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Healthcare utilization and costs in adults with type 2 diabetes treated with first or second-generation basal insulins in England

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ABSTRACT

Introduction The prevalence of people with type 2 diabetes (T2D) on basal insulin (BI) is rising to improve glucose control and minimize complications. However, limited evidence exists regarding the economic impact of second-generation BI analogs compared with first-generation BI in the United Kingdom.

Research design and methods In this comparative retrospective, observational study, adults with T2D who initiated treatment with a first-generation BI (eg, glargine 100 U/mL, detemir) and switched to another first-generation or a second-generation BI (glargine 300 U/mL (Gla-300) or degludec) (index date) between 1 July 2014 and 31 March 2021 were analyzed using the Clinical Practice Research Datalink (CPRD) Aurum linked to Hospital Episode Statistics. Subjects were followed from the index date until the end of observation period, deregistration in CPRD or death. Propensity score weighting balanced baseline characteristics and healthcare resource utilization (HCRU) and costs were compared using standardized differences and zero-inflated regression models.

Results A total of 13 975 people with T2D (mean (SD) age: 62.45 (13.59) years) treated with a first-generation BI who switched to another first-generation BI (n=5654), Gla-300 (n=4737) or degludec (n=3584) were included. Mean (SD) follow-up time was 4.98 (4.27), 1.96 (1.62) and 2.05 (1.92) years for the first-generation BI, Gla-300 and degludec groups, respectively. Overall, people who switched to Gla-300 had significantly lower HCRU. Fewer people in the Gla-300 group received hypoglycemia-related healthcare compared with those in the first-generation BI group (9.1% vs 16.4%, incident rate ratio (IRR)=0.41, p<0.001) and the degludec group (9.2% vs 11.7%, IRR=0.51, p<0.001). During follow-up, diabetes-related and diabetic ketoacidosis-related total direct costs were lower for the Gla-300 group compared with the first-generation BI group by 17% and the degludec group by 60%, respectively.

Conclusions These findings suggest that Gla-300 may offer clinical and economic benefits by reducing hypoglycemia incidents and lowering healthcare costs compared with first-generation BI.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Both insulin glargine 300 U/mL and insulin degludec have been thoroughly researched in comparison to the first-generation basal insulin (BI) glargine 100 U/mL. They show similar effectiveness in managing blood sugar levels and reducing the risk of hypoglycemia compared with early insulins or first-generation insulin analogs. However, the specific healthcare utilization and cost impact of second-generation BI analogs over first generation in the UK remain under-researched.

WHAT THIS STUDY ADDS

⇒ Primary and secondary healthcare resource utilization (HCRU) and the associated costs were significantly lower for adults with type 2 diabetes who switched from first-generation BI to glargine 300 U/mL compared with those who switched to another first-generation BI. The main driver for secondary care reduction was hospital admissions.

⇒ Diabetes- and hypoglycemia-related HCRU (mainly for hospital admission) were lower for people who switched from first-generation BI to glargine 300 U/mL compared with those who switched to degludec.

⇒ People who switched to the glargine 300 U/mL had significantly lower hypoglycemic-related and diabetic ketoacidosis-related total direct costs compared with those switched to another first-generation BI and/or to degludec.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study found that people with type 2 diabetes in the UK who switched to glargine 300 U/mL had a lower rate of hypoglycemia and diabetic ketoacidosis and HCRU than those using first-generation BI, which could result in significant cost savings for National Health Services.

INTRODUCTION

In the United Kingdom (UK), more than 2.4 million people are at increased risk of developing type 2 diabetes mellitus (T2D), and approximately 850 000 individuals currently live with T2D but remain undiagnosed. Additionally, the prevalence of T2D is expected to rise further, with estimates

suggesting that the total number of people with diabetes (including undiagnosed cases) will reach 5.5 million by 2030.[1] The National Health Services (NHS) has been working to treat and prevent T2D as part of its long-term plan. Early detection, lifestyle modifications and effective management through a treat to target approach play crucial roles in addressing this health challenge.[2]

The diabetes care pathway includes lifestyle changes, oral antidiabetic drugs and injectables, including insulin.[3] Insulin plays a crucial role in managing T2D and achieving optimal glucose control, thereby reducing risks of acute and long-term complications.[4 5] Insulin can be roughly characterized into slow-acting and fast-acting insulins. Basal insulins (BIs) are slow-acting insulins, which are usually injected once or two times per day to maintain blood sugar levels between meals.[6] BIs have greatly evolved from traditional neutral protamine Hagedorn insulin to first-generation BI analogs (glargine 100 U/mL (Gla-100), detemir) and, more recently, to the second generation of BI analogs (glargine 300 U/mL (Gla-300), degludec).[7] With each generation, BI pharmacodynamic profiles become flatter and last longer.[8] Both insulin Gla-300 and insulin degludec have been extensively studied versus the first-generation BI Gla-100 and demonstrate comparable efficacy in terms of glycemic control and a lower risk of hypoglycemia.[8]

Increased survival rates and changes in the clinical management of people with T2D have led to more people progressing to insulin therapy in the UK.[4 9] However, there is limited published real-world evidence (RWE) in the UK regarding the economic value of second-generation BIs compared with first-generation BIs and between the second-generation insulins available. This study aimed to assess healthcare resource utilization (HCRU) and cost–benefits associated with switching adults with T2D from a first-generation BI to a second-generation BI. Additionally, we compared HCRU and costs among different second-generation BIs (Gla-300 vs degludec).

RESEARCH DESIGN AND METHODS

Data source and study population

The Clinical Practice Research Datalink (CPRD) Aurum database[10] is a longitudinal database containing routinely collected electronic health record data from UK primary care practices, covering 19.93% of the UK population. The database captures a wide range of health-related information, including demographic characteristics, diagnoses and symptoms, drug exposures, vaccination history, laboratory tests and referrals to hospital and specialist care.[11] The CPRD database is linked at the patient level[12] to Hospital Episode Statistics (HES),[13] which is a secondary care data warehouse that contains pseudonymized records of all patients admitted to NHS hospitals in England, with data stored on hospital diagnoses, procedures, treatment, HCRU (including inpatient admissions, outpatient visits and accident and emergency (A&E) department attendances) and associated costs.

Approval of the study was obtained from CPRD's Research Data Governance process. The study was conducted in accordance with the principles of international ethics guidelines, including the Declaration of Helsinki, and applicable local laws and regulations.

In this retrospective, comparative, observational study, adults with T2D were included if they initiated treatment with a first-generation BI (eg, Gla-100 or detemir) and switched to another first-generation BI or to a second-generation BI (Gla-300 or degludec) (index date) between 1 July 2014 and 31 March 2021 (observation period) in CPRD Aurum. If a person moved from a first-generation BI to another first-generation BI and then to a second-generation BI within the observation period, the person was a part of the second-generation cohort. People who had a diagnosis of type 1 diabetes at any time, aged <18 years at the time of the index date, had <12 months of data available prior to the index date, or had a record of bolus insulin in the 3 months preindex and postindex date in CPRD Aurum were excluded from the study. People were described for the 12-month period prior to the index date (baseline) and followed up from index date until 31 March 2021, deregistration from CPRD or death, whichever occurred first.

Data extracted included patient demographics at the index date (age, sex, ethnicity, index of multiple deprivation (IMD), weight) and baseline clinical characteristics (hospitalization related to diabetes, hypoglycemia, diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS), latest estimated glomerular filtration rate (eGFR) prior to index, number of BI used, oral antidiabetics used, history of retinopathy, neuropathy and nephropathy, baseline hemoglobin A1c (HbA1c)) as well as primary (visits/consultations, prescriptions) and secondary (outpatient visits, inpatient hospitalizations and length of stay, A&E attendances) HCRU during follow-up period. Healthcare Resource Group (HRG) NHS tariff codes were used to define activity-based costs (in GBP).[14] Each HRG has an associated reference cost, which is an average cost of providing that specific type of care. Online supplemental code lists file shows the code lists used for this study.

Statistical analysis

Propensity score-based inverse probability of treatment weighting (IPTW) was applied to balance the baseline characteristics between the comparison groups. All baseline characteristics and comorbidities were included in calculating the propensity score for each person. The comparison groups were then weighted based on the propensity scores.[15] For each baseline covariate, if the standardized mean difference (SMD) between two comparison groups was <10%, the two groups were considered balanced on the covariate.[16] The post-IPTW-weighted HCRU and costs were described, and standardized differences were used to compare the statistical differences between two comparison groups.

Continuous variables were described using mean, SD, median and IQR and compared using student's t-tests or the Mann-Whitney test. Categorical variables were presented using frequency and percentages and compared using Pearson's χ^2 test or Fisher's exact test. The proportion of people with each diabetes-related complication was reported for the follow-up period for each comparison group. To reduce the risk of bias due to different follow-up periods between comparison groups, HCRU and costs were summarized per patient per year (PPY) for all people in a specific group, and the frequency of attendances was also reported. Outcomes were compared between people switching to Gla-300 and each of degludec and an alternative first-generation B1 group separately.

After IPTW, endpoints were compared between the two comparison groups in the weighted sample using regression analyses adjusted for all weighted variables (balanced or imbalanced). Logistic regression was conducted for binary outcomes, including medically attended hypoglycemic events, DKA and HHS. Continuous outcomes including HCRU and cost data are typically characterized by extreme skewness and a high proportion of zero values, as many individuals do not experience events that generate cost or resource use. To address these distributional challenges, we employed zero-inflated negative binomial regression models, which are mixture models combining a logistic model for predicting excess zeros and a count model (negative binomial) for the non-zero portion of the distribution.[17] Therefore, the results are expressed as Estimated HCRU or cost PPY=probability of being zero × 0+probability of not being zero × Estimated PPY when not being zero. This structure enables us to distinguish between individuals who are structurally unlikely to incur HCRU and those who may or may not, better reflecting real-world patterns in healthcare data. This approach is well supported in the literature as an appropriate method for handling zero-inflated and overdispersed cost and utilization data.[18] We also examined distributional characteristics such as skewness and the variance-to-mean ratio to ensure the suitability of this model over alternatives such as two-part or standard negative binomial models.

Missing data were reported, but to comply with CPRD and HES guidance, frequencies estimated in fewer than five people were suppressed to preserve confidentiality. Analyses were performed using Microsoft SQL, R Statistical Software (V.4.2.2) and Microsoft Excel.

RESULTS

Demographic characteristics

A population of 13975 people with T2D using first-generation BI who switched to another first-generation BI (n=5656), Gla-300 (n=4737) or degludec (n=3584) between 1 July 2014 and 31 March 2021 was included in this study (figure 1). The mean (SD) age of the people was 62.45 (13.59) years and did not differ considerably across the groups (table 1). Around half of the people in the first-generation BI group (50.65%) were female compared with 44.29% in the Gla-300 and 46.99% in the degludec group. People in the Gla-300 group had the highest mean (SD) weight (97.27 (22.80) kg vs 88.07 (21.67) kg in the first-generation BI group and 89.84 (23.09) kg in the degludec group). Online supplemental tables 1 and 2 show the baseline demographic characteristics of the people after IPTW. Despite being weighted, there were significant differences, albeit of low magnitude, between people in the Gla-300 group and those in the first-generation BI group (IMD, weight, age).

Baseline clinical characteristics

Overall, people after a mean (SD) of 14.57 (8.17) years from diagnosis of diabetes switched from first-generation BI to either another first-generation BI or second-generation BI (table 1). The majority of people in all three groups (73.47% in the Gla-300 group vs 65.95% in the first-generation BI group and 70.76% in the degludec group) had a reduced eGFR (<90) prior to the index date. People in the degludec group had the highest rate of previous hospitalization related to hypoglycemia (24.30% vs 19.12% in the first-generation BI group and 18.98% in the Gla-300 group), DKA (7.39% vs 3.29% in the first-generation BI group and 4.31% in the Gla-300 group) and HHS (2.32% vs 1.36% in the first-generation BI group and 1.22% in the Gla-300 group). The mean (SD) HbA1c level was the highest in people of the first-generation BI group at baseline (9.26 (2.00)) and the lowest in people of the Gla-300 group (8.98 (1.92)).

There were significant differences, although of low magnitude, between people in the Gla-300 and the first-generation BI groups (history of retinopathy, neuropathy, nephropathy, baseline diabetes-related hospitalization, baseline eGFR, medication) and between people in the Gla-300 group and those in the degludec group (medication) after IPTW (online supplemental tables 3 and 4).

The mean (SD) follow-up time was 4.54 (3.99) years for people in the first-generation BI group and 1.97 (1.64) years for those in the Gla-300 group (p<0.001). People in the Gla-300 and degludec groups were followed for 1.99 (1.60) and 2.25 (2.01) years after switching from first-generation BI (p<0.001) (online supplemental tables 3 and 4).

Diabetes-related complications

A higher proportion of people in the first-generation BI group had hypoglycemia-related (19.6% vs 11.1%), DKA-related (3.2% vs 1.1%) and HHS-related events (1.6% vs 0.7%) during follow-up compared with those in the Gla-300 group (table 2). However, the mean number of hypoglycemic, DKA and HHS events per patient-year did not significantly differ between the two groups during follow-up. People in the degludec group were more likely to have hypoglycemic (13.6% vs 11.2%, p=0.002) and DKA (2.1% vs 1.4%, p=0.027) events compared with those in the Gla-300 group, and the mean (SD) number

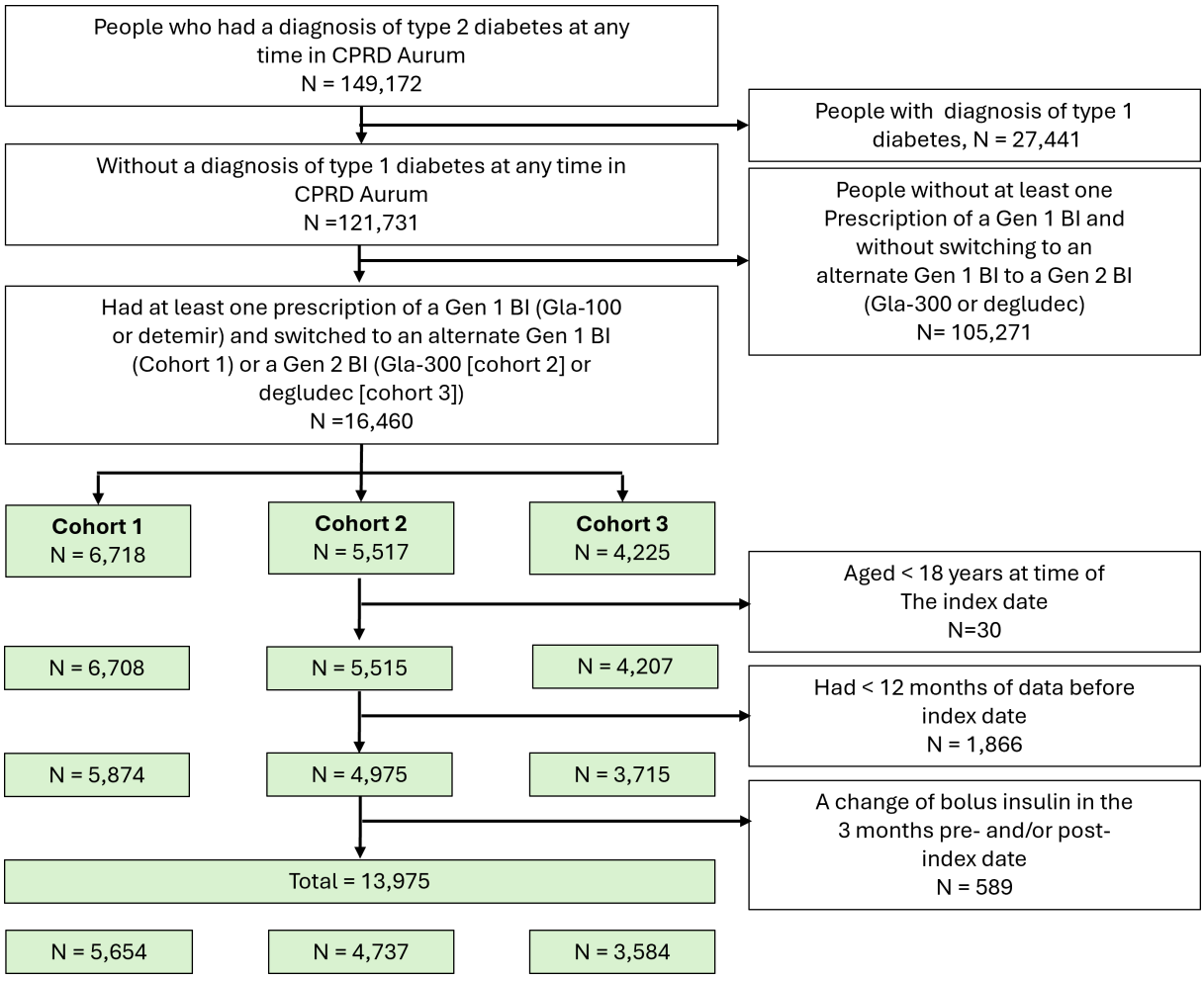

Figure 1 People selection flowchart. BI, basal insulin; CPRD, Clinical Practice Research Datalink; Gen 1, first-generation; Gen 2, second-generation; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL.

of hypoglycemic events per patient-year was slightly higher for people in the degludec group (1.42 (3.66) vs 1.03 (1.57)) compared with those in the Gla-300 group.

Consistently, the regression analyses showed that people in the Gla-300 group had 59% (incident rate ratio (IRR)=0.41, p<0.001) fewer hypoglycemic events, 45% (IRR=0.55, p=0.001) fewer DKA events, and 54% (IRR=0.46, p=0.002) fewer HHS events per patient-year than those in the first-generation BI group (table 2) and 49% (IRR=0.51, p<0.001) fewer hypoglycemic events and 55% (IRR=0.45, p<0.001) fewer DKA events per patient-year than those in the degludec group.

A small proportion of the study population (n=2874) had a record of HbA1c at 6 months after the index date (online supplemental table 5). Among people who had HbA1c recorded at 6 months during follow-up, the post-IPTW mean (SD) HbA1c was higher for people in the Gla-300 group compared with those in the first-generation BI (9.67 (2.61) vs 8.96 (1.58), p<0.001) and the degludec group (9.49 (1.96) vs 9.21 (1.85), p=0.054). The HbA1c level was recorded at both baseline and 6 months' follow-up for 2825 (20.2% of the study population) individuals (data not shown). The mean (SD) HbA1c level decreased from 10.01 (2.00) at baseline to 9.44 (1.90) in people of the Gla-300 group (n=423) at 6 months' follow-up, from 9.47 (1.89) to 9.01 (1.77) in people of the first-generation BI group (2,083), and from 9.81 (1.91) to 9.27 (1.92) in people of the degludec group (n=319).

HCRU and associated costs

Post-IPTW-weighted comparisons

The post-IPTW-weighted analyses showed that primary and secondary HCRU were significantly lower for people in the Gla-300 group than those in the first-generation BI group (online supplemental table 6). People in the Gla-300 group also had lower diabetes-related and hypoglycemic-related primary care use, fewer diabetes-related and DKA-related hospital admissions, and a slightly higher diabetes-related outpatient visits (mean (SD): 0.01 (0.13), p=0.04) compared with those in the degludec group (0 (0.07)).

The costs associated with all-cause primary care use and prescriptions (all cause and antidiabetics) were higher for people in the Gla-300 group than those in the first-generation BI group, while the costs associated with diabetes-related primary care were lower for the Gla-300 group (mean (SD): 19.6£ (61.7) vs 23.2£ (76.5), p=0.013)

Table 1 Baseline demographic and clinical characteristics of adults with type 2 diabetes mellitus, overall and by comparison groups

	Overall	First-generation BI	Gla-300	Degludec
	N=13975	N=5654	N=4737	N=3584
Age at index, years				
Mean (SD)	62.45 (13.59)	62.88 (14.39)	62.13 (12.37)	62.20 (13.83)
Median (Q1–Q3)	63.00 (53.00–72.00)	63.00 (53.00–74.00)	62.00 (54.00–71.00)	62.00 (53.00–72.00)
Sex, N (%)				
Female	6646 (47.56%)	2864 (50.65%)	2098 (44.29%)	1684 (46.99%)
Male	7329 (52.44%)	2790 (49.35%)	2639 (55.71%)	1900 (53.01%)
Ethnicity, N (%)				
White	7031 (50.31%)	2954 (52.25%)	2303 (48.62%)	1774 (49.50%)
Black	430 (3.08%)	235 (4.16%)	110 (2.32%)	85 (2.37%)
Asian	1298 (9.29%)	589 (10.42%)	448 (9.46%)	261 (7.28%)
Mixed	4613 (33.01%)	1568 (27.73%)	1721 (36.33%)	1324 (36.94%)
Other	360 (2.58%)	177 (3.13%)	107 (2.26%)	76 (2.12%)
Unknown	243 (1.74%)	131 (2.32%)	48 (1.01%)	64 (1.79%)
IMD, N (%)				
1 (most deprived quintile)	3494 (25.00%)	1389 (24.57%)	1264 (26.68%)	841 (23.47%)
2	3019 (21.60%)	1335 (23.61%)	1024 (21.62%)	660 (18.42%)
3	2548 (18.23%)	1003 (17.74%)	878 (18.53%)	667 (18.61%)
4	2364 (16.92%)	917 (16.22%)	780 (16.47%)	667 (18.61%)
5 (least deprived quintile)	2055 (14.70%)	834 (14.75%)	641 (13.53%)	580 (16.18%)
Unknown	495 (3.54%)	176 (3.11%)	150 (3.17%)	169 (4.72%)
Weight, kg				
Mean (SD)	91.65 (22.80)	88.07 (21.67)	97.27 (22.80)	89.84 (23.09)
Median (Q1–Q3)	89.90 (75.60–105.70)	86.00 (72.60–101.00)	95.60 (81.60–111.00)	88.00 (73.80–104.00)
Duration from diabetes diagnosis to index, years				
Mean (SD)	14.57 (8.17)	13.01 (8.09)	15.85 (7.93)	15.34 (8.23)
Median (Q1–Q3)	13.85 (8.78–19.11)	11.92 (7.23–17.36)	15.34 (10.74–20.25)	14.70 (9.68–19.96)
Previous hospitalization related to diabetes, N (%)	10884 (77.88%)	4070 (71.98%)	3935 (83.07%)	2879 (80.33%)
Previous hypoglycemia, N (%)	2851 (20.40%)	1081 (19.12%)	899 (18.98%)	871 (24.30%)
Previous DKA, N (%)	655 (4.69%)	186 (3.29%)	204 (4.31%)	265 (7.39%)
Previous HHS, N (%)	218 (1.56%)	77 (1.36%)	58 (1.22%)	83 (2.32%)
Latest eGFR prior to index, N (%)				
Normal and high (≥ 90)	3207 (22.95%)	1054 (18.64%)	1186 (25.04%)	967 (26.98%)
Mild reduction (60–89)	5895 (42.18%)	2105 (37.23%)	2211 (46.68%)	1579 (44.06%)
Mild to moderate reduction (45–59)	1752 (12.54%)	693 (12.26%)	612 (12.92%)	447 (12.47%)
Moderate to severe reduction (30–44)	1384 (9.90%)	582 (10.29%)	460 (9.71%)	342 (9.54%)
Severe reduction (15–29)	579 (4.14%)	281 (4.97%)	163 (3.44%)	135 (3.77%)
Kidney failure (<15)	135 (0.97%)	68 (1.20%)	34 (0.72%)	33 (0.92%)
No record of eGFR	1023 (7.32%)	871 (15.41%)	71 (1.50%)	81 (2.26%)
Number of basal insulins used, N (%)				
1	12916 (92.42%)	5645 (99.84%)	4192 (88.49%)	3079 (85.91%)
≥2	1059 (7.58%)	9 (0.16%)	545 (11.51%)	505 (14.09%)
Oral antidiabetics used, N (%)				
Metformin	12810 (91.66%)	5066 (89.60%)	4493 (94.85%)	3251 (90.71%)
Sulfonylurea	10357 (74.11%)	4302 (76.09%)	3515 (74.20%)	2540 (70.87%)

Continued

Table 1 Continued

	Overall	First-generation BI	Gla-300	Degludec
	N=13975	N=5654	N=4737	N=3584
Dipeptidyl peptidase 4 inhibitors	5016 (35.89%)	1321 (23.36%)	2176 (45.94%)	1519 (42.38%)
SGLT-2	2727 (19.51%)	366 (6.47%)	1477 (31.18%)	884 (24.67%)
GLP-1s	3330 (23.83%)	603 (10.67%)	1710 (36.10%)	1017 (28.38%)
Number of oral antidiabetic classes, N (%)				
≤ 2	7750 (55.46%)	4192 (74.14%)	1866 (39.39%)	1692 (47.21%)
> 2	6225 (44.54%)	1462 (25.86%)	2871 (60.61%)	1892 (52.79%)
History of retinopathy, N (%)	12227 (87.49%)	4653 (82.30%)	4355 (91.94%)	3219 (89.82%)
History of neuropathy, N (%)	2976 (21.30%)	1071 (18.94%)	1122 (23.69%)	783 (21.85%)
History of nephropathy, N (%)	3654 (26.15%)	1533 (27.11%)	1213 (25.61%)	908 (25.33%)
Latest HbA1c prior to index, N (%)	11920 (85.30%)	5130 (90.73%)	3948 (83.34%)	2842 (79.30%)
Mean (SD)	9.13 (1.98)	9.26 (2.00)	8.98 (1.92)	9.11 (2.01)
Median (Q1–Q3)	8.90 (7.70–10.30)	9.00 (7.80–10.40)	8.70 (7.60–10.10)	8.90 (7.70–10.30)

BI, basal insulin; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; Gla-300, glargine 300 U/mL; GLP-1s, glucagon-like peptide-1; HbA1c, hemoglobin A1c; HHS, hyperosmolar hyperglycaemic state; IMD, Index of Multiple Deprivation; Q, quartile; SGLT-2, sodium glucose cotransporter 2.

than the first-generation BI group (online supplemental table 7). The costs associated with diabetes-related and hypoglycemic-related primary care and antidiabetic medication were lower for people in Gla-300 group compared with those in the degludec group (online supplemental table 7). The all-cause secondary care use, diabetes-related and DKA-related hospitalization and diabetes-related A&E attendances were lower in the Gla-300 group compared with the first-generation BI group.

Total direct costs (all-cause, diabetes-related, DKA-related) were significantly lower in people in the Gla-300 group compared with those in the first-generation BI group during the follow-up period (online supplemental table 8). Compared with people in the degludec group, those in the Gla-300 group had lower mean (SD) costs of hospital admissions for DKA (65.4£ (1156.4) vs 244.9£ (4866.3), p=0.051) (online supplemental table 8).

Zero-inflated regression analyses

The regression analyses showed that people switched to Gla-300 had 11% (IRR=0.89, p<0.001) fewer all-cause primary care visits per patient-year than those who switched to another first-generation BI (table 3). The number of primary care visits related to diabetes (IRR=0.88, p=0.001) and hypoglycemia (IRR=0.25, p<0.001) was also significantly lower in the Gla-300 group compared with the first-generation BI group. There were 42% (IRR=0.58, p<0.001), 37% (IRR=0.63, p<0.001), 31% (IRR=0.69, p<0.001), 68% (IRR=0.32, p<0.001) and 59% (IRR=0.41, p=0.001) fewer all-cause, diabetes-related, hypoglycemia-related, DKA-related and HHS-related hospital admissions for the people in the Gla-300 group than for those in the first-generation BI group. However, the length of hospital stays for diabetes-related (1.5 times) and hypoglycemia-related (1.43 times) admissions was higher for people in the Gla-300 group (table 3).

The study showed fewer all-cause (5%), diabetes-related (25%), hypoglycemia-related (78%) and HHS-related primary care visits (99.8%) for the Gla-300 group than the degludec group. There were 43% (IRR=0.57, p<0.001), 41% (IRR=0.59, p<0.001) and 68% (IRR=0.32, p<0.001) fewer diabetes-related, hypoglycemia-related and DKA-related hospital admissions in the Gla-300 group than in the degludec group. People in the Gla-300 group had 42% fewer diabetes-related A&E attendances (IRR=0.58, p=0.003) per patient-year than those in the degludec group (table 3).

The total direct costs of all-cause and diabetes-related HCRU were lower for people in the Gla-300 group (14% and 17%, respectively) compared with those in the first-generation BI group while the total cost of hypoglycemia was higher in the Gla-300 group (1.7 times) during follow-up (table 4). Total direct costs of all-cause and DKA-related HCRU were lower for people in the Gla-300 group (11% and 60%, respectively) compared with those in the degludec group, while the total cost of HHS-related HCRU was 2.9 times higher in the Gla-300 group during follow-up (table 4).

CONCLUSIONS

This retrospective comparative study showed that people with T2D who switched from a first-generation BI to Gla-300 had lower primary and secondary HCRU than those switched to another first-generation BI or degludec. In terms of total direct costs, people who switched to Gla-300 had, in general, lower all-cause, diabetes-related and DKA-related costs compared with those switched to another first-generation BI during the follow-up period

Table 2 Post-IPTW rate (number of events per patient-year) and incidence rate ratio for diabetes-related complications events per patient-year in adults with type 2 diabetes mellitus

Diabetes-related complications	First-generation BI, N=4971	Gla-300, N=3940	St. dif.	P value	Gla-300, N=3855	Degludec, N=2925	St. dif.	P value
Medically attended hypoglycemic events, N (%)	977 (19.6%)	437 (11.1%)	0.24	<0.001	431 (11.2%)	398 (13.6%)	0.07	0.002
Mean (SD)	0.86 (3.47)	1.04 (1.38)	0.07	0.164	1.03 (1.57)	1.42 (3.66)	0.14	0.053
Median (Q1–Q3)	0.35 (0.17–0.67)	0.62 (0.36–1.22)	--	--	0.59 (0.35–1.14)	0.58 (0.31–1.04)	--	--
IRR (95% CI)	Ref.	0.41 (0.33–0.50)	--	<0.001	0.51 (0.39–0.66)	Ref.	--	<0.001
Diabetic ketoacidosis events, N (%)	160 (3.2%)	41 (1.1%)	0.15	<0.001	55 (1.4%)	62 (2.1%)	0.05	0.027
Mean (SD)	0.82 (2.25)	1.50 (3.14)	0.25	0.196	1.10 (2.26)	1.41 (1.85)	0.15	0.418
Median (Q1–Q3)	0.22 (0.12–0.45)	0.50 (0.26–1.00)	--	--	0.56 (0.27–1.06)	0.62 (0.36–1.65)	--	--
IRR (95% CI)	Ref.	0.55 (0.39–0.77)	--	0.001	0.45 (0.30–0.67)	Ref.	--	<0.001
Hyperosmolar hyperglycemic state events, N (%)	79 (1.6%)	26 (0.7%)	0.08	<0.001	31 (0.8%)	20 (0.7%)	0.01	0.616
Mean (SD)	0.86 (2.68)	0.94 (1.69)	0.04	0.863	0.86 (1.65)	0.77 (1.15)	0.06	0.835
Median (Q1–Q3)	0.29 (0.14–0.82)	0.45 (0.27–0.53)	--	--	0.39 (0.27–0.53)	0.38 (0.18–0.88)	--	--
IRR (95% CI)	Ref.	0.46 (0.29–0.75)	--	0.002	0.96 (0.52–1.79)	Ref.	--	0.908

Analysis conducted among all patients, including those with and without any complication events.
BI, basal insulin; DKA, diabetic ketoacidosis; Gla-300, glargine 300 U/mL; HHS, hyperosmolar hyperglycaemic state; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio; St. dif, standardized difference.

Table 3 Post-IPTW regression analysis for HCRU outcomes in adults with type 2 diabetes mellitus

	Gla-300 vs first-generation BI		Gla-300 vs degludec	
HCRU outcomes	IRR (95% CI)	P value	IRR (95% CI)	P value
Primary care visits				
All-cause	0.89 (0.86 to 0.93)	<0.001	0.95 (0.90 to 0.99)	0.016
Diabetes-related	0.88 (0.81 to 0.94)	0.001	0.75 (0.68 to 0.82)	<0.001
Hypoglycemiaa-related	0.25 (0.18 to 0.35)	<0.001	0.22 (0.11 to 0.45)	<0.001
DKA-related	1.63 (0.46 to 5.73)	0.446	0.79 (0.24 to 2.63)	0.699
HHS-related	0.69 (0.01 to 33.38)	0.853	0.002 (0.00 to 0.15)	0.005
Hospital admissions				
All-cause	0.58 (0.54 to 0.63)	<0.001	0.90 (0.82 to 0.98)	0.014
Diabetes-related	0.63 (0.54 to 0.73)	<0.001	0.57 (0.48 to 0.68)	<0.001
Hypoglycemia-related	0.69 (0.60 to 0.81)	<0.001	0.59 (0.49 to 0.70)	<0.001
DKA-related	0.32 (0.22 to 0.48)	<0.001	0.32 (0.21 to 0.49)	<0.001
HHS-related	0.41 (0.25 to 0.69)	0.001	0.95 (0.49 to 1.85)	0.876
Length of hospital stay				
All-cause	0.81 (0.73 to 0.91)	<0.001	0.78 (0.67 to 0.90)	0.001
Diabetes-related	1.53 (1.17 to 1.99)	0.002	0.93 (0.67 to 1.28)	0.639
Hypoglycemia-related	1.43 (1.08 to 1.89)	0.012	0.90 (0.65 to 1.25)	0.526
DKA-related	0.68 (0.34 to 1.36)	0.272	0.46 (0.19 to 1.10)	0.080
HHS-related	1.80 (0.61 to 5.32)	0.287	1.47 (0.34 to 6.28)	0.603
Outpatient visits				
All-cause	1.01 (0.95 to 1.07)	0.814	0.91 (0.83 to 0.98)	0.019
Diabetes-related	0.97 (0.59 to 1.60)	0.895	1.42 (0.77 to 2.65)	0.265
A&E attendances				
All-cause	0.57 (0.52 to 0.61)	<0.001	0.85 (0.76 to 0.94)	0.002
Diabetes-related	0.47 (0.35 to 0.64)	<0.001	0.58 (0.41 to 0.83)	0.003

A&E, accident and emergency; BI, basal insulin; DKA, diabetic ketoacidosis; Gla-300, glargine 300 U/mL; HCRU, healthcare resource utilization; HHS, hyperosmolar hyperglycaemic state; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio.

and lower DKA-related costs compared with those switched to degludec.

Microvascular complications that commonly affect people with T2D can lead to serious health issues if not managed properly.[19] A retrospective cohort study that utilized electronic medical records from people with T2D from the Heart of England Foundation Trust showed that 22.6%, 20.8% and 3.1% of the study population had comorbid nephropathy, retinopathy or neuropathy, respectively.[20] Consistently, in our study, people had a high proportion of microvascular complications (26.15% nephropathy, 87.5% retinopathy and 21.3% neuropathy). Moreover, reduced eGFR was observed for approximately 70% of total population prior to the index date. These findings highlight the significant burden of microvascular complications in people with T2D, indicating that our study population likely has more severe diabetes and is more prone to resource utilization than most patients with T2D.

We found that people who switched to Gla-300 had a lower HCRU rate and fewer associated costs, particularly for diabetes-related, hypoglycemia-related and DKA-related services, compared with those who switched to another first-generation BI or degludec. Notably, the Gla-300 group experienced 51%–59% fewer hypoglycemia events and 45%–55% fewer DKA events, along with shorter hospital stays for these acute complications. These are clinically meaningful differences, as both hypoglycemia and DKA are serious events associated with substantial morbidity, hospital admissions and even mortality. Fewer episodes not only reduce healthcare burden but also improve patient safety, treatment adherence and quality of life. These findings align with prior real-world studies in the USA, showing that switching to insulin Gla-300 reduced hypoglycemia risk and associated HCRU, supporting both clinical and economic benefits.[21–23] The follow-up period in these studies (6–12 months) was shorter than the follow-up time in our study but comparable to most randomized controlled trials. Another recent US study evaluating the value and affordability of Gla-300 over a 3-year model horizon for a hypothetical one million member US health plan

Table 4 Post-IPTW regression analysis for cost of HCRU in adults with type 2 diabetes mellitus

	Gla-300 vs first-generation BI		Gla-300 vs degludec	
HCRU costs	IRR (95% CI)	P value	IRR (95% CI)	P value
Primary care costs				
All-cause	1.18 (1.13 to 1.22)	<0.001	0.93 (0.89 to 0.98)	0.003
Diabetes-related	0.96 (0.89 to 1.03)	0.259	0.77 (0.70 to 0.83)	<0.001
Hypoglycemia-related	0.42 (0.23 to 0.79)	0.007	0.28 (0.15 to 0.52)	<0.001
DKA-related	--	--	0.88 (0.38 to 2.00)	0.752
HHS-related	0.43 (0.08 to 2.22)	0.314	0.14 (0.01 to 2.56)	0.183
Costs of prescriptions				
All-cause	1.24 (1.20 to 1.28)	<0.001	0.95 (0.92 to 0.98)	0.003
Diabetes-related	1.54 (1.49 to 1.60)	<0.001	0.92 (0.88 to 0.95)	<0.001
Hospital admissions costs				
All-cause	1.15 (1.04 to 1.27)	0.006	0.92 (0.81 to 1.04)	0.172
Diabetes-related	1.06 (0.97 to 1.16)	0.221	0.96 (0.86 to 1.08)	0.494
Hypoglycemia-related	1.48 (1.24 to 1.76)	<0.001	0.98 (0.80 to 1.20)	0.830
DKA-related	1.06 (0.60 to 1.86)	0.853	0.45 (0.26 to 0.77)	0.004
HHS-related	1.98 (1.10 to 3.57)	0.023	2.78 (1.39 to 5.55)	0.004
Outpatient visits costs				
All-cause	1.05 (1.00 to 1.10)	0.047	1.04 (0.98 to 1.10)	0.215
Diabetes-related	1.20 (0.68 to 2.11)	0.528	1.15 (0.68 to 1.95)	0.609
A&E attendance costs				
All-cause	1.14 (1.05 to 1.24)	0.001	1.02 (0.93 to 1.12)	0.655
Diabetes-related	1.31 (1.03 to 1.68)	0.031	0.74 (0.56 to 0.97)	0.027
Total HCRU costs				
All-cause	0.86 (0.80 to 0.94)	<0.001	0.89 (0.80 to 0.98)	0.019
Diabetes-related	0.83 (0.78 to 0.89)	<0.001	0.93 (0.87 to 1.01)	0.082
Hypoglycemia-related	1.69 (1.35 to 2.13)	<0.001	1.07 (0.84 to 1.38)	0.579
DKA-related	0.93 (0.53 to 1.62)	0.788	0.40 (0.22 to 0.70)	0.002
HHS-related	1.83 (0.97 to 3.44)	0.062	2.91 (1.33 to 6.38)	0.008

A&E, accident and emergency; BI, basal insulin; DKA, diabetic ketoacidosis; Gla-300, glargine 300 U/mL; HCRU, healthcare resource utilization; HHS, hyperosmolar hyperglycaemic state; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio.

population using HCRU parameters from the DELIVER-2 and DELIVER-naïve studies showed economic benefits driven by reductions in HCRU and costs.[24] However, market shares were projected based on clinicians' opinions rather than real-world patient data. A systematic review on cost-effectiveness, measured by cost per quality-adjusted life year, suggested that insulin degludec may be of lower value compared with insulin glargine. Differences in costs and benefits were mainly driven by hypoglycemic event models based on systematic reviews of RCTs, which often excluded individuals at the highest risk of hypoglycemia, making severe hypoglycemia rare and the event estimates unstable.[25]

Our data provide real-world evidence that switching to Gla-300 from first-generation BI is associated with reduced hypoglycemia-related and DKA-related HCRU. People in the Gla-300 group had lower rates of hypoglycemia and DKA events and shorter hospital stays for these conditions compared with those switched to an alternate first-generation or degludec. A European multicenter prospective study demonstrated that switching the BI to Gla-300 significantly enhanced metabolic control and treatment satisfaction in many people with T2D within 12 months.[26] This switch reduced the risk of symptomatic and nocturnal hypoglycemia without causing weight gain.[26] Insulins with a lower risk of hypoglycemia may lead to better adherence to and persistence with therapy, and potentially, to longer-term glycemic control.[27 28] Although people in the Gla-300 group had fewer hypoglycemia-related and HHS-related events overall, the zero-inflated regression analysis showed that conditional on experiencing an event, the per-episode costs were higher compared with the other groups (1.7 times higher for hypoglycemia than the first-generation

BI, and 2.9 times higher for HHS than the degludec). These findings may reflect greater severity or complexity of cases that did require HCRU among people in the Gla-300 group, or potential differences in how these events were managed (eg, more intensive treatment or inpatient services). These results highlight the importance of interpreting total cost alongside per-event cost, as the overall burden was still lower in the Gla-300 group due to fewer events overall. Further research is warranted to explore the drivers of higher per-episode costs in this subgroup.

Gla-300 and degludec are both long-acting insulins. In this study, HbA1c decreased by 0.57 (from 10.01 to 9.44) at 6 months' follow-up in people of the Gla-300 compared with a 0.54 decrease (from 9.81 to 9.27) in the degludec group. In line with our study, a small retrospective comparative study (degludec: n=171, Gla-300: n=123) indicated that degludec and Gla-300 have a similar impact on HbA1c levels (0.5–0.6 reduction) after switching from other BIs in Japanese patients with T2D.[29] Another retrospective comparative study among insulin-naïve patients found that Gla-300 or degludec led to comparable improvements in glycemic control and hypoglycemia rates.[30] One US RWE study did report that insulin degludec led to a larger reduction in HbA1c and hypoglycemia rates compared with Gla-300 in insulin-naïve adults,[31] but some methodological questions have been raised over these findings.[32] While not adjusting for baseline differences between studies, we note the HbA1c changes reported in this study are broadly consistent with those reported in previous studies (0.6 to 1.8).[29 30 33–35] According to a trial-level meta-analysis, Gla-300 showed similar HbA1c reduction to Gla-100, with a lower risk of hypoglycemia at night and any time of day.[36]

In this study, the rate of hypoglycemia and DKA events was generally lower in the Gla-300 group compared with the degludec group. As these analyses were adjusted for baseline clinical characteristics, this may suggest that people in the Gla-300 group experienced fewer diabetes-related complications than those in the degludec group, and possibly insulin Gla-300 was more effective at reducing complications compared with insulin degludec. The CONCLUDE trial showed that both insulins improved HbA1c similarly, with no significant differences in overall hypoglycemia events.[37] However, nocturnal symptomatic and severe hypoglycemia rates were lower with degludec compared with Gla-300. These results are inconclusive due to the primary endpoint not being met and glucometer reliability issues. In the BRIGHT trial including insulin-naive people with uncontrolled T2D, Gla-300 and IDeg-100 (degludec insulin) provided similar glycemic control improvements, with comparable hypoglycemia incidence and rates.[38] Results from clinical trials may differ from those observed in real-world settings due to controlled environments, strict protocols, strict inclusion/exclusion criteria, predefined outcomes, and shorter follow-up times. Integrating clinical trial data with RWE is essential for a comprehensive understanding of the efficacy and safety of therapeutic interventions.

Research indicates that insulin resistance is closely linked to inflammatory responses, which play a crucial role in the development of conditions like T2D.[39–41] Inflammatory markers such as cytokines and chemokines can interfere with insulin signaling pathways, leading to insulin resistance.[42] By reducing inflammation, BIs can improve insulin sensitivity and enhance glucose uptake by cells.[43] By mitigating inflammation, BIs may help preserve beta-cell function and improve endogenous insulin production. Additionally, they can manage other metabolic disturbances, such as dyslipidemia and atherosclerosis, which are common in T2D and associated with inflammation, leading to better overall metabolic control.[43 44] Understanding and managing inflammation are crucial for optimizing the effectiveness of BI in type 2 diabetes treatment. The findings of this study may be partly related to insulin's impact on inflammation markers; however, more research is needed to fully understand these mechanisms.

Once weekly administered BIs represent a significant innovation in the pharmacological management of T2D. They appear to be at least equally efficient in glycemic management and as safe as once-daily injections for people with T2D.[45 46] Continuous glucose monitoring (CGM) metrics are crucial for managing diabetes, especially when using once-weekly BI analogs.[47] Recent studies have shown that CGM-based metrics such as time in range, time above range, and time below range are comparable between once-weekly insulin and once-daily BI analogues.[48] Further research is required to evaluate the cost-effectiveness of these treatments.

The results of the study should be interpreted considering certain limitations due to its retrospective real-world design. First, only high-cost drug treatments are recorded in HES; therefore, treatment for T2D with non-high-cost drugs in hospitals is not captured. Additionally, ambulance call-out and societal costs are not available in HES, potentially underestimating HCRU and the costs associated with diabetes-related short-term complications. The study's short timescale also limits consideration of long-term effects of insulin treatment at primary and secondary HCRU. Despite these limitations, HES data play a pivotal role in shaping healthcare policies, improving patient care and advancing medical knowledge. Second, because not all general practitioners in CPRD overlap with secondary care settings in HES, the data are limited to CPRD. Additionally, HES is limited to England, which affects the sample size and generalizability of results to other UK nations and countries with similar populations. The findings may not be directly applicable to other healthcare systems with different cost structures, insulin-prescribing patterns or reimbursement policies. However, CPRD-HES studies are considered high standard for secondary data research.[11 12] Third, the IPTW method assumes that all relevant confounders are measured and included in the propensity score model. If important confounders are unmeasured, bias may still occur. To assess the robustness of our findings,

we conducted several diagnostic checks. We evaluated covariate balance using SMDs, all of which were <0.1 after weighting, indicating strong balance. We also examined the distribution of weights and applied weight truncation at the 1st and 99th percentiles to minimize the influence of extreme weights. These analyses showed consistent results, suggesting that our findings are robust to model specification and relatively insensitive to moderate unmeasured confounding. Nevertheless, we acknowledge this limitation and recommend cautious interpretation of the results. Moreover, as an observational study with possible residual confounding, this research cannot establish causality, unlike randomized controlled trials. The shorter follow-up period in the Gla-300 and degludec groups compared with the first-generation BI group may introduce bias and affect conclusions about long-term effectiveness and cost savings. While adjusted analyses mitigate this to some extent, the longer follow-up in the first-generation BI group could inflate HCRU and cost differences. Additionally, the observed changes in clinical outcomes may be due to uncontrolled confounders or may be limited to patients with high event frequency. Fourth, the study used secondary data sources recorded for non-research purposes, with inherent limitations such as data availability (eg, no data on the reason for the switch), potential misclassification, HRG-based HCRU costs, which are average costs of providing a specific type of care, instead of a sum of costs for individual procedures/diagnoses. The validity and completeness of individual patient records cannot be assessed due to the nature of electronic health records. Finally, the study did not evaluate the progression of long-term diabetes complications, which should be a focus of future research.

In conclusion, this study showed that people with T2D in the UK transitioning to Gla-300 had a lower rate of hypoglycemia and DKA events and HCRU than those in first-generation BI, which could result in significant cost savings for NHS, and that within second-generation BI, insulin Gla-300 may offer economic advantages over degludec. However, given the limitations of the study, additional research is necessary to substantiate these results.

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Patient consent for publication Not applicable.

Ethics approval This study is a retrospective observational study. Only de-identified secondary data were used for the study. Approval of the study was obtained from the data governance framework for the Clinical Practice Research Datalink, underpinned by the Research Data Governance process (RDG Protocol Reference ID: 22_001997). The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments.

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