Healthcare resource utilization and related financial costs associated with glucose lowering with either exenatide or basal insulin: a retrospective cohort study

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Abstract

Aims

Type 2 diabetes is a major health problem placing increasing demands on healthcare systems. Our objective was to estimate healthcare resource use and related financial costs following treatment with exenatide-based regimens prescribed as once-weekly

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(EQW) or twice-daily (EBID) formulations, compared with regimens based on basal insulin (BI).

Materials and methods

This retrospective cohort study used data from the UK Clinical Practice Research Datalink (CPRD) linked to Hospital Episode Statistics (HES). Patients with type 2 diabetes prescribed exenatide or BI between 2009 to 2014 as their first recorded exposure to injectable therapy were selected. Costs were attributed to primary care contacts, diabetes-related prescriptions and inpatient admissions using standard UK healthcare costing methods (2014 prices). Frequency and costs were compared between cohorts before and after matching by propensity score using Poisson regression.

Results

8,723, 218 and 2,180 patients prescribed BI, EQW and EBID were identified. 188 and 1,486 patients prescribed EQW and EBID, respectively, were matched 1:1 to BI patients by propensity score. Among unmatched cohorts, total crude mean costs per patient-year were £2,765 for EQW, £2,549 for EBID and £4,080 for BI. Compared with BI, the adjusted annual cost ratio (aACR) was 0.92 (95% CI 0.91–0.92) for EQW and 0.82 (0.82–0.82) for EBID. Corresponding costs for the propensity-matched subgroups were £2,646 versus £3,283 (aACR 0.80, 0.80–0.81) for EQW versus BI and £2,532 versus £3,070 (0.84, 0.84–0.84) for EBID versus BI.

Conclusion

Overall, treatment with EQW and EBID was associated with reduced healthcare resource use and costs compared with BI.

Introduction

Type 2 diabetes (T2DM) is a major health problem and places increasing demands on healthcare systems. The direct and indirect cost of type 2 diabetes in the UK in 2010/2011 has been estimated to be £21.8 billion.[1] Normoglycaemia remains a primary aim in the management of type 2 diabetes. Although, in the early stages, the condition can be managed using diet and lifestyle adjustments alone, glucose-lowering therapies are usually required for the management of hyperglycaemia. As glucose control deteriorates, intensification using combination therapy and eventually insulin injection is recommended. However, the achievement of adequate glucose control often needs to be weighed against the risk of inducing side effects such as hypoglycaemia and weight gain. Glucagon-like peptide-1 (GLP-1) receptor agonists have been recommended as an alternative to insulin.[2] Exenatide, the first GLP-1 receptor agonist to reach the market has been reported to be associated with similar or greater reductions in glycated haemoglobin (HbA1c) when compared with long-acting insulin analogues[3–10] and is associated with weight reductions.[3] In addition to the immediate-release formulation to be used twice a day, exenatide is also available as an extended-release formulation, thereby offering the advantage of a simpler dosing regimen.

In the CHOICE (CHanges to Treatment and Outcomes in Patients With Type 2 Diabetes Initiating InjeCtablE Therapy) observational study based in six European countries, total healthcare costs were higher over a 24-month period in those prescribed twice-daily exenatide when compared with those prescribed insulin (€3,998 versus €3,267).[11] However, following the exclusion of the cost attributed to

insulin or twice-daily exenatide, the cost of other healthcare resource utilization was lower for exenatide (€1792 versus €2466).[11]

In addition to clinical factors, cost can be an important consideration when selecting the most appropriate glucose-lowering therapy to initiate in patients with type 2 diabetes.[2] In this retrospective, observational cohort study, we aim to estimate, using UK primary and secondary care data, NHS resource use and related costs in patients who are prescribed regimens that include exenatide in its once-weekly (EQW) or twice-daily formulation (EBID), compared with regimens including basal insulin (BI). To our knowledge, this is the first study to compare the use and cost of NHS healthcare resources in patients treated with exenatide and insulin.

Materials and methods

Data sources

Retrospective data were extracted from the United Kingdom Clinical Practice Research Datalink (CPRD). CPRD is a proprietary healthcare data resource containing clinically rich, anonymized data on 14 million research-quality patients registered at 689 UK primary care practices, of which 4.9 million patients are actively registered (representing approximately 7% of the UK population). These data are collected in a non-interventional manner and include patient demographics, consultations, medical history, test results and prescriptions. Patients registered in CPRD are broadly representative of the UK population in terms of age and sex.[12] The geographical distribution of patients and practices in CPRD has been described previously. Briefly, the percentage of acceptable patients registered in CPRD by region varies between 3.9% from Yorkshire and the Humber to 11.1% from the North West of England.[12] Patient-level data from a proportion of consenting English CPRD practices are linked to Hospital Episode Statistics (HES) inpatient data. Data were available from 1987 until June 2015. Approval for this study was granted by the CPRD Independent Scientific Advisory Committee (reference number 15_178R).

Patients

Patients with type 2 diabetes and naïve to injectable therapies were selected if they received their first recorded prescription for EQW, EBID or BI between 1 January 2009 and 31 December 2014. Patients were classified as having type 2 diabetes if they met at least one of the following criteria: more than one diagnosis for type 2

diabetes, prescriptions for more than one class of glucose-lowering therapy, or at least one diagnosis of type 2 diabetes plus at least one prescription for an oral glucose-lowering therapy. Analysis was restricted to those English practices that were part of the CPRD linkage scheme. The percentage of CPRD practices linked to HES records varied from 83.6% in the South West to 52.0% in the East Midlands. This allowed access to hospital data recorded in HES. Patients were excluded if they had secondary diabetes.

The index date was defined as the date of the first recorded prescription for exenatide or BI. For the main analysis, no minimum wash-in period prior to index date was required. The censor date was defined as the earliest of: end of therapy (defined as last prescription +90 days), date of death, end of CPRD follow-up and the end of HES follow-up (31 March 2015). End of CPRD follow-up was defined as the earlier of: the patient's transfer out date and the practice's last data collection date. Continuous periods of therapy were identified as such if there were no more than 112 days between prescriptions for the same drug, with this interval being based on the 95th percentile of the maximum number of days prescribed for each patient.

Primary care contacts

Primary care consultations were classified by consultation type (e.g. surgery appointment, clinic, home visit, telephone consultation) and staff type (e.g. general practitioner (GP), practice nurse, district nurse) and then assigned a unit cost as listed in the Unit Cost of Health and Social Care 2015 from the Personal Social Services Research Unit (PSSRU).[13] For some staff roles, the cost per consultation was

not published in the Unit Cost of Health and Social Care. Therefore, mean length of consultation was obtained from the UK GP workload survey[14] and used to calculate the average cost per consultation from the unit cost per hour. Where a member of staff in an administrative role recorded the consultation, it was assumed that the consultation itself was carried out by a GP.

Prescriptions

Prescriptions for glucose-lowering therapies (including glucose-lowering therapies other than BI or exenatide prescribed concomitantly), injection equipment (needles and syringes), equipment used for the self-monitoring of blood glucose (strips and lancets), drugs used for the treatment of obesity, antihypertensives, antiplatelets and lipid-lowering therapies were identified in CPRD. Each prescription was matched to the corresponding product listed in the Prescription Cost Analysis (PCA) report for 2014[15] and attributed a net ingredient cost (NIC) per quantity. The NIC refers to the cost of the drug before discounts and does not include any dispensing costs or fees.[15] For those products that were discontinued before 2014 and therefore not included in the 2014 PCA, the NIC per quantity listed in the most recent prior version of the PCA was used and the cost inflated to 2014 prices using the Gross Domestic Product Deflator from Her Majesty's Treasury.[16]

The quantity of medication entered in each of the relevant prescriptions was determined and its unit converted, if necessary, to the Standard Quantity Unit used for the corresponding product in the PCA. This quantity was then multiplied by the NIC per quantity in order to determine the cost of each prescription.

Secondary care resource use

Data from inpatient admissions recorded in HES were processed into Healthcare Resource Groups (HRGs) using HRG-4 grouper. The allocated Healthcare Resource Groups (HRGs) were linked to the 2013–14 National Tariff,[17] adjusting for the nature of the admission (elective versus emergency) and excess length of stay.

Statistical analysis

Continuous baseline characteristics were compared using the independent *t*-test or Mann–Whitney U test depending on their distribution. Categorical variables were compared using the chi-squared test. Frequency and cost of primary care contacts and inpatient admissions were compared using adjusted annual cost ratios (aACR). These were estimated from a Poisson regression model that adjusted for the following baseline characteristics: age, gender, glycated haemoglobin (HbA1c), body mass index (BMI), Charlson comorbidity index,[18] the number of GP contacts in the year prior to index date, smoking status and the duration of diagnosed diabetes.

Sensitivity analysis

As a sensitivity analysis, patients were required to have been registered at their GP practice for at least 90 days before the index date in order to identify incident therapies.

Additional sensitivity analyses were performed based on cohorts matched by propensity score. The following baseline criteria were used to generate the propensity score: age at index date, sex, BMI, duration of diagnosed diabetes, index year, HbA1c, smoking status, serum creatinine, systolic blood pressure (BP), total cholesterol and Charlson index. For BMI, HbA1c, serum creatinine, systolic blood pressure, and total cholesterol the nearest recorded measurement to the index date was selected providing this was no more than 365 days before or 30 days after the index date. The search was conducted in the following order: -30, +30 and -365 days. For smoking, the nearest recorded status prior to the index date was selected. Where no status was recorded prior to the index date, the nearest recorded status after the index date was used. The duration of diabetes was calculated as the time between the diabetes presentation date and the index date. The Charlson comorbidity index was calculated by identifying relevant medical diagnoses recorded prior to the index date. Where the patient history prior to index date was shorter than 365 days, then the shorter period prior to index date was searched for the relevant baseline criteria. The caliper was set at 0.1. Patients with missing values for any of the characteristics used to generate the propensity score were excluded from the matching process. Propensity score matching produced four treatment cohorts: patients prescribed EQW and the corresponding matched BI cohort and patients prescribed EBID and the corresponding matched BI cohort.

Results

8,723 patients prescribed BI, 218 patient prescribed EQW and 2,180 patients prescribed EBID were identified. Total exposure time was 8,715 years. Mean follow-up was as follows: 0.75 years for BI, 0.85 years for EQW and 0.93 years for EBID.

Baseline characteristics

Patients prescribed BI were older than those prescribed EQW (mean age 64.8 versus 55.7 years, p <0.001) and EBID (64.8 versus 56.6 years, p <0.001), with a longer duration of diagnosed diabetes (median 9.1 years for BI; 8.0 years, p<0.005, for EQW; 7.4 years, p<0.001, for EBID). HbA1c at baseline was higher for patients prescribed BI in comparison with those prescribed EQW (9.7% versus 9.3%, p<0.001) and EBID (9.7% versus 9.2%, p<0.001). More patients prescribed BI had a history of major adverse cardiac events and cancer when compared with those prescribed EQW (19% versus 9%, p<0.001, for major adverse cardiac events and 14% versus 6%, p=0.001, for cancer) and EBID (19% versus 9%, p<0.001, for major adverse cardiac events and 14% versus 6%, p<0.001, for cancer). Patients prescribed BI also had a higher Charlson index (3.0 versus 2.0, p<0.001, for BI versus EQW and 3.0 versus 2.0, p <0.001, for BI versus EBID). Prior antiplatelet therapy was also more common in patients prescribed BI than in those prescribed EQW (44% versus 36%, p=0.020). However, patients prescribed BI had a lower BMI when compared with those prescribed EQW (30.0 versus 38.0 kg/m^2, p<0.001) and EBID (30.0 versus 38.6 kg/m^2, p<0.001). Fewer patients prescribed BI had received prescriptions for lipid-lowering therapy when compared with EQW (72% versus 78%, p=0.037) and EBID (72% versus

79%, p<0.001), and fewer patients prescribed BI had received prescriptions for antihypertensive therapy when compared with EBID (72% versus 85%, p<0.001).

5,987 patients prescribed BI, 193 patients prescribed EQW and 1,913 patients prescribed EBID had no missing data for any of the characteristics used to generate the propensity score. 188 patients prescribed BI were successfully matched to 188 patients prescribed EQW, and 1,486 patients prescribed BI were matched to 1,486 patients prescribed EBID. Following propensity-score matching, more patients prescribed EQW had previously been prescribed lipid-lowering therapy compared with those prescribed BI (79% versus 69%, p=0.019). Duration of diagnosed diabetes was longer for those prescribed EBID than in those receiving BI (median 7.8 versus 7.4 years, p=0.018), and diastolic blood pressure (78.8 versus 78.1 mmHg, p=0.039) and BMI (36.9 versus 36.1 kg/m^2, p<0.001) were also higher in those prescribed EBID. No other significant differences in the baseline characteristics between matched cohorts were observed.

A sensitivity analysis was carried out using those patients with a minimum wash-in of 90 days between the patient's current registration date with their GP practice and the study index date. Baseline characteristics of these patients are detailed in Supplementary Table 1.

Healthcare Resource Use

Overall, the cost of glucose-lowering therapies was higher in patients prescribed EQW than in those prescribed BI (£914 versus £507 per patient year (ppy), aACR 1.55, 95% CI 1.55–1.56, Table 2a). Following propensity-score matching this

difference remained (£926 versus £556 ppy, aACR 1.69, 1.68–1.71). However, lower costs were observed in those prescribed EQW for primary care contacts (£976 versus £1,178 ppy, aACR 0.95, 0.94–0.95), hospital admissions (£760 versus £2,096 ppy, aACR 0.65, 0.65–0.66) and total costs (£2,765 versus £4,080 ppy, aACR 0.92, 0.91–0.92). The corresponding costs for patients prescribed EQW and BI in the propensity-matched subgroup were £944 versus £1,059 ppy (aACR 0.89, 0.89–0.90) for primary care contacts, £654 versus £1,349 ppy (0.48, 0.47–0.48) for hospital admissions and £2,646 versus £3,283 ppy (0.80, 0.80–0.81) total costs, respectively.

When compared with those prescribed BI, lower total costs were observed in those prescribed EBID in the mains analysis (£2,549 versus £4,080 ppy, aACR 0.82, 0.82–0.82) and following propensity-score matching (£2,532 versus £3,070 ppy, 0.84, 0.84–0.84). A detailed breakdown of resource use and cost for those prescribed BI and EBID is provided in Table 2b.

In the sensitivity analysis selecting only those patients with a wash-in of ≥90 days between current registration date and index date, patients prescribed EQW had lower overall costs compared with those allocated to the BI cohort overall (£2,809 versus £3,857 ppy, aACR 0.99, 95% CI 0.99–0.99) and in the subgroup matched by propensity score (£2,782 versus £3,616, 0.92, 0.91–0.92, Supplementary Table 2a). Patients prescribed EBID had lower total costs when compared with those treated with BI in the overall analysis (£2,534 versus £3,857 ppy, aACR 0.86, 95% CI 0.86–0.86) and following propensity score matching (£2,543 versus £3,032, 0.82, 0.82–0.82, Supplementary Table 2b).

Discussion

Compared with patients treated with BI, patients treated with exenatide in its once-weekly (EQW) and twice-daily (EBID) formulations had significantly lower rates of primary care contacts and inpatient admissions and, consequently, lower total financial costs in spite of exenatide's higher pharmacy cost. Lower total costs for patients treated with EQW or EBID were also observed in the propensity-score-matched analysis. However, total costs were lower in the subgroup of BI patients matched by propensity score than in the original BI cohort. This is likely to be related to the decrease in mean age of patients prescribed BI following propensity-score matching where age is related to increased disease severity, increased morbidity and patient frailty.

In several studies, exenatide has been reported to have numerous clinical benefits when compared with insulin. In a meta-analysis by Wang and colleagues, GLP-1 receptor agonists were associated with greater reductions in HbA1c and weight (which may help to mitigate cardiovascular risk) in comparison with insulin.[19] Furthermore, in randomized trials, EQW has been reported to provide improved glycaemic control versus EBID.[20,21] In a retrospective study, exenatide was associated with a reduced cardiovascular risk versus insulin.[22]

It is important for patented products such as exenatide to demonstrate not only efficacy but also cost-effectiveness. In this study, despite the higher drug costs, overall costs were lower in the exenatide cohorts than in the BI cohort due largely to fewer primary care contacts and hospital admissions. Several studies have investigated the cost-effectiveness of exenatide versus insulin. In a systematic

review and economic evaluation carried out by Waugh and colleagues, the cost-effectiveness of EBID versus insulin glargine was estimated as approximately £20,000 per quality-adjusted life years (QALY), decreasing to £1,600 per QALY in patients with a BMI of 35kg/m^2.[23] Insulin dose increases with weight whereas exenatide is prescribed as a fixed dose and, indeed, the authors reported an improvement in the cost of EBID relative to insulin glargine as BMI increased.[23] A further small benefit for EBID in terms of QALY was reported due to its association with weight loss.[23] Several other studies have investigated the cost-effectiveness of EBID versus insulin glargine and EBID was shown to be cost-effective in Germany,[24] Switzerland[25] and the UK.[26] For EQW, the cost per QALY gained when compared with insulin glargine has been reported to be within the range that NICE normally considers as cost-effective both in the base-case scenario (incremental cost-effectiveness ratio, ICER, £10,597 per QALY gained) and in each of the BMI subgroups investigated (BMI <30k/m^2, 30–35kg/m^2 and >35kg/m^2 resulted in ICERs of £9425 to £12,956 per QALY gained).[27] However, as the study was conducted prior to the launch of EQW, the price was derived from GLP-1 receptor agonists already on the market.[27] When compared with insulin glargine, EQW has also been reported to cost-effective in the USA ($15,936 per QALY) and for patients with BMI of >30kg/m^2 in Spain (ICER €12,084 per QALY gained).[28] In the CHOICE study, total healthcare costs over a 24-month period post-initiation of the study drugs were higher in those prescribed EBID than in those prescribed insulin (€3997.9 versus €3265.5)[29] when drug costs were taken into account but were lower for exenatide when drug costs were excluded (€1791.9 versus €2465.5).[11] However, the CHOICE study took place in several European countries excluding the UK and included secondary care contacts.[11] In a study carried

out by Brice and colleagues, initiation with a GLP-1 receptor agonist was less costly than with a BI due to lower staff costs and fewer clinic visits (mean cost for GLP-1 receptor agonists was £43.81 in primary care, £243.49 in intermediate care and £518.99 in secondary care, whereas mean cost for BI was £473.63 in intermediate care and £571.11 in secondary care).[30]

Limitations

In this study, we were able to investigate healthcare resource utilization in real-world clinical practice. However, this study had a number of inherent limitations that are associated with retrospective observational studies. Patients were not randomized to each treatment cohort, and patient characteristics that were not known or could not be fully accounted for may have driven the decision to prescribe a particular therapy. We have aimed to reduce this risk of bias through the use of multivariate models and propensity-score matching. However, it is possible that confounding by indication and residual confounding from factors that are difficult to measure or quantify in retrospective data, such as diabetes severity and patient frailty, may exist. The purpose of the propensity matching process was to equalise the difference in baseline characteristics. However, it should be considered that those BI patients that were included in the propensity score matched cohort are likely to be atypical of the cohort as whole. This may affect the generalisability of the results.

As with other routine data, the data sources used for this study are likely to contain coding imperfections, misclassifications or the omission of diagnoses. It is also likely

that data were not missing at random but reflected patient characteristics. 27% of patients had missing data for one or more of the characteristics used to generate the propensity score and therefore were excluded from the matching process. Missing data were more common in people treated with BI (32% versus 21% for EQW and 22% for EBID). Missing data could have also affected the study outcomes. The HES inpatient dataset does not contain information on private treatments. As prescriptions are generated electronically, we expect that the completeness of the data was relatively high for prescriptions issued in primary care. However, prescriptions issued in secondary care are unlikely to be recorded in CPRD. Although this is difficult to quantify, we have no reason to suspect any issue of missing data in the recording of primary care consultations or secondary care inpatient admissions; should data be missing, however, this is unlikely to affect one treatment cohort more than another.

Some assumptions were required when applying costs to healthcare resource use. Costs were only applied to consultations involving a verbal contact (face-to-face or via the telephone) with the patient. As discontinued medicines are no longer listed in the Prescription Cost Analysis for England 2014, the most recently recorded costs from earlier Prescription Cost Analyses were used and inflated.

Exposure to study therapy was based on a record for one or more prescriptions in CPRD. However, we were not able to determine whether this prescription was then filled at the pharmacy or taken by the patient. Adherence to the prescribed medicine may have also differed between study cohorts. Misclassification of drug exposure

was possible. However, a consistent approach was maintained throughout the selection of the therapies of interest.

Baseline characteristics were derived using data recorded prior to index date. For those with a short or no registration period prior to index date, we needed to rely on the recording of prior and current medical conditions and monitoring information at registration. For BMI, HbA1c, total cholesterol, blood pressure and serum creatinine, the nearest recorded result to index date was selected, where records were searched in the following order: 30 days prior to index, 30 days post-index and 365 days prior to index date. The use of data up to 365 days prior was considered appropriate in order to reduce the percentage of missing data.

Conclusion

Type 2 diabetes places an increasing burden on the NHS. In this study we have shown that treatment with EQW and EBID was associated with reduced healthcare resource use and costs than BI -based regimens. Although the analysis adjusted for key baseline characteristics, the possibility of residual and unmeasured confounding should be considered when interpreting these results.

Tables

Table 1 | Baseline characteristics

a) EQW

	Unmatched					Propensity score matched				
	EQW		BI		p-value	EQW		BI		p-value
N	218		8,723			188		188		
Males, N (%)	125	(57%)	4,902	(56%)	0.737	106	(56%)	102	(54%)	0.678
Age at index, mean (SD), years	55.7	(11.3)	64.8	(15.1)	<0.001	56	(11.3)	55.4	(12.7)	0.631
Duration of diagnosed diabetes, median (IQR), years	8.0	(4.5–11.3)	9.1	(4.6–14.1)	0.005	8.0	(4.5–11.5)	7.7	(3.5–11.3)	0.207
Smoking status, N (%)[a]										0.730
Non smoker	96	(44%)	3,708	(43%)		87	(46%)	80	(43%)	
Ex-smoker	90	(41%)	3,397	(39%)		74	(39%)	77	(41%)	
Current smoker	29	(13%)	1,465	(17%)		27	(14%)	31	(16%)	
BMI, mean (SD), kg/m^{2}[b]	38	(6.5)	30	(6.4)	<0.001	37.7	(5.9)	37.4	(7.9)	0.625
HbA1c[b]										
Mean (SD), %	9.3	(1.5)	9.7	(2)	<0.001	9.3	(1.5)	9.4	(1.7)	0.676
Mean (SD), mmol/l	77.8	(16.7)	82.3	(21.9)		78.3	(16.4)	79.1	(19)	
Concomitant glucose-lowering therapies, N (%)										<0.001
2 oral GLTs	93	(43%)	2,222	(25%)		82	(44%)	47	(25%)	
1 oral GLT	79	(36%)	2,175	(25%)		68	(36%)	40	(21%)	
None	26	(12%)	2,156	(25%)		21	(11%)	39	(21%)	
3 oral GLTs	18	(8%)	610	(7%)		15	(8%)	17	(9%)	
4 oral GLTs	1	(0%)	13	(0%)		1	(1%)	1	(1%)	
GLP-1 receptor agonist plus other insulin	1	(0%)	4	(0%)		1	(1%)	0	(0%)	
Other insulin	0	(0%)	997	(11%)		0	(0%)	21	(11%)	
1 oral GLT plus other insulin	0	(0%)	440	(5%)		0	(0%)	15	(8%)	
2 oral GLTs plus other insulin	0	(0%)	73	(1%)		0	(0%)	6	(3%)	
3 oral GLTs plus other insulin	0	(0%)	10	(0%)		0	(0%)	0	(0%)	
1 oral GLT plus GLP-1 receptor agonist	0	(0%)	7	(0%)		0	(0%)	1	(1%)	
GLP-1 receptor agonist	0	(0%)	7	(0%)		0	(0%)	0	(0%)	
1 oral GLT plus GLP-1 receptor agonist plus other	0	(0%)	5	(0%)		0	(0%)	1	(1%)	

insulin										
2 oral GLTs plus GLP-1 receptor agonist	0	(0%)	4	(0%)	<0.001	0	(0%)	0	(0%)	
Serum creatinine, median (IQR), µmol/l[b]	74	(61–85)	84	(68–110)	<0.001	75	(62–85.5)	71	(60–82)	0.056
Systolic BP, mean (SD), mmHg[b]	132.6	(13.4)	132.8	(17.1)	0.838	132.8	(13.6)	134.2	(14.5)	0.331
Diastolic BP, mean (SD), mmHg[b]	78.7	(8.9)	75.5	(10.5)	<0.001	78.6	(9.2)	80.4	(9.8)	0.072
Total cholesterol, mean (SD), mmol/l[b]	4.4	(1.1)	4.4	(1.4)	0.707	4.5	(1.1)	4.6	(1.6)	0.519
Charlson index, median (IQR)	2	(1–3)	3	(2–5)	<0.001	2	(1–3)	2	(1–3)	0.503
GP contacts in the year prior										
N (%)[a]	190	(87%)	6,032	(69%)		170	(90%)	144	(74%)	
Median (IQR)	9.5	(6–15)	12	(7–19)	<0.001	9	(5–15)	10	(3.5–17)	0.013
History of major adverse cardiac event, N (%)	20	(9%)	1,627	(19%)	<0.001	16	(9%)	19	(10%)	0.594
History of cancer, N (%)	12	(6%)	1,188	(14%)	0.001	8	(4%)	10	(5%)	0.629
Prior prescriptions for antiplatelets, N (%)	78	(36%)	3,809	(44%)	0.02	69	(37%)	55	(29%)	0.125
Prior prescriptions for antihypertensives, N (%)	155	(71%)	6,096	(70%)	0.699	138	(73%)	131	(70%)	0.424
Prior prescriptions for lipid-lowering therapy, N (%)	170	(78%)	6,241	(72%)	0.037	149	(79%)	129	(69%)	0.019

N = number of patients, SD = standard deviation, IQR = interquartile range, BMI = body mass index, GLT = glucose-lowering therapy, HbA1c = glycated haemoglobin, BP = blood pressure, GP = general practitioner.

[a] Nearest status recorded prior to index date. Where no status is recorded prior to index date, nearest recorded status post-index is used.

[b] The nearest record to the index date providing it was no more than 365 days before or 30 days after the index date. The search was conducted in the following order: −30, +30 and −365 days.

b) EBID

	Unmatched					Propensity score matched				
	EBID		BI		p-value	EBID		BI		p-value
N	2,180		8,723			1,486		1,486		
Males, N (%)	1,207	(55%)	4,902	(56%)	0.485	838	(56%)	841	(57%)	0.912
Age at index, mean (SD), years	56.6	(10.5)	64.8	(15.1)	<0.001	58.1	(10.2)	58.6	(12.5)	0.238
Duration of diagnosed diabetes, median (IQR), years	7.4	(4.4–10.6)	9.1	(4.6–14.1)	<0.001	7.8	(4.8–11)	7.4	(3.8–11.3)	0.018
Smoking status, N (%)[a]					<0.001					0.120
Non smoker	864	(40%)	3,708	(43%)		571	(38%)	582	(39%)	
Ex-smoker	989	(45%)	3,397	(39%)		693	(47%)	647	(44%)	
Current smoker	312	(14%)	1,465	(17%)		222	(15%)	257	(17%)	
BMI, mean (SD), kg/m^{2}[b]	38.6	(6.6)	30	(6.4)	<0.001	36.9	(6)	36.1	(6.5)	<0.001
HbA1c[b]										
Mean (SD), %	9.2	(1.6)	9.7	(2)	<0.001	9.3	(1.6)	9.3	(1.8)	0.946
Mean (SD), mmol/l	77	(18)	82.3	(21.9)		78.2	(18)	78.1	(19.3)	
Concomitant glucose-lowering therapies, N (%)										<0.001
2 oral GLTs	955	(44%)	2,222	(25%)		683	(46%)	518	(35%)	
1 oral GLT	756	(35%)	2,175	(25%)		499	(34%)	333	(22%)	
None	275	(13%)	2,156	(25%)		161	(11%)	264	(18%)	
3 oral GLTs	185	(8%)	610	(7%)		138	(9%)	130	(9%)	
Other insulin	3	(0%)	997	(11%)		0	(0%)	117	(8%)	
1 oral GLT plus other insulin	3	(0%)	440	(5%)		2	(0%)	88	(6%)	
4 oral GLTs	3	(0%)	13	(0%)		3	(0%)	1	(0%)	
2 oral GLTs plus other insulin	0	(0%)	73	(1%)		0	(0%)	30	(2%)	
3 oral GLTs plus other insulin	0	(0%)	10	(0%)		0	(0%)	0	(0%)	
1 oral GLT plus GLP-1 receptor agonist	0	(0%)	7	(0%)		0	(0%)	1	(0%)	
GLP-1 receptor agonist	0	(0%)	7	(0%)		0	(0%)	2	(0%)	
1 oral GLT plus GLP-1 receptor agonist plus other insulin	0	(0%)	5	(0%)		0	(0%)	1	(0%)	
2 oral GLTs plus GLP-1 receptor agonist	0	(0%)	4	(0%)		0	(0%)	1	(0%)	
GLP-1 receptor agonist plus other insulin	0	(0%)	4	(0%)	<0.001	0	(0%)	0	(0%)	<0.001
Serum creatinine, median (IQR), µmol/l[b]	75	(63–90)	84	(68–110)	<0.001	76	(65–92)	76	(64–90)	0.280
Systolic BP, mean (SD), mmHg[b]	134.3	(14.7)	132.8	(17.1)	<0.001	134.2	(14.8)	134.6	(15.7)	0.456
Diastolic BP, mean (SD), mmHg[b]	79.3	(9.3)	75.5	(10.5)	<0.001	78.8	(9.1)	78.1	(10)	0.039

Total cholesterol, mean (SD), mmol/l[b]	4.3	(1.1)	4.4	(1.4)	<0.001	4.3	(1.1)	4.3	(1.1)	0.658
Charlson index, median (IQR)	2	(1–3)	3	(2–5)	<0.001	2	(1–3)	2	(1–3)	0.629
GP contacts in the year prior										
N (%)	1,916	(88%)	6,032	(69%)		1,342	(90%)	1127	(76%)	
Median (IQR)	10	(6–15.5)	12	(7–19)	<0.001	10	(6–16)	12	(7–19)	<0.001
History of major adverse cardiac events, N (%)	191	(9%)	1,627	(19%)	<0.001	139	(9%)	168	(11%)	0.080
History of cancer, N (%)	127	(6%)	1,188	(14%)	<0.001	99	(7%)	103	(7%)	0.771
Prior prescriptions for antiplatelets, N (%)	996	(46%)	3,809	(44%)	0.089	705	(47%)	645	(43%)	0.027
Prior prescriptions for antihypertensives, N (%)	1,722	(79%)	6,096	(70%)	<0.001	1,180	(79%)	1,100	(74%)	0.001
Prior prescriptions for lipid-lowering therapy, N (%)	1,847	(85%)	6,241	(72%)	<0.001	1,291	(87%)	1,183	(80%)	<0.001

N = number of patients, SD = standard deviation, IQR = interquartile range, BMI = body mass index, GLT = glucose-lowering therapy, HbA1c = glycated haemoglobin, BP = blood pressure, GP = general practitioner.

[a] Nearest status recorded prior to index date. Where no status is recorded prior to index date, nearest recorded status post-index is used.

[b] The nearest record to the index date providing it was no more than 365 days before or 30 days after the index date. The search was conducted in the following order: −30, +30 and −365 days.

Table 2 | Primary and secondary care contacts and costs after treatment with exenatide versus basal insulin

a) EQW

Healthcare resource post-index	Unmatched						Matched on propensity score					
	EQW		BI				EQW		BI			
	Total	Rate ppy	Total	Rate ppy	Adjusted rate ratios (95% CI)		Total	Rate ppy	Total	Rate ppy	Adjusted rate ratios (95% CI)	
Primary care contacts												
Number of contacts	5,413	29.1	230,172	35.4	0.92	(0.89–0.95)	4,665	28.5	3,893	31.8	0.89	(0.85–0.93)
Cost of contacts, £	181,661	976	7,664,456	1178	0.95	(0.94–0.95)	154,839	944	129,723	1,059	0.89	(0.89–0.90)
Primary care prescriptions												
Glucose-lowering therapies, £	170,589	914	3,309,968	507	1.55	(1.55–1.56)	152,295	926	68,410	556	1.69	(1.68–1.71)
Other diabetes related products, £[1]	7,828	42	1,455,679	223	0.20	(0.20–0.21)	7,382	45	28,459	231	0.20	(0.19–0.20)
All diabetes related prescriptions, £	178,416	956	4,765,648	730	1.19	(1.19–1.20)	159,677	971	96,869	787	1.25	(1.24–1.26)
Weight management drugs, £	0	0	6,498	1			0	0	113	1		
Lipid-lowering therapy, £	4,970	27	204,442	31	0.66	(0.64–0.68)	4,496	27	4,009	33	0.90	(0.86–0.94)
Antihypertensives, £	6,587	35	220,087	34	0.97	(0.95–1.00)	6,088	37	4,238	35	1.11	(1.06–1.15)
Antiplatelets, £	1,560	8	47,336	7	1.46	(1.38–1.54)	1,509	9	1,964	16	1.45	(1.34–1.58)
Secondary care admissions												
Number of admissions	109	0.6	8,466	1.3	0.69	(0.55–0.85)	84	0.5	79	0.6	0.78	(0.57–1.07)
Number of emergency admissions	45	0.2	3,573	0.5	0.81	(0.58–1.1)	38	0.2	35	0.3	0.86	(0.54–1.40)
Total length of stay, days	184	1.0	39,760	6.1	0.42	(0.36–0.49)	123	0.8	288	2.4	0.30	(0.24–0.37)
Total cost of hospital admissions, £	141,403	760	13,637,849	2,096	0.65	(0.65–0.66)	107,254	654	165,263	1,349	0.48	(0.47–0.48)
Total	**514,598**	**2,765**	**26,546,316**	**4,080**	**0.92**	**(0.91–0.92)**	**433,863**	**2,646**	**402,179**	**3,283**	**0.80**	**(0.80–0.81)**

ppy = per patient year

[1] Other diabetes-related products comprised injection equipment (needles and syringes) and appliances used for the self-monitoring of blood glucose (strips and lancets)

b) EBID

Healthcare resource post-index	Unmatched						Matched on propensity score					
	EBID		BI		Adjusted rate ratios (95% CI)		EBID		BI		Adjusted rate ratios (95% CI)	
	Total	Rate ppy	Total	Rate ppy			Total	Rate ppy	Total	Rate ppy		
Primary care contacts												
Number of contacts	48,052	24	230,172	35	0.76	(0.75–0.77)	32,875	24	43,209	32	0.76	(0.75–0.77)
Cost of contacts, £	1,591,677	787	7,664,456	1,178	0.77	(0.76–0.77)	1,079,548	779	1,405,408	1,031	0.77	(0.76–0.77)
Primary care prescriptions												
Glucose-lowering therapies, £	1,686,164	832	3,309,968	507	1.53	(1.53–1.53)	1,159,326	834	759,680	556	1.50	(1.49–1.50)
Other diabetes related products, £[1]	262,124	129	1,455,679	223	0.61	(0.61–0.62)	181,052	130	285,690	209	0.63	(0.63–0.63)
All diabetes related prescriptions, £	1,948,288	961	4,765,648	730	1.26	(1.26–1.27)	1,340,377	964	1,045,369	764	1.26	(1.26–1.26)
Weight management drugs, £	12,855	6	6,498	1	3.22	(3.10–3.34)	6,446	5	2,797	2	2.34	(2.23–2.44)
Lipid-lowering therapy, £	65,657	32	204,442	31	0.82	(0.81–0.83)	45,034	32	52,586	39	0.86	(0.85–0.87)
Antihypertensives, £	78,381	39	220,087	34	1.04	(1.03–1.06)	51,525	37	47,852	35	1.12	(1.10–1.13)
Antiplatelets, £	10,561	5	47,336	7	0.90	(0.88–0.92)	8,190	6	9,611	7	0.90	(0.88–0.93)
Secondary care admissions												
Number of admissions	854	0	8,466	1	0.53	(0.48–0.57)	571	0	957	1	0.60	(0.54–0.67)
Number of emergency admissions	301	0	3,573	1	0.49	(0.42–0.56)	201	0	451	0	0.46	(0.39–0.54)
Total length of stay, days	2,557	1	39,760	6	0.49	(0.47–0.51)	1,684	1	3,650	3	0.51	(0.48–0.54)
Total cost of hospital admissions, £	1,444,848	715	13,637,849	2,096	0.58	(0.58–0.59)	979,195	706	1,622,372	1,190	0.62	(0.62–0.62)
Total	**5,152,268**	**2,549**	**26,546,316**	**4,080**	**0.82**	**(0.82–0.82)**	**3,510,315**	**2,532**	**4,185,995**	**3,070**	**0.84**	**(0.84–0.84)**

ppy = per patient year

[1] Other diabetes-related products comprised injection equipment (needles and syringes) and appliances used for the self-monitoring of blood glucose (strips and lancets).

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Conflict of Interest statement

CC is a director of, SH, SJJ and EB are employed by and CLIM consults for Pharmatelligence, a research consultancy that receives funding from various pharmaceutical companies and other healthcare-related organizations. QQ is an employee of AstraZeneca who commercialize exenatide.

Contributor statement

CC, CLIM and QQ designed the study. SJ-J and CLIM extracted and prepared the data. CLIM, ERB and SEH analysed the data. All authors interpreted the results. SEH prepared the first draft of the manuscript and CC, CLIM, QQ and SJJ commented on this version.

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