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Switching to insulin glargine 300 units/mL in real-world older patients with type 2 diabetes (DELIVER 3)

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Abstract

Aim: To compare the second-generation basal insulin glargine 300 units/mL (Gla-300) and first-generation basal insulins on glycaemic control and hypoglycaemia risk in older adults with type 2 diabetes (T2D).

Materials and methods: DELIVER 3 was a retrospective observational cohort study of electronic medical records. A total of 1176 older adults (aged ≥ 65 years) with T2D and ≥1 HbA1c value during 6 month baseline and 3 to 6 month follow-up who switched from basal insulin to Gla-300 were propensity score-matched to 1176 older adults who switched to a first-generation basal insulin [insulin detemir (IDet) or insulin glargine 100 units/mL (Gla-100)]. Outcomes were follow-up HbA1c, achievement of HbA1c <7% and <8%, hypoglycaemia incidence and event rates, and healthcare resource utilization.

Results: Following basal insulin switching, HbA1c reductions were greater/similar with Gla-300 versus IDet/Gla-100 (variable follow-up: −0.45% ± 1.40% vs. −0.29% ± 1.57%; P = .021; fixed follow-up: −0.48% ± 1.49% vs. −0.38% ± 1.59%; P = .114), while HbA1c goal attainment was similar in both cohorts. Gla-300 was associated with less hypoglycaemia [event rate: adjusted rate ratio (aRR): 0.63, 95% CI: 0.53-0.75; P < .001] and inpatient/emergency department-associated hypoglycaemia (adjusted hazard ratio: 0.58, 95% CI: 0.37-0.90; P = .016; aRR: 0.43, 95% CI: 0.31-0.60; P < .001) by variable follow-up. By fixed follow-up, hypoglycaemia results significantly or numerically favoured Gla-300.

Conclusion: Among older adults with T2D, switching to Gla-300 versus Gla-100/IDet was associated with greater/similar improvements in glycaemic control, and generally less hypoglycaemia.

KEYWORDS

hypoglycaemia, insulin glargine 300 units/mL, real-world study, type 2 diabetes

1 | INTRODUCTION

Data from the National Health and Nutrition Examination Survey showed that the prevalence of diagnosed diabetes was 9.7% in 2013 to 2016.[1] Of these people, ~12 million were aged ≥65 years, resulting in a prevalence of diabetes in this age group of 25%.[2] Diabetes was estimated to be associated with direct medical costs of US $237 billion in the USA in 2017; >60% of this cost was for those aged ≥65 years.[3]

Older adults with type 2 diabetes (T2D) have an elevated risk of hypoglycaemia compared with younger adults.[4,5] Not surprisingly, hypoglycaemia has been associated with increased healthcare resource utilization and hospitalizations.[6] Additionally, among older adults with T2D, hypoglycaemia has been associated with cognitive decline, dementia, falls, accidents and fractures.[7-10] Therefore, the American Diabetes Association recommends that treatments for older adults with T2D should focus on minimizing the risk of hypoglycaemia.[11] Treatments with a lower risk of hypoglycaemia may also lead to better adherence.[12]

To reduce the risk of hypoglycaemia, glycaemic goals for older adults are less strict than for younger adults, ranging from <7.5% (for otherwise healthy individuals) and from <8.5% (for those with complex/poor health),[13] compared with <7% for younger adults.[11,13] The first-line pharmacologic treatment for older adults with T2D is metformin; other options include oral dipeptidyl peptidase-4 inhibitors, sodium glucose co-transporter 2 inhibitors, glucagon-like peptide-1 receptor agonists and basal insulin.[11]

First-generation basal insulins include insulin glargine 100 units/mL (Gla-100; Lantus[14]) and insulin detemir (IDet; Levemir[15]). Insulin glargine 300 units/mL (Gla-300; Toujeo[16]), a second-generation basal insulin, has a more stable pharmacokinetic/pharmacodynamic profile and a longer duration of action than Gla-100, leading to lower within-day variability and better day-to-day reproducibility.[17,18] In the EDITION randomized controlled trials (RCTs), there was a comparable to lower risk of hypoglycaemia with Gla-300 than with Gla-100 in adults with T2D.[19-22] Similar results have recently been reported in the SENIOR RCT, which enrolled patients aged ≥65 years with T2D.[23]

Although the observed glycaemic control is poorer in real-world settings than in RCTs,[24] real-world evidence is useful to support decision-making.[25] Therefore, the outcomes of switching to Gla-300 or another basal insulin among adults with T2D in real-world clinical practice have been investigated in the DELIVER studies.[26-28] In DELIVER 2, which compared adults who switched basal insulin to Gla-300 or another basal insulin, Gla-300 was associated with less hypoglycaemia and lower healthcare resource utilization, while providing similar glycaemic control.[26] Although 37% of patients in DELIVER 2 were aged ≥65 years, results in this age group were not reported separately. This age group is important because they account for ~40% of patients with diabetes,[2] are at an increased risk of hypoglycaemia[4,5] and its sequelae,[7-10] and are underrepresented in clinical trials.[29]

Therefore, the objective of DELIVER 3 was to examine clinical outcomes (HbA1c and hypoglycaemia) and healthcare resource utilization in patients aged ≥65 years with T2D who switched to Gla-300 or to a first-generation basal insulin (IDet or Gla-100) in real-world clinical practice.

2 | MATERIALS AND METHODS

2.1 | Data source

Data were sourced from Accenture's Predictive Health Intelligence Environment (IBM Explorys, Cleveland, Ohio), which provides electronic medical record (EMR) data for ~18% of the US population. It is used by 39 major integrated healthcare systems and captures >315 billion clinical, financial and operational data elements, spanning 55 million patients, 420 hospitals and >400 000 providers.

2.2 | Study design

DELIVER 3 was a retrospective cohort study. The study period was 1 March 2014 to 28 February 2018, and the identification period was 1 March 2015 to 31 August 2017. The index date was the date of first prescription of Gla-300, IDet or Gla-100 during the identification period. The baseline basal insulin was defined as the most recent basal insulin. The baseline period was 12 months before the index date and the follow-up period was 6 months after the index date.

2.3 | Study population

Inclusion criteria were ≥1 diagnosis of T2D (Table S1)[30] in the EMR database; EMR activity during the identification period, and for ≥12 months before and ≥6 months after the index date; ≥1 prescription of Gla-300, IDet or Gla-100 during the identification period; ≥1 prescription of a different basal insulin during the 12 month baseline; age ≥ 65 years at the index date; and ≥1 valid HbA1c value (≤15%) during the 6 month baseline and 3 to 6 month follow-up. Exclusion criteria were type 1 diabetes (Table S1)[30] and prescriptions for >1 basal insulin on the index date.

Baseline data extracted from the EMRs included sex, race, insurance type, USA geographic region, age (on the index date), body mass index (BMI) (last value during 12 month baseline), HbA1c (last value during 6 month baseline), hypoglycaemia (defined in Table S1), healthcare resource utilization, basal insulin prescription (during 6 month baseline), comorbidities/diabetic complications (identified by International Classification of Diseases [ICD] codes, as detailed in Table S2), non-basal insulin diabetes medications, and non-diabetes medications (during 12 month baseline). Comorbidities were used to calculate the Elixhauser comorbidity index (which predicts in-hospital mortality) and Charlson comorbidity index (which predicts 1 year mortality).[31]

2.4 | Propensity score-matching

To minimize confounding by indication, patients switching to Gla-300 were matched[32] (1:1) to those switching to IDet/Gla-100 using propensity scores, which were derived using a logistic regression model. This included the baseline demographic and clinical characteristics detailed in Table 1, excluding estimated glomerular filtration rate (eGFR), with BMI being categorized as <25 kg/m^2, 25 to <30 kg/m^2, 30 to <35 kg/m^2, ≥35 kg/m^2, or missing. A "greedy nearest neighbour" algorithm was

TABLE 1 Baseline patient characteristics after propensity score-matching

	Gla-300 (n = 1176)	IDet/Gla-100† (n = 1176)	*P*	SMD
Age, years, mean ± SD	71.8 ± 5.5	71.7 ± 5.8	.739	.01
≥75 years, n (%)	330 (28.1)	326 (27.7)	.876	.01
Female, n (%)	626 (53.2)	627 (53.3)	.977	.00
BMI, kg/m^2, mean ± SD[a,b]	33.9 ± 6.8	33.8 ± 7.2	.812	.01
HbA1c, %, mean ± SD[c]	8.60 ± 1.68	8.56 ± 1.66	.520	0.03
Hypoglycaemia, n (%)[c]	196 (16.7)	197 (16.8)	.960	0.00
Comorbidities and/or diabetic complications, n (%)[b]				
Hypertension	1071 (91.1)	1059 (90.1)	.795	0.03
Hyperlipidaemia	1043 (88.7)	1052 (89.5)	.844	0.02
Obesity	419 (35.6)	422 (35.9)	.918	0.01
Neuropathy	319 (27.1)	313 (26.6)	.811	0.01
Depression	181 (15.4)	187 (15.9)	.754	0.01
Retinopathy	130 (11.1)	127 (10.8)	.852	0.01
Nephropathy	116 (9.9)	88 (7.5)	.049	0.08
eGFR, mL/min/1.73 m^2, mean ± SD[d]	60.1 ± 22.2	59.3 ± 23.4	.419	0.04
Elixhauser index, mean ± SD	4.4 ± 2.6	4.5 ± 2.6	.857	0.01
Charlson comorbidity index score, mean ± SD	1.7 ± 1.9	1.7 ± 1.9	.430	0.03
Most common diabetes treatments, n (%)[b]				
Oral antihyperglycaemia drugs	782 (66.5)	735 (62.5)	.228	0.08
Metformin	520 (44.2)	516 (43.9)	.901	0.01
Sulphonylureas	345 (29.3)	325 (27.6)	.440	0.04
Dipeptidyl peptidase-4 inhibitor	233 (19.8)	208 (17.7)	.234	0.05
Sodium glucose co-transporter-2 inhibitor	102 (8.7)	92 (7.8)	.473	0.03
Injectables	704 (59.9)	675 (57.4)	.435	0.05
Rapid-acting insulin	624 (53.1)	586 (49.8)	.275	0.06
Glucagon-like peptide-1 receptor agonist	148 (12.6)	148 (12.6)	1.00	0.00
Concomitant medications, n (%)[b]				
Statins	844 (71.8)	882 (75.0)	.360	0.07
Beta-blockers	472 (40.1)	461 (39.2)	.719	0.02
Angiotensin-converting-enzyme inhibitors	461 (39.2)	492 (41.8)	.315	0.05
Calcium channel blockers	176 (15.0)	184 (15.6)	.673	0.02
Angiotensin receptor blockers	169 (14.4)	155 (13.2)	.437	0.03
Diuretics	98 (8.3)	107 (9.1)	.530	0.03
Healthcare resource utilization, n (%)[c]				
Inpatient visit	158 (13.4)	157 (13.4)	.955	0.00
ED visit	270 (23.0)	276 (23.5)	.797	0.01
Outpatient endocrinologist visit	186 (15.8)	185 (15.7)	.959	0.00

(Continues)

TABLE 1 (Continued)

	Gla-300 (n = 1176)	IDet/Gla-100[†] (n = 1176)	*P*	SMD
Last basal insulin prior to switch, n (%)[c]				
Gla-100	788 (67.0)	786 (66.8)	.960	0.00
IDet	348 (29.6)	346 (29.4)	.939	0.00
Insulin degludec	40 (3.4)	44 (3.7)	.663	0.02

Abbreviations: BMI, body mass index; ED, emergency department; eGFR, estimated glomerular filtration rate; Gla-100, insulin glargine 100 units/mL; Gla-300, insulin glargine 300 units/mL; IDet, insulin detemir; SD, standard deviation; SMD, standardized mean difference.
[a]BMI data were only available for 1166 Gla-300 and 1156 IDet/Gla-100 switchers.
[b]During 12 month baseline (latest measurement for BMI).
[c]During 6 month baseline (latest measurement for HbA1c).
[d]eGFR data were only available for 961 Gla-300 and 917 IDet/Gla-100 switchers.
[e]IDet (n = 798; 67.9%) or Gla-100 (n = 378; 32.1%).

used to match patients using the propensity scores with a calliper width of 0.01. Once matched, patients were not reconsidered. Propensity scores were matched using 2 to 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 switched to Gla-300 and those who switched to a first-generation basal insulin (IDet or Gla-100). HbA1c outcomes were follow-up HbA1c (last value during 3-6 month follow-up), HbA1c reduction from baseline, and HbA1c goal attainment (<7% and <8%). HbA1c was assessed by both variable follow-up (on treatment) and fixed follow-up (intention-to-treat).

Hypoglycaemia outcomes (defined in Table S1) included overall hypoglycaemia and hypoglycaemia associated with an inpatient/emergency department (ED) encounter. They are reported as the incidence of hypoglycaemia (i.e. the proportion of patients with ≥1 event) and the number of events per patient per year. Hypoglycaemia outcomes were assessed in two ways. Firstly, hypoglycaemia events were captured at the earliest time of discontinuation or at 6 months using variable follow-up (on treatment). Secondly, hypoglycaemia events were assessed during 0 to 3 months and 3 to 6 months of follow-up using fixed follow-up (intention-to-treat).

All-cause, diabetes-related and hypoglycaemia-related healthcare resource utilization (incidence and event rates) were assessed using variable follow-up (to discontinuation or 6 months) and fixed follow-up (to 6 months).

Discontinuation was defined as no active prescription of the initiated basal insulin analogue after 45 days from the latest prescription end date, termination of the initiated basal insulin analogue, or switch between basal insulin analogue brands.

2.6 | Statistical analysis

Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations. Baseline characteristics were compared using the χ^2 test for categorical variables and Student's *t* test for continuous variables; standardized mean differences were also calculated.

Follow-up versus baseline HbA1c reductions within each cohort were tested using paired *t* tests. HbA1c reductions were compared between cohorts using Student's *t* test, while HbA1c goal attainment was compared between cohorts using the χ^2 test.

By variable follow-up, odds ratios adjusted (aOR) for baseline hypoglycaemia were calculated for the incidence of hypoglycaemia using logistic regression. Hazard ratios adjusted for baseline hypoglycaemia were calculated for the first event of hypoglycaemia using a Cox proportional hazards model. Rate ratios adjusted for baseline hypoglycaemia were calculated for all hypoglycaemia event rates using Poisson's regression. By fixed follow-up, aORs were calculated for the incidence of hypoglycaemia using logistic regression. Baseline hypoglycaemia-adjusted least-squares mean differences were calculated for hypoglycaemia event rates using a generalized linear model procedure.

Healthcare resource utilization statistical methods were the same as those for hypoglycaemia, but with adjustment for baseline healthcare use rather than hypoglycaemia. HbA1c and hypoglycaemia outcomes were analyzed post hoc in matched patients aged ≥75 years.

3 | RESULTS

3.1 | Patient selection and matching

The study flow diagram is shown in Figure 1. Outcomes were analyzed in 1176 propensity score-matched patients in each cohort (Gla-300 and IDet/Gla-100).

3.2 | Baseline characteristics

Prior to propensity score-matching, there were some statistically significant differences between the two groups, including age, BMI, HbA1c, comorbidities (including neuropathy, depression and dementia), eGFR, hypoglycaemia, comorbidity index and healthcare resource utilization (see Table S3). These baseline differences were ameliorated after propensity score-matching (Table 1).

In the matched cohorts, the mean age was 71.8 years and 53.3% of patients were female (Table 1). Most patients were Caucasian

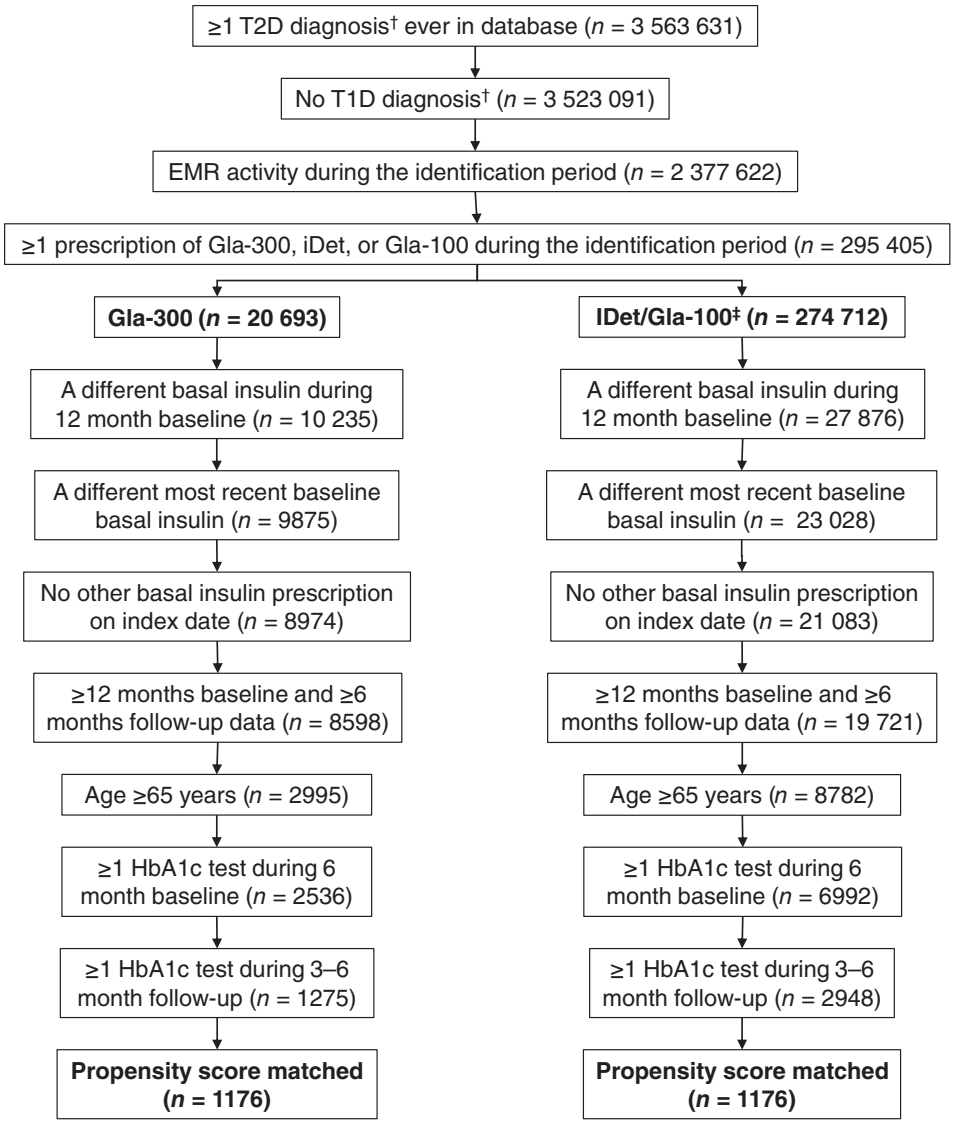

FIGURE 1 Study flow chart. EMR, electronic medical record; Gla-100, insulin glargine 100 units/mL; Gla-300, insulin glargine 300 units/mL; IDet, insulin detemir; T1D, type 1 diabetes; T2D, type 2 diabetes. †See Table S1 for the conditions used to identify patients with T1D and T2D. ‡No Gla-300 prescription during the identification period

(79.3%) or African American (13.6%), and the majority were covered by Medicare (69.6%) or had commercial insurance (14.0%). Most patients were from the Midwest (62.6%) and South (27.3%) USA geographic regions. In the IDet/Gla-100 group, 67.9% of patients switched to IDet and 32.1% to Gla-100. Baseline HbA1c was 8.60% ± 1.68% in the Gla-300 group and 8.56% ± 1.66% in the IDet/Gla-100 group. Nearly 17% of patients in both groups had hypoglycaemia during the 6 month baseline.

3.3 | HbA1c

Mean HbA1c decreased significantly from the 6 month baseline to the 3 to 6 month follow-up in the Gla-300 and IDet/Gla-100 cohorts, with significantly greater HbA1c reductions in the Gla-300 cohort by variable follow-up (Figure 2A) and comparable HbA1c reductions in the two cohorts by fixed follow-up (Figure 2B). Attainment of HbA1c <7% and <8% was comparable in both cohorts by both follow-up methods (Figure 2C,D).

3.4 | Hypoglycaemia

By variable follow-up, all hypoglycaemia outcomes (overall and inpatient/ED-associated; incidence and event rates) were significantly in favour of Gla-300 (Figure 3).

By fixed follow-up, overall hypoglycaemia incidence and event rates decreased significantly from baseline to 3 month follow-up among those who switched to Gla-300, but not among those who switched to IDet/Gla-100 (Figure S1). Switching to Gla-300 was associated with significantly less hypoglycaemia (incidence [Figure S2A] and event rates [Figure S2B]) than switching to IDet/Gla-100 at 0-3 and 3-6 month follow-ups. Switching to Gla-300 was also associated with significantly less inpatient/ED hypoglycaemia during 3 to 6 month follow-up but not 0 to 3 month follow-up.

3.5 | Healthcare resource utilization

By variable follow-up, hypoglycaemia-related inpatient incidence and event rates and inpatient days were all significantly lower among

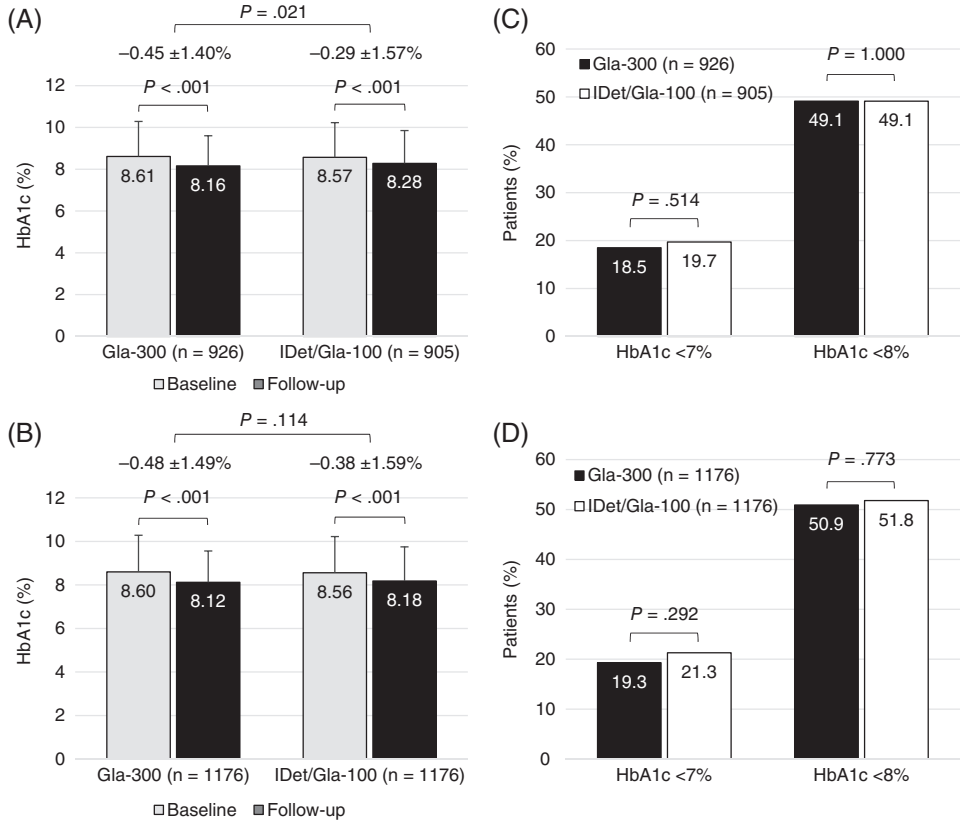

FIGURE 2 HbA1c outcomes among matched patients: mean ± SD values during 6 month baseline and 3-6 month follow-up using (A) variable (on treatment) or (B) fixed (intention-to-treat) follow-up; attainment of goals (HbA1c <7% and <8%) during follow-up using (C) variable or (D) fixed follow-up. Gla-100, insulin glargine 100 units/mL; Gla-300, insulin glargine 300 units/mL; IDet, insulin detemir; SD, standard deviation

	Gla-300 (*n* = 1176)	IDet/Gla-100 (*n* = 1176)	aOR/aHR/aRR (95% CI)†	*P*‡
All hypoglycaemia				
Patients with ≥1 event, n (%)	128 (10.9)	171 (14.5)	aOR: 0.70 (0.54–0.90)	.006
Crude incidence rate, PPY	0.32	0.44	aHR: 0.72 (0.58–0.91)	.006
Events, n	222	335	–	–
Event rate, PPY	0.52	0.80	aRR: 0.63 (0.53–0.75)	<.001
Inpatient/ED-associated hypoglycaemia				
Patients with ≥1 event, n (%)	30 (2.6)	55 (4.7)	aOR: 0.54 (0.34–0.86)	.010
Crude incidence rate, PPY	0.07	0.13	aHR: 0.58 (0.37–0.90)	.016
Events, n	49	114	–	–
Event rate, PPY	0.12	0.27	aRR: 0.43 (0.31–0.60)	<.001

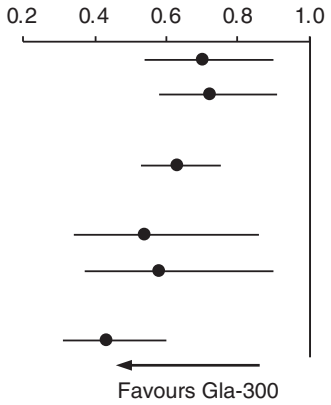

FIGURE 3 Hypoglycaemia outcomes using variable (on treatment) follow-up. aHR, hazard ratio adjusted for baseline hypoglycaemia; aOR, odds ratio adjusted for baseline hypoglycaemia; aRR, rate ratio adjusted for baseline hypoglycaemia; CI, confidence interval; ED, emergency department; Gla-100, insulin glargine 100 units/mL; Gla-300, insulin glargine 300 units/mL; IDet, insulin detemir; PPY, per patient year. †aOR for patients with ≥1 event (logistic regression); aHR for crude incidence rate (Cox proportional hazards model); aRR for event rate (Poisson's regression). ‡*P* values adjusted for baseline hypoglycaemia incidence

those who switched to Gla-300 versus IDet/Gla-100 (Table 2). There was also a trend toward less diabetes-related inpatient days with Gla-300.

By fixed 6 month follow-up, inpatient, ED and outpatient endocrinologist visit incidences were similar in both cohorts, regardless of whether it was all-cause or related to diabetes or hypoglycaemia (Figure S3A). Event rates were also generally similar between cohorts (Figure S3B). The numbers of inpatient days were lower in the Gla-300 cohort, reaching statistical significance for hypoglycaemia-related inpatient days (0.27 vs. 0.61 days; *P* = .048; Figure S3C).

3.6 | Subgroup analysis

Among matched patients aged ≥75 years, mean HbA1c decreased significantly from 6 month baseline to 3 to 6 month follow-up in the Gla-300 and IDet/Gla-100 cohorts, with comparable reductions in

TABLE 2 Healthcare resource utilization during variable follow-up for those who switched to Gla-300 (n = 1176) versus IDet/Gla-100 (n = 1176)

	Incidence		Event rate	
	aOR[a] (95% CI)	*P*	aRR[b] (95% CI)	*P*
All-cause				
Inpatient visit	1.00 (0.75-1.33)	.985	1.03 (0.85-1.25)	.769
ED visit	0.91 (0.72-1.14)	.399	0.92 (0.78-1.09)	.323
Outpatient endocrinologist visit	1.30 (0.92-1.83)	.132	1.21 (1.02-1.45)	.030
Inpatient days	–	–	0.97 (0.88-1.06)	.468
Diabetes-related				
Inpatient visit	1.00 (0.70-1.42)	.988	0.82 (0.62-1.08)	.153
ED visit	0.92 (0.69-1.22)	.560	0.92 (0.73-1.17)	.506
Outpatient endocrinologist visit	1.05 (0.75-1.48)	.782	0.92 (0.74-1.13)	.407
Inpatient days	–	–	0.90 (0.80-1.01)	.072
Hypoglycaemia-related				
Inpatient visit	0.38 (0.18-0.83)	.015	0.27 (0.12-0.58)	<.001
ED visit	0.82 (0.41-1.63)	.563	0.84 (0.44-1.63)	.608
Outpatient endocrinologist visit	0.45 (0.15-1.35)	.153	0.53 (0.21-1.34)	.181
Inpatient days	–	–	0.34 (0.26-0.45)	<.001

Abbreviations: aOR, odds ratio adjusted for baseline healthcare resource utilization; aRR, rate ratio adjusted for baseline healthcare resource utilization; CI, confidence interval; ED, emergency department; Gla-100, insulin glargine 100 units/mL; Gla-300, insulin glargine 300 units/mL; IDet, insulin detemir.
[a]aOR for patients with ≥1 event (logistic regression).
[b]aRR for event rate (Poisson's regression).

both cohorts (fixed follow-up: −0.35% ± 1.31% and −0.35% ± 1.43%; *P* = .991; Figure S4A). Attainment of HbA1c <8% was also comparable in both cohorts, while attainment of HbA1c <7% was significantly better in the IDet/Gla-100 cohort (Figure S4B).

By fixed 6 month follow-up, patients aged ≥75 years were generally more likely to have hypoglycaemia than the overall population; however, because of insufficient patient numbers, only descriptive statistics can be provided (Figure S5).

4 | DISCUSSION

In this real-world EMR study with propensity score-matched cohorts, patients aged ≥65 years with T2D who switched to Gla-300 achieved greater or similar (by variable or fixed follow-up, respectively) HbA1c reductions than those who switched to a first-generation basal insulin (IDet or Gla-100), but experienced significantly less hypoglycaemia and hypoglycaemia-related inpatient healthcare resource utilization (by variable follow-up). A preliminary analysis of DELIVER 3[33] compared unmatched cohorts of patients aged ≥65 years (March 2015 to March 2016), 468 of whom switched to Gla-300 and 1142 to IDet, Gla-100 or insulin degludec, after adjustment for baseline variables. The current analysis used a longer inclusion period to increase patient numbers in the database, thus allowing propensity score-matching. It did not include patients who switched to the second-generation basal insulin insulin degludec, because switching to Gla-300 or insulin degludec has been studied in DELIVER D[27] and DELIVER D+.[28] Despite these differences, the preliminary[33] and current analyses of DELIVER 3 found that Gla-300 was associated with significantly less hypoglycaemia.

The current results are also in line with those from DELIVER 2, which analyzed matched cohorts of adults (37% of whom were aged ≥65 years) with T2D who switched to Gla-300 or another basal insulin (IDet, Gla-100 or insulin degludec).[26] In DELIVER 2, both cohorts achieved similar, significant HbA1c reductions, but Gla-300 was associated with significantly less hypoglycaemia, significantly fewer patients utilizing hypoglycaemia-related healthcare services (hospitalization, ED and outpatient), and significantly less all-cause and diabetes-related ED use.[26] Lack of a significant benefit of Gla-300 on most healthcare resource utilization outcomes in the current study may have been a result of the higher level of comorbidities in the more elderly population (mean Charlson comorbidity index: 1.7 vs. 1.2 in DELIVER 2).[26]

Baseline and follow-up HbA1c levels in DELIVER 3 were lower than those in DELIVER 2[26] (Gla-300: 8.60% to 8.12% vs. 8.95% to 8.43%; other basal insulins: 8.56% to 8.18% vs. 8.93% to 8.43%). Also, HbA1c target attainment was better in DELIVER 3 than in DELIVER 2 (<7%: Gla-300: 19.3% vs. 16.8%; other basal insulins: 21.3% vs. 18.4%; <8%: Gla-300: 50.9% vs. 44.0%; other basal insulins: 51.8% vs. 44.2%).[26] Given that HbA1c targets are less strict for older adults (<7.5% to <8.5%[12] vs. <7% for most adults[11,13]), realistic target attainment in DELIVER 3 was actually much better than in DELIVER 2. This could indicate that older patients are more adherent to treatment, which has previously been reported for non-insulin T2D treatments.[34,35]

To our knowledge, no other real-world studies have compared older adult patients switching to Gla-300 or a first-generation basal insulin. However, the Gla-300 cohort results of DELIVER 3 are in line with a medical chart-review study from the USA (n = 184; mean age: 56 ± 11 years), which reported that switching from basal insulin to Gla-300 was associated with significantly lower HbA1c (8.57% to 7.61%; $P < .001$) and significantly fewer hypoglycaemia events (0.75-0.17 per patient year [PPY], $P < .001$).[36] Similarly, in a retrospective observational study of adults who switched from Gla-100 or IDet to Gla-300 (n = 163; mean age: 56 ± 10 years),[37] HbA1c fell significantly (8.50% to 7.55%; $P < .001$) and there were significantly fewer hypoglycaemia events (0.78 to 0.13 PPY; $P < .001$) after switching.

The DELIVER 3 results are also in line with those from the three EDITION RCTs that randomized adults with T2D already using a basal insulin to Gla-300 or Gla-100 (EDITION 1, 2, and JP 2).[19,20,22] These all reported similar reductions in HbA1c for the Gla-300 and Gla-100 cohorts and comparable to less hypoglycaemia with Gla-300. Recently, data from two of the EDITION RCTs (EDITION 2 and 3) have been pooled and results in different age groups (<55, 55-59, 60-64 and ≥65 years) reported.[38] Glycaemic control was generally comparable across age groups and, although hypoglycaemia varied slightly with age, this interaction did not reach statistical significance. There was, however, significantly less confirmed/severe hypoglycaemia with Gla-300 versus Gla-100 across all age groups. In a recent meta-analysis of three EDITION RCTs (EDITION 1, 2, and 3), patients with mild-to-moderate renal impairment had a similar reduced risk of hypoglycaemia with Gla-300 versus Gla-100 to patients without renal impairment.[39] These data may be particularly relevant for older adults who are more likely to have such comorbidities.

In the recent SENIOR RCT,[23] 1014 patients aged ≥65 years with T2D who were inadequately controlled on their antihyperglycaemia regimen (including no insulin or basal insulin as their only insulin) were randomized to Gla-300 or Gla-100. HbA1c reductions were comparable in both groups, but patients randomized to Gla-300 had similar to significantly lower risks of hypoglycaemia (depending on the definition of hypoglycaemia).

Baseline and follow-up HbA1c levels in DELIVER 3 were higher than in SENIOR[23] (Gla-300: 8.60% to 8.12% vs. 8.20% to 7.31%; other basal insulins: 8.56% to 8.18% vs. 8.22% to 7.28%). This could be because of differences in HbA1c inclusion criteria (3%-15% in DELIVER 3 vs. 7%-10% [for basal insulin-treated] or 7.5%-11% [for insulin-naïve] patients in SENIOR) and/or study design (real-world treatment in DELIVER 3 vs. dose titration to target fasting plasma glucose of 5.0 to 7.2 mmol/L in SENIOR). It could also indicate that real-world treatment may not be sufficiently intensified and/or that patients are more likely to adhere to treatment in the context of a clinical trial. This is supported by the poorer HbA1c target attainment (<7%) in DELIVER 3 versus SENIOR[23] (<7%: Gla-300: 19.3% vs. 33.3%; other basal insulins: 21.3% vs. 35.2%). Such differences in HbA1c control in real-world settings versus RCTs have already been identified; these differences are thought to be driven largely by lower treatment adherence in a real-world setting[24] and highlight the importance and added value of real-world studies.

Although RCTs provide reliable information, the specialized conditions and strict inclusion/exclusion criteria may not reflect real-world conditions and patients. Therefore, the real-world DELIVER 3 study provides complementary information that may be more generalizable and pertinent to clinicians, healthcare-delivery systems, patients and payers.[25]

However, the results from DELIVER 3 should be interpreted with caution because of various limitations, including its retrospective design and short follow-up. Healthcare resource utilization and diagnoses for diabetes were based on ICD version 9 or 10 codes,[30] but as EMR data may not include the actual diagnosis name, this could have resulted in misclassification. Further, EMRs only capture information on medication prescription, not dispensing or consumption. They also do not include the reason for switching, so selection bias may not be completely excluded, even after propensity score-matching. Patients who switched basal insulin as a result of poor glycaemic control could have received further education about the importance of taking their basal insulin as directed. This could have improved glycaemic control but would have probably affected both cohorts similarly. Because dose information was missing in many EMRs, this could not be addressed.

Glycaemic goals for older adults should be individualized, ranging from <7.5% for otherwise healthy individuals and from <8.5% for those with complex/poor health.[11] However, it was not possible to set individual targets for different patients, so all patients were measured against two frequently recommended HbA1c targets (<7% and <8%).

Although inpatient/ED-associated hypoglycaemia events should be well captured in the EMRs, it is probable that some less serious hypoglycaemia events were not recorded. This is particularly relevant in this population because hypoglycaemia is underdiagnosed and underreported in older adults.[9] However, this probably affected both cohorts similarly. Further, as there were no self-monitored blood glucose or continuous blood glucose monitoring data, the diagnosis and treatment effect on hypoglycaemia could be underestimated.

Patients were only studied for 6 months after switching basal insulins; however, EDITION extension trials (up to 12 months) have shown that the 6 month results are generally maintained.[40-42] It should be noted, however, that ~43% of patients in each cohort had discontinued their initial basal insulin by 6 months in the current study compared with <10% in the 6 month EDITION RCTs.[19,20,22] Most of those who discontinued Gla-300 or IDet/Gla-100 (80% and 72%, respectively) switched to another basal insulin brand. Interestingly, 30% and 25%, respectively, restarted their original basal insulin brand during the study. Lastly, although the older adults in DELIVER 3 represent a real-life USA population, the results may not be generalizable to all geographic regions, as most patients (89.9%) were from either the Midwest or the South.

DELIVER 3 is the first real-world analysis to compare the second-generation basal insulin Gla-300 with first-generation basal insulins exclusively in patients aged ≥65 years with T2D. In this population, switching to Gla-300 was associated with greater or similar

improvements in glycaemic control compared with switching to IDet or Gla-100, and generally lower hypoglycaemia incidence and event rates and less hypoglycaemia-related inpatient healthcare resource utilization (by variable follow-up). This real-world study provides complementary findings that support the results of RCTs and other real-world studies. The lower risk of hypoglycaemia with Gla-300, probably because of its more evenly distributed and stable pharmacokinetic exposure and pharmacodynamic profile,[17,18] is particularly important for older adults with T2D, who are at an increased risk of hypoglycaemia and its associated adverse events.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

J. Wu, F.L.Z., R.A.G., P.B., J. Westerbacka and J.V.V. designed the study. R.A.G. and A.A.M. analyzed the data. All authors contributed to the interpretation of the data, and 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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