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Patient Reported Outcomes following initiation of Glucagon-like peptide-1 Receptor agonists in patients with type 2 Diabetes in a specialist endocrinology practice of the LMC diabetes registry: The PROGRESS-Diabetes study

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ABSTRACT

Aims: To compare patient-reported outcomes and clinical outcomes in patients who initiated dulaglutide or liraglutide as part of usual clinical therapy.

Methods: This observational study enrolled adults with type 2 diabetes who initiated dulaglutide or liraglutide between April 2017 and January 2018. A prospective patient cohort completed questionnaires at baseline and at their usual follow-up visit three to six months later. Clinical outcomes were assessed in a post-hoc retrospective analysis using propensity score matching.

Results: In the per-protocol analysis, 146 dulaglutide and 79 liraglutide patients had similar significant improvements in diabetes treatment satisfaction scores (dulaglutide 9.6 ± 1.1, $p < 0.001$; liraglutide 10.6 ± 1.4, $p < 0.001$) and follow-up scores for diabetes device satisfaction. Only dulaglutide had significant improvements in medication adherence scores. In the overall cohort, 754 matched patients showed similar reductions in A1C (dulaglutide −0.8% [9 mmol/mol]; liraglutide −0.7% [8 mmol/mol]). Liraglutide patients had a greater reduction in weight than those initiating dulaglutide (−2.8 kg vs. −1.8 kg; $p < 0.001$).

Conclusions: Patients who initiated dulaglutide or liraglutide in a real-world specialist practice had similar improvements in diabetes medication satisfaction and diabetes device satisfaction. Only dulaglutide patients had significant improvements in medication adherence scores. Both treatment cohorts had similar patterns of A1C change, and liraglutide had significantly greater weight loss, which are similar to findings from clinical trials.

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1. Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) are injectable, non-insulin therapies for patients with T2D that improve glycemic control through several mechanisms, including stimulating glucose-dependent insulin release, slowing gastric emptying, inhibiting post-meal glucagon release and reducing appetite [1]. In addition to having proven glucose-lowering efficacy, GLP-1 RA therapies promote weight loss and are associated with a low risk for hypoglycemia, thus making them an attractive treatment option for patients with T2D [2]. GLP-1 RA therapy is recommended as a treatment option after metformin in patients with established cardiovascular disease (CVD), or for patients prioritizing weight loss or low risk of hypoglycemia. In addition, GLP-1 RA therapy is recommended prior to initiating insulin if patients are intensifying to injectable therapies [3].

Daily and weekly dosing options are available within the GLP-1 RA drug class. Dulaglutide, semaglutide and exenatide QW are administered once-weekly, liraglutide and lixisenatide are administered once-daily, and exenatide is also available for twice-daily dosing. In RCT's comparing GLP-1 RA's head-to-head, varying results within the class have been seen in A1C and weight reduction, as well as in gastrointestinal adverse effects [1,3,4].

Patient-reported outcomes (PROs), reported by participants through self-reported questionnaires, can add to RCT findings by offering a unique patient perspective on the effectiveness of a therapy. Several clinical trials of GLP-1 RA on clinical outcomes have also evaluated PRO's. In the first head-to-head trial between GLP-1 RA, comparing once-daily liraglutide to twice-daily exenatide (LEAD 6), the liraglutide group reported significantly greater overall treatment satisfaction, and a greater reduction in perceived hypoglycemia and hyperglycemia, compared to the exenatide group [5]. In the AWARD-6 trial, both dulaglutide and liraglutide had significant improvements on impact of weight on self-perception scores and the European Quality of Life Scale, with no differences between groups [6]. In the more recent SUSTAIN-7 trial, semaglutide and dulaglutide patients had similar improvements in self-reported health status and diabetes treatment satisfaction [7].

Although RCT's are the gold standard for determining efficacy and safety of therapeutic agents, their results may not be fully generalizable to real-world clinical practice due to their strict and limited patient inclusion criteria, as well as a bias favouring the enrollment of participants with better overall adherence. This selection bias in RCTs may be especially relevant to PRO comparisons. Evidence from studies using observational clinical data is increasingly valued and can be used to complement data from RCT's, thus enabling clinicians to make well-informed treatment decisions for their patients [8].

To better understand the influence of once-weekly versus once-daily administration of GLP-1 RA's on PRO's and clinical outcomes in a real-world specialist setting, this study prospectively investigated patient and provider reported outcomes as the primary objective in patients who initiated a GLP-1 RA as part of usual therapy in a large, specialist diabetes practice in Canada. We hypothesized that patients initiating a once-weekly GLP-1 RA therapy would report greater diabetes medication satisfaction, diabetes device satisfaction, and diabetes medication adherence compared to patients initiating a once-daily GLP-1 RA therapy. Additionally, we performed a post-hoc analyses comparing clinical outcomes in a larger prospective cohort of patients initiating GLP-1 RA, using propensity score matching.

2. Subjects, materials and methods

The study used a prospective, observational design to evaluate PRO's and clinical outcomes in patients initiating GLP-1 RA therapy during routine clinical practice. The study was conducted in compliance with the ethics principles of the Declaration of Helsinki and in compliance with all International Council on Harmonization Good Clinical Practice Guidelines. An independent ethics committee approved the protocol, and written informed consent was obtained from all study participants.

Between April 1, 2017 and January 30, 2018, all patients with T2D attending an LMC Diabetes & Endocrinology specialist clinic in Ontario, Canada, who were prescribed a GLP-1 RA therapy (liraglutide: available in Canada since 2010, dulaglutide: available in Canada since 2016, or exenatide QW: available in Canada since 2016) by their endocrinologist, were invited to participate in the study. Patients were eligible to participate if they met the following inclusion criteria: clinical diagnosis of T2D $\geq$6 months, >18 years of age, and ability to read and respond to the questionnaires. The questionnaires were available in English, Hindi and Punjabi, the major languages spoken by the patient populations. Patients were excluded if they were pregnant or nursing, initiating or switching from liraglutide 3.0 mg, had a recent eGFR <40 ml/min/1.73 m^2, undergoing treatment for cancer, had a history of medullary thyroid carcinoma, multiple endocrine neoplasia syndrome type 2 (MEN 2), severe gastroparesis, pancreatitis, or bariatric surgery, or if they were participating in a research study with an Investigational Product. Patients were either GLP-1 RA naïve (defined as never having used a GLP-1 RA therapy) or were switching from another GLP-1 RA that they had used for $\geq$three months.

The GLP-1 RA prescription date was considered the baseline date. At baseline and the follow-up visit, patients completed questionnaires including the Diabetes Medication Satisfaction (DiabMedSat) [9], Adherence to Refills and Medications Scale – Diabetes (ARMS-D) [10], and the Treatment-Related Impact Measure for Diabetes – Devices (TRIM-D Device) [11]. Patients also indicated their satisfaction with glycemic control, body weight and cost of diabetes medications, fear of injection, and the frequency of nausea, vomiting and diarrhea in the prior 4 weeks (Supplementary Fig. 1).

At baseline, HCP's rated the extent that each of the following parameters influenced their decision to prescribe the GLP-1 RA: glucose lowering, weight reduction, hypoglycemia risk reduction, insulin sparing/avoidance, and cardiovascular benefit (Supplementary Fig. 2). At follow-up, the HCP completed a questionnaire that investigated for each patient, their satisfaction with glycemic control and weight, with teaching the

GLP-1 RA device, concern regarding adverse effects, and likelihood to prescribe the GLP-1 RA again (Supplementary Fig. 3).

Age, sex, duration of T2D, ethnicity, and education were recorded at baseline. Clinical characteristics collected at baseline included A1C, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), history of macrovascular complications (coronary artery disease, cerebrovascular disease, or peripheral arterial disease), and history of microvascular complications (neuropathy, nephropathy or retinopathy). Concomitant classes of antihyperglycemic agents were assessed during the pre-index period. Self-reported incidence of hypoglycemia (all and severe) were recorded at each clinic visit. Follow-up values were the last available value three to six months (±six weeks) following the index date.

2.1. *Outcomes*

The primary outcome was the change in DiabMedSat at three to six months follow-up. Secondary patient-reported outcomes included change in ARMS-D, TRIM-D Device scores at follow-up, and change in the LMC questionnaire scores. Secondary clinical outcomes included change in A1C, weight, SBP, and DBP, the proportion of patients who achieved A1C <7.0% (<53 mmol/mol), the proportion of patients who achieved an A1C reduction of ≥0.5% (≥6 mmol/mol), and the proportion of patients who achieved a weight reduction of ≥5%. Outcomes for PRO's, A1C, weight and hypoglycemia were also assessed in pre-planned subgroups of non-insulin and insulin users. Exploratory endpoints included responses to HCP questionnaires at baseline and follow-up, the proportion of patients who self-reported ≥one incidence of hypoglycemia in the prior week and ≥one incidence of severe hypoglycemia in the prior year, change in insulin dose (where applicable) and the proportion of patients who discontinued GLP-1 RA therapy, and the reason for discontinuation.

For clinical outcomes, we also performed a post-hoc retrospective analysis of the larger cohort of GLP-1 RA naïve patients initiating and maintaining dulaglutide or liraglutide during the same time period as the prospective study, with a documented baseline and follow-up A1C.

2.2. *Data analysis*

The main analysis population was the per-protocol population, including all patients who had baseline and follow-up PRO scores, and who persisted on GLP-1 RA therapy until follow-up. Change in DiabMedSat scores and ARMS-D scores were analyzed with multivariable regression, with baseline value, insulin use, and discontinuation of a DPP-4i at baseline as covariates. TRIM-D score at follow-up between the 2 cohorts was analyzed with multivariable regression, with insulin use as a covariate. Patient and HCP questionnaire scores were analyzed descriptively. Change in A1C, weight, BMI, SBP and DBP were compared between treatment cohorts using multivariable regression, with baseline value, duration of T2D and insulin use as covariates. Differences between groups in the proportion of patients achieving A1C <7.0% (<53 mmol/mol), and reductions in A1C of ≥0.5% (≥6 mmol/mol), were compared with chi-square tests. Missing data was not replaced. Alpha was considered statistically significant at $p < 0.05$. All analyses were performed with SAS 9.4 (Cary, NC).

In the retrospective analysis of clinical outcomes, patients were matched 1:1 using propensity scores. The propensity score was estimated using a logistic regression model with treatment as the dependent variable and the following variables as covariates: age, gender, duration of T2D, baseline A1C, baseline weight, baseline blood pressure, history of macrovascular disease, history of microvascular disease, concomitant diabetes therapy during the pre-index period, ethnicity and education level. Patients were matched using a greedy, nearest neighbour process, with a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score [12]. The baseline characteristics of the pre-matched and post-matched cohorts were compared using a standardized difference. Baseline characteristics with a standardized difference <0.10 were considered to be balanced between the cohorts [12].

3. Results

There were only limited numbers of patients initiating exenatide QW (n = 2), or switching GLP-1 RA's (n = 24) and these groups were not analyzed. Albiglutide had been approved but not marketed, and semaglutide had not yet been approved in Canada. Overall, 888 GLP-1 RA naive patients initiated dulaglutide and 853 GLP-1 RA naïve patients initiated liraglutide at the six participating LMC sites between April 1, 2017 and January 30, 2018. In the prospective study portion, 318 participants were enrolled, of which 27 did not start the prescribed therapy, 38 discontinued therapy prior to follow-up, and 28 became lost-to-follow-up (LTFU), resulting in 225 individuals in the main per-protocol (PP) analyses (dulaglutide n = 146, liraglutide n = 79).

Baseline characteristics of the cohorts are presented in Table 1. Patients prescribed dulaglutide were significantly younger, had a lower prevalence of macrovascular disease, and had less insulin use compared to those initiated on liraglutide. Dulaglutide patients had a numerically lower baseline weight compared to liraglutide patients (97.8 kg vs. 101.9 kg). Baseline A1C was similar between dulaglutide (8.3%) [67 mmol/mol] and liraglutide (8.4%) [68 mmol/mol] cohorts. Other than two patients in the dulaglutide cohort, all study patients who used a DPP-4i during the pre-index period discontinued the DPP-4i on the index date. Overall, 12.4% of the dulaglutide cohort and 5.1% of the liraglutide cohort added another diabetes therapy on the index date; whereas 19.1% of the dulaglutide cohort and 15.2% of the liraglutide cohort discontinued other non-DPP-4i diabetes therapies on the index date. Mean follow-up time was similar between cohorts (dulaglutide: 4.1 ± 1.3 months; liraglutide 3.9 ± 1.3 months). By follow-up, 62% of dulaglutide patients had titrated to the full 1.5 mg weekly dose, and 52% of liraglutide patients had titrated to the full 1.8 mg daily dose.

3.1. *Patient reported outcomes*

Baseline scores for the DiabMedSat were similar between dulaglutide (67.9 ± 16.2) and liraglutide (69.8 ± 14.8). Both

Table 1 – Baseline characteristics of the per-protocol cohort of patients who initiated dulaglutide or liraglutide.

Cohort	Dulaglutide	Liraglutide
N total	146	79
Age (years)	53.6 ± 11.0	56.7 ± 9.0*
Males, N (%)	85 (57.1)	46 (58.2)
Duration T2D (years)	8.9 ± 5.9	10.7 ± 8.3
Ethnicity, n (%)		
Caucasian	71 (47.7)	45 (57.0)
Asian	40 (26.9)	12 (15.2)*
Other	17 (11.4)	9 (11.4)
Declined response	21 (14.1)	13 (16.5)
Education, N (%)		
Post-secondary	81 (54.4)	45 (57.0)
Secondary	28 (18.8)	12 (15.2)
Declined response	40 (26.9)	15 (19.0)
Income, N (%)		
0–30,000	16 (10.7)	9 (11.4)
30–60,000	19 (12.8)	15 (19.0)
60–90,000	24 (16.1)	12 (15.2)
90–120,000	19 (12.8)	4 (5.1)
>120,000	22 (14.8)	16 (20.3)
Declined response	49 (32.9)	23 (29.1)
A1C (%)	8.3 ± 1.4	8.4 ± 1.4
A1C (mmol/mol)	67 ± 15	68 ± 15
Weight (kg)	97.8 ± 22.0	101.9 ± 22.8
BMI (kg/m^2)	34.4 ± 7.1	35.8 ± 8.1
Waist circumference (cm)	109.8 ± 15.1	114.0 ± 15.0
SBP (mmHg)	124.5 ± 12.8	125.3 ± 12.4
DBP (mmHg)	74.2 ± 8.7	74.4 ± 10.4
Macrovascular disease, N (%)	12 (8.1)	13 (16.5)*
Microvascular disease, N (%)	16 (10.7)	15 (19.0)
Diabetes therapies during the pre-index period, N (%)		
Metformin	137 (93.8)	74 (93.7)
Sulfonylurea	54 (37.0)	21 (26.6)
SGLT2i	78 (53.4)	44 (55.7)
DPP4-i	90 (61.6)	38 (48.1)
Insulin	41 (28.1)	44 (55.7)*
Basal only	21 (14.4)	31 (39.2)*
Basal-bolus	19 (13.0)	13 (16.5)
Number of oral diabetes therapies	2.5 ± 1.0	2.2 ± 0.9

Data is presented as mean ± SD, or as N (%).
* = significantly different compared to dulaglutide ($p < 0.05$). T2D = type 2 diabetes; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure. The per-protocol cohort contains patients in the full cohort who completed baseline and follow-up questionnaires, and who did not discontinue GLP-1 RA therapy prior to follow-up.

cohorts had significant improvements in the total score from baseline (LS mean ± SE: dulaglutide 9.6 ± 1.1, $p < 0.001$; liraglutide 10.6 ± 1.4, $p < 0.001$), as well as for the efficacy, symptoms and burden subscale scores (Fig. 1a), with no significant differences between treatment cohorts, regardless of prior insulin use. Medication adherence scores as assessed by the ARMS-D were similar between cohorts at baseline (dulaglutide 15.5 ± 3.7; liraglutide 15.2 ± 4.0). Medication adherence scores significantly improved for dulaglutide (−0.5 ± 0.2; $p = 0.03$) but not for liraglutide (−0.2 ± 0.3, $p = 0.56$). Results were consistently better for dulaglutide in the medication taking subscale (dulaglutide (−0.4 ± 0.2, $p = 0.02$; liraglutide −0.2 ± 0.2, $p = 0.30$), however, there was not a significant difference between cohorts. Neither cohort had a significant change in the refills subscale (Fig. 1b). In the sub-group of patients not using insulin, both cohorts had significantly improved adherence scores (dulaglutide −1.1 ± 0.30, $p < 0.001$; liraglutide −1.0 ± 0.4, $p = 0.03$) with no significant difference between cohorts ($p = 0.85$). Satisfaction with the diabetes device was also similar between dulaglutide and liraglutide based on the TRIM-D Device total scores at follow-up (dulaglutide 80.3 ± 1.4 and liraglutide 83.3 ± 1.8), and on device function and device bother subscale scores (Fig. 1c), regardless of prior insulin use. Both treatment cohorts had significant improvements in scores for satisfaction with glycemia and weight, and fear of injectable therapy, with no significant differences between cohorts (Supplementary Table 1).

3.2. *Provider reported outcomes*

All the HCP's prescribed both therapies to varying degrees. Overall at baseline, 20 HCP's rated each of the following variables evenly in their decision to choose a therapy: glucose

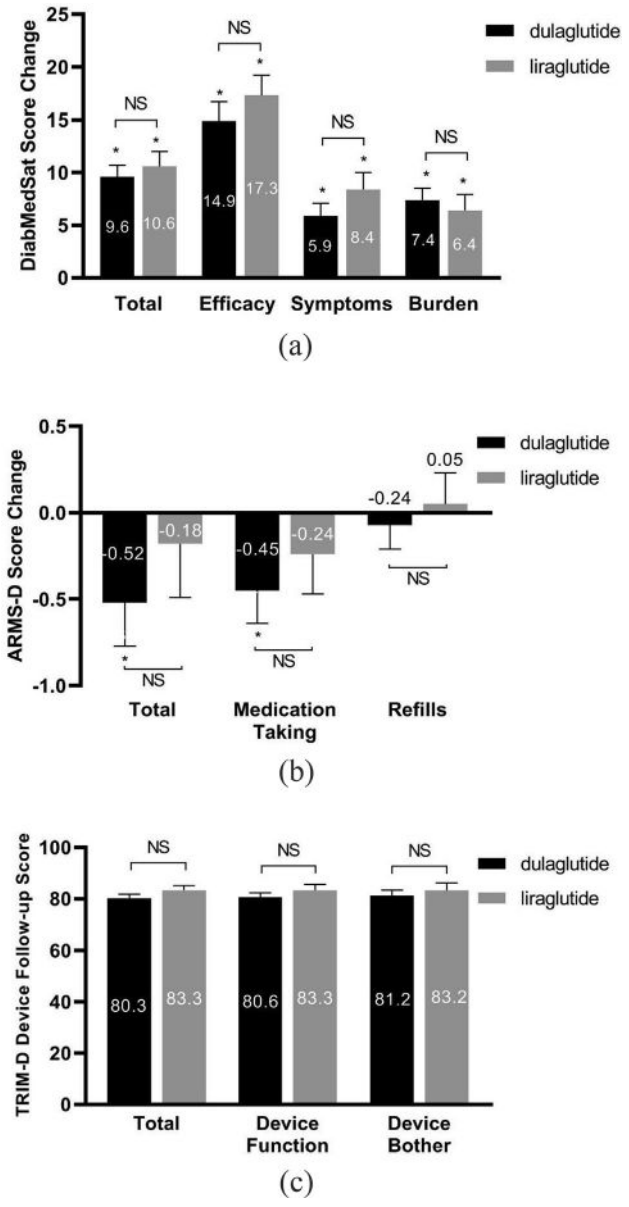

Fig. 1 – DiabMedSat change scores (panel A), ARMS-D change scores (panel B) and TRIM-D Device follow-up scores (panel C) in the dulaglutide (black bars) and liraglutide (grey bars) treatment cohorts. DiabMedSat: the total score and the three sub-scales range from 0 to 100. A higher score indicates higher satisfaction. ARMS-D: the total score ranges from 11 to 44. Scores for the refill subscale range from 4 to 16. Scores for the medication taking subscale range from 7 to 28. A lower score indicates greater adherence. TRIM-D Device: the transformed scores for the total score and the two sub-scales range from 0 to 100. A higher score indicates a higher health status. * = significant change from baseline value ($p < 0.05$).

lowering, weight reduction, insulin sparing or avoidance, and hypoglycemia risk reduction. Providers did report higher scores for cardiovascular benefit for liraglutide (3.5/5) compared to dulaglutide (2.3/5) ($p < 0.01$) (Supplementary Fig. 4).

At follow-up, >75% of providers reported that they were either somewhat or very satisfied with the change in their patients' glycemia and weight, for each therapy. For the dulaglutide cohort, 91% of providers reported being very satisfied with the ease of teaching the GLP-1 RA device, compared to 85% of providers for liraglutide. In terms of adverse effects, 60% of providers reported being very unconcerned or somewhat unconcerned about adverse effects with dulaglutide, compared to approximately 40% of providers for liraglutide. The majority of providers reported being either very likely or somewhat likely to prescribe either dulaglutide or liraglutide again (Supplementary Table 2).

3.3. *Clinical outcomes*

Clinical outcomes were assessed as secondary outcomes in the prospective cohort. Both treatment groups showed significant improvements in A1C, with no difference between groups (LS mean ± SE) in any of absolute decline (dulaglutide −1.0 ± 0.1% [−11 ± 1 mmol/mol]; liraglutide −0.9 ± 0.1%) [−10 ± 0.1 mmol/mol] ($p = 0.63$), proportion achieving A1C ≤7.0% (≤53 mmol/mol) (dulaglutide 43.8%, liraglutide 41.8%), nor A1C reduction ≥0.5% (≥6 mmol/mol) (dulaglutide 59.4%, liraglutide 59.7%). Weight was significantly reduced in both treatment cohorts, with no statistically significant between group difference (dulaglutide −2.2 ± 0.3 kg; liraglutide −2.7 ± 0.3 kg). Neither cohort had a significant change in SBP or DBP.

In the larger post hoc analysis of the retrospective cohort initiating GLP-1 RA therapy, the dulaglutide cohort was similarly younger and had lower body weight, lower prevalence of macrovascular disease, and fewer proportions using insulin, prior to matching (Supplementary Table 4). After matching, each treatment cohort included 377 patients, well balanced in their baseline characteristics (Supplementary Table 4). During the follow-up period (dulaglutide 4.8 ± 1.4 months; liraglutide 6.0 ± 1.9 months), 55 (14.6%) of dulaglutide cohort and 61 (16.2%) of liraglutide cohort discontinued GLP-1 RA therapy, leaving 322 dulaglutide and 316 liraglutide patients in the on-treatment analysis population. Both groups had a significant reduction in A1C, with no significant difference between groups (dulaglutide −0.8 ± 0.1% [−9 ± 1 mmol/mol]; liraglutide −0.7 ± 0.1% [−8 ± 1 mmol/mol]). Similar results were observed for the non-insulin subgroup (dulaglutide −0.9 ± 0.1% [−10 ± 1 mmol/mol]; liraglutide −0.8 ± 0.1% [−9 ± 1 mmol/mol]) and insulin subgroup (dulaglutide −0.8 ± 0.1% [−9 ± 1 mmol/mol]; liraglutide −0.7 ± 0.1% [−8 ± 1 mmol/mol]) (Fig. 2). The proportion of patients who achieved an A1C ≤ 7.0% (≤53 mmol/mol) (dulaglutide 35.1%, liraglutide 37.4%) and an A1C reduction ≥0.5% (≥6 mmol/mol) (dulaglutide 54.0%, liraglutide 52.9%), was similar between dulaglutide and liraglutide. Both treatment cohorts had a significant reduction in weight from baseline. Liraglutide had a significantly greater change in weight (−2.8 ± 0.2 kg) compared to dulaglutide (−1.8 ± 0.2 kg) ($p < 0.001$), with similar observations in the non-insulin and insulin sub-groups (Fig. 3). The proportion of patients who achieved ≥5% weight loss was significantly lower for dulaglutide patients (12.1%) compared to liraglutide patients (21.2%) ($p = 0.002$). Both treatment cohorts had small but significant reductions in SBP, with no significant differ-

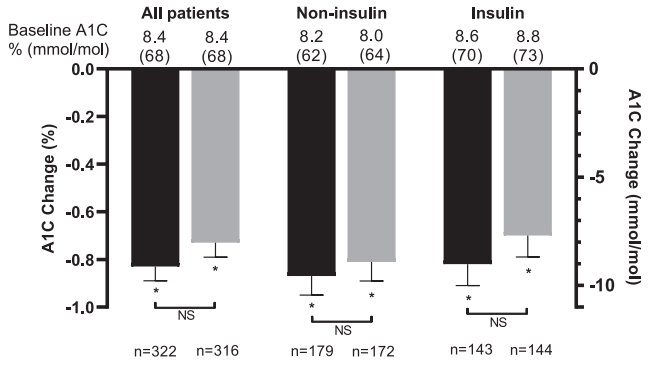

Fig. 2 – A1C change in the overall cohort, non-insulin and insulin subgroups from the retrospective matched dulaglutide (black bars) and liraglutide (grey bars) cohorts. * = significant change from baseline ($p < 0.05$).

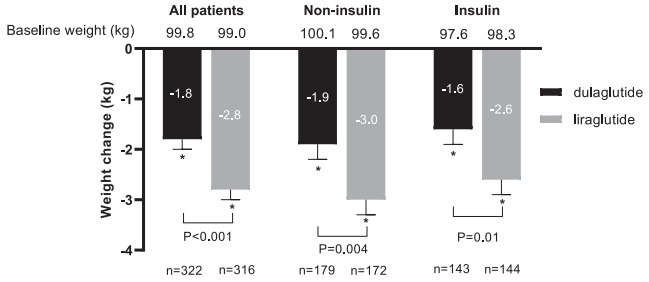

Fig. 3 – Weight change in the overall cohort, non-insulin and insulin subgroups from the retrospective matched dulaglutide (black bars) and liraglutide (grey bars) cohorts. * = significant change from baseline ($p < 0.05$).

ence between treatment cohorts (dulaglutide −2.6 ± 0.6 mmHg; liraglutide −1.6 ± 0.6 mmHg). Only dulaglutide group had a small but statistically significant reduction in DBP (−0.9 ± 0.4, p = 0.04).

3.4. *Exploratory outcomes*

In the pre-specified prospective cohorts, the proportion of patients reporting severe hypoglycemia was <2% in either cohort. The proportion of patients who reported ≥one episode/week of hypoglycemia was similar for both cohorts (dulaglutide: 8.9% vs. 11.0%; liraglutide: 10.1% vs. 10.1%) and was similar for insulin users and non-insulin users.

Dulaglutide and liraglutide cohorts using insulin at baseline had a similar median total daily dose of insulin (dulaglutide 0.56 U/kg; liraglutide 0.58 U/kg). Dulaglutide sub-cohort had a significant reduction in median total daily dose of insulin at follow-up (−0.10 U/kg; $p < 0.01$), whereas there was no significant change in the liraglutide sub-cohort (−0.05 U/kg; p = 0.45).

The proportion of patients who discontinued GLP-1 RA therapy prior to follow-up was similar between treatment cohorts (dulaglutide 13.1%; liraglutide 16.8%; p = 0.39). The most common reason for discontinuing GLP-1 RA therapy was due to gastrointestinal adverse effects. Reasons for discontinuing the GLP-1 RA therapy are listed in Supplementary Table 3.

4. Discussion

The present study investigated the patient experience prospectively, and clinical outcomes retrospectively, in participants with T2D initiating GLP-1 RA therapies in a large Canadian specialist practice group. Our hypothesis that participants initiating dulaglutide would have greater diabetes medication satisfaction, diabetes device satisfaction and diabetes medication adherence, was not confirmed. Dulaglutide and liraglutide cohorts had similar score gains for diabetes medication satisfaction and diabetes device satisfaction but only the dulaglutide cohort improved their score for diabetes medication adherence. In clinical outcomes, cohorts initiating dulaglutide and liraglutide each had similar reductions in A1C, with nearly one third of cohorts in each group, achieving A1C < 7.0% at three to six months. Both cohorts had significant reductions in weight, with a greater weight loss observed in the liraglutide cohort, particularly in non-insulin users.

Patient reported outcomes provide unique patient perspectives about GLP-1 RA therapy. The similar improvements in diabetes medication satisfaction scores are an important outcome to assess given the association between treatment satisfaction and medication adherence [13] which remains a challenge for persons with T2D. An estimated 55% of individuals do not adhere to their therapy regimen [14] because of factors including complexity or frequency of dosing regimens, medication cost, age, overall health, and patient preference [14]. The greater medication adherence scores in the dulaglutide group may be explained by a more convenient once-weekly dosing of dulaglutide. In line with our results, two retrospective analyses of medical and pharmacy claims data reported greater adherence in adults who initiated dulaglutide compared to liraglutide [15,16]. Despite improved adherence scores, the dulaglutide cohort A1C reduction was similar to that of liraglutide. A longer follow-up period may be needed to observe a potential difference in glycemic control related to adherence. In fact, a recent real-world analysis of U.S. claims data which found higher adherence with dulaglutide did show that by 12 months, dulaglutide was associated with a statistically significant greater reduction in A1C (−0.98% vs −0.77%) [16].

Interestingly, device satisfaction scores were similar between dulaglutide and liraglutide, surprising given the advanced injection system in the dulaglutide single-dose pen that does not require reconstitution, includes a “hidden” needle and offers automated insertion with retraction of the needle [17]. It is possible that experienced people who inject regularly may not find the liraglutide injection pen to be any more burdensome than the dulaglutide injection device, however there were no apparent differences even in those participants not on insulin. As an alternate explanation to the observed similar device satisfaction, it is plausible that any actual differences between therapy injections may only have been visible within the first few weeks of use, and may not be

apparent at the mean follow-up time of approximately 4 months in our study.

Discontinuation rates in the prospective cohort (dulaglutide 13.1%; liraglutide 16.8%) were similar to the larger retrospective cohort (dulaglutide 14.6%; liraglutide 16.2%). These discontinuation rates are higher than what has been reported in RCT's [6], but lower than what has been reported in other retrospective observational analyses [15,16,18]. The cohorts in the present study were attending specialist-led, multidisciplinary diabetes clinics which may have improved persistence.

In the present study, the mean change in A1C was similar between dulaglutide and liraglutide, consistent with results from clinical trials [6] but mean reduction in A1C (-dulaglutide −0.8% [−9 mmol/mol] and liraglutide −0.7% [−8 mmol/mol] in the retrospective analyses) was lower than what has been previously reported in RCT's [6,19]. This finding may be due to the more pragmatic approach to patient inclusion, which included individuals with a broader age range, multiple comorbidities, and various combinations of concomitant antihyperglycemic agents. Similar to our results, recent retrospective analyses have similarly reported A1c reductions of 0.9% [10 mmol/mol] [18] and 0.5% [6 mmol/mol] [20] in separate small cohorts of dulaglutide users.

In the retrospective cohort, prior to matching, the mean weight in the liraglutide cohort was nearly 8 kg higher than the dulaglutide cohort, implying that HCP's may be favouring liraglutide for higher weight patients. However, HCP's rated weight reduction as a reason for their GLP-1 RA choice similarly between each of dulaglutide and liraglutide. The resulting greater weight loss with liraglutide in our retrospective analysis had also been observed in an RCT comparing liraglutide to dulaglutide (AWARD-6) [6]. The greater weight loss observed in the liraglutide cohort was also consistent among insulin users, despite the observation that dulaglutide, but not liraglutide, was associated with a significant reduction in total daily insulin dose. A recent retrospective uncontrolled analysis of dulaglutide initiators reported a slightly greater weight loss (−2.7 kg) compared to the present study[20], possibly attributable to a higher mean weight at baseline (108.8 kg vs. 97.6 kg). Of note, HCP's in this study rated liraglutide higher for cardiovascular benefit for their GLP-1 RA choice, although this study was conducted prior to the REWIND trial results, which reported that dulaglutide reduces the risk of cardiovascular outcomes [21].

A strength of this study is the availability of a large sample of adults with T2D initiating dulaglutide or liraglutide, within one practice group all following the national clinical practice guidelines [22] within a public health system. The cohort study design may have specific advantages compared to an RCT[23], especially in investigations of adherence, and may be more generalizable to clinical practice. There was a high completion rate for the questionnaires (90%). The inclusion of both patient and provider outcomes may provide a more holistic assessment of the real-world experience in initiating dulaglutide and liraglutide.

As in all non-randomized observational research, our therapy cohorts may reflect selection bias. Although we tried to adjust for important baseline characteristics by propensity score matching in the retrospective cohort, residual and unknown confounding may have occurred. Voluntary participants in a PRO study tend to be younger, healthier and/or more compliant. Participating in the study may have also led to a bias in perceptions of the therapies. We were unable to directly assess actual medication compliance, other than drug discontinuation during follow-up. Finally, since the sample for this study came from a referral-based diabetes specialist practice, the results may not be generalizable to all individuals with T2D.

In conclusion, the results of this observational cohort study indicate that adults initiating dulaglutide and liraglutide had similar satisfaction with their diabetes medications and device, but only the dulaglutide cohort had improved scores for diabetes medication adherence. The results also confirm the clinical trial findings that dulaglutide and liraglutide result in similar reductions in A1C, and that liraglutide is superior to dulaglutide for weight reduction, albeit with a modest weight differential.

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Declaration of Competing Interest

R.E.B. has no conflicts of interest to declare.

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Author contributions

All authors designed the study. R.E.B. performed the data analysis and wrote the first draft of the manuscript. All authors provided critical revisions to the manuscript and approved the final version.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107820.

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