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Treatment persistence in patients with type 2 diabetes treated with glucagon-like peptide-1 receptor agonists in clinical practice in Sweden

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Abstract

Aim: To compare treatment persistence in patients with type 2 diabetes initiating the glucagon-like peptide-1 receptor agonists (GLP-1 RAs) dulaglutide, exenatide once-weekly (QW), liraglutide or lixisenatide in routine clinical practice in Sweden and assess clinical outcomes.

Materials and Methods: We performed a retrospective study using data from several nationwide Swedish health registries, including the National Diabetes Register and other mandatory and population-based registries. Individual level data were collected from 17 361 patients who initiated GLP-1 RA treatment from 23 May 2015 to 15 October 2017, up to 2.5 years postindex (treatment start date). Treatment persistence and modification, predictors of discontinuation, HbA1c and body weight were recorded. Non-persistence was defined as a treatment gap of more than 45 days. Treatment modification included switching and augmentation. Confounding was addressed through the use of propensity scores.

Results: Treatment persistence was higher and treatment modifications were lower in patients initiating dulaglutide compared with those on exenatide QW, liraglutide and lixisenatide. Patients who remained on the same treatment for 1-year postindex experienced greater HbA1c reductions and a steadier decrease in body weight.

Conclusions: Our study suggests that in clinical practice in Sweden there is a greater persistence of treatment among patients initiating dulaglutide compared with those on exenatide QW, liraglutide and lixisenatide. Persistence with the index GLP-1 RA was closely correlated with positive clinical outcomes and thus should be considered a critical factor of patient-centric treatment in Sweden.

KEYWORDS
antidiabetic drug, GLP-1 analogue, population study, type 2 diabetes

1 | INTRODUCTION

Current guidelines from the American Diabetes Association and European Association for the Study of Diabetes recommend metformin as a first-line monotherapy along with comprehensive lifestyle management for the treatment of type 2 diabetes (T2D). If HbA1c levels remain above the desired target, injectables can be added to the treatment plan as a second-line treatment option. In general, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are recommended as the first injectable medication ahead of insulin. They

can be used in combination with many oral glucose-lowering medications and basal insulin but not dipeptidyl peptidase-4 inhibitors because of overlapping mechanisms of action.[1,2] GLP-1 RAs are an attractive therapy option as they control glycaemia with a low risk of hypoglycaemia, promote proper β-cell function in the pancreas via the incretin system, facilitate weight loss, and significantly reduce the risk of major cardiovascular complications independent of weight loss.[3–5] Combination treatment with a GLP-1 RA and basal insulin has yielded positive clinical outcomes in patients with diabetes.[6]

Poor persistence (continuation of the index treatment) to treatment of T2D can lead to reduced glycaemic control, increased healthcare resource utilization, increased risk of complications and greater cost.[7–11] 11 A meta-analysis of six separate studies estimated the mean persistence as 56% with oral treatments in patients with T2D, over a period of 6 months to 2 years.[12] Real-world evidence studies on injectable treatments, including glargine and the first GLP-1 RAs, show low levels of persistence with index treatments.[13–15] It is therefore important to consider the facilitation of medication persistence and factors that might influence it, with the aim of improving clinical patient outcomes.

The prevalence of diabetes in Swedish adults is projected to rise from 6.8% in 2013 to 10.4% by 2050.[16] As 85%-90% of patients have T2D,[16] this disease is a growing health concern in Sweden. Several GLP-1 RAs are available on the market in Sweden. Exenatide twice-daily (BID) was first-in-class and available in Sweden from 2007, followed by liraglutide (2010), exenatide once-weekly (QW) (2012), lixisenatide (2015), dulaglutide (2015) and, most recently, semaglutide (2018). Real-world studies on the persistence of GLP-1 RAs have been conducted in the United States, Canada and several European countries, including Sweden.[14,15,17–20] Our study is the first comparative (as opposed to descriptive) analysis of the persistence within the GLP-1 RA class using comprehensive statistical methods to account for substantial potential bias, and the first to include data on persistence with lixisenatide and dulaglutide, in Sweden. The objective of the current study was to compare the treatment persistence of patients initiated on dulaglutide, liraglutide, exenatide or lixisenatide in routine clinical practice in Sweden and identify predictors and outcomes of discontinuation. It was not feasible for semaglutide to be included as it was not available on the market during the study period. To this end, we performed a retrospective study using information collected from several Swedish health registries at an individual patient level, including the National Diabetes Register (NDR), which has a coverage of 90% of patients with diabetes, and other mandatory and population-based registries. We present data on treatment patterns surrounding discontinuation, switching and augmentation, in addition to treatment outcomes of HbA1c and body weight.

2 | MATERIALS AND METHODS

2.1 | Data source

We used data from national health and administrative registers in Sweden. In this retrospective study, data from adult patients with T2D were collected from the NDR, and demographic, prescription and health registries maintained by the Swedish government, including The Prescribed Drug Register, The Patient Registry, The Registry for Cause-Specific Mortality, and The Longitudinal Integration Database for Health Insurance and Labor Market Studies. Except for the NDR, all databases are mandatory governmental registries with coverage of the total population of the nation. All are administered by the National Board of Health and Welfare except for The Longitudinal Integration Database for Health Insurance and Labor Market Studies, which is administered by Statistics Sweden. The availability of individual patient level data allowed for combination of the various sources. Linkage was performed by the National Board of Health and Welfare, and after linkage, the data were anonymized and provided to us for analysis. Outcomes data came from The Prescribed Drug Register (persistence and treatment patterns) and the NDR (HbA1c and body weight). All the registries contributed to baseline information essential for describing and matching cohorts before comparative analyses. The study was approved by the Swedish Ethical Review Authority.

2.2 | Study design

The intake period of the study was from 23 May 2015 to 31 December 2017. The index date specified the date of initiation of GLP-1 RA treatment for the first time. Baseline characteristics were collected from 3 months up to 10 years preindex (see section [2.4] on Outcome measures for more details). Postindex data were collected for a minimum of 75 days. To allow for this 75-day period, patients initiating GLP-1 RA treatment after 15 October 2017 could not be included.

2.3 | Patient population

The study population included adult patients with T2D initiating any GLP-1 RA for the treatment of T2D for the first time, at a time when exenatide, liraglutide, lixisenatide and dulaglutide were available on the market. Inclusion criteria included the following: initiating treatment with dulaglutide, liraglutide, exenatide BID, exenatide QW or lixisenatide from 23 May 2015 to 15 October 2017; being aged 18 years or older on the index date; and a diagnosis of T2D according to registration in the NDR. Exclusion criteria included the following: initiating treatment with a GLP-1 RA prior to the index treatment; initiating treatment with liraglutide for obesity as an index treatment; and less than 75 days follow-up postindex.

2.4 | Outcome measures

Over 50 baseline characteristics across clinical measures, prior treatment, cardiovascular health, co-morbidities/complications/treatments, lifestyle and socioeconomic status were collected up to 10 years preindex. Previous events and diagnoses were noted during the full preindex period. Other baseline characteristics were recorded within the

12 months preindex. For HbA1c and body weight, baseline values were restricted to within 3 and 6 months prior to index, respectively.

Patients were considered persistent on the index medication until the first gap of 45 days or more between the end of days' supply of one claim and the date of the next claim for the same medication, in line with a previous method.[18] In cases of overlapping claims suggestive of early refills, days' supply of the next claim was appended to previous claims. Persistence (days to discontinuation or switching) was measured in days as the length of days' supply from the index date to the end of days' supply of the last claim before the 45-day gap. Persistence was censored at the last day of follow-up. The sensitivity of the 45-day gap was assessed against a 60-day gap. Only patients with at least 75 days of follow-up after initiation were included in the study. This was to allow for the possibility of a treatment discontinuation based on the minimum possible days covered by the first dispensing (28-30 days) plus the 45-day treatment gap.

Discontinuation was defined as a treatment gap of the index medication without the start of a new glucose-lowering medication within the defined gap. Switch was defined as a treatment gap of the index medication with a start of a new glucose-lowering medication within the defined gap. Augmentation was defined as a start of a new glucose-lowering medication before or on the date of the last dispensing of the index medication. Modification included discontinuation, switching and/or augmentation.

Monthly average daily dose of the index therapy was assessed for all patients at the patient level while persistent. Daily dose was calculated by dividing the total amount of drug prescribed by the number of days between two consecutive prescriptions. Average daily dose was reported by monthly intervals from date of initiation.

HbA1c and body weight measurements taken 61-135 days postindex date were categorized as an outcome at 3 months, and those taken 136-225 days postindex date were categorized as 6 months. Postbaseline HbA1c values (mmol/mol) and body weight (kg) were reported as mean change from baseline.

2.5 | Statistical methods

2.5.1 | Determination of sample size

The sample size was imposed by the capacity of the NDR database. We checked that the available data would allow us to detect meaningful differences between GLP-1 RAs in terms of persistence. Detecting a 10% difference in rate of persistence (hazard ratio = 0.9) between dulaglutide and liraglutide, for example, with 90% power at a two-sided type 1 error rate of 0.05 required ~4700 events (lack of persistence). Given that ~13 000 patients initiated liraglutide and ~5000 initiated dulaglutide from May 2015 to November 2017, were followed up for ~15 months on average, and assuming an event rate of 50% at 15 months, we expected to reach ~80% power to detect a 2% difference between dulaglutide and liraglutide. The minimally detectable differences with dulaglutide were not as small as for liraglutide but remained above 15% for lixisenatide and exenatide QW (1200 and 1000 patients, respectively).

2.5.2 | Adjustments for bias and confounding

Where applicable, the effect of confounding factors was addressed through the use of propensity scores estimated using gradient boosting for a multinomial-dependent variable.[21–23] All relevant baseline information was used to calculate propensity scores. The propensity scores were used to create weights (inverse probability of treatment weight [IPTW]) that allow estimation of the average treatment effect.[24] The performance of the adjustment process was assessed using the standardized mean differences (SMDs) of baseline variables where a sufficient value was defined as 0.1. SMD was defined using the tableone package in R.[25] Propensity adjustment and IPTW generation were performed with more than 50 variables captured in the NDR across clinical measures, prior treatment, cardiovascular health, co-morbidities/complications/treatments, lifestyle and socioeconomic status, all found to be related to diabetes severity and outcome of diabetes treatment in our previous research.[26,27] The model used was a gradient boosting/tree-based machine learning method that automatically selects the most important variables to split on in each step and disregards the variables it deems irrelevant. Thus, we did not impose any model restrictions or preselect variables for inclusion.

2.5.3 | Missing data

Summary statistics are presented based on observed values only. The estimation of propensity scores were based on data imputed using multiple chained equations[28] where at least five imputed datasets were created. The performance of the imputation process was evaluated by checking convergence and by plotting distribution of the observed and imputed observations for each variable.

2.5.4 | Significance levels and multiplicity

Comparative analyses were performed at an alpha level of .05. No adjustments were made for multiplicity.

2.5.5 | Statistical analyses of baseline characteristics and outcomes

Baseline characteristics were compared between treatment groups using F-tests for continuous variables and Chi-square tests for categorical variables.

Treatment persistence was evaluated using a time-to-event approach where the event time is defined as the time from treatment initiation to treatment switch or treatment discontinuation. The time-to-event may be censored because of death, or at the end of follow-up. The time to treatment switch or discontinuation was described for each treatment group using the Kaplan–Meier method and compared between treatment groups using an IPTW Cox regression with treatment as the only covariate. The analysis was based on robust standard

TABLE 1 Key patient baseline characteristics

Characteristic	Exenatide QW	Liraglutide	Lixisenatide	Dulaglutide	SMD	*P*
Patient number, n	713	12 461	797	3390	—	
Age, years (SD)	60.4 (12.0)	60.6 (11.6)	61.1 (11.4)	61.2 (11.6)	0.039	.073
Female, n (%)	318 (44.6)	5230 (42.0)	309 (38.8)	1350 (39.8)	0.066	.016
Diabetes duration, years (SD)	9.9 (7.3)	10.7 (7.7)	11.9 (7.7)	10.3 (7.4)	0.146	<.001
HbA1c, mmol/mol (SD)	72.8 (17.2)	71.0 (16.2)	71.8 (15.3)	70.2 (16.0)	0.088	.003
BMI, kg/m^2 (SD)	33.8 (6.1)	34.4 (5.8)	33.6 (5.5)	33.4 (6.0)	0.090	<.001
eGFR, mL/min (SD)	89.8 (28.1)	87.2 (28.0)	89.1 (27.9)	87.8 (27.3)	0.055	.057
AMI, n (%)	59 (8.3)	1112 (8.9)	66 (8.3)	261 (7.7)	0.022	.149
Stroke, n (%)	36 (5.0)	597 (4.8)	43 (5.4)	172 (5.1)	0.014	.805
Heart failure, n (%)	40 (5.6)	802 (6.4)	49 (6.1)	179 (5.3)	0.028	.088
Prior insulin treatment, n (%)						
Any insulin	272 (38.1)	6751 (54.2)	565 (70.9)	1391 (41.0)	0.388	<.001
Basal insulin	216 (30.3)	5488 (44.0)	494 (62.0)	1075 (31.7)	0.374	<.001
Mealtime insulin	100 (14.0)	2470 (19.8)	241 (30.2)	504 (14.9)	0.221	<.001
Mix insulin	75 (10.5)	1630 (13.1)	115 (14.4)	407 (12.0)	0.065	.046
Prior other treatment, n (%)						
Metformin	569 (79.8)	9720 (78.0)	627 (78.7)	2632 (77.6)	0.029	.614
Sulphonylurea	177 (24.8)	2578 (20.7)	167 (21.0)	747 (22.0)	0.054	.030
Metglitides	33 (4.6)	458 (3.7)	41 (5.1)	159 (4.7)	0.036	.011
TZD	6 (0.8)	121 (1.0)	12 (1.5)	71 (2.1)	0.061	<.001
DPP-4 inhibitors	220 (30.9)	3089 (24.8)	196 (24.6)	1018 (30.0)	0.090	<.001
AGI inhibitors	1 (0.1)	54 (0.4)	5 (0.6)	14 (0.4)	0.041	.539
SGLT2 inhibitors	92 (12.9)	919 (7.4)	78 (9.8)	499 (14.7)	0.135	<.001

Abbreviations: AGI, alpha-glucosidase inhibitor; AMI, acute myocardial infarction; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; n, number of patients; QW, once weekly; SD, standard deviation; SGLT2, sodium-glucose co-transporter-2; SMD, standardized mean difference; TZD, thiazolidinedione.
Unweighted key baseline characteristics (please see Table S3 for data on additional baseline characteristics).

errors taking the weights into account. As a sensitivity analysis, a stratified log-rank test was used to formally compare GLP-1 RAs where the propensity score (categorized in five equally sized ordered categories) served as the stratification variable.

The change from baseline for continuous variables such as body weight and HbA1c were summarized using standard descriptive measures and, where relevant, were compared between treatment options using IPTW ANCOVA models where the baseline observation was included as a covariate.

Predictors of discontinuation were evaluated using gradient boosting with a proportional hazards loss function fitted to an imputed dataset. The shrinkage factor was set to 0.01 and the optimal number of trees (568) was determined using 10-fold cross validation.

3 | RESULTS

3.1 | Patient sample

The patient selection process according to the inclusion and exclusion criteria presented 17 384 eligible patients. Patients on exenatide BID were excluded from further analysis at this point because of a low number of patients (n = 23; 0.1%), resulting in a final patient number of 17 361 (Figure S4).

3.2 | Baseline characteristics

The numbers of patients included in the study were 713, 12 461, 797 and 3390 for exenatide QW, liraglutide, lixisenatide and dulaglutide, respectively. Baseline characteristics of patients who initiated exenatide QW, liraglutide, lixisenatide or dulaglutide are shown in Tables 1 and S3. All four groups were similar in age, sex, diabetes duration, HbA1c, body mass index, estimated glomerular filtration rate (eGFR), acute myocardial infarction, stroke, heart failure, prior treatment other than insulin, cardiovascular health, clinical measures, co-morbidities/complications/treatments and lifestyle/socioeconomic status (Tables 1 and S3). The greatest differences between groups were observed for prior insulin treatment, specifically any insulin, basal insulin and mealtime insulin but not premixed insulin (Table 1). A higher proportion of patients prescribed liraglutide and lixisenatide had previously been treated with basal and/or mealtime insulin at baseline (Table 1).

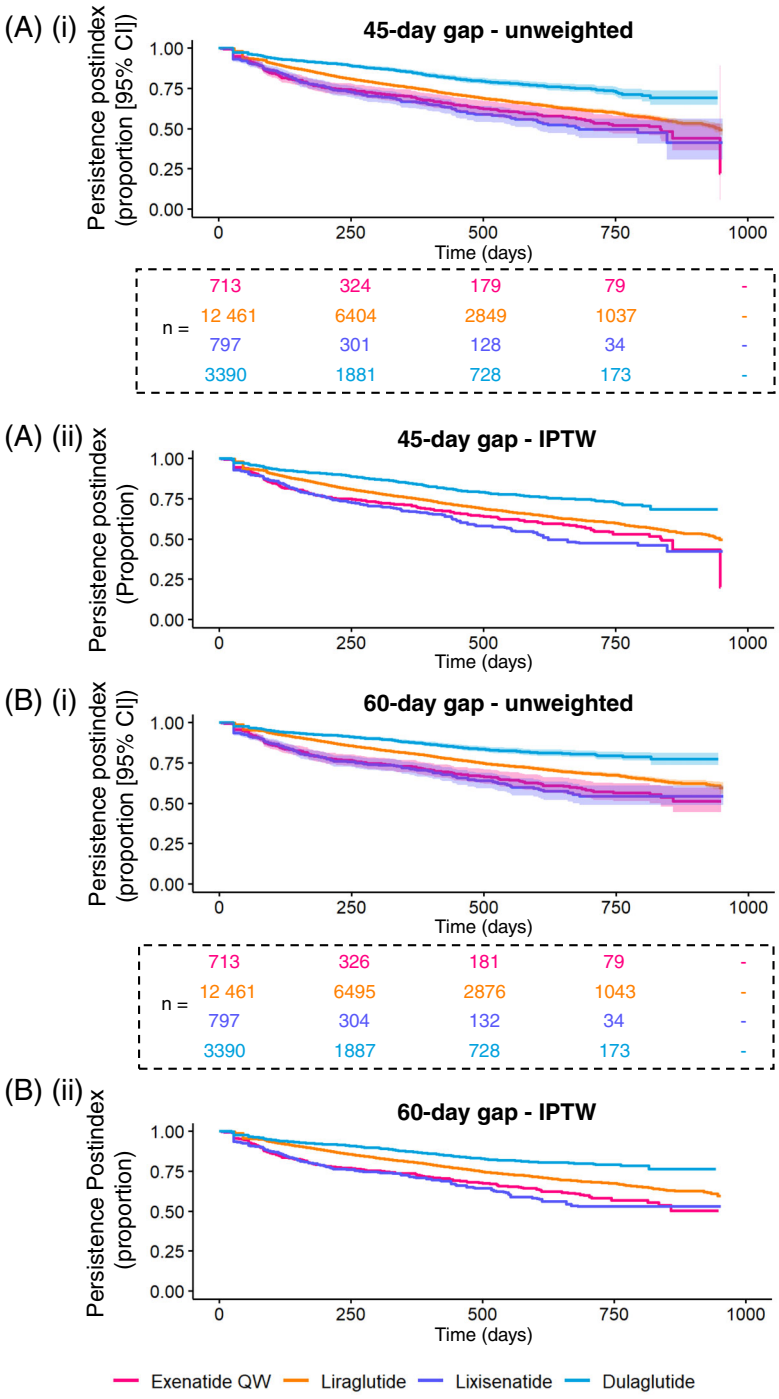

FIGURE 1 Proportion of persistent patients on exenatide QW, liraglutide, lixisenatide or dulaglutide during the 2.5 years postindex. The proportions of persistent patients are shown using A, 45-day and B, 60-day (sensitivity) gaps, for A(i) and B(i) unweighted, and A(ii) and B(ii) following inverse probability of treatment weight (IPTW); 95% confidence intervals are shown by shaded areas. The number of patients (n) for each time point per treatment group is shown

Weighting with IPTW with more than 50 variables did not alter the results in a significant way and resulted in SMD values of all variables to within close to 10% of each other (data not shown).

3.3 | Monthly average daily dose

The monthly average daily dose for exenatide QW, liraglutide, lixisenatide and dulaglutide consumed by patients between two consecutive prescriptions is shown in Figure S5. It should be noted that exenatide QW and dulaglutide are approved for once-weekly dosing, whereas liraglutide and lixisenatide are dosed once-daily.[1] The range of values for average daily dose for each drug was generally within the range of clinical dosing[1] (Figure S5; dotted lines) with a steady increase in average daily dose observed for liraglutide as patients remained persistent.

3.4 | Treatment persistence

Figure 1 shows the proportion of persistent patients across groups in the 2.5 years postindex, for both 45- and 60-day (sensitivity) gap analyses, before and with IPTW. These data show that persistence during

TABLE 2 Treatment persistence with exenatide QW, liraglutide, lixisenatide and dulaglutide

		Exenatide QW	Liraglutide	Lixisenatide	Dulaglutide
45-day gap	Proportion persistent at 1 year, % (95% CI)	69.4 (65.5-73.4)	75.5 (74.7-76.4)	66.6 (62.6-70.9)	85.0 (83.6-86.4)
	Time to 75% persistence, median days (95% CI)	213 (169-324)	375 (355-395)	211 (170-273)	704 (588-757)
	Time to 50% persistence, median days (95% CI)	835 (703-NA)	947 (927-NA)	681 (602-NA)	Not calculable[a]
	Hazard ratio for treatment discontinuation vs. dulaglutide (95% CI)	2.2 (1.9-2.6)	1.7 (1.5-1.8)	2.5 (2.1-2.9)	1.0
	Hazard ratio for treatment discontinuation vs. dulaglutide (95% CI) - IPTW	2.1 (1.8-2.5)	1.6 (1.5-1.8)	2.4 (2.0-2.9)	1.0
60-day gap	Proportion persistent at 1 year, % (95% CI)	72.6 (68.9-76.6)	80.9 (80.0-81.7)	71.2 (67.3-75.2)	87.7 (86.3-89.0)
	Time to 75% persistence, median days (95% CI)	278 (198-389)	497 (473-524)	266 (201-370)	Not calculable[a]
	Time to 50% persistence, median days (95% CI)	Not calculable[a]	Not calculable[a]	Not calculable[a]	Not calculable[a]
	Hazard ratio for treatment discontinuation vs. dulaglutide (95% CI)	2.5 (2.1-3.0)	1.6 (1.5-1.8)	2.8 (2.3-3.3)	1.0
	Hazard ratio for treatment discontinuation vs. dulaglutide (95% CI) - IPTW	2.4 (2.0-2.8)	1.6 (1.4-1.8)	2.6 (2.2-3.2)	1.0

Abbreviations: CI, confidence intervals; IPTW, inverse probability of treatment weight; NA, not applicable; QW, once weekly.
Unweighted analysis except for those highlighted in grey.
[a]Not calculable as the proportion of persistent patients remained above 50%/75% in the first year postindex.

this 2.5-year period was highest among patients on dulaglutide, followed by patients on liraglutide, exenatide QW and lixisenatide (Figure 1). As shown, IPTW did not alter the results in a significant way. The first year postindex had the highest patient numbers, with less patient numbers contributing to the time points thereafter (Figure 1).

Following a 45-day gap analysis, the proportion of persistent patients at 1-year postindex was highest for dulaglutide (85.0%), followed by liraglutide (75.5%), exenatide QW (69.4%) and lixisenatide (66.6%) (Table 2). The median number of days for groups to reach 75% and 50% persistence is shown in Table 2. Dulaglutide had the highest number of days for 75% persistence (704), followed by liraglutide (375). All groups except for dulaglutide had a 50% persistence value (Table 2), as the proportion of persistent patients remained above 50% for the full period of observation postindex for dulaglutide (Figure 1). Patients on exenatide QW, liraglutide and lixisenatide were 2.2, 1.7 and 2.5 times more probable to discontinue treatment than patients on dulaglutide, as shown by the hazard ratios (Table 2). IPTW analysis of the hazard ratio revealed a similar finding (Table 2). A 60-day gap sensitivity analysis did not impact the results more than minimally, including the relative results between drugs, compared with the 45-day gap analysis (Table 2).

In the 2.5 years postindex, the highest proportion of switching took place in the exenatide QW group, followed closely by lixisenatide, and with a similarly low proportion of switchers in the liraglutide and dulaglutide groups (Figure S6A). Augmentation of treatment occurred in more than 50% of patients across all groups (Figure S6B). Overall, dulaglutide had the lowest number and lixisenatide the highest number of patients with treatment modifications in the 2.5 years postindex (Figure S7). The proportion of patients who had modified their treatment at 1-year postindex was highest for lixisenatide (63.6%), followed by exenatide QW (55.5%), liraglutide (44.4%) and dulaglutide (39.2%) (Table S4). Patients on exenatide QW, liraglutide and lixisenatide were 1.6, 1.1 and 1.9 times more probable to modify their treatment than patients on dulaglutide, respectively, as shown by the hazard ratios (Table S4). IPTW analysis of the hazard ratio revealed a similar finding (Table S4). Proportions of patients at 1-year postindex and hazard ratios for switching and augmentation are also shown in Table S4.

3.5 | HbA1c levels

Mean change from baseline in HbA1c levels following IPTW at 3, 6, 9 and 12 months postindex are shown in Figure 2. For patients across all groups, HbA1c levels decreased from baseline following treatment but remained above a 10 mmol/mol change from baseline at 12 months (Figure 2A). For patients who remained on the same index treatment throughout the first year, greater HbA1c reductions occurred and lowered to more than a 10 mmol/mol change from baseline by 12 months (Figure 2B).

3.6 | Body weight

Mean change from baseline in body weight following IPTW at 3, 6, 9 and 12 months postindex date are shown in Figure 3. For patients across all groups, their body weight decreased from baseline following treatment and remained lower than baseline but fluctuated during the

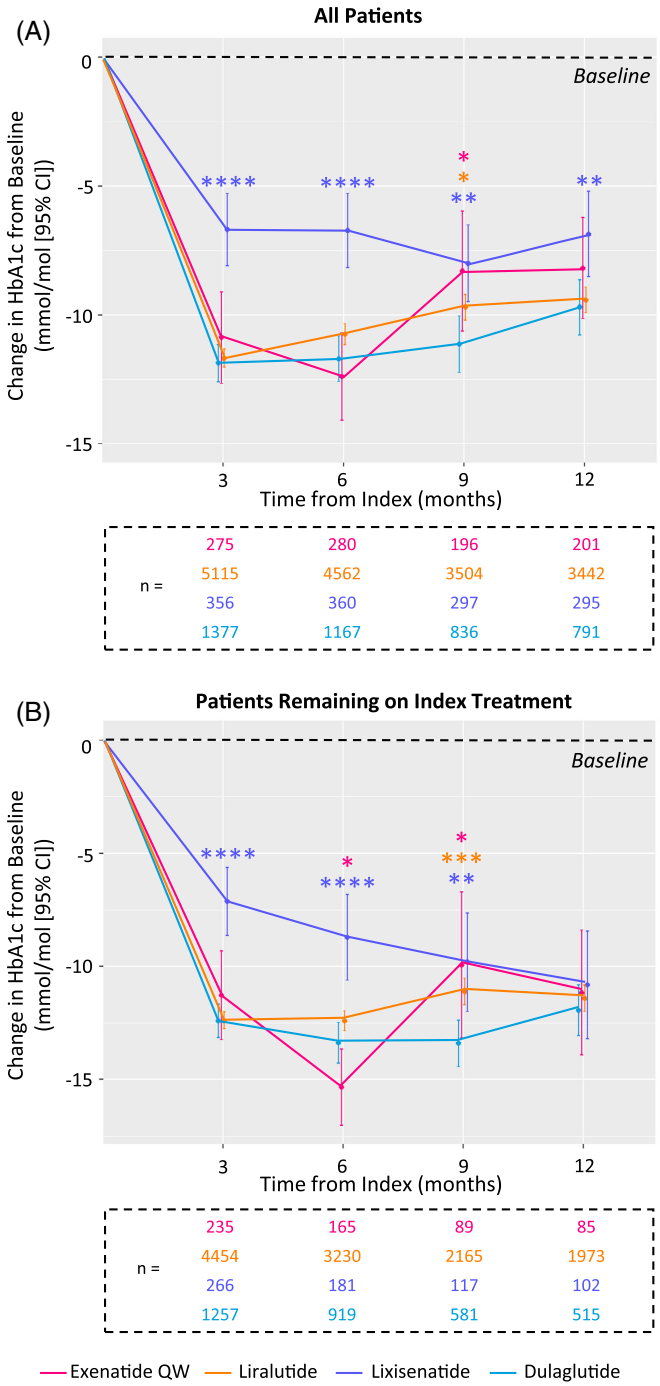

FIGURE 2 Change from baseline in HbA1c levels of patients on exenatide QW, liraglutide, lixisenatide or dulaglutide, at 3, 6, 9 and 12 months postindex. Least squares estimates (95% confidence intervals [CI]) of HbA1c levels following inverse probability of treatment weight (IPTW) are shown for either A, all patients or B, patients who remained on the index treatment in those 12 months. Each time point was analysed separately and included all patients with data for that time point. The number of patients (n) for each time point per treatment group is shown. *P < .05, **P < .01, ***P < .001 and ****P < .0001 for dulaglutide compared with other treatment groups at each time point

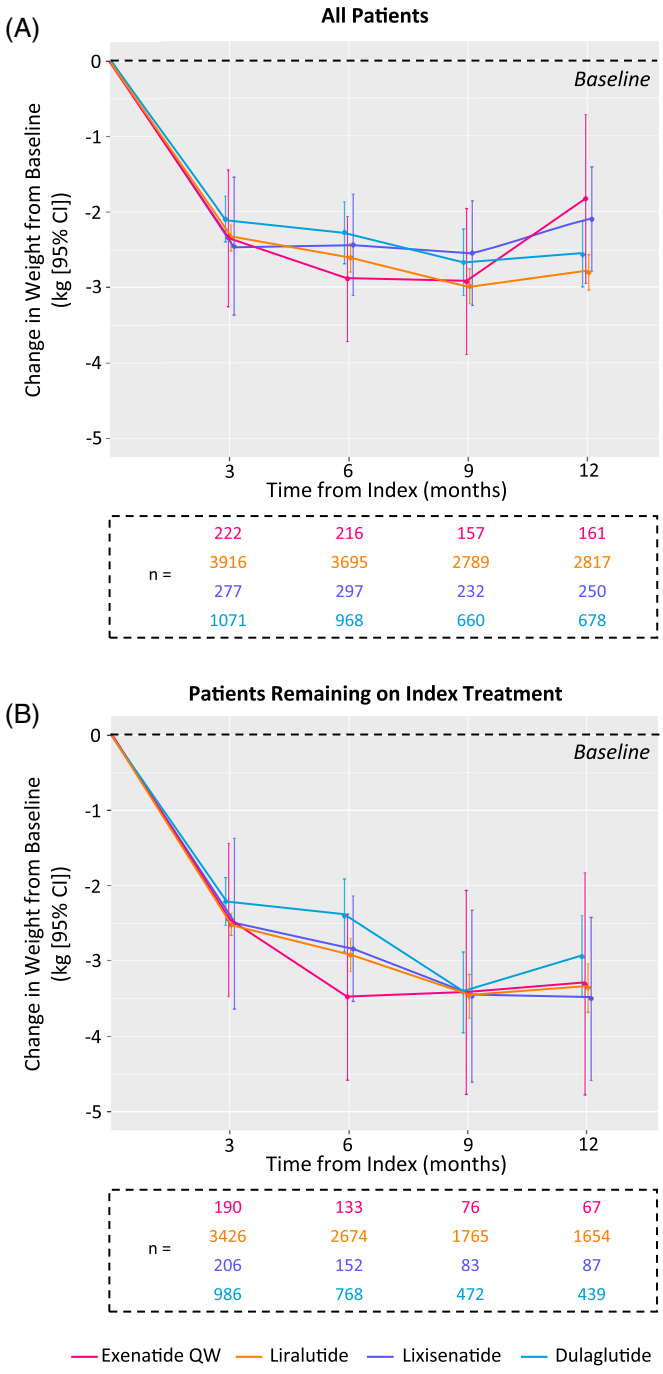

FIGURE 3 Change from baseline in body weight of patients on exenatide QW, liraglutide, lixisenatide or dulaglutide, at 3, 6, 9 and 12 months postindex. Least squares estimates (95% confidence intervals [CI]) of body weight following inverse probability of treatment weight (IPTW) are shown for either A, all patients or B, patients who remained on the index treatment in those 12 months. Each time point was analysed separately and included all patients with data for that time point. The number of patients (n) for each time point per treatment group is shown

12 months (Figure 3A). For patients who remained on the same index treatment throughout the first year, their body weight decreased more steadily in those 12 months (Figure 3B).

3.7 | Predictors of discontinuation

We assessed more than 50 patient characteristics for predictors of discontinuation. This analysis highlighted that the GLP-1 RA used

(exenatide QW, liraglutide, lixisenatide or dulaglutide) was the main influencer in this model, closely followed by the country of birth of the patient. The next top influencers were HbA1c and age, which had relative influences approximately half those of GLP-1 RA used and country of birth. These were followed by eGFR and income, which had relative influences of approximately one third those of GLP-1 RA used and country of birth (data not shown).

4 | DISCUSSION

In this study, using nationwide registers, we present data on the persistence of GLP-1 RAs within the Swedish population with T2D. This is the first comparative (as opposed to descriptive) analysis of the persistence within the GLP-1 RA class, comprehensively controlling for bias, and the first to include data on persistence with lixisenatide and dulaglutide, in Sweden. Baseline characteristics were similar between patients on exenatide QW, liraglutide, lixisenatide or dulaglutide, except for treatment with any insulin, basal insulin and mealtime insulin. A higher proportion of patients prescribed liraglutide and lixisenatide had previously been treated with basal and/or mealtime insulin at baseline compared with exenatide QW and dulaglutide. This could be explained by differences in indications and/or reimbursement criteria during the study period. Our findings show the greatest level of persistence with those patients who initiated dulaglutide as their first GLP-1 RA treatment compared with exenatide QW, liraglutide and lixisenatide over a 2.5-year period. In addition, the proportion of patients who modified their treatment was lowest for dulaglutide. Importantly, patients who remained on the index treatment showed greater decreases in HbA1c levels and, to a lesser extent, body weight, after 1 year of treatment. The greatest predictor of persistence for patients on exenatide QW, liraglutide, lixisenatide or dulaglutide was the specific type of GLP-1 RA used.

Persistence of treatment is a critical determinant of clinical outcomes and thus an integral factor in patient-centric treatment for T2D.[7–11,29–31] In line with our results on persistence in Sweden, greater treatment persistence has also been shown for dulaglutide compared with exenatide QW, exenatide BID, liraglutide and lixisenatide in real-world studies from other European countries as well as from the United States and Canada.[17–19] The relative difference between GLP-1 RAs was similar but the absolute persistence at 1-year postindex was higher in our study than in other real-world analyses.[15,17,18,20] We do not have a clear explanation for this, but propose that differences in healthcare systems, data collection (e.g. claims databases vs. registries) and varying time periods could be contributing factors, all of which make comparisons of absolute persistence between studies difficult. Varying time periods in particular will have influenced the availability of treatments, and thus the number of patients taking them if they were comparatively new to the market, along with experience in use and prescription among patients and physicians, respectively. It is also worth noting that the percentage range of patients persistent on the index GLP-1 RA treatment 1-year postindex in real-world settings varies significantly between countries, as evidenced by previous reports (exenatide QW: 25%-51%; liraglutide: 22%-61%; lixisenatide: 4.2%-50%; dulaglutide: 37%-67%).[15,17,18,20] It is thus not surprising perhaps that the data from our study expand this documented broad range further. We found a higher absolute persistence in Swedish patients compared with a previous real-world study.[15] The difference in persistence at 1-year postindex between this previous study (31%-59%) and the current study (66.6%-85.0%) could be explained by the GLP-1 RAs included in the studies. In the previous study dulaglutide was not on the market and thus not evaluated,[15] but it accounted for the greatest persistence in the current study (85.0%). The lowest level of persistence reported in the previous study was with exenatide BID, which was not included in the current analysis because of the low number of patients in this group. Greater treatment persistence in patients taking dulaglutide, compared with exenatide QW, liraglutide and lixisenatide, could be attributed at least in part to its once-weekly dosing regimen[32] and ease of use.[32] The percentage of patients who had modified their treatment at 1-year postindex was generally lower compared with previous real-world studies in Canada and Europe, including Sweden.[15,17] However, similar to treatment persistence, it is worth noting that the percentage range of patients who underwent treatment modifications at 1-year postindex in real-world settings varied significantly between countries.[15,17]

4.1 | Strengths and limitations

Propensity adjustment and IPTW generation with more than 50 variables across several group of covariates such as clinical measures, prior treatment, cardiovascular health, co-morbidities/complications/treatments, lifestyle and socioeconomic status allowed for elimination of both potential bias owing to differences between patients starting different GLP-1 RAs and confounding in our results. However, while the propensity adjustment used in the analysis accounts for bias in measured confounders, the potential for bias from unmeasured confounders remains possible. The potential for patients to switch to GLP1-RA/insulin mixes has not been accounted for in the analyses. Our analyses on HbA1c and weight are limited to within 1-year postindex. This is because of decreasing patient numbers with each consecutive time point, from which we reasoned that data beyond 1 year would not contribute to any well-founded understanding. Low patient numbers beyond 1 year were largely attributable to the design of the study, with a long index period and set end date, and partly attributable to the basic recommendation of the NDR to report at least one HbA1c measurement per patient per year. Treatment adherence was not assessed in our study but probably closely mimics persistence results considering the comparatively short treatment gap we employed.

In conclusion, this retrospective study of nationwide data from Swedish health registries suggests that in clinical practice, more patients starting dulaglutide remained on treatment over 2.5 years compared with patients starting exenatide QW, liraglutide or lixisenatide. Our findings suggest that patients' persistence with GLP-1 RA treatment has positive clinical outcomes for patients; thus,

it is a factor worth considering and closely monitoring as part of patient-centric treatment in Sweden. This information will be of importance for decision-making among payers, policymakers and healthcare practitioners. The treatment of diabetes is a long-time effort and requires collaboration between healthcare professionals and people with diabetes. Using treatments shown to have long treatment persistence would probably help to achieve treatment goals.

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CONFLICT OF INTEREST

AMS, MM and SF have no competing interests to declare. AT is an employee and stockholder of Eli Lilly and Company. JL is a consultant for HaaPACS GmbH, Schriesheim, Germany. BE reports personal fees (expert panels, lectures) from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Merck Sharp & Dohme, Mundipharma, Navamedic, NovoNordisk and RLS Global, as well as grants and personal fees from Sanofi, all outside the submitted work.

AUTHORS CONTRIBUTIONS

All the authors contributed to conception and/or study design. AMS and MM contributed to acquisition of the data. AT, JL, SF and BE contributed to analysis of the data. All the authors contributed to drafting and/or critical revision of the manuscript for important intellectual content. All the authors have given final approval of the version to be published and agreed to be accountable for all aspects of the work.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

As social security numbers were required/used in the study, the appropriate approvals were granted from the Swedish Ethical Review Authority and health registries. Linkage was performed by the Swedish Board of Health and, after linkage, the data were anonymized and provided to us for analyses.

DATA SHARING

The data that we have acquired from a combination of registers cannot be shared, but they are accessible, after relevant permissions from an ethics board and application to the registers in question.

DATA AVAILABILITY STATEMENT

The data that we have acquired from a combination of registers cannot be shared, but they are accessible, after relevant permissions from an ethics board and application to the registers in question.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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