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ORIGINAL ARTICLE

Glycaemic goal attainment and hypoglycaemia outcomes in type 2 diabetes patients initiating insulin glargine 300 units/mL or 100 units/mL: Real-world results from the DELIVER Naïve cohort study

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Aims: To compare HbA1c and hypoglycaemia in insulin-naïve patients with type 2 diabetes (T2D) who initiated insulin glargine 300 units/mL (Gla-300) or 100 units/mL (Gla-100).

Materials and methods: This retrospective cohort study examined electronic medical records of insulin-naïve adults with T2D who initiated Gla-300 or Gla-100 during March 2015 through to December 2016 with active records for ≥12 months before and ≥6 months after initiation, and ≥1 valid HbA1c value during 6-month baseline and 90–180-day follow-up. Outcomes included HbA1c and hypoglycaemia. Cohorts were propensity score-matched (1:2) on baseline demographic and clinical characteristics. Sensitivity analyses were conducted using broader inclusion criteria.

Results: The matched cohorts included 1004 Gla-300 and 2008 Gla-100 initiators (mean age 60.4 years; 53.2% male). During 6-month follow-up, Gla-300 versus Gla-100 initiators had a greater mean HbA1c decrease (−1.52 ± 2.08% vs. −1.30 ± 2.12%; $P = 0.003$) and more patients achieved HbA1c <7% (25.0% vs. 21.5%; $P = 0.029$) and <8% (55.0% vs. 49.2%; $P = 0.002$); and HbA1c <7% (21.9% vs. 17.4%; $P = 0.003$) and <8% (49.1% vs. 41.8%; $P < 0.001$) without hypoglycaemia. Gla-300 initiators were similarly or less likely to have any or inpatient/emergency department-associated hypoglycaemia during 3- and 6-month follow-up (e.g. any hypoglycaemia to 6 months: 9.7% vs. 12.5%; adjusted odds ratio 0.61; $P = 0.057$).

Conclusions: Among insulin-naïve adults with T2D, Gla-300 was associated with significantly better HbA1c reductions (latest value during 90–180-day follow-up) and similar or improved hypoglycaemia outcomes (3- and 6-month follow-up) than Gla-100.

KEYWORDS

basal insulin, cohort study, hypoglycaemia, type 2 diabetes

1 | INTRODUCTION

The Centers for Disease Control and Prevention has estimated that 30 million Americans (9.4% of the population) had diabetes in 2015, the vast majority of whom had type 2 diabetes (T2D).[1] Although metformin is the preferred initial pharmacological treatment, along with lifestyle modifications, most patients with T2D may require additional treatments (e.g. sulphonylurea, thiazolidinedione, dipeptidyl peptidase-4 inhibitor, sodium glucose co-transporter 2 inhibitor or glucagon-like peptide-1 receptor antagonist [GLP-1 RA]), and some will ultimately require basal insulin.[2,3]

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Insulin glargine 100 units/mL (Gla-100[4]), a first-generation basal insulin, is widely used among patients with T2D. It is injected once daily to provide basal insulin levels to help meet glycaemic control needs between meals and at night. Insulin glargine 300 units/mL (Gla-300[5]), a second-generation basal insulin analog, has been available in the United States since February 2015. Gla-300 has more stable pharmacokinetic and pharmacodynamic profiles and a longer duration of action than Gla-100.[6] Gla-300 has been shown to achieve similar reduction in HbA1c levels as Gla-100, with lower risks of overall and nocturnal hypoglycaemia.[6]

Gla-300 and Gla-100 have been compared in EDITION 3, a randomized controlled trial of 878 insulin-naïve T2D patients on oral antihyperglycaemic drugs who were treated to a target self-monitored fasting plasma glucose level of 4.4–5.6 mmol/L (80–100 mg/dL) without hypoglycaemia.[7] Both formulations elicited comparable reductions in HbA1c, but hypoglycaemia outcomes were generally more favourable among those taking Gla-300, although statistical significance varied depending on the hypoglycaemia definition used.[7]

Although randomized controlled trials provide essential information on the efficacy and safety of pharmacologic agents, the strict inclusion and exclusion criteria and the specialized clinical research settings are vastly different from the real-world settings in which medications are ultimately used. For example, Saunders et al.[8] have reported that only 4–50% of real-world patients with T2D would have been eligible for various randomized controlled trials that have assessed the impact of glycaemic control on macrovascular disease.

Real-world studies can therefore provide complementary clinical effectiveness information that may be more generalizable and pertinent to clinicians and healthcare-delivery systems.[9,10] The interest in comparative effectiveness research[11] and a growing demand for real-world data[9] to support clinical decision-making have increased the use of other data sources (e.g. electronic medical records [EMRs] and/or claims data). Therefore, a series of studies examining the use of first-generation (Gla-100 and insulin detemir) and second-generation (Gla-300 and insulin degludec) basal insulins among patients with T2D in real-world clinical practice have been carried out. The DELIVER series of studies examined the effects of basal insulin switching, and include: DELIVER D (patients switched from Gla-100 to Gla-300 or insulin degludec);[12] DELIVER D+ (patients switched from Gla-100 or insulin detemir to Gla-300 or insulin degludec);[13] DELIVER 2 (patients switched to Gla-300 or another basal insulin);[14] and DELIVER 3 (patients aged ≥65 years who switched to Gla-300 or another basal insulin).[15]

The objectives of the current study, the DELIVER Naïve study, were to examine HbA1c reduction and goal attainment (overall and without hypoglycaemia) and hypoglycaemia outcomes in insulin-naïve patients who newly initiated Gla-300 or Gla-100 in real-world clinical practice.

2 | MATERIALS AND METHODS

2.1 | Study design

The study period for the retrospective DELIVER Naïve cohort study was 1 March 2014 through to 30 June 2017. Patients were identified during 1 March 2015 through to 31 December 2016 (the identification period). The date of first prescription of Gla-300 or Gla-100 during the identification period was defined as the index date. The 12 months prior to the index date was the baseline period; outcomes were evaluated during the 6-month follow-up period.

2.2 | Data source

Data were obtained from Accenture's Predictive Health Intelligence Environment (PHIE) which, based on IBM Watson Health Explorys database, provides real-world, real-time EMR data for ~18% of the US population. PHIE, which is used by 39 major integrated healthcare delivery systems, captures more than 315 billion clinical, financial and operational data elements, spanning 55 million unique patients, 420 hospitals and more than 400 000 providers.

Data (i.e. demographics, diagnoses, treatment, laboratory results, encounter-level data, etc.) were standardized and normalized using common ontologies. Data from multiple health systems (e.g. ambulatory, outpatient, emergency and inpatient) were available, with a combination of data from clinical EMRs, healthcare system outgoing bills and adjudicated payer claims.

2.3 | Study population

Patients were included if they: had ≥1 diagnosis of T2D by International Classification of Diseases (ICD) codes[16] (Supporting Information Table S1) at any time in the EMR database; had ≥1 prescription of Gla-300 or Gla-100 during the identification period; received treatment with an oral antihyperglycaemic drug or GLP-1 RA, but did not use insulin during the 12-month baseline period; were active in the EMR system for ≥12 months before and ≥6 months after the index date; were aged ≥18 years on the index date and had ≥1 valid HbA1c value (3–15%) during both 6-month baseline and 90–180-day follow-up.

Patients were excluded if they had prescriptions for >1 basal insulin on the index date or had type 1 diabetes (ICD codes and definitions to distinguish from T2D; Supporting Information Table S1).

Baseline data extracted from the EMRs included: gender, age, race, insurance type, United States geographic region, physician specialty associated with basal insulin initiation, body mass index (last value during 12-month baseline), HbA1c (last value during 6-month baseline), hypoglycaemia (definitions in Supporting Information Table S1) and healthcare utilization (during 6-month baseline), and comorbidities/diabetic complications and diabetes/other medications (during 12-month baseline).

2.4 | Propensity score matching

To minimize confounding by indication, patients were propensity score-matched[17] (1:2, Gla-300:Gla-100) based on all available (39) baseline demographics and clinical characteristics using a greedy nearest neighbour algorithm. This selected a patient treated with Gla-300 and then selected two patients treated with Gla-100 with the closest propensity scores. Once matched, patients were not reconsidered. Propensity scores were matched using 2–8

decimal places. This was performed sequentially from highest to lowest digit match.

2.5 | Outcomes

Outcomes were compared between propensity score-matched patients who initiated Gla-300 versus Gla-100. Primary outcomes were follow-up HbA1c (last value during 90–180-day follow-up) and HbA1c reduction from baseline. Secondary outcomes were: HbA1c goal attainment (<7% and <8%), overall and without experiencing hypoglycaemia during 6-month follow-up and hypoglycaemia (based on ICD diagnoses or blood glucose ≤3.9 mmol/L [70 mg/dL]; Supporting Information Table S1), overall and associated with an inpatient or emergency department (ED) encounter. Hypoglycaemia outcomes are reported as incidence (proportion of patients with ≥1 events) and event rate (number of events per patient per year [PPPY]).

2.6 | Statistical analysis

Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations (SDs). To measure the balance before and after propensity score matching, baseline characteristics were compared using chi-square tests for categorical variables and two-sample t-tests for continuous variables; and standardized mean differences (SMDs) were also calculated.

Follow-up versus baseline HbA1c reductions within each matched cohort were tested by paired t-tests. HbA1c reductions were compared between cohorts using a linear mixed model with repeated measures. A Cochran–Mantel–Haenszel test was used to assess difference in the HbA1c goal attainment (overall and without hypoglycaemia) between cohorts.

Odds ratios (ORs), adjusted for baseline hypoglycaemia incidence, were calculated to compare the risk of hypoglycaemia between the two cohorts using a generalized linear model. Adjusted least squares mean (LSM) differences for event rates of hypoglycaemia in the two cohorts were calculated using a mixed-effect model with repeated measures adjusted for baseline hypoglycaemic events.

Variables that remained significantly different between the cohorts after propensity score matching were controlled in the models as confounders.

2.7 | Sensitivity analysis

For the hypoglycaemia outcomes, the requirement for HbA1c data during the 90–180-day follow-up was removed to capture a broader patient cohort, and also because hypoglycaemia can occur independently of HbA1c level. These patients were propensity score-matched using the same procedure as for the main cohort. This sensitivity analysis was preplanned in the study and protocol design stage.

3 | RESULTS

3.1 | Patient selection and matching

As shown in Figure 1, 1044 and 15 901 patients who initiated Gla-300 and Gla-100, respectively, met the inclusion criteria. Outcomes were analysed in 1004 Gla-300 and 2008 Gla-100 propensity score-matched patients.

3.2 | Baseline characteristics

Baseline patient characteristics before propensity score matching are shown in Supporting Information Table S2. Patients who initiated Gla-300 versus Gla-100 were younger, were more likely to have commercial insurance and be treated by an endocrinologist, had a higher mean baseline HbA1c and lower mean Charlson comorbidity index score, were more likely to have been prescribed a GLP-1 RA, were prescribed a higher mean number of oral antihyperglycaemic drugs, were less likely to have experienced hypoglycaemia during the 6-month baseline period, and had lower ED and inpatient healthcare resource utilization. These baseline differences were balanced after propensity score matching, except for unknown insurance type (Table 1).

In the matched cohorts, the mean age was 60.4 years and 53% of patients were male (Table 1). Mean ± SD baseline HbA1c was similar in the Gla-300 and Gla-100 cohorts (9.59 ± 1.96% and 9.56 ± 1.94%, respectively), and similar proportions had hypoglycaemia during the 6-month baseline period (5.7% and 6.7%, respectively; Table 1).

3.3 | HbA1c endpoints

During 90–180-day follow-up, mean HbA1c decreased significantly ($P < 0.001$) from baseline in both cohorts (Figure 2). Patients who initiated Gla-300 had a significantly greater mean HbA1c reduction than those who initiated Gla-100 (−1.52 ± 2.08% vs. −1.30 ± 2.12%; $P = 0.003$; Figure 2).

During 6-month follow-up, patients who initiated Gla-300 versus Gla-100 were significantly more likely to reach the HbA1c goals of <7% (25.0% vs. 21.5%; $P = 0.029$) and <8% (55.0% vs. 49.2%; $P = 0.002$) (Figure 3A) and to reach the goals without experiencing hypoglycaemic events (<7% goal: 21.9% vs. 17.4%; $P = 0.003$; <8% goal: 49.1% vs. 41.8%; $P < 0.001$) (Figure 3B).

3.4 | Hypoglycaemia endpoints

During 3-month follow-up, inpatient/ED-associated hypoglycaemia incidence (OR 0.35; $P = 0.009$) and event rate (LSM difference −0.13; $P = 0.003$) were significantly lower for Gla-300 initiators in the main analysis (Figure 4A,B).

During 6-month follow-up, the all hypoglycaemia incidence (OR 0.77; $P = 0.057$) and event rate (LSM difference −0.11; $P = 0.077$), and the inpatient/ED incidence (OR 0.61; $P = 0.051$) and event rate (LSM difference −0.07; $P = 0.093$), were numerically in favour of Gla-300 (Figure 4A,B).

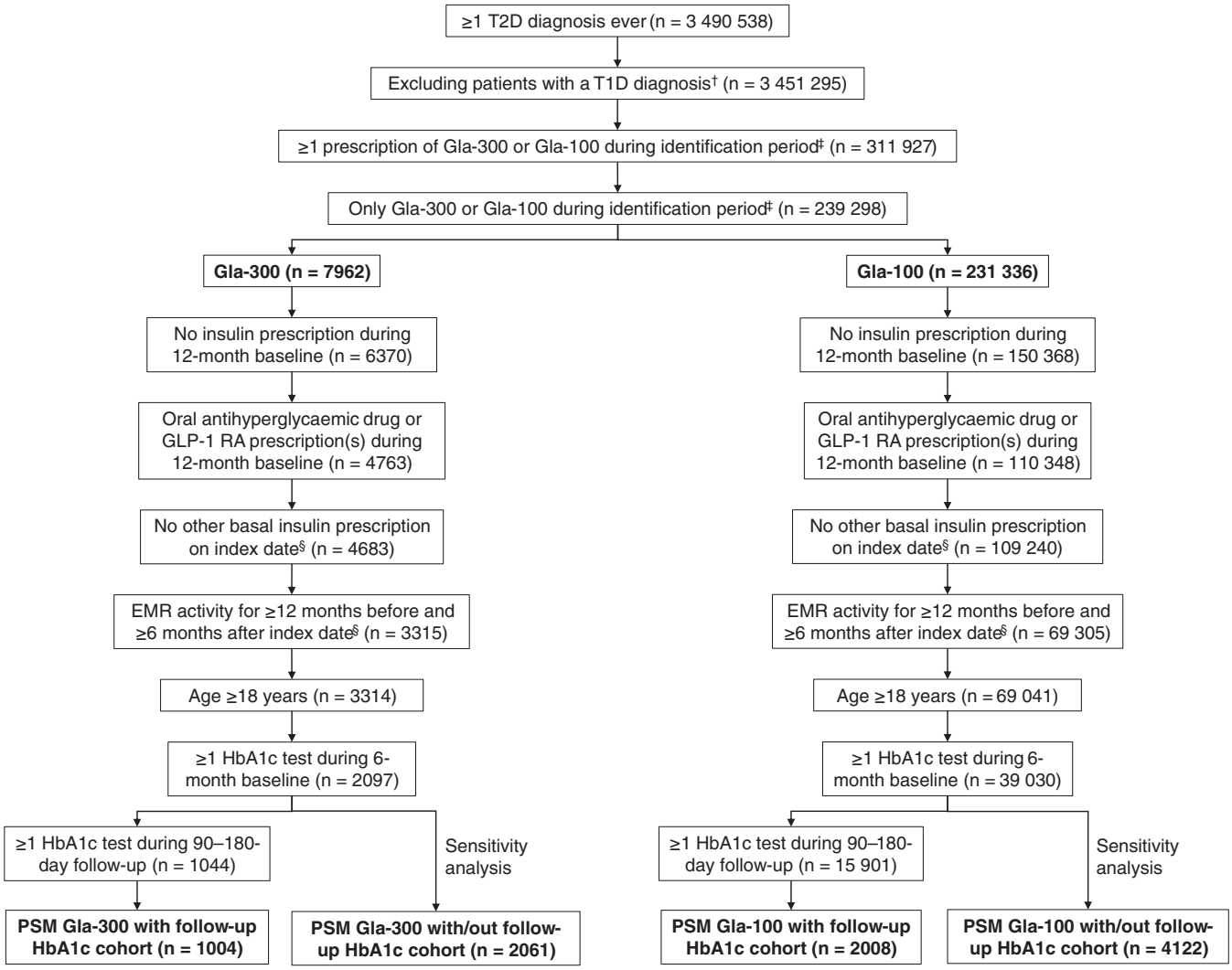


FIGURE 1 Patient flow chart. Abbreviations: EMR, electronic medical record; Gla-100, insulin glargine 100 units/mL; Gla-300, insulin glargine 300 units/mL; GLP-1 RA, glucagon-like peptide-1 receptor antagonist; PSM, propensity score matching; T1D, type 1 diabetes; T2D, type 2 diabetes. †See Supporting Information Table S1 for the conditions used to identify patients with T1D. ‡Identification period: 1 March 2015 to 31 December 2016. §Index date: date of first Gla-100 or Gla-300 prescription

3.4.1 | Sensitivity analysis

In the sensitivity analysis, hypoglycaemia was analysed among patients without requirement of follow-up HbA1c. This resulted in matched Gla-300 and Gla-100 cohorts of 2061 and 4122 patients, respectively. The baseline characteristics of the sensitivity analysis population are shown in Supporting Information Table S3. Similar proportions had hypoglycaemia during the 6-month baseline period (5.6% and 5.3%, respectively; Supporting Information Table S3).

During 3-month follow-up, all hypoglycaemia and inpatient/ED-associated hypoglycaemia incidences (all: OR 0.62; $P < 0.001$; inpatient/ED: OR 0.37; $P < 0.001$) and event rates (all: LSM difference −0.18; $P < 0.001$; inpatient/ED: LSM difference −0.08; $P = 0.009$) were all significantly lower in the Gla-300 cohort (Figure 4C,D).

During 6-month follow-up, all hypoglycaemia and inpatient/ED-associated hypoglycaemia incidences (all: OR 0.71; $P < 0.001$; inpatient/ED: OR 0.57; $P = 0.003$) and all hypoglycaemia event rate (LSM difference −0.12; $P = 0.002$) were significantly in favour of Gla-300, while the inpatient/ED-associated hypoglycaemia event rate was numerically in favour of Gla-300 (Figure 4C,D).

4 | DISCUSSION

In this large real-world EMR study with propensity score-matched cohorts, insulin-naïve T2D patients who initiated Gla-300 achieved significantly better HbA1c reductions and a trend for improved hypoglycaemia outcomes than those who initiated Gla-100. This trend became statistically significant when a larger pool of matched patients was examined as part of the sensitivity analyses. These analyses, without the requirement for follow-up HbA1c levels, appropriately mirror hypoglycaemia evaluation in the real-world clinical setting, where hypoglycaemia can occur irrespective of HbA1c levels.[18,19]

Absolute HbA1c reductions in this study were of the same magnitude as those observed in the EDITION 3 randomized controlled trial of 878 insulin-naïve T2D patients who initiated Gla-300 or Gla-100, although both baseline and follow-up HbA1c were higher in the

TABLE 1 Baseline patient characteristics after propensity score matching

	Gla-300 (*n* = 1004)	Gla-100 (*n* = 2008)	*P*	SMD
Age, years	60.2 ± 12.3	60.5 ± 12.3	0.539	0.02
Male	523 (52.1)	1080 (53.8)	0.548	0.03
Body mass index,[a,b] kg/m^2	33.6 ± 7.0	33.9 ± 7.3	0.302	0.04
Race				
Caucasian	777 (77.4)	1576 (78.5)	0.748	0.03
African American	135 (13.4)	236 (11.8)	0.212	0.05
Other	51 (5.1)	99 (4.9)	0.862	0.01
Unknown	41 (4.1)	97 (4.8)	0.367	0.04
Insurance type				
Commercial	386 (38.4)	803 (40.0)	0.525	0.03
Medicare	287 (28.6)	634 (31.6)	0.162	0.07
Medicaid	42 (4.2)	84 (4.2)	1.000	0.00
Other	51 (5.1)	102 (5.1)	1.000	0.00
Unknown	238 (23.7)	385 (19.2)	0.010	0.11
United States geographic region				
Midwest	565 (56.3)	1194 (59.5)	0.281	0.06
South	365 (36.4)	666 (33.2)	0.159	0.07
West	46 (4.6)	101 (5.0)	0.600	0.02
Northeast	28 (2.8)	46 (2.3)	0.411	0.03
Unknown	0	1 (<0.1)	0.480	0.03
Physician specialty associated with basal insulin initiation				
Primary care practitioner	500 (49.8)	932 (46.4)	0.204	0.07
Internal medicine	193 (19.2)	442 (22.0)	0.116	0.07
Endocrinologist	91 (9.1)	190 (9.5)	0.736	0.01
Other/unknown	220 (21.9)	444 (22.1)	0.913	0.00
HbA1c[c]	9.59 ± 1.96	9.56 ± 1.94	0.669	0.02
<7%	69 (6.9)	140 (7.0)	0.922	0.00
7% to <8%	128 (12.7)	252 (12.5)	0.885	0.01
8% to <9%	235 (23.4)	476 (23.7)	0.874	0.01
≥9%	572 (57.0)	1140 (56.8)	0.946	0.00
Hypoglycaemia during 6-month baseline	57 (5.7)	134 (6.7)	0.306	0.04
Comorbidities/diabetic complications during 12-month baseline				
Hyperlipidaemia	788 (78.5)	1566 (78.0)	0.884	0.01
Hypertension	780 (77.7)	1491 (74.3)	0.306	0.08
Obesity	310 (30.9)	577 (28.7)	0.307	0.05
Neuropathy	141 (14.0)	260 (12.9)	0.437	0.03
Retinopathy	43 (4.3)	100 (5.0)	0.408	0.03
Nephropathy	46 (4.6)	92 (4.6)	1.000	0.00
Charlson comorbidity index score	0.83 ± 1.38	0.85 ± 1.38	0.708	0.01
Treatments during 12-month baseline				
Injectable GLP-1 RA	180 (17.9)	354 (17.6)	0.854	0.01
Oral antihyperglycaemic drugs	736 (73.3)	1453 (72.4)	0.774	0.02
Number of oral antihyperglycaemic drugs	1.5 ± 0.9	1.5 ± 1.0	0.671	0.02
Metformin	503 (50.1)	1007 (50.1)	0.985	0.00
Sulphonylureas	441 (43.9)	917 (45.7)	0.502	0.04
Dipeptidyl peptidase-4 inhibitors	304 (30.3)	577 (28.7)	0.460	0.03
Sodium glucose co-transporter-2 inhibitors	183 (18.2)	350 (17.4)	0.624	0.02
Thiazolidinediones	80 (8.0)	147 (7.3)	0.542	0.02
Meglitinides	20 (2.0)	24 (1.2)	0.088	0.06
Alpha-glucosidase inhibitor	8 (0.8)	16 (0.8)	1.000	0.00

TABLE 1 (Continued)

	Gla-300 (*n* = 1004)	Gla-100 (*n* = 2008)	*P*	SMD
Other				
Statins	503 (50.1)	999 (49.8)	0.898	0.01
Angiotensin-converting enzyme inhibitors	322 (32.1)	609 (30.3)	0.417	0.04
Beta-blockers	224 (22.3)	419 (20.9)	0.419	0.04
Angiotensin receptor blockers	77 (7.7)	145 (7.2)	0.669	0.02
Calcium channel blockers	74 (7.4)	166 (8.3)	0.411	0.03
Diuretics	34 (3.4)	61 (3.0)	0.612	0.02
Healthcare utilization during 6-month baseline				
Emergency department	168 (16.7)	338 (16.8)	0.950	0.00
Endocrine outpatient	153 (15.2)	317 (15.8)	0.720	0.02
Inpatient	74 (7.4)	130 (6.5)	0.373	0.04

Abbreviations: Gla-100, insulin glargine 100 units/mL; Gla-300, insulin glargine 300 units/mL; GLP-1 RA, glucagon-like peptide-1 receptor antagonist; SD, standard deviation; SMD, standardized mean difference.
Data are presented as mean ± SD or *n* (%).
[a]Last value during 6-month baseline.
[b]Data available for 967 Gla-300 and 1948 Gla-100 initiators.
[c]Last value during 12-month baseline.

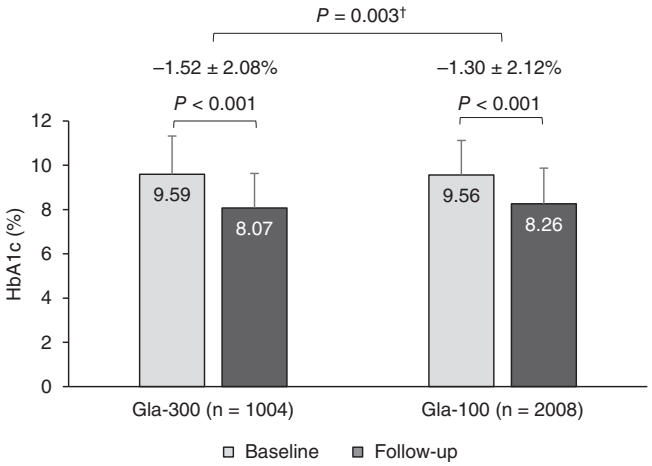


FIGURE 2 HbA1c values (mean ± SD) during 6-month baseline and 90–180-day follow-up in Gla-300 and Gla-100 cohorts. Abbreviations: Gla-100, insulin glargine 100 units/mL; Gla-300, insulin glargine 300 units/mL. †With payer as covariate

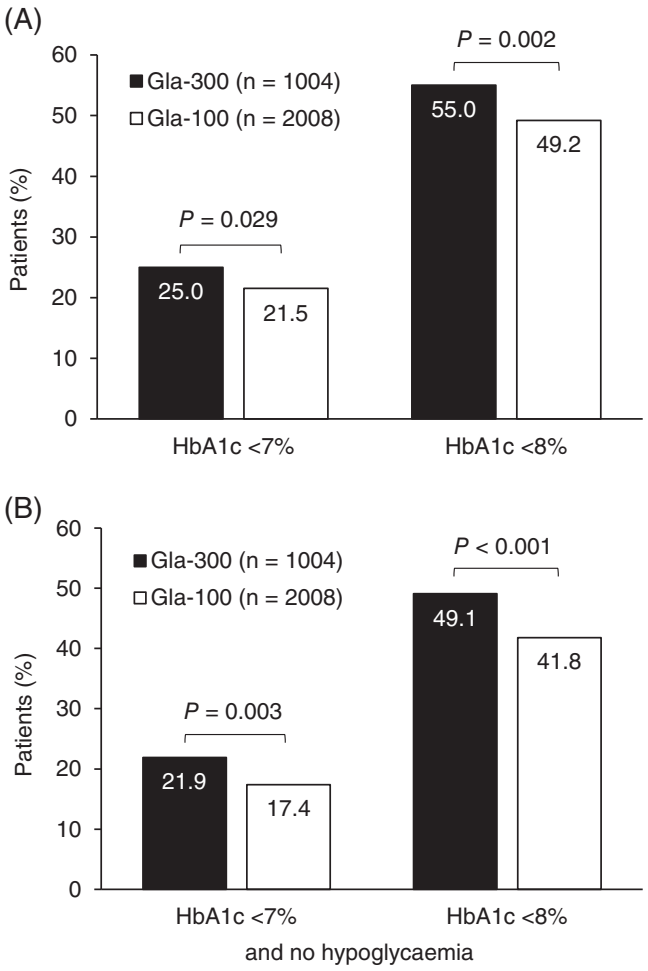


FIGURE 3 Attainment of HbA1c goals (<7% and <8%): A, overall and B, without experiencing hypoglycaemia. Abbreviations: Gla-100, insulin glargine 100 units/mL; Gla-300, insulin glargine 300 units/mL

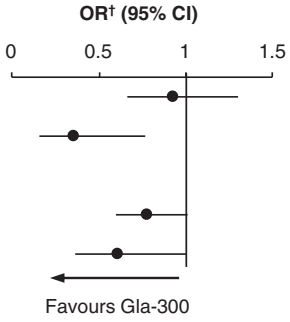
current study than in EDITION 3.[7] However, Gla-300 was associated with significantly better HbA1c reductions than Gla-100 in the current study, while EDITION 3 reported similar mean HbA1c reductions at 6 months (−1.42 ± 0.05% and −1.46 ± 0.05%, respectively), meeting the study's non-inferiority criterion.[7] Achieve Control, a randomized, open-label, prospective, pragmatic trial that included 3304 insulin-naïve patients initiating Gla-300 versus Gla-100 or insulin detemir in real-world clinical settings, also reported similar HbA1c reductions (−1.41% vs. −1.36%; *P* = 0.32).[20,21]

The magnitudes of the lower incidence and event rates of hypoglycaemia in favour of Gla-300 versus Gla-100 in the current study were greater during 3-month than 6-month follow-up, especially in the larger cohort sensitivity analyses without HbA1c requirement (Figure 4C,D). It is probable that the lower incidence of hypoglycaemia during the initial 3 months allowed for better dose titration, with less fear of hypoglycaemia, resulting in the better HbA1c reduction in favour of Gla-300 versus Gla-100. However, insulin dose information was not readily available in this retrospective database analysis to confirm this.

Regarding glycaemic goals, the most widely applicable glycaemic control (HbA1c) target is <7%,[2,3] although more or less stringent

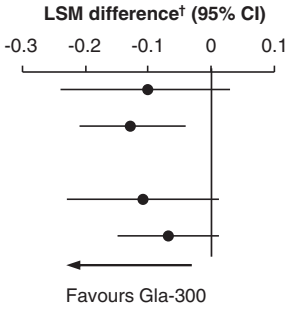
(A)

	Incidence (%) Gla-300 (n = 1004)	Incidence (%) Gla-100 (n = 2008)	OR† (95% CI)	P†
3-month follow-up				
All hypoglycaemia	56 (5.58)	130 (6.47)	0.93 (0.66 to 1.30)	0.656
Inpatient/ED hypoglycaemia	8 (0.80)	43 (2.14)	0.35 (0.16 to 0.77)	0.009
6-month follow-up				
All hypoglycaemia	97 (9.66)	250 (12.45)	0.77 (0.60 to 1.01)	0.057
Inpatient/ED hypoglycaemia	24 (2.39)	69 (3.44)	0.61 (0.37 to 1.00)	0.051



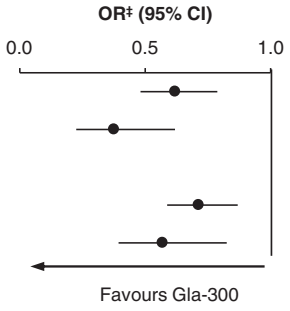
(B)

	Events (PPPY) Gla-300 (n = 1004)	Events (PPPY) Gla-100 (n = 2008)	LSM difference† (95% CI)	P†
3-month follow-up				
All hypoglycaemia	78 (0.31)	226 (0.45)	–0.10 (–0.24 to 0.03)	0.135
Inpatient/ED hypoglycaemia	10 (0.04)	85 (0.17)	–0.13 (–0.21 to –0.04)	0.003
6-month follow-up				
All hypoglycaemia	175 (0.35)	489 (0.49)	–0.11 (–0.23 to 0.01)	0.077
Inpatient/ED hypoglycaemia	45 (0.09)	147 (0.15)	–0.07 (–0.15 to 0.01)	0.093



(C)

	Incidence (%) Gla-300 (n = 2061)	Incidence (%) Gla-100 (n = 4122)	OR‡ (95% CI)	P‡
3-month follow-up				
All hypoglycaemia	115 (5.58)	325 (7.88)	0.62 (0.48 to 0.79)	<0.001
Inpatient/ED hypoglycaemia	19 (0.92)	96 (2.33)	0.37 (0.23 to 0.62)	<0.001
6-month follow-up				
All hypoglycaemia	162 (7.86)	424 (10.29)	0.71 (0.59 to 0.87)	<0.001
Inpatient/ED hypoglycaemia	39 (1.89)	127 (3.08)	0.57 (0.39 to 0.83)	0.003



(D)

	Events (PPPY) Gla-300 (n = 2061)	Events (PPPY) Gla-100 (n = 4122)	LSM difference‡ (95% CI)	P‡
3-month follow-up				
All hypoglycaemia	188 (0.36)	552 (0.54)	–0.18 (–0.28 to –0.08)	<0.001
Inpatient/ED hypoglycaemia	37 (0.07)	153 (0.15)	–0.08 (–0.13 to –0.02)	0.009
6-month follow-up				
All hypoglycaemia	294 (0.29)	810 (0.39)	–0.12 (–0.19 to –0.04)	0.002
Inpatient/ED hypoglycaemia	78 (0.08)	216 (0.10)	–0.03 (–0.07 to 0.01)	0.155

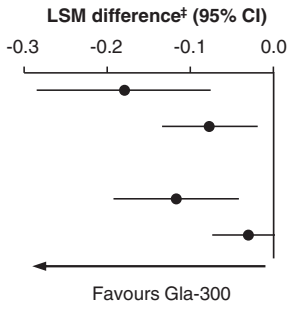


FIGURE 4 Overall and inpatient/ED-associated hypoglycaemia during follow-up in the main analysis (patients with ≥1 follow-up HbA1c) and the sensitivity analysis (with the requirement for ≥1 follow-up HbA1c removed): A, main analysis incidences; B, main analysis event rates; C, sensitivity analysis incidences; and D, sensitivity analysis event rates. Abbreviations: CI, confidence interval; ED, emergency department; Gla-100, insulin glargine 100 units/mL; Gla-300, insulin glargine 300 units/mL; LSM, least squares mean; OR, odds ratio; PPPY, per person per year. †With baseline hypoglycaemia and payer as covariates. ‡With baseline hypoglycaemia as covariate

targets of <6.5% or <8% may be appropriate for some patients.[2] In the current study, HbA1c goal attainment was significantly better in the matched Gla-300 versus Gla-100 cohort, which is consistent with the greater HbA1c reduction from baseline in the Gla-300 cohort. Conversely, in the EDITION 3 trial, there was little difference in HbA1c goal attainment between the Gla-300 and Gla-100 cohorts (43.1% and 42.1%, respectively), as would be expected given that patients in EDITION 3 were treated to the same target fasting plasma glucose levels.[7] The overall proportion of patients who achieved HbA1c <7% was considerably higher in EDITION 3[7] than in the

current study (42.6% vs. 25.0%). This difference in attainment is probably because matched patients in this DELIVER Naïve study had substantially higher mean baseline HbA1c than patients in EDITION 3 (9.58% vs. 8.54%, respectively). This difference is probably because of the broader HbA1c inclusion criteria in the current study (3–15% vs. 7–11% in EDITION 3) and because, in practice, clinicians often delay the initiation of insulin. Additionally, it has been shown that improvement in HbA1c and glycaemic goal attainment are usually greater within the strictly defined environment of randomized controlled trials than in real-world studies.[10,22] Another contributory factor may be that randomized controlled trials, such as the EDITION studies, include a period of active insulin dose titration, while in DELIVER Naïve patients, dose titration was according to routine clinical practice in a real-world setting and, as such, would probably have been less intensive or consistent, and may have occurred over a longer period. This could indicate that real-world titration is often not sufficiently intensified. Furthermore, low treatment adherence has been identified as one of the main factors for the gap in HbA1c goal attainment that is commonly observed in randomized, controlled trials versus real-world clinical settings.[10]

In the current study, significantly more Gla-300 patients achieved HbA1c goals (<7% or <8%) without hypoglycaemia. Similarly, in the Achieve Control pragmatic study, significantly more patients randomized to Gla-300 versus Gla-100 or insulin detemir achieved the composite primary endpoint (reaching an individualized HbA1c target [<8% if age ≥65 years or with defined comorbidities; <7% otherwise] without documented symptomatic and/or severe hypoglycaemia) (31.3% vs. 27.9%; $P = 0.03$).[21]

For the various hypoglycaemia outcomes in the main analysis of the current DELIVER Naïve study (Figure 4A,B), all were numerically better among patients who were initiated on Gla-300 versus Gla-100, but only inpatient/ED-associated hypoglycaemia incidence and event rate during 3-month follow-up reached statistical significance. With the removal of the requirement for a follow-up HbA1c result, however, the sample size was approximately doubled and all but one of the differences in hypoglycaemia outcomes favouring Gla-300 became statistically significant (Figure 4C,D). Similarly, in a retrospective observational study by Gupta et al.,[23] the risk of hypoglycaemia was statistically significantly lower among insulin-naïve patients who initiated Gla-300 versus Gla-100 (relative risk 0.31; 95% confidence interval 0.12–0.81; $P = 0.018$), although there were similar reductions in HbA1c with Gla-300 and Gla-100. EDITION 3 reported on 48 different hypoglycaemia endpoints, based on incidence/event rates, nocturnal/any time, confirmed (≤3.9/<3.0 mmol/L [≤70/<54 mg/dL]) or severe, documented symptomatic (≤3.9/<3.0 mmol/L [≤70/<54 mg/dL]) and follow-up time (0–6 months/0–8 weeks/9 weeks–6 months).[7] Of these, 13 were significantly in favour of Gla-300, 32 were numerically in favour of Gla-300, and three were numerically in favour of Gla-100.[7]

It should be noted that the hypoglycaemia event rates in the three above-mentioned studies were very different, namely, 0.04 versus 0.08 events PPPY in the study by Gupta et al.,[23] 0.35 versus 0.49 events PPPY (main analysis) or 0.29 versus 0.39 events PPPY (sensitivity analysis) in DELIVER Naïve, and 2.33 versus 3.76 documented symptomatic hypoglycaemia ≤3.9 mmol/L (70 mg/dL) events PPPY in EDITION 3[7] for Gla-300 versus Gla-100, respectively. This is probably because of the very different data collection methods, potential differences between the patient populations, and differences in insulin titration. In their observational study, Gupta et al.[23] asked physicians "Since being initiated on Gla-300 or Gla-100, has this patient reported experiencing any hypoglycaemic events?" and "How many hypoglycaemic events has this patient reported experiencing since being initiated on Gla-300 or Gla-100?", which probably underestimated hypoglycaemia as it relied upon physician recall. Moreover, the physicians were not blinded to the therapy their patients were receiving. DELIVER Naïve included hypoglycaemia events that were captured in the PHIE database, which also probably underestimated hypoglycaemia events, but to a lesser extent. In EDITION 3, patients had 11 assessment visits or telephone contacts during their 6-month follow-up, thus increasing the likelihood of capturing hypoglycaemia events.[7] However, regardless of the methodology used, hypoglycaemia events were consistently lower among insulin-naïve patients who initiated Gla-300 versus Gla-100 in these three studies. This is consistent with the implications of the comparatively more stable pharmacokinetic and pharmacodynamic profiles of Gla-300 versus Gla-100.[6]

4.1 | Strengths and limitations

The results of DELIVER Naïve should be interpreted with caution because of its retrospective design and short follow-up duration (6 months). Also, diagnoses were based on ICD codes,[16] but as EMR data may not link the actual diagnosis name, this could have resulted in misclassification. Furthermore, the reasons for choice of basal insulin were not available in the EMRs, so selection bias may not be completely excluded even after propensity score matching. It should also be considered that EMRs only capture medication prescription, not dispensing or consumption. As dosage data were missing in most of the EMRs, dose information and titration intensity/timing could not be addressed in this study. Even in cases where dosage information was present in the EMRs, it did not adequately capture dose changes during titration.

Although hypoglycaemia associated with an inpatient/ED event should be well captured in the EMR, it is probable that some less severe hypoglycaemia events were not captured as there were no self-monitored blood-glucose or continuous blood-glucose monitoring data. Additionally, not all EMRs contain hospital and ED data, in which case, data on hypoglycaemia are derived from providers' clinical notes, further reducing the capture of these events. Thus, the treatment effect on hypoglycaemia could be underestimated. Also, as the study was powered to evaluate HbA1c outcomes, it may have been underpowered to detect differences in hypoglycaemia. Removing the requirement for a follow-up HbA1c in the sensitivity analysis allowed us to compare hypoglycaemia outcomes in a much larger cohort. However, while the sensitivity analyses appropriately mirror hypoglycaemia evaluation in the real-world clinical setting, where hypoglycaemia can occur irrespective of known HbA1c levels, it should be noted that it is then unclear whether differences in glycaemic attainment levels have contributed to differences in hypoglycaemia.

As discussed above, there were some significant differences between the Gla-300 and Gla-100 cohorts prior to matching. As Gla-300 only became available after 2015, many more patients in the database had initiated Gla-100. If the study period had been longer and/or started later, there would have been more patients in the database who had initiated Gla-300. The larger Gla-100 population was also potentially more heterogeneous. As propensity score matching was used to select Gla-100 initiators based on the characteristics of the Gla-300 initiators, this could limit the generalizability of the results. Finally, although the patients included in this study represented a real-world US population, the results may not be generalizable to the entire US population as most patients (93%) in the current database were from the Midwest or South regions and there were significant prescribing differences between these two regions (Supporting Information Table S2).

In conclusion, data from real-world studies such as the current DELIVER Naïve study can provide additional and complementary information to randomized controlled trials. In this study, initiation of Gla-300 versus Gla-100 by insulin-naïve patients with T2D was associated with significantly improved glycaemic control (based on the latest HbA1c value during the 90–180-day follow-up) and similar or fewer hypoglycaemia events (during 3- and 6-month follow-up, with a greater benefit seen during the first 3 months) in real-world clinical settings. Furthermore, significantly more patients who initiated Gla-300 versus Gla-100 achieved HbA1c targets of <7% and <8% without experiencing hypoglycaemia during the 6-month follow-up. These benefits may contribute to improved patient adherence and better glycaemic control as well as potentially lower healthcare resource utilization and costs as previously reported in a similar real-world evidence study.[14] These findings could be important for patients, their healthcare professionals, integrated delivery networks/healthcare systems, and payers.

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CONFLICT OF INTEREST

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Author contributions

F.L.Z. and R.A.G. designed the study. F.L.Z., R.A.G. and V.E.G. acquired and analysed the data. T.S.B., R.P., P.B. and L.B. interpreted the data. All authors contributed to the drafting, critical review and revision of the manuscript.

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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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