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Original Research

Real-World Health Outcomes of Insulin Glargine 300 U/mL vs Insulin Glargine 100 U/mL in Adults With Type 1 and Type 2 Diabetes in the Canadian LMC Diabetes Patient Registry: The REALITY Study

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Key Messages

- In clinical trials, Gla-300 had similar glycated hemoglobin (A1C) reduction and a lower risk of hypoglycemia than Gla-100 in patients with type 1 diabetes (T1D) and type 2 diabetes (T2D).
- In a real-world clinical setting, insulin-naïve patients with T2D initiating Gla-300 or Gla-100 had similar A1C reduction and weight change.
- Patients with T1D or T2D switching to Gla-300 had significant reductions in A1C with no change in weight or insulin dose.

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ABSTRACT

Objectives: This study evaluated real-world clinical outcomes of patients with type 1 diabetes (T1D) and type 2 diabetes (T2D) initiating or transferring to insulin glargine 300 U/mL (Gla-300) vs insulin glargine 100 U/mL (Gla-100).
Methods: This is a retrospective cohort study using data from the Canadian LMC Diabetes Patient Registry. The 4 following cohorts were analyzed: 1) insulin-naïve patients with T2D who initiated Gla-300 or Gla-100, 2) patients with T2D who switched from neutral protamine Hagedorn (NPH) or detemir to Gla-300 or Gla-100, 3) patients with T2D who switched from Gla-100 to Gla-300 and 4) patients with T1D who switched from Gla-100, NPH or detemir to Gla-300.
Results: Of 376 propensity score-matched insulin-naïve patients, 6-month reduction in glycated hemoglobin (A1C) was similar between Gla-300 (−1.78%±1.85%; $p<0.001$) and Gla-100 (−1.74%±1.87%; $p<0.001$). In 114 propensity score-matched patients who switched from NPH or detemir, 6-month reduction in A1C was similar between Gla-300 (−0.78%±1.14%) and Gla-100 (−0.70%±1.57%). The 396 patients who switched from Gla-100 to Gla-300 had a significant reduction in A1C (−0.45%±1.39%; $p<0.001$). In 196 patients with T1D who switched from Gla-100, NPH or detemir to Gla-300, there was a significant reduction in A1C of −0.17%±1.19% ($p=0.04$).
Conclusions: In a real-world clinical setting, insulin-naïve patients who initiated Gla-300 or Gla-100 showed similar changes in A1C and weight. Patients with T1D or T2D using Gla-300 transferred from another basal insulin had significant reductions in A1C with no change in weight or insulin dose.

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RÉSUMÉ

Objectifs : La présente étude avait pour objet l'évaluation des résultats cliniques en contexte réel des patients atteints de diabète de type 1 (DT1) et de diabète de type 2 (DT2) qui commençaient l'insuline glargine 300 U/ml (Gla-300) *vs* l'insuline glargine 100 U/ml (Gla-100), ou y transféraient.
Méthodes : Ceci est une étude de cohorte rétrospective réalisée à partir des données du registre canadien de diabète LMC. L'analyse portait sur les 4 cohortes suivantes: 1) les patients atteints du DT2 n'ayant jamais reçu d'insuline qui ont commencé la Gla-300 ou la Gla-100; 2) les patients atteints du DT2 qui sont passés de la protamine neutre Hagedorn (NPH pour *neutral protamin Hagedorn*) ou de la détémir à la Gla-300 ou la Gla-100; 3) les patients atteints du DT2 qui sont passés de la Gla-100 à la Gla-300; 4) les patients atteints du DT1 qui sont passés de la Gla-100, de la NPH ou de la détémir à la Gla-300.
Résultats : Parmi les 376 patients n'ayant jamais reçu d'insuline qui étaient appariés par score de propension, la réduction de l'hémoglobine glyquée (A1c) après 6 mois était similaire entre la Gla-300 ($-1,78\ \% \pm 1,85\ \%$; $p < 0,001$) et la Gla-100 ($-1,74\ \% \pm 1,87\ \%$; $p < 0,001$). Chez les 114 patients appariés par score de propension qui étaient passés de la NPH ou de la détémir, la réduction de l'A1c après 6 mois était similaire entre la Gla-300 ($-0,78\ \% \pm 1,14\ \%$) et la Gla-100 ($-0,70\ \% \pm 1,57\ \%$). Les 396 patients qui étaient passés de la Gla-100 à la Gla-300 montraient une réduction significative de l'A1c ($-0,45\ \% \pm 1,39\ \%$; $p < 0,001$). Les196 patients atteints du DT1 qui étaient passés de la Gla-100, de la NPH ou de la détémir à la Gla-300 montraient une réduction significative de l'A1c de $-0,17\ \% \pm 1,19\ \%$ ($p = 0,04$).
Conclusions : Dans le contexte clinique réel, les patients n'ayant jamais reçu d'insuline qui ont amorcé la Gla-300 ou la Gla-100 montraient des changements similaires de l'A1c et du poids. Les patients atteints du DT1 ou du DT2 qui recevaient la Gla-300, mais qui avaient pris une autre insuline basale montraient des réductions significatives de l'A1c sans changement de poids ou de dose d'insuline.

Introduction

Type 1 diabetes (T1D) and type 2 diabetes (T2D) are progressively worsening global health challenges. The foundation of T1D treatment is life-long insulin replacement therapy because of permanent insulin deficiency. Because of the progressive loss of beta-cell dysfunction associated with T2D, many patients treated with oral and/or injectable therapies ultimately require the addition of insulin therapy to improve glycemic control (1).

Basal insulin represents the mainstay of insulin therapy in clinical practice. Since 1946, neutral protamine Hagedorn (NPH), an intermediate-acting basal insulin, has been predominantly used. Its main limitation is the need for resuspension and a duration of action of approximately 10 to 16 h. In the 1980s, insulin glargine 100 U/mL (Gla-100) (Lantus) became the first long-acting basal insulin approved for clinical use. Gla-100 has been established to be both safe and effective, and is associated with less nocturnal hypoglycemia than NPH insulin (2). Most clinicians use Gla-100 as first-line therapy when initiating basal insulin. Insulin detemir is another long-acting basal insulin analogue. It is rapidly absorbed after subcutaneous injection, and contains a fatty acid group that forms a complex with albumin in blood, leading to a slow disassociation and a prolonged duration of action. Insulin glargine 300 U/mL (Gla-300) (Toujeo) is a recently approved ultralong-lasting basal insulin that has a flatter pharmacokinetic profile than Gla-100, with a duration of action >36 h (3). Gla-300 also offers only one-third of the volume per unit of insulin compared with Gla-100. Insulin degludec (Tresiba) is the latest prolonged-acting insulin approved for use in Canada that forms long subcutaneous multihexamers, which delay insulin absorption and prolong duration of action up to 42 h.

In the EDITION phase III randomized clinical trial program, Gla-300 had a similar glucose lowering effect and was associated with a lower risk of nocturnal hypoglycemia than Gla-100 in patients with T1D and T2D (4–7). There is limited real-world clinical evidence evaluating patients with T1D and T2D initiating or transferring to Gla-300 or Gla-100.

The Real-World Health Outcomes of Insulin Glargine 300 U/mL vs Insulin Glargine 100 U/mL in Adults With Type 1 and Type 2 Diabetes in the Canadian LMC Diabetes Patient Registry study is a retrospective cohort study. We sought to investigate the real-world clinical outcomes of patients with T1D and T2D initiating Gla-300 by analyzing the medical records of patients from one of the largest global registries of patients with diabetes (LMC Diabetes Registry). Four separate cohorts were analyzed, and the primary outcome was the change in glycated hemoglobin (A1C) at 3 to 6 months.

Methods

Patient data were retrieved from the LMC Diabetes Registry between January 2015 and January 2018 (observation period). The LMC Diabetes Registry represents the active health records of 39,000 patients with diabetes from one of the largest endocrine practice groups globally (LMC Diabetes & Endocrinology). LMC Diabetes & Endocrinology has 11 clinics in Canada, representing >50 endocrinologists who share a common electronic medical record system that is integrated with the provincial laboratory information system. The registry contains sociodemographic information, medical history, prescriptions and laboratory investigations. A detailed description of this registry has been previously described (8,9). Patients provided written consent for their electronic medical records to be used for research purposes, and this study was approved by a local ethics review board.

Patients were included in the analysis if they were prescribed Gla-300 or Gla-100 by an LMC Diabetes & Endocrinology physician between July 2015 and July 2017, if they had a clinical diagnosis of T1D or T2D for >6 months, if they used Gla-300 or Gla-100 for at least 6 weeks and if they had ≥1 A1C value in the 6 months prior to the index date (baseline period) and ≥1 A1C value 3 to 6 months after the index date (follow-up period). Four separate cohorts were analyzed: 1) insulin-naïve patients with T2D who initiated Gla-300 or Gla-100, 2) patients with T2D who switched from NPH or insulin detemir to Gla-300 or Gla-100, 3) patients with T2D who switched from Gla-100 to Gla-300 and 4) patients with T1D who switched

Table 1
Baseline characteristics of the 4 study cohorts

Characteristic	T2D							T1D
	Insulin naïve			Switch from NPH or detemir			Switch from Gla-100	Switch from Gla-100, NPH or detemir
	Gla-300 (n=188)	Gla-100 (n=188)	*d*	Gla-300 (n=57)	Gla-100 (n=57)	*d*	Gla-300 (n=396)	Gla-300 (n=187)
Age, years	53.9±10.1	53.9±11.2	0.003	61.8±9.1	60.9±12.9	0.076	58.0±10.0	45.4±15.7
Sex (% men)	110 (58.5)	102 (54.3)	0.090	33 (57.9)	35 (61.4)	0.080	250 (63.1)	105 (56.2)
Duration T2D, years	11.0±7.4	11.3±8.6	0.043	17.4±10.0	16.2±8.2	0.136	15.1±8.4	21.1±15.9
A1C, %	9.76±1.75	9.72±1.83	0.023	8.58±1.42	8.54±1.54	0.026	8.53±1.57	8.35±1.54
Weight, kg	87.7±20.9	87.7±23.3	0.003	91.7±24.6	92.6±24.7	0.035	101.3±26.3	77.2±17.4
BMI, kg/m^2	30.9±6.8	30.8±6.8	0.008	31.7±7.7	32.8±6.8	0.141	34.8±7.5	26.9±7.3
Basal insulin dose, U	12.3±3.6	12.3±6.4	0.002	48.5±30.7	48.8±45.8	0.008	62.2±39.2	28.5±18.0
Basal insulin dose, U/kg	0.14±0.07	0.14±0.08	0.002	0.51±0.27	0.51±0.30	0.009	0.60±0.32	0.36±0.17
Education								
Postsecondary school	104 (55.3)	97 (51.6)	0.075	26 (45.6)	25 (43.9)	0.035	171 (43.2)	13 (17.7)
Secondary school	49 (26.1)	57 (30.3)	0.095	14 (24.6)	13 (22.8)	0.041	112 (28.3)	106 (56.7)
Declined response	35 (18.6)	34 (18.1)	0.014	17 (29.8)	19 (33.3)	0.076	113 (28.5)	48 (25.7)
Ethnicity								
Caucasian	78 (41.5)	73 (38.8)	0.054	32 (56.1)	32 (56.1)	0.000	257 (64.9)	140 (74.9)
Asian	57 (30.3)	54 (28.7)	0.035	8 (14.0)	8 (14.0)	0.000	62 (15.7)	17 (9.1)
Other	33 (17.6)	41 (21.8)	0.107	12 (21.1)	11 (19.3)	0.044	38 (9.6)	14 (7.5)
Declined response	20 (10.6)	20 (10.6)	0.000	5 (8.8)	6 (10.5)	0.059	39 (9.9)	16 (8.6)
Microvascular disease	27 (14.4)	27 (14.4)	0.000	11 (19.3)	15 (26.3)	0.168	106 (26.8)	47 (25.1)
Macrovascular disease	15 (8.0)	7 (3.7)	0.182	11 (19.3)	12 (21.1)	0.044	85 (21.5)	10 (5.4)
Diabetes therapy								
Rapid-acting insulin	9 (4.8)	12 (6.4)	0.070	33 (57.9)	36 (63.2)	0.108	207 (52.3)	187 (100)
Metformin	165 (87.8)	163 (86.7)	0.032	45 (79.0)	41 (71.9)	0.164	319 (80.6)	0 (0)
SU	111 (59.0)	107 (56.9)	0.043	16 (28.1)	14 (24.6)	0.080	107 (27.0)	0 (0)
GLP-1 RA	23 (12.2)	20 (10.6)	0.050	4 (7.0)	3 (5.3)	0.073	102 (25.8)	0 (0)
DPP-4i	113 (60.1)	111 (59.0)	0.022	29 (59.0)	24 (42.1)	0.177	135 (34.1)	0 (0)
SGLT2i	57 (30.3)	63 (33.5)	0.069	21 (36.8)	20 (35.1)	0.037	176 (44.4)	0 (0)

Note: Data are presented as mean ± SD, n (%) or as otherwise indicated. A standardized difference of <0.1 indicates a negligible difference in the mean or prevalence of a baseline characteristic between treatment groups.
A1C, glycated hemoglobin; *BMI,* body mass index; *d,* standardized difference; *DPP-4i,* dipeptidyl peptidase-4 inhibitors; *Gla-100,* insulin glargine 100 U/mL; *Gla-300,* insulin glargine 300 U/mL; *GLP-1 RA,* glucagon-like peptide-1 receptor agonist; *NPH,* neutral protamine Hagedorn; *SGLT2i,* sodium-glucose co-transporter 2 inhibitors; *SU,* sulfonylurea; *T1D,* type 1 diabetes; *T2D,* type 2 diabetes.

from Gla-100, NPH or detemir to Gla-300. Patients switching from another basal insulin were included if they had been using the preswitch insulin for ≥6 months. Baseline and follow-up data were the latest available information during the baseline and follow-up period, respectively.

The primary outcome was the change in A1C at follow up. Secondary outcomes were change in weight, proportion of patients achieving A1C <7.0% and <8.0% at follow up, proportion of patients achieving A1C reduction ≥0.3%, ≥0.5% and ≥1.0% at follow up, proportion of patients self-reporting at least 1 weekly incidence of hypoglycemia and at least 1 yearly incidence of severe hypoglycemia and proportion of patients who discontinued Gla-300 or Gla-100. Hypoglycemia was assessed by a third-party interviewer at each office visit. The patient reported the number of times in the past week they experienced any hypoglycemia, and the number of times in the past year they experienced severe hypoglycemia, defined as requiring the assistance of a third party to recover.

To minimize confounding between groups in the insulin-naïve cohort and in the NPH/detemir switch cohort, patients on Gla-300 and Gla-100 were matched 1:1 using propensity scores. Propensity scores were estimated by a logistic regression analysis with treatment as the outcome and the following variables as covariates: age, sex, ethnicity, education, baseline basal insulin dose, duration of diabetes, baseline A1C, baseline weight, macrovascular disease, microvascular disease and baseline concomitant diabetes therapy. Patients were matched using a greedy, nearest neighbour process, with a caliper width equal to 0.2 of the SD of the logit of the propensity score (10). The baseline characteristics of the matched samples were compared using a standardized difference.

Change in A1C and weight was compared using paired *t* tests. Differences between groups in the proportion of patients achieving A1C <7.0% and <8.0%, and reductions in A1C of 0.3%, 0.5% and 1.0%, were compared with McNemar test. Alpha was considered statistically significant at p<0.05. All analyses were performed with SAS 9.4 (SAS Institute, Cary, North Carolina, United States).

Results

Cohort: T2D insulin naïve

The unmatched insulin-naïve cohort included 194 patients initiating Gla-300 who were significantly younger, had a shorter duration of diabetes and a higher A1C and body weight than the 900 patients initiating Gla-100 (Supplementary Table 1). After propensity score matching, there were 188 patients in each group, who were well balanced in baseline characteristics (Table 1). There was a significant reduction in A1C in the patients on Gla-300 (−1.78%±1.85%; p<0.001) and Gla-100 (−1.74%±1.87%; p<0.001), with no difference between groups (−0.04%; p=0.82) (Figure 1A). Both groups had a significant increase in weight from baseline (Gla-300: 2.3±4.0 kg, p<0.01; Gla-100: 1.7±3.8 kg, p<0.01), with no significant difference between groups (0.4±5.3 kg, p=0.33). The proportion of patients with A1C <7.0% and <8.0% at follow up, and the proportion who had an A1C reduction of ≥0.3%, ≥0.5% or ≥1.0%, was similar between Gla-300 and Gla-100 (Figure 2A).

Baseline basal insulin dose was 0.14 U/kg in both groups. During follow up, patients on Gla-300 titrated to a numerically higher basal insulin dose (mean, 0.35±0.22 U/kg; median, 0.28 U/kg) than patients on Gla-100 (mean, 0.30±0.18 U/kg; median, 0.26 U/kg). Of the 296 patients who had complete data for self-reported hypoglycemia, the proportion of patients reporting at least 1 incidence per week of hypoglycemia increased from 3.3% at baseline to 8.7% at follow up for Gla-300 (p=0.03), and from 5.5% to 11.0% for Gla-100

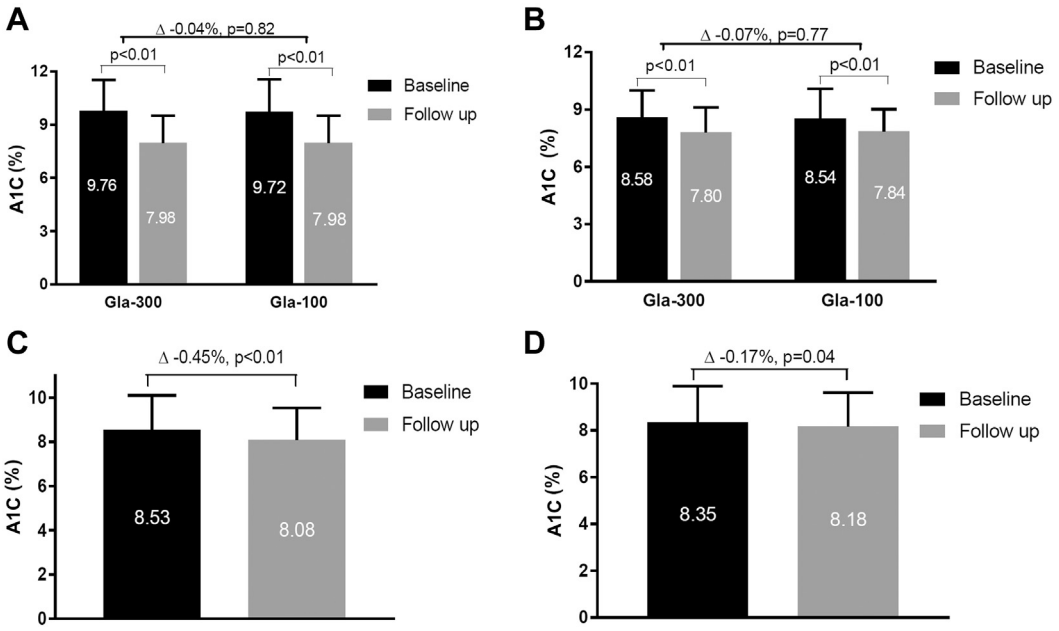

Figure 1. A1C at baseline (black bars) and follow up (grey bars) in the 4 cohorts: (A) type 2 diabetes-matched insulin-naïve cohort, (B) type 2 diabetes neutral protamine Hagedorn or detemir to Gla-300 switch cohort, (C) type 2 diabetes Gla-100 to Gla-300 switch cohort and (D) type 1 diabetes basal insulin to Gla-300 switch cohort. *A1C*, glycated hemoglobin; *Gla-100*, insulin glargine 100 U/mL; *Gla-300*, insulin glargine 300 U/mL.

(p=0.07). The proportion of patients reporting severe hypoglycemia was small and negligible. During follow up, 10.6% of patients on Gla-300 and 11.7% of patients on Gla-100 discontinued therapy.

Cohort: T2D switch from NPH or detemir to Gla-300

In the unmatched sample of patients switching from NPH or detemir, the 122 patients who switched to Gla-300 were significantly younger, had a shorter duration of diabetes and had a higher body weight than the 133 patients who switched to Gla-100 (Supplementary Table 1). After propensity score matching, there were 57 patients in each group, with comparable baseline characteristics (Table 1). Of the patients who switched to Gla-300, 82% and 18% switched from detemir and NPH, respectively, whereas in the Gla-100 group, 59% and 41% switched from detemir and NPH, respectively.

The reduction in A1C was similar between Gla-300 (−0.78%± 1.14%) and Gla-100 (−0.70%±1.57%) (between-group difference, −0.07%±1.92%; p=0.77) (Figure 1B). Neither groups had a significant change in body weight (Gla-300: 0.5±3.1 kg, p=0.25; Gla-100: 1.0±4.7 kg, p=0.13). The proportion of patients who achieved A1C <7.0% and <8.0% at follow up, and who had an A1C

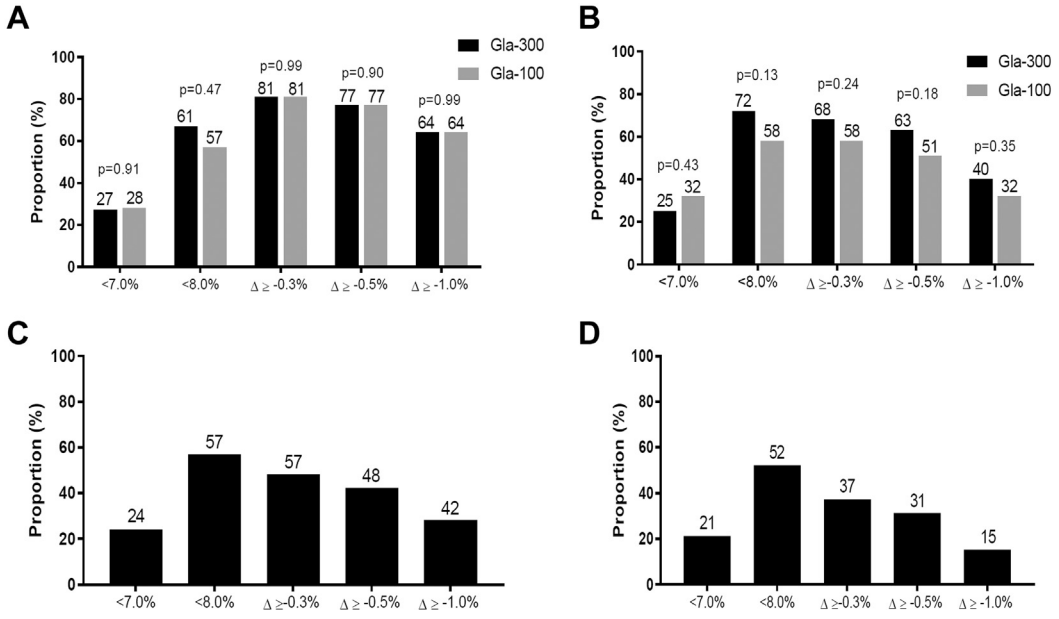

Figure 2. Proportion of patients who achieved glycated hemoglobin <7.0% and <8.0% at follow up, and a glycated hemoglobin reduction of ≥0.3%, ≥0.5% and ≥1.0%: (A) type 2 diabetes-matched insulin-naïve cohort, (B) type 2 diabetes neutral protamine Hagedorn or detemir to Gla-300 switch cohort, (C) type 2 diabetes Gla-100 to Gla-300 switch cohort and (D) type 1 diabetes basal insulin to Gla-300 switch cohort. *Gla-100*, insulin glargine 100 U/mL; *Gla-300*, insulin glargine 300 U/mL.

reduction ≥0.3%, ≥0.5% and ≥1.0%, was similar between Gla-300 and Gla-100 (Figure 2B).

Basal insulin dose was similar at baseline and follow up for both Gla-300 (baseline mean, 0.51±0.27 U/kg; median, 0.42 U/kg; follow-up mean, 0.51±0.30 U/kg; median, 0.43 U/kg) and Gla-100 (baseline mean, 0.51±0.28 U/kg; median, 0.46 U/kg; follow-up mean, 0.51±0.29 U/kg median, 0.47 U/kg). Of the 69 patients who had complete information for self-reported hypoglycemia, the proportion of patients who reported at least 1 incidence per week of hypoglycemia was similar at baseline and follow up for Gla-300 (25.0% vs 28.1%, respectively) and Gla-100 (40.5% at baseline and follow up). The proportion of patients reporting severe hypoglycemia was small and negligible. During follow up, only 3.5% of patients on Gla-300 and Gla-100 discontinued their respective therapies.

Cohort: T2D switching from Gla-100 to Gla-300

There were 396 patients with T2D who switched from Gla-100 to Gla-300. Patients had a mean age of 58.0 years, a mean duration of diabetes of 15.1 years and approximately one-half were using rapid-acting insulin at baseline (Table 1). A1C significantly decreased from 8.53%±1.57% at baseline to 8.08%±1.45% at follow up (Δ −0.45%±1.39%, p<0.001) (Figure 1C), with no significant change in weight (−0.2±3.3 kg; p=0.30). At follow up, 57.0% of patients had an A1C <8.0%, and 28% had an A1C reduction of ≥1.0% (Figure 2C).

Preswitch basal insulin dose (0.59±0.32 U/kg) was similar to baseline dose of Gla-300 (0.60±0.32 U/kg), with no change in dose during follow up (0.61±0.34 U/kg). Of the 312 patients who had complete information for self-reported hypoglycemia, the proportion of patients reporting at least 1 incidence per week of hypoglycemia decreased from 27.2% at baseline to 25.3% at follow up (p=0.51). During follow up, 12.9% of patients discontinued Gla-300.

Cohort: T1D switching from Gla-100, NPH or detemir to Gla-300

There were 187 patients with T1D who switched from another basal insulin to Gla-300. Patients had a mean age of 45.4 years, mean duration of diabetes of 21 years and mean A1C of 8.35%. The preswitch basal insulin was Gla-100 for 73% of patients, detemir for 23% of patients and NPH for 3% of patients. During follow up, there was a significant reduction in A1C of −0.17%±1.19% (p=0.04) (Figure 1D), with no significant change in weight (0.1±3.4 kg; p=0.74). At follow up, 52% of patients had an A1C <8.0%, and 31% had a reduction in A1C of ≥0.5% (Figure 2D).

Preswitch basal insulin dose (0.36±0.16 U/kg) was similar to baseline dose (0.36±0.17 U/kg) and follow-up basal insulin dose (0.38±0.17 U/kg). Of the 128 patients who had complete information for self-reported hypoglycemia, the proportion of patients who reported ≥1 incidence per week of any hypoglycemia was 74.2% at baseline and 79.7% at follow up (p=0.19). Self-reported yearly incidence of severe hypoglycemia was 9.4% at baseline and 4.7% at follow up (p=0.15). During follow up, 21 patients (11.2%) discontinued Gla-300.

Discussion

To our knowledge, this study provides the first analysis evaluating real-world clinical outcomes in patients with both T1D and T2D initiating or transferring to Gla-300 vs Gla-100.

Insulin-naïve patients with T2D initiating Gla-300 or Gla-100 showed similar significant reductions in A1C and increases in weight at follow up compared with baseline, with no appreciable differences between treatment groups. Prior to matching, patients initiating Gla-300 tended to be younger, had a shorter duration of diabetes and a higher baseline A1C and weight. A younger age among Gla-300 initiators was expected because of the lack of provincial reimbursement for Gla-300 for patients ≥65 years of age during the study period. In the matched cohort, patients on Gla-300 titrated to a higher basal insulin dose than patients on Gla-100, which may have been influenced by greater insulin resistance despite the matching process, or possibly because of less prescriber perceived risk of hypoglycemia. There may also be unexplained molecular differences accounting for this difference in dose, hypothesized to be related to a lower bioavailability of Gla-300. Similar results were observed for insulin-naïve participants with T2D in the EDITION 3 trial, which showed 17% higher final mean insulin dose for Gla-300 than Gla-100 for equivalent A1C reductions (6). However, a recent retrospective study using physician survey data to compare insulin-naïve patients with T2D initiating Gla-300 or Gla-100, did not show a difference in dose for equivalent A1C reductions but is limited by volunteer bias among the reporting physicians and selection bias in the charts reviewed (11).

In this real-world retrospective analysis, both Gla-100 and Gla-300 led to similar increases in self-reported hypoglycemia. In EDITION 3, subjects assigned to Gla-300 showed a 24% reduction in each of confirmed nocturnal or severe hypoglycemic rates compared with Gla-100, and a 25% reduction in risk of hypoglycemia at any time of day. Again, a retrospective survey study of physicians who had treated insulin-naïve people with T2D with either Gla-300 or Gla-100 did demonstrate lower hypoglycemic event rates for equivalent A1C reductions but is limited to only late physician recall of their patient's hypoglycemia reporting during routine office visits (11).

Our second and third cohorts evaluated patients with T2D switching their basal insulin. Patients who had switched to Gla-300 from insulin detemir or NPH showed similar A1C reductions, basal insulin dose, self-reported hypoglycemic events and discontinuation rates compared with switchers to Gla-100, and neither group showed a significant change in weight. Prior to matching, switchers to Gla-300 from detemir or NPH were significantly younger with a higher baseline weight and a greater preswitch insulin dose than switchers to Gla-100. Nonetheless, propensity-matched patients had a similar basal insulin dose at baseline, which remained consistent throughout the follow-up period.

Patients with T2D who switched to Gla-300 from Gla-100 demonstrated a significant A1C reduction of 0.45% over 6 months, with the same insulin dose, and with no significant change in weight or hypoglycemia. These results are consistent with the DELIVER 2 study, a recent retrospective analysis of electronic medical record systems in the United States that similarly reported equal A1C reductions among patients switching to Gla-300 or other basal insulins (22% Gla-100, 67% detemir, 11% degludec). Interestingly, DELIVER 2 also found reduced hypoglycemia as measured by the number of patients reporting hypoglycemia that generated a *International Classification of Diseases* visit code of hypoglycemia (12). The EDITION 2 clinical trial compared Gla-300 and Gla-100 in participants previously using either Gla-100 or NPH in combination with oral antidiabetic medications and showed results that differ from this retrospective analysis in some respects. EDITION 2 found that participants using Gla-300 did require a 10% higher basal insulin dose compared with Gla-100 for similar efficacy, and showed less increase in weight with Gla-300. EDITION 2 also demonstrated a 23% reduction in risk of confirmed nocturnal or severe hypoglycemia after 9 weeks with Gla-300 and reductions across all nonsevere hypoglycemic categories throughout the 6-month period.

Patients with T1D who switched from another basal insulin (Gla-100, NPH or detemir) to Gla-300 demonstrated a small A1C reduction of 0.17% at 6 months, with no significant change in weight

or insulin dose and similar rates of hypoglycemia. There was an interesting numerical 50% reduction in severe hypoglycemic event rates with numbers too small to reach statistical significance. The EDITION 4 trial, in contrast, did not find a benefit of Gla-300 in patients with T1D switching from a different basal insulin (7). In that controlled trial, hypoglycemic event rates did not differ overall, but the rate of nocturnal confirmed or severe hypoglycemia was 31% lower with Gla-300 compared with Gla-100 during the first 8 weeks of the study.

Our study had several limitations. As in all real-world outcomes research, our therapy cohorts may reflect selection bias that may not have been controlled by the propensity matching process. The LMC Diabetes Patient Registry represents a referral-based specialist practice, and findings may not be generalizable to the general insulin-using diabetes population. Despite the large sample size, only 76% of the study sample had an evaluable outcome for A1C within the defined time frame. Although the LMC Diabetes Registry collects information about any and severe self-reported hypoglycemia, information for confirmed hypoglycemia is not readily available. Furthermore, we were unable to directly assess medication compliance, and it is likely that patients in this study were less compliant than patients in randomized clinical trials. Although we report rates of discontinuation, this assessment is limited to patients who had actually returned for reassessment and may be underestimated. Finally, because this study was observational, causality cannot be inferred.

This retrospective real-world analysis confirms the clinical trial findings of similar to greater improvements in glycemic control with Gla-300 compared with Gla-100, with a trend towards lower rates of self-reported hypoglycemia among insulin-naïve patients. Our results are in line with a similar trend observed in the recently presented LIGHTNING study (13). A propensity-matched cohort switching from basal insulin to Gla-300 showed significantly lower severe hypoglycemic event rates vs Gla-100. In our study, basal insulin switchers in patients with T1D, and patients with T2D switching from Gla-100 to Gla-300, also had significant improvements in A1C, with no change in weight or basal insulin dose. Further studies are warranted evaluating comparisons between Gla-300 and newer basal insulins, particularly insulin degludec, and combinations of basal insulin and glucagon-like peptide-1 receptor agonists (as these become available), in continued assessments of health outcomes, and treatment satisfaction and cost-effectiveness.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Diabetes* at www.canadianjournalofdiabetes.com.

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Author Contributions

A.A., R.E.B., L.S. and R.A. designed the study. R.E.B. and D.J. analyzed the data. A.A., R.E.B. and R.A. wrote the manuscript. All authors provided critical revisions to the manuscript and approved the final version.

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Supplementary Table 1
Baseline characteristics of the insulin-naïve cohort and the NPH or detemir switch cohort prior to propensity score matching

Characteristic	Naïve			Switch from NPH or detemir		
	Gla-300 (n=194)	Gla-100 (n=900)	p value	Gla-300 (n=122)	Gla-100 (n=133)	p value
Age, years	53.8±10.0	64.5±12.7	<0.001	58.5±9.4	65.8±12.2	<0.001
Males	113 (58.3)	491 (54.6)	0.35	68 (55.7)	73 (54.9)	0.89
Duration T2D, years	10.9±7.3	12.7±8.4	0.005	15.4±8.6	17.8±7.7	0.02
A1C, %	9.80±1.79	9.46±1.76	0.02	8.67±1.67	8.54±1.47	0.50
Weight, kg	88.1±21.2	83.0±21.4	0.003	99.9±26.9	84.9±21.2	<0.001
BMI, kg/m^2	31.0 ± 6.9	30.0 ± 6.5	0.06	34.0 ± 76.0	31.0 ± 6.3	0.001
Basal insulin dose, U	12.5±4.2	10.6±4.6	<0.01	66.6±47.2	38.8±35.0	<0.001
Basal insulin dose, U/kg	0.15±0.05	0.13±0.06	0.01	0.65±0.44	0.44±0.27	<0.001
Education						
Postsecondary school	107 (55.2)	306 (34.0)	<0.001	68 (55.7)	42 (31.6)	<0.001
Secondary school	51 (26.3)	309 (34.3)	0.03	34 (27.9)	35 (26.3)	0.78
Declined response	36 (18.9)	285 (31.7)	<0.001	20 (16.4)	56 (42.1)	<0.001
Ethnicity						
Caucasian	81 (41.8)	428 (47.6)	0.14	79 (64.8)	58 (43.6)	<0.001
Asian	57 (29.4)	230 (25.6)	0.27	15 (12.3)	43 (32.3)	0.001
Other	35 (18.0)	116 (12.9)	0.06	19 (15.6)	19 (14.3)	0.77
Declined response	21 (10.8)	126 (14.0)	0.24	9 (7.4)	13 (9.8)	0.50
Microvascular disease	27 (13.9)	151 (16.8)	0.33	30 (24.6)	34 (25.6)	0.86
Macrovascular disease	15 (7.7)	190 (21.1)	<0.001	16 (13.1)	39 (29.3)	0.002
Diabetes therapy						
Rapid-acting insulin	9 (4.6)	70 (7.8)	0.13	70 (57.4)	77 (57.9)	0.93
Metformin	171 (88.1)	712 (79.1)	0.003	92 (75.4)	102 (76.7)	0.81
SU	115 (59.3)	576 (64.0)	0.22	29 (23.8)	31 (23.3)	0.93
GLP-1 RA	26 (13.4)	77 (8.6)	0.04	41 (33.6)	3 (2.3)	<0.001
DPP-4i	115 (59.3)	617 (68.6)	0.01	40 (32.8)	63 (47.4)	0.02
SGLT2i	59 (30.4)	250 (27.8)	0.45	55 (45.1)	34 (25.6)	0.001

Note: Data are presented as mean ± SD, n (%) or as otherwise indicated.
A1C, glycated hemoglobin; *BMI,* body mass index; *DPP-4i,* dipeptidyl peptidase-4 inhibitors; *Gla-100,* insulin glargine 100 U/mL; *Gla-300,* insulin glargine 300 U/mL; *GLP-1 RA,* glucagon-like peptide-1 receptor agonist; *NPH,* neutral protamine Hagedorn; *SGLT2i,* sodium-glucose co-transporter 2 inhibitors; *SU,* sulfonylurea; *T2D,* type 2 diabetes.