severe patients by using the upper limit of 95% confidence interval of the HbA1c value at baseline. A second scenario considered a treatment duration based on disease progression according to UKPDS 68 risk equations; patients remain on active treatment until their level of HbA1c reached 7.5%, at which point they were assumed to switch to insulin glargine. A third scenario analysis tested the impact of using a dose of 1.35 mg/day for liraglutide, reflective of the average daily dose in UK [27], for which costs and effects were linearly interpolated between the 1.2 and 1.8 mg doses. Finally, a fourth scenario explored the impact of comparing liraglutide with SGLT-2is as a class. Data from QuintilesIMS MIDAS was used to derive the current market shares of liraglutide 1.2 and

Table 3 Health-related utility and disutility values based on a systematic review of T2DM utility values [23]

Health state/event	Health-related utility/disutility	References
T2DM no complications	0.785	[46]
Myocardial infarction event	−0.055	[46]
Post MI	0.730	[46]
Angina	0.695	[46]
Congenital heart failure	0.677	[46]
Stroke event	−0.164	[46]
Post stroke	0.621	[46]
Peripheral vascular disease	0.724	[24]
Microalbuminuria	0.785	[46][a]
Gross renal proteinuria	0.785	[46][a]
Hemodialysis	0.621	[47]
Peritoneal dialysis	0.581	[47]
Renal transplant	0.762	[48]
Background diabetic retinopathy (BDR)	0.745	[49]
BDR wrongly treated	0.745	[49]
Proliferative diagnostic retinopathy laser treated (proliferative diabetic retinopathy)	0.785	[46][a]
Proliferative diagnostic retinopathy no laser (proliferative diabetic retinopathy)	0.785	[46][a]
Macular edema	0.745	[49]
Severe vision loss/blindness	0.711	[46]
Cataract	0.769	[50]
Neuropathy	0.701	[24]
Healed ulcer	0.785	[46]
Active ulcer	0.615	[24]
Amputation, year of event	−0.280	[46]
Post-amputation (2+ years after event)	0.505	[46]
Severe hypoglycemia events	−0.062	[51][b]
Non-severe hypoglycemia event	−0.005	[51][b]
Nausea event	−0.01	[51]
Depression not treated	0.785	[46][a]
Depression treated	0.785	[46][a]

Table 3 continued

Health state/event	Health-related utility/disutility	References
Each unit of BMI over 25 kg/m^2	−0.0061	[24]

[a] Assumed same as no complications
[b] Value for UK population

1.8 mg, dapagliflozin 5 and 10 mg, empagliflozin 10 and 25 mg, and canagliflozin 100 and 300 mg in the UK. A weighted average of the treatment effects of included SGLT-2i treatments from the NMA was applied for this scenario analysis.

Finally, probabilistic sensitivity analysis was conducted for all base case analyses, using 500 simulations with 25,000 patients throughout.

RESULTS

Base Case: Dual Therapy

In the base case analysis, liraglutide 1.2 mg generated higher QALYs (0.039 per patient) and lower costs (GBP 11 per patient) compared with dapagliflozin 10 mg. Liraglutide 1.2 mg also showed increases in life expectancy compared to dapagliflozin 10 mg. Whilst higher treatment costs were observed for liraglutide 1.2 mg than for dapagliflozin 10 mg (GBP 1532 per patient), complication costs were on average lower for liraglutide 1.2 mg, overall resulting in lower total costs with liraglutide. Differences in complication cost between liraglutide 1.2 mg and dapagliflozin 10 mg were due to lower incidence of renal, eye, ulcer, amputation, and neuropathy-related complications associated with liraglutide 1.2 mg. Patients treated with liraglutide 1.2 mg on average were free of complications for three additional months compared with patients on dapagliflozin 10 mg. Base case results are reported in Table 4.

In the base case analysis of liraglutide 1.8 mg compared with dapagliflozin 10 mg, liraglutide 1.8 mg produced higher life expectancy and QALYs than dapagliflozin 10 mg. Liraglutide 1.8 mg was also associated with higher total costs relative to dapagliflozin 10 mg (GBP 888 per patient). As with liraglutide 1.2 mg, liraglutide 1.8 mg was associated with higher treatment costs but lower complication costs compared to dapagliflozin 10 mg, with fewer renal, ulcer, amputation, neuropathy, and eye-related complications. Overall, liraglutide 1.8 mg compared to dapagliflozin 10 mg generated an ICER of GBP 13,227 per QALY gained.

Base Case: Triple Therapy

In the base case analysis of liraglutide 1.2 mg versus dapagliflozin 10 mg, liraglutide 1.2 mg yielded a QALY gain of 0.064 and lower costs of GBP −261, resulting in liraglutide 1.2 mg dominating dapagliflozin 10 mg. In the base case analysis of liraglutide 1.8 mg compared with dapagliflozin 10 mg, liraglutide 1.8 mg produced a QALY gain of 0.067 and incremental costs of GBP 791, giving an ICER of GBP 11,857 per QALY gained.

Sensitivity Analyses

In both dual and triple therapy, liraglutide 1.2 mg remained either dominant (more effective and less costly) or cost-effective compared to dapagliflozin 10 mg in the majority of sensitivity analyses. The cost-effectiveness of liraglutide 1.2 mg was most sensitive to a discount rate of 0% applied to costs and outcomes, to a treatment switch at 5 years, and to a lowering of the time horizon to 10 years. Liraglutide 1.8 mg also remained cost-effective across the majority of analyses performed in both dual and triple therapy, mostly generating ICERs below GBP 20,000 per QALY gained. Overall, sensitivity analysis calculating undiscounted costs and outcomes, shortening the time horizon to 10 years, and extending the treatment

Table 4 Base case results: liraglutide vs dapagliflozin

	Liraglutide 1.2 mg	Dapagliflozin 10 mg	Incremental	Liraglutide 1.8 mg	Dapagliflozin 10 mg	Incremental
Dual therapy						
QALYs	10.169	10.131	0.039	10.198	10.131	0.067
Life expectancy (years)	15.223	15.197	0.027	15.258	15.197	0.061
Lifetime costs (GBP)	64,239	64,250	−11	65,137	64,250	888
ICER (incremental costs/incremental life expectancy)	Dominant					13,227.00
ICER (incremental costs/incremental QALYs)	Dominant					14,432.00
Triple therapy						
QALYs	10.184	10.12	0.064	10.187	10.12	0.067
Life expectancy (years)	15.345	15.294	0.051	15.35	15.294	0.056
Lifetime costs (GBP)	63,158	63,229	−71	64,020	63,229	791
ICER (incremental costs/incremental life expectancy)	Dominant					11,857.00
ICER (incremental costs/incremental QALYs)	Dominant					14,250.00

duration to 5 years had the most significant impact on the ICER. Results of all univariate sensitivity analyses for dual and triple therapy are presented in Table 5 and 6, respectively.

Scenario analysis explored the cost-effectiveness when comparing liraglutide to the weighted average costs and effects of SGLT-2is as an entire class. Assuming a willingness-to-pay (WTP) threshold between GBP 20,000 and GBP 30,000 per QALY gained, both liraglutide doses remained cost-effective versus the entire class of SGLT-2is, with ICERs ranging between GBP 2000 and GBP 21,000.

Finally, probabilistic sensitivity analysis (PSA) for the dual therapy analysis yielded respective ICERs for liraglutide 1.2 and 1.8 mg of GBP 2178 and GBP 18,154 per QALY gained. In the triple therapy comparison, PSA generated ICERs of GBP 1850 and GBP 16,156 per QALY gained for liraglutide 1.2 and 1.8 mg, respectively. Cost-effectiveness planes from PSA in dual and triple therapy for liraglutide 1.2 and 1.8 mg are presented in Fig. 1 and

suggest that the majority of bootstrap samples were located in the north-eastern quadrant, denoting higher QALYs as well as higher costs for liraglutide 1.2 and 1.8 mg compared to dapagliflozin 10 mg. Cost-effectiveness acceptability curves (CEACs) presented in Fig. 2 suggest a respective probability for liraglutide 1.2 and 1.8 mg of 85% and 49% of being cost-effective in triple therapy at a willingness-to-pay (WTP) threshold of GBP 20,000, whereas the probability of cost-effectiveness of liraglutide 1.2 and 1.8 mg in dual therapy amounted to 70% and 48%, respectively, at the same WTP threshold.

DISCUSSION

This analysis explored the cost-effectiveness of liraglutide compared to dapagliflozin, the most commonly used GLP-1RA and SGLT-2i treatments in the UK, for the treatment of T2DM in patients on dual and on triple antidiabetic

Table 5 Summary of sensitivity analyses: dual therapy

	Liraglutide 1.2 mg vs. dapagliflozin 10 mg			Liraglutide 1.8 mg vs. dapagliflozin 10 mg		
	Incremental costs (GBP)	Incremental QALYs	ICER (GBP per QALY gained)	Incremental costs (GBP)	Incremental QALYs	ICER (GBP per QALY gained)
Base case	−11	0.039	Dominant	888.00	0.067	13,227
Probabilistic sensitivity analysis	83	0.04	2178	1024.00	0.06	18,154
Treatment switch						
Treatment switch at 7.5%	225	0.038	5926	864.00	0.050	17,359
Treatment switch at 5 years	863	0.039	21,856	2752.00	0.056	49,140
Time horizon: 10 years	825	0.016	52,203	2008.00	0.019	104,063
Time horizon: 20 years	286	0.031	9195	1062.00	0.037	28,944
Time horizon: 30 years	−66	0.033	Dominant	850.00	0.059	14,354
Time horizon: 40 years	−68	0.045	Dominant	896.00	0.060	14,964
Treatment effects						
Abolish BMI treatment differences	−24	0.051	Dominant	913.00	0.062	14,611
Abolish SBP treatment differences	−237	0.058	Dominant	458.00	0.075	6119
Discount rate						
0% discount rate, costs and outcomes	−840	0.071	Dominant	95.00	0.126	754
6% discount rate, costs and outcomes	77,042	7.881	9776	95.00	0.126	754
Costs						
Costs of complications −10%	−243	0.039	Dominant	841.00	0.067	12,535

Table 5 continued

	Liraglutide 1.2 mg vs. dapagliflozin 10 mg			Liraglutide 1.8 mg vs. dapagliflozin 10 mg		
	Incremental costs (GBP)	Incremental QALYs	ICER (GBP per QALY gained)	Incremental costs (GBP)	Incremental QALYs	ICER (GBP per QALY gained)
Costs of complications +10%	−10,469	0.039	Dominant	1215.00	0.067	18,110
Complications costs from Alva et al.	70	0.039	1815	1176.00	0.067	17,533
Management costs −20%	−13	0.039	Dominant	884.00	0.067	13,176
Management costs +20%	−9	0.039	Dominant	891.00	0.067	13,279
UKPDS 82 equations applied	95	0.035	2741	1006.00	0.059	17,027
Liraglutide average dose of 1.35 mg	296	0.062	4748	296	0.062	4748
Higher baseline HbA1c (upper 95% CI)	−54	0.043	Dominant	907.00	0.066	13,742
Comparator: SLGT-2i class	104	0.019	5516	1003.00	0.047	21,200

therapy. For T2DM patients on dual and on triple antidiabetic therapy, analysis results suggested modest cost savings and health benefits for liraglutide 1.2 mg when compared to dapagliflozin 10 mg. Liraglutide 1.8 mg was found to be cost-effective vs. dapagliflozin 10 mg with an ICER below cost-effectiveness thresholds set by NICE (GBP 20,000–30,000) in both dual and triple therapy. Overall, observed differences between treatments in terms of costs and outcomes were modest, however, therefore both liraglutide doses and dapagliflozin 10 mg may be considered comparable in terms of cost-effectiveness.

A range of scenario and sensitivity analyses were conducted to test the robustness of model results and generally found these to be robust to plausible variations in input parameters and modelling assumptions. Notable exceptions were sensitivity analyses of liraglutide 1.8 mg reducing the time horizon to 10 years in the dual therapy analysis and extending the duration on treatment to 5 years in the triple therapy analysis.

The study has a number of limitations. Relative treatment effects of liraglutide and dapagliflozin have yet to be established in head-to-head RCTs; therefore, indirect estimates were derived from a network meta-analysis. As the NMA only included studies investigating dual therapy, relative estimates of effectiveness were assumed equivalent in patients on triple therapy. The CDM predicts long-term outcomes of T2DM patients based on the impact of therapies in short-term studies; although the CDM has been validated [8–10] as capable of reliably predicting long-term patient outcomes, direct evidence is lacking. The

Table 6 Summary of sensitivity analyses: triple therapy

	Liraglutide 1.2 mg vs. dapagliflozin 10 mg			Liraglutide 1.8 mg vs. dapagliflozin 10 mg		
	Incremental costs (GBP)	Incremental QALYs	ICER (GBP per QALY gained)	Incremental costs (GBP)	Incremental QALYs	ICER (GBP per QALY gained)
Base case	−71.00	0.0640	Dominant	791.00	0.07	11,857
Probabilistic sensitivity analysis	117.00	0.06	1850	893.00	0.06	16,156
Treatment switch						
Treatment switch at 7.5%	−116.00	0.0490	Dominant	2713.00	0.05	52,269
Treatment switch at 5 years	1080.00	0.0670	16,168	2061.00	0.02	130,413
Time horizon: 10 years	948.00	0.0230	40,698	1135.00	0.05	24,666
Time horizon: 20 years	220.00	0.0470	4705	924.00	0.05	18,219
Time horizon: 30 years	69.00	0.0720	957	850.00	0.05	15,712
Time horizon: 40 years	32.00	0.0640	503	2713.00	0.05	52,269
Treatment effects						
Abolish BMI treatment differences	−85.00	0.0710	Dominant	739.00	0.07	11,151
Abolish SBP treatment differences	−388.00	0.0830	Dominant	170.00	0.08	2230
Discount rate						
0% discount rate, costs and outcomes	−909.00	0.1120	Dominant	−271.00	0.13	Dominant
6% discount rate, costs and outcomes	−909.00	0.1120	Dominant	−271.00	0.13	Dominant
Costs						
Costs of complications −10%	−57.00	0.0640	Dominant	1094.00	0.07	16,404

Table 6 continued

	Liraglutide 1.2 mg vs. dapagliflozin 10 mg			Liraglutide 1.8 mg vs. dapagliflozin 10 mg		
	Incremental costs (GBP)	Incremental QALYs	ICER (GBP per QALY gained)	Incremental costs (GBP)	Incremental QALYs	ICER (GBP per QALY gained)
Costs of complications +10%	−416.00	0.0640	Dominant	993.00	0.06	16,770
Complications costs from Alva et al.	−169.00	0.0640	Dominant	978.00	0.07	14,663
Management costs −20%	−74.00	0.0640	Dominant	788.00	0.07	11,812
Management costs +20%	−69.00	0.0640	Dominant	794.00	0.07	11,903
UKPDS 82 equations applied	212.00	0.0620	3404	1052.00	0.06	19,087
Liraglutide average dose of 1.35 mg	235.00	0.0660	3555	235.00	0.07	3555
Higher baseline HbA1c (upper 95% CI)	−112.00	0.0810	Dominant	425.00	0.08	5123
Comparator: SLGT-2i class	120.00	0.0630	1913	983.00	0.07	14,956

generalizability of the findings is limited by potential differences between RCT populations and patients who would receive these drugs in usual practice in the UK. Future research is warranted to generate evidence from real-world clinical data to help provide insights into the comparative real-life effectiveness of liraglutide and dapagliflozin and other SGLT-2is in terms of life expectancy or microvascular complications, including scenarios when these treatments are used in addition to insulin glargine.

Many different classes of products are available to treat T2DM. Often, new drugs are evaluated against very similar agents or against placebo. Liraglutide was previously compared with other GLP-1RA products in the UK [4, 5, 28] and was recommended by the Scottish Medicines Consortium on the basis of acceptable cost-effectiveness compared to other

GLP-1RAs [29, 30]. Treatment decisions, however, need to weigh the merits and risks of different drug classes for a patient, but UK studies comparing liraglutide against drugs from other classes are infrequent. A 2011 study found that liraglutide at a dose of 1.2 and 1.8 mg was associated with a cost per QALY gained of GBP 9851 and GBP 10,405, respectively, when compared to sitagliptin, and a cost per QALY gained of GBP 9449 and GBP 16,501, respectively, compared to glimepiride [31]. This study is the first of which we are aware that compares the cost-effectiveness of liraglutide to dapagliflozin from a UK perspective.

Whereas guidelines from the American Diabetes Association and the European Association for the Study of Diabetes suggest that GLP1-RA drugs are considered as options at first treatment escalation after failure on metformin [32],
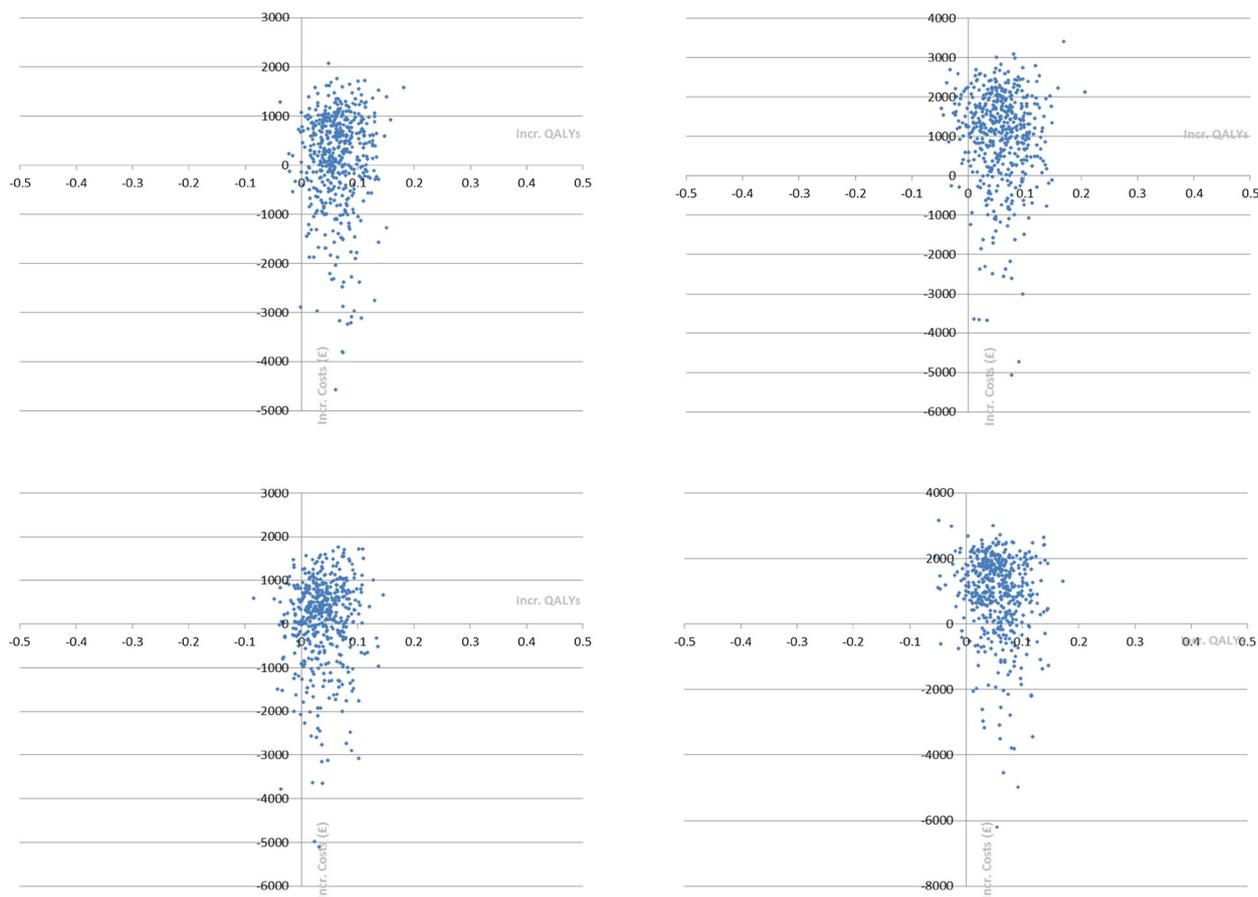
Fig. 1 Cost-effectiveness planes, liraglutide 1.2 and 1.8 mg vs. dapagliflozin 10 mg. *Upper left* Liraglutide 1.2 mg vs dapagliflozin 10 mg in dual therapy; *upper right* liraglutide 1.8 mg vs dapagliflozin 10 mg in dual therapy; *lower left* liraglutide 1.2 mg vs dapagliflozin 10 mg in triple therapy; *lower right* liraglutide 1.8 mg vs dapagliflozin 10 mg in triple therapy

NICE guidelines recommend that GLP1-RA drugs are considered as an option after triple therapy with OADs (including SGLT-2is) has failed to achieve glycemic control. Potential reasons for placing GLP1-RA after OADs in the NICE pathway include the injected route of administration, gastrointestinal side effects, and higher cost. This study therefore evaluated the cost-effectiveness of treatment options which are recommended at different positions in the treatment pathway as per UK clinical guidelines.

In common with other studies, this economic evaluation relied on a simulation model to estimate the occurrence of long-term complications based on changes in diabetic risk factors shown in studies of 6–12 months

duration. Long-term direct data on the impact of therapy on outcomes would be preferable to modelling. A recent study found that liraglutide reduces the incidence of cardiovascular events [33] in patients at high risk of cardiovascular disease, though results of similar studies with other agents have been mixed. Future evaluations might consider this direct evidence of impact on outcomes as well as making estimates based on risk factors.

CONCLUSION

This long-term health economic modelling analysis found that liraglutide 1.2 mg was cost-effective when compared to dapagliflozin
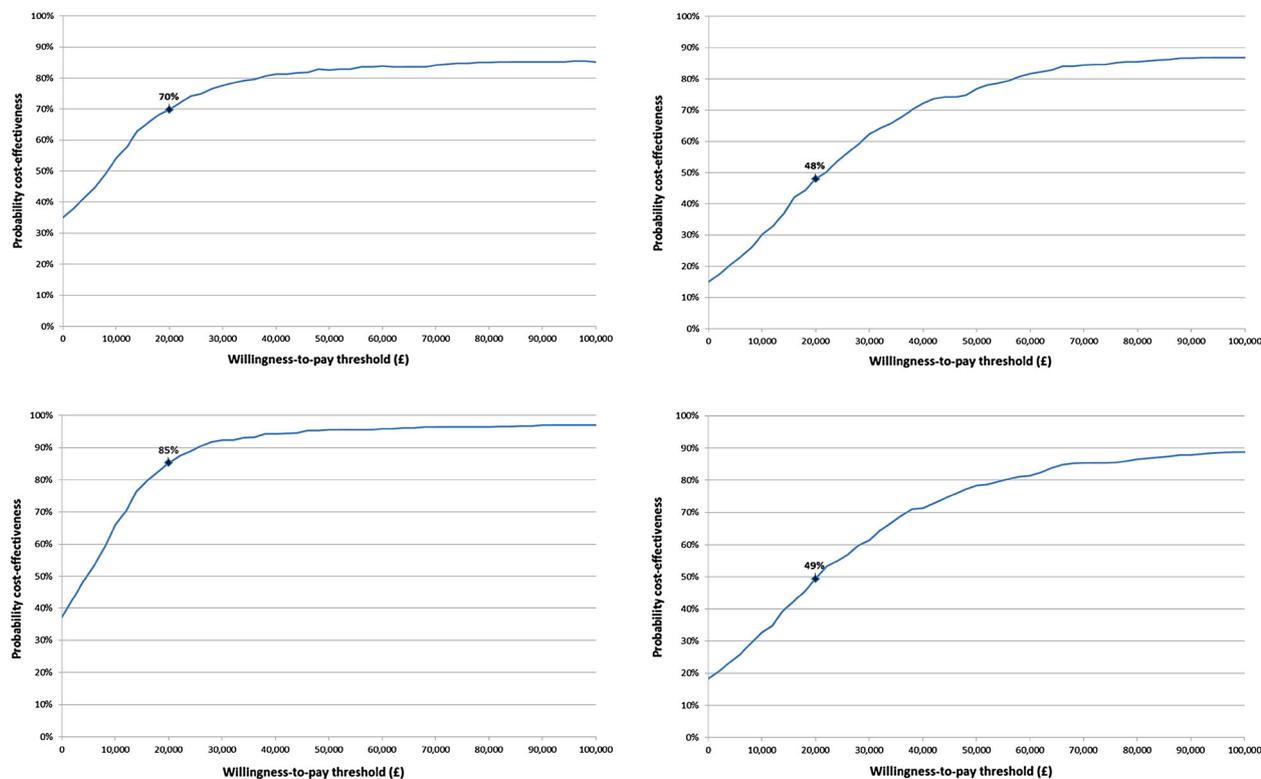
Fig. 2 Cost-effectiveness acceptability curves, liraglutide 1.2 and 1.8 mg vs. dapagliflozin 10 mg. *Upper left* Liraglutide 1.2 mg vs dapagliflozin 10 mg in dual therapy; *upper right* liraglutide 1.8 mg vs dapagliflozin 10 mg in dual therapy; *lower left* liraglutide 1.2 mg vs dapagliflozin 10 mg in triple therapy; *lower right* liraglutide 1.8 mg vs dapagliflozin 10 mg in triple therapy

10 mg in patients with T2DM as part of a dual and a triple antidiabetic therapy in the UK setting. Additionally, liraglutide 1.8 mg is cost-effective vs. dapagliflozin 10 mg under the cost-effectiveness thresholds set by NICE in both a dual and a triple combination therapy. Both dosages of liraglutide may therefore present a cost-effective treatment alternative in patients for whom an SGLT-2i therapy is considered.

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