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REVIEW ARTICLE

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Insulin glargine 300 units/mL for the treatment of individuals with type 2 diabetes in the real world: A review of the DELIVER programme

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Abstract

Evidence from randomized controlled trials (RCTs) has shown that second-generation basal insulin (BI) analogues, insulin glargine 300 U/mL (Gla-300) and insulin degludec (IDeg), provide similar glycaemic control, with a lower risk of hypoglycaemia compared with the first-generation BI analogue insulin glargine 100 U/mL (Gla-100) in people with type 2 diabetes (T2D). However, the highly selected participants and frequent follow-up of RCTs may not be truly representative of real-life clinical practice. It is important to assess the safety and effectiveness of these second-generation BI analogues in real-life clinical practice settings. The DELIVER programme utilized electronic healthcare records from the United States to compare clinical outcomes in people with T2D who received either Gla-300 or other BI analogues in real-world clinical practice. This review provides a concise overview of the results of the DELIVER studies. Overall, Gla-300 provided similar antihyperglycaemic effectiveness and a lower risk of hypoglycaemia versus the first-generation BI analogues Gla-100 and insulin detemir in people with T2D who had switched BIs. In those who were insulin-naïve, initiation with Gla-300 versus Gla-100 was associated with significantly better antihyperglycaemic effectiveness and similar or lower hypoglycaemic risk. Both glycaemic control and hypoglycaemia risk were also shown to be similar with Gla-300 and IDeg, in people who had switched BIs and in those who were insulin-naïve. In addition, the DELIVER 2 study reported that people with T2D who switched to Gla-300 had reduced healthcare resource utilization, with an overall saving of US $1439 per person per year compared with those who switched to another BI analogue. Overall, the real-world DELIVER programme showed that the glycaemic control with a low risk of hypoglycaemia observed with Gla-300 in RCTs was also seen in standard clinical practice.

KEYWORDS
basal insulin, glycaemic control, hypoglycaemia, insulin analogues, insulin therapy, type 2 diabetes

1 | INTRODUCTION

Maintaining good glycaemic control is important in people with diabetes to avoid the microvascular and macrovascular complications associated with hyperglycaemia.[1] However, the right balance between good glycaemic control and minimizing the risk of hypoglycaemia is required.

Insulin glargine 300 U/mL (Gla-300) and insulin degludec (IDeg) are second-generation basal insulin (BI) analogues with improved pharmacokinetic and pharmacodynamic properties and a prolonged duration of action compared with the first-generation BI analogue, insulin glargine 100 U/mL (Gla-100).[2,3] The results of two large randomized controlled trial (RCT) programmes, EDITION and BEGIN, showed that these second-generation BI analogues provided similar glycaemic control compared with Gla-100, with a lower risk of hypoglycaemia, in people with type 2 diabetes (T2D).[4,5] Gla-300 and IDeg have been compared directly in two RCTs of people with T2D, the BRIGHT and CONCLUDE trials, which reported differing results. In BRIGHT, Gla-300 and the 100 U/mL formulation of IDeg were compared in insulin-naïve individuals with T2D inadequately controlled on oral antihyperglycaemic drugs with or without glucagon-like peptide-1 receptor agonists.[6] The primary endpoint (non-inferiority of HbA1c change from baseline to week 24 with Gla-300 vs. IDeg) was achieved. A similar risk of hypoglycaemia with Gla-300 and IDeg over 24 weeks, but significantly lower incidences and rates of anytime (24-hour) confirmed hypoglycaemia with Gla-300 during the first 12 weeks, were reported. In CONCLUDE, Gla-300 and the 200 U/mL formulation of IDeg were compared in people with T2D with one or more hypoglycaemia risk factor, previously treated with BI (insulin glargine 100 U/mL [Gla-100], insulin detemir [IDet] or neutral protamine Hagedorn insulin), with or without oral antihyperglycaemic drugs (excluding sulphonylureas and glinides).[7] The rate of 'overall symptomatic' hypoglycaemia during the 36-week maintenance period was similar with Gla-300 and IDeg 200 U/mL, so the primary endpoint of hypoglycaemia superiority was not achieved.[7,8] Rates of the prespecified secondary endpoints, nocturnal symptomatic hypoglycaemia, and severe hypoglycaemia were nominally significantly lower during the maintenance period with IDeg 200 U/mL versus Gla-300, but these analyses remain exploratory as the primary endpoint was not met.

While RCTs are invaluable, providing evidence with high internal validity of the efficacy and safety of new therapies and technologies, the highly selected participants, strict clinical protocols, specialist investigators, and the high degree of participant follow-up, means that the results of these trials may not be generalizable to clinical practice. Indeed, adherence to insulin therapy is an important factor in diabetes management, which may not be appropriately represented in RCTs of antihyperglycaemic therapies.[9] Real-world evidence (RWE) studies can provide information on the effectiveness and safety of therapies in real-life clinical practice, often utilizing electronic healthcare records (EHRs) and claims data,[10] trading lower internal validity for higher external validity.

The DELIVER programme was a series of studies undertaken to assess clinical outcomes and healthcare-resource utilization (HCRU) using EHRs of people with T2D who received either Gla-300 or other BI analogues in real-world clinical settings in the United States (Table 1), the results of which have been reported in eight separate publications.[11–18] The purpose of the current paper is to provide a concise overview of the DELIVER studies published to date, and to consider whether the clinical benefits and risks observed in RCTs with Gla-300 are replicated in this real-world programme that reflects standard clinical practice.

2 | THE DELIVER PROGRAMME

2.1 | Overview/methodology/data source

In the DELIVER real-world programme, the effectiveness and safety of Gla-300 were compared with those of other BIs, that is, the second-generation BI analogue IDeg, and/or the first-generation BI analogues Gla-100 or IDet, in people with T2D who were either initiating insulin (i.e. insulin-naïve individuals) or switching their BI.[11–18] The DELIVER programme consisted of multiple retrospective observational cohort studies using data from the Explorys IBM Watson Health database of EHRs, which provides medical record data from over 360 hospitals and 920 000 providers for 64 million people, including more than 3 million people with T2D.[13]

Individuals were eligible for inclusion in the analyses if they were aged 18 years or older at their index date (the date of their first prescription for the index BI [first or switched]), had T2D (identified using International Classification of Diseases codes version 9 or 10 [ICD-9/ICD-10]), had one or more valid HbA1c measurement during the 6-month baseline period, and one or more valid HbA1c measurement during 3-6 months of follow-up (9-12 months in DELIVER HIGH RISK). Individuals diagnosed with type 1 diabetes or who had been prescribed more than one BI on their index date were excluded. The size of the study populations and the BIs used as comparators differed among the DELIVER studies (Table 1).

One factor to be considered when analysing EHRs in a retrospective manner is the lack of randomization to treatment groups and thus potential for systematic bias. In RCTs, randomization is key to ensuring that treatment groups being compared differ only on the basis of chance, to minimize both known and unknown confounders. In the DELIVER studies, similar groups for treatment comparisons were generated using propensity score matching (PSM), which matches cohorts of people according to their observed baseline characteristics. Outcomes were then compared between matched cohorts. While PSM can provide a good balance between cohorts based on observed baseline characteristics, unlike randomization, it cannot account for differences of any unobserved/unmeasured characteristics and therefore cannot be assured to provide completely unbiased estimates of treatment effect.

Outcomes assessed in all DELIVER studies included the change in HbA1c between baseline (within 6 months prior to the index date) and the last value after 3-6 months of follow-up (described as '6-month follow-up' herein). For the DELIVER HIGH RISK study, this

TABLE 1 Overview of publications in the DELIVER programme, undertaken to investigate the effectiveness and safety of Gla-300

	BI switch						Insulin-naïve	
Study	DELIVER 1[16]	DELIVER 2[17]	DELIVER 2 BB[11]	DELIVER 3[18]	DELIVER D+[13]	DELIVER HIGH RISK[14]	DELIVER NAÏVE[12]	DELIVER NAÏVE D[15]
Patient numbers (PSM)[a]	881	3638	2972	2352	3184	5100	3012	1276
Comparator	None	IDet/Gla-100 or IDeg	Gla-100 or IDet	Gla-100 or IDet	IDeg	Gla-100 or IDet	Gla-100	IDeg
Distinguishing features[b]	No comparator group	HCRU endpoints	BB subgroup from DELIVER 2	Older adult population (≥65 y of age) HCRU endpoints	High-risk subgroups Discontinuation endpoints	High-risk subgroups	HbA1c target achievement without hypoglycaemia	HbA1c target achievement without hypoglycaemia Discontinuation endpoints

Abbreviations: BB, basal-bolus insulin therapy; BI, basal insulin; Gla-100, insulin glargine 100 units/mL; Gla-300, insulin glargine 300 units/mL; HCRU, healthcare-resource utilization; IDeg, insulin degludec; IDet, insulin detemir; PSM, propensity score matched; T2D, type 2 diabetes.
[a]No PSM performed for DELIVER 1, as there was no comparator group.
[b]Distinguishing features of the DELIVER programme.

follow-up period was 9-12 months (described as '12-month follow-up'). The other outcomes assessed across all DELIVER studies included the incidence and event rates of any hypoglycaemia (identified using ICD-9/ICD-10 codes or blood glucose ≤70 mg/dL [≤3.9 mmol/L]) and those associated with inpatient/emergency department (ED) visits up to the last reported values in the 3-6–month follow-up period (9-12 months for DELIVER HIGH RISK). In addition to this 'fixed-follow-up' approach (whereby all patients were followed for a fixed period of time, regardless of whether or not they persisted with the BI treatment they received at the start of the follow-up period) in some DELIVER studies, change from baseline in HbA1c and/or hypoglycaemia events were also assessed using a variable follow-up approach (whereby patients were followed up to discontinuation of treatment or 6-month follow-up [12 months for DELIVER HIGH RISK], whichever occurred earlier). To facilitate comparisons across the DELIVER studies, the current review focuses on results from the fixed follow-up analyses.

2.2 | Effectiveness and safety in individuals who switched BIs

2.2.1 | HbA1c

There were significant reductions in HbA1c between baseline and follow-up in adults with T2D who switched their BI therapy (Figure 1A). The changes in HbA1c from baseline were similar between the treatment arms in the fixed follow-up analyses (Figure 1A). However, it is notable that in the DELIVER 3 study of older adults (aged ≥65 years of age), significantly greater reductions in HbA1c from baseline were seen with Gla-300 compared with first-generation BIs (Gla-100/IDet) when using variable follow-up analyses (−0.45% ± 1.40% vs. −0.29% ± 1.57%; $P = .021$).[18] Similar proportions of people with T2D who switched to Gla-300 and comparator BIs achieved HbA1c targets of less than 7% or less than 8% across all DELIVER studies (-Figure S1A,B).

2.2.2 | Hypoglycaemia

Consistent with the findings in the EDITION RCT programme, Gla-300 was associated with a lower risk of hypoglycaemia compared with first-generation BI analogues in the DELIVER programme (Figure 1B, C). Event rates for any hypoglycaemia and for hypoglycaemia associated with inpatient/ED visits were significantly lower with Gla-300 versus other BIs at 6-month follow-up in the DELIVER 2 study ($P = .041$ for both). Similar results were observed when comparing Gla-300 versus first-generation BIs in individuals aged 65 years or older (the DELIVER 3 study), with lower event rates for any hypoglycaemia ($P = .012$) and hypoglycaemia associated with inpatient/ED visits ($P = .014$) at 6-month follow-up (Figure 1B,C).[17,18]

In the DELIVER HIGH RISK study, rates of any hypoglycaemia were similar with Gla-300 and first-generation BIs in the overall high-risk population and in most high-risk subgroups (Table S1); however, event rates of any hypoglycaemia were statistically significantly lower with Gla-300 versus first-generation BIs in older adults (aged ≥65 years; $P = .037$) and individuals with renal impairment (estimated glomerular filtration rate <60 mL/min/1.73 m^2; $P = .006$). Rates of hypoglycaemia associated with inpatient/ED visits were lower with Gla-300 than first-generation BIs in the overall population ($P < .0001$) and in all high-risk subgroups assessed ($P \leq .036$).[14]

Similar event rates for any hypoglycaemia or hypoglycaemia associated with inpatient/ED visits at 6-month follow-up were seen with both second-generation BI analogues, Gla-300 and IDeg, in the

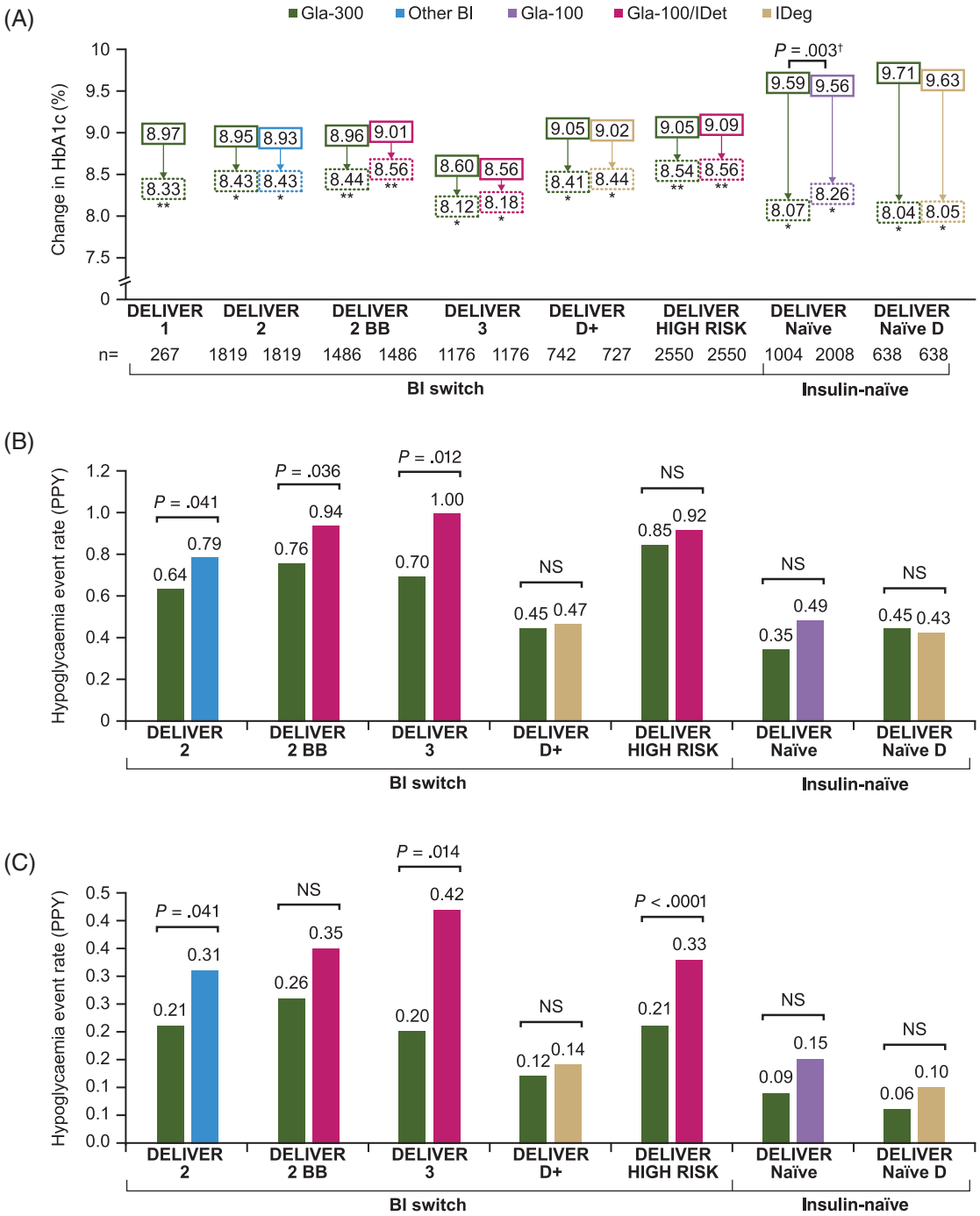

FIGURE 1 (A) Change in HbA1c from baseline to follow-up, (B) adjusted event rate of any hypoglycaemia‡, and (C) adjusted event rate of hypoglycaemia associated with inpatient/emergency department (ED) visits‡, in the DELIVER programme. Fixed 6-month follow-up approach (12-month follow-up in DELIVER HIGH RISK[14]); *P < .001; **P < .0001; †with payer as covariate[12]; ‡P values adjusted for baseline hypoglycaemia. BI, basal insulin; Gla-100, insulin glargine 100 units/mL; Gla-300, insulin glargine 300 units/mL; IDeg, insulin degludec; IDet, insulin detemir; NS, non-significant; PPY, per person-year

DELIVER D+ study overall (Figure 1B,C).[13] Across all high-risk subgroups assessed, the incidence of any hypoglycaemia was also similar between Gla-300 and IDeg (Table S2). The proportions of patients with any hypoglycaemia or hypoglycaemia associated with inpatient/ED visits were also assessed in DELIVER D+ and were similar between Gla-300 and IDeg (Figure S2), consistent with the results for event rates.

2.3 | Effectiveness and safety in insulin-naïve individuals

2.3.1 | HbA1c

Among insulin-naïve individuals, there were significant reductions in HbA1c from baseline to 6 months in those who initiated BI therapy

with Gla-300, Gla-100 or IDeg (Figure 1A).[12,15] In the DELIVER Naïve study, HbA1c reductions were significantly greater with Gla-300 compared with Gla-100 (−1.52% ± 2.08% vs. −1.30% ± 2.12%; $P = .003$), whereas similar HbA1c reductions were seen with Gla-300 versus IDeg in DELIVER Naïve D (Figure 1A).[12,15] Significantly more people with T2D achieved an HbA1c of less than 7% or less than 8% with Gla-300 than with Gla-100 ($P \leq .029$ for both; Figure S1), and significantly more people achieved either of these targets without hypoglycaemia with Gla-300 than with Gla-100 ($P \leq .003$ for both targets) in DELIVER Naïve.[12] The absolute HbA1c reductions in this study were similar to those observed in the EDITION 3 RCT, which also studied insulin-naïve people with T2D initiating either Gla-300 or Gla-100, although baseline HbA1c levels were lower compared with the DELIVER Naïve study (EDITION 3: ∼8.5% [∼69 mmol/mol]; DELIVER ∼9.6% [81 mmol/mol]).[19]

2.3.2 | Hypoglycaemia

The rates of any hypoglycaemia and hypoglycaemia associated with inpatient/ED visits were similar with Gla-300 and Gla-100 in the DELIVER Naïve study during the 6-month follow-up (Figure 1B,C).[12] However, the DELIVER Naïve study also assessed the initial 3-month follow-up period, during which hypoglycaemia associated with inpatient/ED visit event rate was significantly lower with Gla-300 than Gla-100 (0.04 vs. 0.17 events per person year [PPY]; least-squares mean difference: −0.13; $P = .003$).[12]

Similar hypoglycaemia rates were observed during the 6-month follow-up in insulin-naïve adults with T2D who initiated BI treatment with Gla-300 or IDeg in the DELIVER Naïve D study.[15] These findings are consistent with those in the 6-month BRIGHT RCT, which also compared Gla-300 and IDeg in insulin-naïve people with T2D. However, participants in the DELIVER Naïve D study had considerably higher mean baseline HbA1c values than those in the BRIGHT trial; mean baseline HbA1c in the Gla-300 group was 9.7% in DELIVER and 8.7% in BRIGHT (83 and 72 mmol/mol, respectively) and for the IDeg group it was 9.6% and 8.6% (81 and 70 mmol/mol), respectively.[6,15]

2.4 | Healthcare resource utilization

HCRU was reported for two studies, both including people with T2D who had switched their BIs: the DELIVER 2 and DELIVER 3 studies.[17,18] In the DELIVER 2 study, people who switched to Gla-300 had a significantly lower incidence of HCRU associated with hypoglycaemia than those who had switched to another BI, including hospitalization (2.8% vs. 4.3%; $P = .037$), ED visits (3.1% vs. 5.1%; $P = .007$) and outpatient visits (12.6% vs. 15.4%; $P = .011$).[17] People who switched to Gla-300 had an overall saving of US$1439 per person per year in HCRU compared with those who switched to another BI.[17]

In the DELIVER 3 study, the number of hypoglycaemia-associated inpatient days was significantly lower in people who switched to Gla-300 than in those who switched to first-generation BI analogues, based on a fixed 6-month follow-up analysis (0.27 vs. 0.61 days; $P = .048$).[18] Using an on-treatment/variable follow-up analysis, Gla-300 was associated with significantly lower hypoglycaemia-associated inpatient visit incidence ($P = .015$), event rate ($P < .001$), and number of inpatient days ($P < .001$) than first-generation BIs.[18]

2.5 | Discontinuation

The proportion of people who discontinued BI therapy (i.e. switched to another BI or had a prescription gap of >45 days) was reported for two DELIVER studies, both comparing Gla-300 and IDeg.[13,15] The proportions of people who discontinued BI by the end of the 6-month follow-up were similar in the Gla-300 and IDeg groups in people switching BIs in the DELIVER D+ study (32.0% and 28.5%, respectively)[13] and in insulin-naïve participants in the DELIVER Naïve D study (29.2% and 32.6%, respectively).[15]

3 | DELIVER AND OTHER RWE STUDIES OF EHRs

The results of the DELIVER programme are consistent with those of the retrospective, observational LIGHTNING study, in which clinical outcomes in adults with T2D who had newly initiated or switched to Gla-300, IDeg, Gla-100 or IDet were investigated.[20] The LIGHTNING study analysed EHRs from the US Optum Humedica database, which included 831 456 individuals with T2D treated with a BI analogue. Severe hypoglycaemia was defined using ICD-9/ICD-10 codes, inpatient/ED visit, blood glucose less than 54 mg/dL (<3.0 mmol/L), glucagon administration or natural language processing (a method of capturing events from free-text notes contained within EHRs in an automated manner). In cohorts matched using PSM, there were significantly lower rates of severe hypoglycaemia with Gla-300 versus first-generation BIs IDet and Gla-100 ($P < .05$ for both) and similar rates to IDeg, in a broad spectrum of people with T2D. Interestingly, the rate of any hypoglycaemia was significantly lower with Gla-300 versus IDeg in the LIGHTNING study in both those switching BIs and insulin-naïve individuals ($P < .05$ for both), while this was not observed in the DELIVER programme. HbA1c reductions were similar with Gla-300 versus Gla-100, IDet and IDeg in people switching BIs and in insulin-naïve individuals in the LIGHTNING study, in line with the results of the DELIVER programme.

By contrast, in the CONFIRM study, which assessed EHRs of insulin-naïve adults with T2D extracted from the same database used in the DELIVER studies (the Explorys IBM Watson Health database), there was a significantly greater HbA1c reduction with IDeg than with Gla-300 after 6 months (180 days) of treatment (estimated treatment difference: −0.27 [$P = .03$]).[21] In addition, CONFIRM reported significantly greater reductions in the incidence and event rates of hypoglycaemia from baseline to 6 months with IDeg versus Gla-300 (odds ratio 0.64 [$P < .01$] and 0.70 [$P < .05$], respectively), and a 27% lower risk of discontinuation with IDeg than Gla-300 (hazard ratio

0.73, $P < .001$). However, despite the use of 1:1 PSM to minimize confounding in CONFIRM, it has been observed that the treatment groups were inadequately matched at baseline, particularly for hypoglycaemia but also for HbA1c.[22] Whether these baseline differences fully explain the greater reduction in the incidence of hypoglycaemia with IDeg versus Gla-300 is unknown, but it is clear that hypoglycaemia event rates while on treatment were similar in both treatment groups (0.391 and 0.389 events per patient year for IDeg and Gla-300, respectively).[22]

4 | APPLICATIONS OF RWE

While RCTs are the gold standard for regulatory evidence on comparative efficacy and safety of therapies, they have a number of constraints that limit full generalizability to clinical practice.[10,23]

RWE provides an opportunity to examine the comparative effectiveness and safety of new therapies in varied clinical practice settings in individuals who are often excluded from RCTs, including older individuals, pregnant women and children. RWE can also provide information beyond treatment effectiveness, such as cost-effectiveness, HCRU and geographic patterns of prescription data. They can also highlight differences between guideline recommendations and implementation.[10,24] Furthermore, findings from observational RWE studies can be hypothesis-generating and can be used to design further prospective studies.[10]

Consequently, RWE has increasingly become recognized as a valuable source of information on the safety and effectiveness of therapies. While use of real-world pharmacovigilance data has provided RWE on the safety of approved therapies, increasing recognition is being given to the potential for RWE to provide effectiveness data, with position statements from the US Food and Drug Administration and European Medicines Agency highlighting the importance of, and providing guidance for, the greater integration of RWE for regulatory decision-making.[25–27] In addition, the GetReal Initiative, launched in 2018, is a project designed to drive adoption of tools, methodologies and best practices, and to increase the quality of RWE generation in medicine development and regulatory processes across Europe.[28] RWE is probable to become an increasingly important source of comparative effectiveness and safety information for regulatory approval of new therapies or new indications, and has already been used to support regulatory approval of new medication indications without the need for further clinical trials.[29]

However, RWE is not without limitations, including the lack of participant selection and incomplete data sources (such as EHRs), which can introduce bias. Increasingly advanced methods are being used to attempt to control for potential confounding factors, including PSM and predictive modelling.[23] Of note, the previously mentioned LIGHTNING study also included a separate predictive modelling analysis that largely confirmed the results of the PSM analysis of data from the same EHR dataset.[20] Natural language processing is a technique that can also help improve the incomplete data sources used for most RWE studies by facilitating capture of valuable information from clinical notes, leading to increased hypoglycaemia identification[30] and, potentially, information about insulin dosing and therapeutic choices. Randomization can also be applied to prospective real-world studies. Pragmatic randomized studies can preserve the internal validity of RCTs while providing RWE from usual clinical practice.[23] Such studies include the ACHIEVE, REACH and REGAIN pragmatic real-world studies of the effectiveness and safety of Gla-300.[31,32] However, while findings from the 12-month ACHIEVE study suggested lower hypoglycaemia risk with Gla-300 than with standard of care BI, comparison of outcomes between treatment arms in the REACH and REGAIN studies was limited by suboptimal insulin dose titration. This highlights that real-world behaviour may differ substantially from that seen in a classical RCT, which should be considered when assessing results from RWE studies.[31,32]

Further attempts to improve the quality of RWE include designing such studies with the same methodological rigour as RCTs, including detailed study protocols and statistical analysis plans, and comprehensive reporting of data sources, data ranges, exclusion criteria, care setting exposure to study drugs, outcomes, attrition and analytical strategies.[24,33] In addition, the validity of RWE would be further supported if consistency can be shown across studies utilizing similar data sources (e.g. EHR), as well as those utilizing different data sources (e.g. patient registries, pharmacy/health insurance databases, patient-powered research networks).

In the context of applying RWE to clinical practice, the DELIVER programme has important benefits that may increase utility to clinicians and patients, including minimal exclusion criteria and a large number of individuals with T2D represented, including high-risk groups of people. DELIVER also applied PSM to achieve a good balance between the cohorts for known observable confounders[15]; although, as participants were not randomized to treatment, it is not possible to control for unknown or unobserved confounders and thus these analyses are not fully unbiased. The DELIVER study programme had other limitations similar to those generally observed in RWE studies, such as use of EHRs, which are not designed for research use and may be less complete than data captured in RCTs. In addition, as the DELIVER studies shared a common data source, data from a participant may be included in more than one DELIVER study, depending on their characteristics. Nevertheless, the DELIVER programme provides real-world comparative effectiveness and safety data of both first- and second-generation BI analogues, assessed using a robust real-world study methodology, to support and enhance the broad evidence base generated from RCTs.

5 | DISCUSSION

The results of the DELIVER programme, which represents prescribing patterns and clinical outcomes in real-life people with T2D in the United States who initiated or switched to Gla-300, complement those from RCTs in which Gla-300 was compared with first- and second-generation BI analogues (Gla-100 and IDeg, respectively) in people with T2D.[5–7] DELIVER studies showed similar

antihyperglycaemic effectiveness and a lower risk of hypoglycaemia with Gla-300 versus the first-generation BIs Gla-100 and IDet in people switching BIs and extended those findings most notably to older adults and those at a high risk of hypoglycaemia. In insulin-naïve individuals, the DELIVER Naïve study showed better antihyperglycaemic effectiveness with Gla-300 versus Gla-100, accompanied by a similar risk of hypoglycaemia. When comparing the two second-generation BI analogues, Gla-300 and IDeg, it is reassuring that both provided similar improvements in glycaemic control and a similar, low risk of hypoglycaemia, even in individuals at a high risk of hypoglycaemia. The results of the DELIVER studies were also generally consistent with the LIGHTNING RWE study, but there were differences between the results of the DELIVER study and those of the CONFIRM study, which might be explained by methodology.[20–22]

The comparatively high HbA1c levels achieved at the end of the real-world DELIVER studies investigating the second-generation BI analogues (DELIVER D+ and DELIVER Naïve D; Figure 1A) are a potential limitation when interpreting the similarity of hypoglycaemia risk with Gla-300 and IDeg. Suboptimal HbA1c levels are not uncommon in real-world diabetes studies, either prior to the study (particularly in insulin-naïve individuals) or at the end of the study period,[32,34,35] reflecting the clinical reality that many people with diabetes do not achieve glycaemic targets. A recent report of the results of the real-world REACH and REGAIN studies suggested that the high end-of-study HbA1c levels and comparatively low HbA1c reductions observed were driven by a lack of adequate insulin titration, which limited the ability to compare outcomes between treatment groups.[32] While the final HbA1c levels were high in DELIVER Naïve D, the HbA1c reduction seen over the study period was substantial (>1.5%), suggesting that insulin titration was occurring during this study. However, a failure to appropriately titrate insulin is not the only possible cause of high end-of-study HbA1c levels. Intensification inertia may also have contributed, if some individuals required, but did not receive, the addition of other agents such as glucagon-like peptide-1 receptor agonists (either separately or in a fixed ratio combination with a BI) or prandial insulin to reduce their HbA1c levels. It is also important to consider that HbA1c may be a weak predictor of hypoglycaemia[36] as it does not capture information about acute glycaemic excursions,[37] so people with higher HbA1c levels can still experience hypoglycaemia. Differences between treatment groups in baseline HbA1c levels may also influence any interpretation of hypoglycaemia, but in both DELIVER D+ and DELIVER Naïve D baseline HbA1c was similar with Gla-300 and IDeg (9.05% vs. 9.02% and 9.71% vs. 9.63%, respectively).

In conclusion, the DELIVER programme provides valuable RWE showing similar effectiveness and a lower risk of hypoglycaemia with Gla-300 compared with first-generation BI analogues in a diverse population with T2D who were switching their BI. In an insulin-naïve population, the DELIVER Naïve study showed that initiation with Gla-300 versus Gla-100 was associated with a greater HbA1c reduction, and significantly improved or similar hypoglycaemia outcomes at 3 and 6 months, respectively. The results of the DELIVER programme support the wealth of evidence from RCTs and other RWE studies regarding the use of Gla-300 in people with T2D.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors contributed to the interpretation of data, drafting and critical review of the manuscript and approved the final version for submission.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated

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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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