The Safety and Efficacy of Second-Generation Basal Insulin Analogues in Adults with Type 2 Diabetes at Risk of Hypoglycemia and Use in Other Special Populations: A Narrative Review

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ABSTRACT

Hypoglycemia is a major barrier impeding glycemic control in persons with type 2 diabetes mellitus and creates a substantial burden on the healthcare system. Certain populations that require special attention, such as older adults and individuals with renal impairment, a longer duration of diabetes or those who have experienced prior hypoglycemia, may be at a higher risk of hypoglycemia, particularly with insulin treatment. Second-generation basal insulin analogues (insulin glargine 300 U/mL and degludec) have demonstrated reductions in hypoglycemia compared with insulin glargine 100 U/mL although evidence of this benefit across specific populations is less clear. In this review we summarize the literature with respect to the efficacy and safety data for second-generation basal insulin analogues in adults with type 2 diabetes mellitus who are at risk of hypoglycemia or who require special attention. Randomized controlled trials, meta-analyses and real-world evidence demonstrate that the use of second-generation basal insulin analogues is associated with less hypoglycemia compared with insulin glargine 100 U/mL without compromising glycated hemoglobin control. A reduced risk of hypoglycemia with second-generation basal insulin analogues was evident in older adults and in individuals with obesity, renal impairment, a history of cardiovascular disease or a long duration of insulin use. Further studies are needed in other populations, including those with more severe renal impairment or hepatic dysfunction, the hospitalized population and those with cognitive impairment. Overall, less hypoglycemia associated with second-generation basal insulin analogues may help reduce barriers for insulin use, improve adherence and offset the costs of
hypothesis of individualizing glycemia targets based on a number of factors, such as the risk of hypoglycemia and the presence of cardiovascular disease (CVD) or chronic kidney disease (CKD) [1]. With disease progression and increased β-cell deterioration, most patients with T2DM eventually require insulin for glycemia management [1]. However, in clinical practice only 38% of people with diabetes achieve a glycated hemoglobin (HbA1c) level target of <7% (<53 mmol/mol) in the first year after starting basal insulin (BI), and only 8% more in the second year [2]. Drug-induced hypoglycemia is a major barrier preventing insulin initiation and adjustment, which can impede glycemia management and increase the risk of diabetes-related complications [3].

Hypoglycemia is associated with increased fear and anxiety in patients, which can lower the quality of life (QoL) and reduce productivity [3]. Moreover, medication-related hospitalization due to hypoglycemia creates a substantial burden on the healthcare system and can result in serious clinical consequences [4]. In particular, severe hypoglycemia, defined as requiring the assistance of another person to raise the patient’s glucose level, is associated with increased cardiovascular (CV) morbidity and mortality [5, 6].

A number of risk factors have been associated with an elevated risk of hypoglycemia in people with T2DM, including older age, renal impairment, long duration of diabetes and the presence of comorbidities [6–12]. Univariate and multivariable analyses from the ADVANCE study have shown that older age, longer duration of diabetes, higher creatinine levels, lower body mass index (BMI), lower cognitive function, use of two or more oral hypoglycemic agents (OHA), history of smoking or microvascular disease and assignment to intensive glucose control are independent risk factors for severe hypoglycemia (p < 0.05 for all comparisons) [6]. Similar results were reported in a small longitudinal cohort study in 616 subjects with T2DM. The independent predictors of the
time to first severe hypoglycemia episode in this latter study were the duration of insulin treatment, estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m², peripheral neuropathy, education beyond primary level and past severe hypoglycemia [13].

Patients who are at risk of hypoglycemia may benefit from individualized, evidenced-based therapies to minimize hypoglycemia, prevent complications and optimize QoL [1]. BI is often the preferred initial insulin regimen in T2DM because it has a lower risk for inducing hypoglycemia and causes less weight gain compared with premixed insulin or basal-bolus insulin therapy [1]. The development and introduction into clinical practice of the first-generation BI analogues (insulin glargine-100 IU/mL [Gla-100; Sanofi] and insulin detemir [IDet; Novo Nordisk) represented a significant advance to reduce hypoglycemia compared to the human BIs. However, despite a reduction in the risk of hypoglycemia, many people with T2DM on first-generation BI still experience low blood glucose levels. The second-generation BI analogues, insulin glargine 300 IU/mL (Gla-300; Sanofi) and insulin degludec (IDeg; Novo Nordisk), have demonstrated a longer duration of action, less glycemic variability and reduced hypoglycemia compared to first-generation BI analogues [14–17]. Whether these benefits are still apparent in populations at high risk for hypoglycemia, without a loss of efficacy, is less evident.

In this review we strive to describe the efficacy and safety of second-generation BI analogues in adults with T2DM, specifically in individuals at risk of hypoglycemia: participants ≥ 65 years; those with renal insufficiency, a long duration of diabetes (> 10 years) or long duration on insulin (> 5 years); and patients with prior severe hypoglycemia. Other populations of interest include those with obesity, a history of CVD and different ethnicities. The clinical implications for these at-risk populations will be discussed.

METHODS

Comprehensive literature searches of the EMBASE, Medline and Cochrane library databases were undertaken in December 2019. Key search terms were ‘insulin glargine 300 U/mL’ OR ‘degludec’ AND ‘type 2 diabetes’ (or ‘non-insulin dependent’ or ‘insulin independent’ or ‘ketosis resistant’ or ‘adult onset’ or ‘maturity onset’ or ‘slow onset’) AND ‘high risk patient’ (or ‘aged’ or ‘elderly’ or ‘frail elderly’ or ‘very elderly’ or ‘geriatrics’ or ‘aging’; ‘unaware or impaired awareness hypoglycemia’, ‘severe hypoglycemia’, ‘cardiovascular’ or ‘myocardial’ or ‘cardiovascular risk’ or ‘cardiovascular disease’, ‘long-duration adult onset diabetes’, ‘obese patient’ or ‘obesity’, ‘multiple daily injection’, ‘basal-bolus’, ‘proteinuria’, ‘insufficient or impaired estimated glomerular function rate’, ‘kidney disease’). The search was narrowed down to English articles involving clinical studies (randomized controlled trials [RCTs], meta-analyses and real-world evidence [RWE]) published in the last 10 years. Studies must have evaluated Gla-300 and/or IDeg versus a control and measured at least one objective outcome measure including hypoglycemia. The decision was made to include RWE in this review because RWE complements the findings from RCTs and meta-analyses. RCTs and meta-analyses determine if there are differences between therapies in the purest, most controlled environment, providing an answer to the question of what can be in the ideal situation. On the other hand, RWE answers the question of what is actually happening in the real world, providing additional information and confidence in the findings when consistent [18].

This article is based on previously conducted and published studies that were compliant with ethics guidelines, and does not involve any new studies performed by any of the authors.

PUBLISHED DATA FOR SECOND-GENERATION BI IN ADULTS WITH T2DM

Second-Generation Compared to First-Generation BI Analogues

The registration trials and subsequent meta-analyses of these studies have demonstrated
non-inferiority in reducing HbA1c with second-generation versus first-generation BI analogues, with less hypoglycemia compared with Gla-100 [19–40]. Although these studies were not designed to specifically address outcomes in populations at risk of hypoglycemia, many participants in these trials had multiple risk factors for hypoglycemia, such as BMI > 30 kg/m², age > 65 years duration of diabetes > 10 years, co-existing morbidities, high creatinine levels and the use of two or more OHA.

The EDITION and BEGIN phase IIIa clinical trial programs compared the efficacy and safety of a second-generation BI analogue (Gla-300 or IDeg, respectively) with the first-generation BI analogue, Gla-100, in a broad range of adults with T2DM. These studies demonstrated non-inferiority of Gla-300 or IDeg in reducing HbA1c (primary endpoint) with less hypoglycemia, particularly nocturnal hypoglycemia, compared with Gla-100 (secondary endpoint) [9, 23–26, 28, 30, 33, 34, 37, 39]. Overall in the phase IIIa registration studies, there was a similar frequency and pattern of AEs in patients treated with a second-generation BI (Gla-300 or IDeg) compared with Gla-100. A summary of these trials can be found in Appendix 1.

The dose of Gla-300 in these studies was higher than that of Gla-100, particularly during the titration phase, in order to achieve comparable fasting plasma glucose levels [19, 33, 34, 37]. However, despite a higher insulin dose, weight gain in patients receiving Gla-300 was significantly less than that in those receiving Gla-100 in several trials [19, 33, 34, 37]. In the BEGIN studies, the dose of IDeg and Gla-100 was similar [3, 26, 39]. However, in two of the BEGIN trials the mean insulin dose was significantly less with IDeg versus Gla-100 [24, 28], although there was a similar increase in body weight in the IDeg- and Gla-100-treated patients [23, 25, 26, 28, 39].

A number of meta-analyses of phase IIIa trials have evaluated Gla-300 or IDeg versus Gla-100. Consistent with the outcomes reported in the phase IIIa RCTs, these meta-analyses support less hypoglycemia with second-generation versus first-generation BI analogues (Appendix 2) [20–22, 27, 29, 31, 32, 35, 36, 38, 40, 41].

A patient-level meta-analysis of the 6-month EDITION studies demonstrated that Gla-300 (n = 2496) was as effective as Gla-100 in terms of glycemia management, with significantly lower confirmed (< 3.9 mmol/L [< 70 mg/dL]) or severe hypoglycemia episodes with Gla-300 than with Gla-100 during the night (relative risk 0.69, 95% confidence interval [CI] 0.58–0.81) and at any time of day (relative risk 0.83, 95% CI 0.77–0.89) [31]. A follow-up meta-analysis showed that the hypoglycemia benefits of Gla-300 versus Gla-100 were maintained at 12 months [32]. Investigators of other meta-analyses of Gla-300 versus Gla-100 trials have reported similar findings [20–22].

A pre-planned meta-analysis of IDeg phase III (BEGIN) trials also revealed significantly lower rates of overall confirmed and nocturnal confirmed episodes of hypoglycemia with IDeg (n = 2262) versus Gla-100 (n = 1110) (rate ratio [RR] 0.83, 95% CI 0.74–0.94 vs. 0.68, 95% CI 0.57–0.82, respectively) in the overall T2DM population [29]. Other investigators have also reported comparable HbA1c control with lower hypoglycemia for IDeg versus Gla-100 [27, 36, 38, 40].

Retrospective RWE corroborates a comparable glycemic control and reduced hypoglycemia with second-generation compared with first-generation BI analogues [42–46], with potential cost offsets from a reduction in healthcare utilization and hospitalizations [44]. These findings have been observed in both insulin-naïve T2DM populations [45, 46] and in participants who switched from another BI analogue [42–44]. The Differentiate Gla-300 clinical and Economic in real-world Via EMR Data study (DELIVER 2) was a retrospective observational study that evaluated two propensity score-matched baseline cohorts consisting of 1819 patients on BI who switched to Gla-300 and 1819 participants who switched to another BI. The change in HbA1c during the 6-month follow-up period was identical (−0.51% in both cohorts; p = 0.928), but there was a significantly lower incidence of hypoglycemia in the group who switched to Gla-300 compared with those switching to other BIs (15.4 vs 18.1%, respectively; p = 0.015). Hypoglycemia was defined by US medical codes for hypoglycemia and/or
plasma glucose ≤ 70 mg/dL. In this study there were also a significant reduction in emergency department (ED) and/or hospitalization admissions associated with hypoglycemia, which translated into lower healthcare resource utilization and costs [44].

Looking at the evidence in totality comparing second-generation with first-generation BIs, it is apparent that the second-generation BIs offer the clinical advantages of glycemic efficacy with less hypoglycemia, which make them the preferred consideration for people living with diabetes.

Comparison of Second-Generation BI Analogues

The more relevant clinical question, however, is how do the second-generation BI analogues compare to each other. A number of studies have compared the second-generation BI analogues Gla-300 and IDeg (100 U/mL or 200 U/mL) (Appendix 3) [45, 47–52], including several RCTs, two of which employed a crossover design with continuous or flash glucose monitoring (CGM) [47, 50]. Many of the patients included in these comparator studies had a number of risk factors for hypoglycemia, although these factors were not independently assessed in these studies.

An open-label, head-to-head, treat-to-target, non-inferiority study (BRIGHT) compared second-generation BI analogues Gla-300 (n = 466) and IDeg (n = 463) 100 U/mL (IDeg-100) in insulin-naïve patients with uncontrolled T2DM. In this multinational, multicenter trial, Gla-300 (n = 466) and IDEG-100 (n = 463) provided similar improvement in HbA1c (primary endpoint). At week 24, the mean baseline HbA1c values improved similarly from a baseline of 8.7% (72 mmol/mol) and 8.6% (70 mmol/mol) in the Gla-300 and IDEG groups, respectively, to a HbA1c level of 7.03% (53.3 mmol/mol) at week 24 in both BI treatment groups (least square mean [LSM] difference – 0.05%, 95% CI – 0.15 to 0.05 and – 0.6 mmol/mol, 95% CI – 1.7 to 0.6; p < 0.0001). There was no statistically significant difference in the incidence or event rates of hypoglycemia at any time of day (24-h) or nocturnal hypoglycemia over 24 weeks. However, during the titration period (0–12 weeks), the incidence and rate of anytime (24-h) confirmed hypoglycemia (≤ 70 or < 54 mg/dL) was lower with Gla-300 versus IDEG. The incidence of confirmed (< 54 mg/dL) anytime hypoglycemia in the Gla-300 group during the titration period was 7.8 vs 11.7% with IDEG (odds ratio [OR] 0.63, 95% CI 0.40–0.99; p = 0.044) and event rate 0.49 versus 0.86, respectively (RR 0.57, 95% CI 0.34–0.97; p = 0.038). Overall, during the 24-week period, only one participant experienced severe hypoglycemia [49].

In 2019, Kawaguchi et al. reported similar findings using CGM in a small, open-label, randomized cross-over designed study involving 30 patients with T2DM from a single center in Japan [47]. These authors reported that patients treated with Gla-300 versus IDEG-100 had a significantly lower mean percentage of time with hypoglycemia (< 70 mg/dL) (1.3 vs. 5.5%; p = 0.002), severe hypoglycemia (< 54 mg/dL) (0.04 vs. 1.8%; p = 0.003) and nocturnal hypoglycemia (< 70 mg/dL from 00:00 to 06:00 hours) (1.1 vs. 4.2%; p = 0.009), respectively. However, there was no difference in the primary endpoint, which was the mean percentage of time with target glucose range 70–180 mg/dL, between the two BIs (77.8 vs. 76.9%; p = 0.848) [47].

The open-label, randomized, head-to-head, treat-to-target study, CONCLUDE, was designed to assess the efficacy and safety of IDEG 200 U/mL versus Gla-300 in T2DM patients who were on a BI analogue and at high risk of hypoglycemia (n = 1609) [48]. The study was designed to test for superiority of IDEG. The primary endpoint was the number of severe (requiring third-party assistance) or blood glucose-confirmed (< 56 mg/dL) symptomatic hypoglycemic episodes during the maintenance period. The investigators found no significant difference between the two groups (RR 0.88, 95% CI 0.73–1.06). Since this primary outcome was not met, the other study outcomes, i.e. showing a lower rate of nocturnal symptomatic and severe hypoglycemia with IDEG-200 compared to Gla-300, were considered to be exploratory. Several factors should be
considered when interpreting CONCLUDE data, such as the exclusion of patients who were taking sulfonylureas and inaccuracy issues with the blood glucose meters initially used in the titration phase and maintenance period of the study; these factors necessitated a substantial amendment to and change of measurement device and follow-up time [48].

RWE studies comparing the two second-generation BI analogues (Gla-300 and IDEg) have shown differing results. In a retrospective, observational, cohort study of US medical records (DELIVER D+), adult patients with T2DM and a number of high-risk characteristics (n = 3184) switching from a first-generation insulin analogue (Gla-100 or IDEt) to a second-generation BI analogue (Gla-300 or IDEg) had comparable improvements in glycemic control [51]. The switchers to Gla-300 or IDEg were propensity score-matched using baseline demographic and clinical characteristics. The mean HbA1c in the Gla-300 switchers (n = 742) decreased from 9.05% to 8.41% (−0.63; p < 0.001) and for IDEg (n = 727) from 9.02% to 8.44% (−0.58; p < 0.001) (p value for difference between the two BIs was 0.488). A total of 15.1% of Gla-300 switchers versus 16.1% IDEg switchers reached an HbA1c target of <7% (p = 0.628). The authors reported no statistically significant difference in hypoglycemia incidence or hypoglycemia event rates between the Gla-300 and IDEg arms of the study. Using 6-month fixed follow-up (intention-to-treat method) the incidence of hypoglycemia for Gla-300 (n = 1592) and IDEg (n = 1592), after adjusted for baseline hypoglycemia incidence, was 12.7% in both treatment cohorts (OR 0.97, 95% CI 0.78–1.20; p = 0.745). Similarly, there was no difference in the adjusted hypoglycemia event rate between the two second-generation BI analogues (LSM difference −0.03, 95% CI −0.13 to 0.08; p = 0.617) [51].

CONFIRM was a retrospective, observational study that compared the effectiveness of IDEg-100 or 200 units/mL and Gla-300 in insulin-naive adult patients with T2DM from electronic health records in the USA [52]. In this study there was a greater reduction in the change in baseline HbA1c from treatment initiation until 180 days of follow-up in the IDEg (n = 671) versus the Gla-300-treated group (n = 749) (estimated treatment difference −0.27%, 95% CI −0.51 to −0.03; p = 0.03 [primary endpoint]). However, this result was not generated from the propensity score-matched population and so may be attributable to fundamental differences in the patient populations rather than attributable to the treatment given. A greater change in the rate of hypoglycemia (RR 0.70; p < 0.05) with IDEg compared with Gla-300 was reported although there were differences in rates of hypoglycemia at baseline between the two groups [52].

Interestingly, another retrospective observational study (DELIVER Naive D) [45] using the same US electronic health records as CONFIRM [52], also compared glycemic control, hypoglycemia and treatment discontinuation of Gla-300 and IDEg in propensity-score matched cohorts (n = 638 per treatment group) in insulin-naive adults with T2DM from baseline to 3–6 months of follow-up. In contrast to CONFIRM, this study demonstrated comparable HbA1c decreases, HbA1c target attainment and treatment discontinuation. Overall and inpatient/ED-associated hypoglycemia incidences and event rates were also similar in both cohorts [45].

Taken all together, it would appear that the two second-generation BI analogues are effective BIs with similar glycemic efficacy and similar overall hypoglycemia. Less hypoglycemia was observed with Gla-300 during the titration period in insulin-naive individuals with T2DM. Similar hypoglycemia was seen during the maintenance phase among those on BI. Therefore, the more important clinical interpretation of these data is that (1) second-generation BI analogues are better than their first-generation counterparts and should be used preferentially and (2) the choice of which second-generation BI analogue to use should be based on practical differences, such as cost, access, device and others.

HIGH-RISK GROUPS
FOR HYPOGLYCEMIA AND OTHER SPECIAL POPULATIONS

Given that one of the primary advantages of the second-generation BI is the reduction in
hypoglycemia in the overall diabetes population, are there data specifically in high-risk groups for hypoglycemia? In particular, older adults (≥ 65 years), those with renal insufficiency, longer duration of diabetes or duration on insulin treatment and those with prior severe hypoglycemia are at higher risk of hypoglycemia. The focus of this section is the evaluation of hypoglycemia risk with second-generation BI analogues in the aforementioned patient populations.

Older Adults

It is estimated that approximately 40% of people with T2DM are ≥ 65 years of age [53]. Population-based cohort studies show that older individuals have a substantially increased risk of morbidity and mortality compared to younger people with T2DM [8]. Older adults with diabetes often have an increased duration of diabetes and other comorbidities, such as CV events, retinopathy and renal impairment [8]. Impaired cognitive function, dementia and falls are also increased in older persons compared to younger people with T2DM [54, 55]. All of these factors increase the complexity of managing older people with T2DM [55] and may substantially increase the risk of hospitalization for hypoglycemia and associated death [8, 56].

Hospitalization rates for hypoglycemia reported in a large retrospective observational study carried out in the USA from 1999 to 2011 were two-fold higher in persons aged ≥ 75 years compared to those aged 65–74 years [57]. In a 2-year prospective study, 124 subjects with T2DM aged ≥ 80 years were hospitalized with hypoglycemia, of whom 31 (25%) had severe hypoglycemia (defined as a symptomatic event requiring treatment with intravenous glucose and confirmed blood glucose level of < 50 mg/dL). This group of patients had marked comorbidity and was found to have HbA1c values of 5.1%, indicating that their diabetes was well controlled [58].

The specific mechanisms for an increased risk of severe or fatal hypoglycemia with age is unclear [59]. Experimental and clinical data in small numbers of subjects suggests that hypoglycemia symptoms and counterregulatory hormone responses in older people with T2DM may be different to those observed in younger people treated with insulin [7, 59–61]. Using a retrospective questionnaire, Japp et al. reported that older adults ≥ 70 years (n = 102) treated with insulin generally had a low intensity of ‘classic’ hypoglycemia symptoms (e.g. lightheadedness and unsteadiness) and more neurological symptoms, with the latter possibly being less readily identified and erroneously attributed to other causes [60]. In an experimental study of healthy men, Matyka et al. found subjects aged 60–70 years of age (n = 7) were more prone to severe cognitive impairment during hypoglycemia compared to younger men (n = 7) and also less likely to report warning symptoms [61]. Using hyperinsulinemic glucose clamp studies, Meneilly et al. reported that older adults with T2DM who did not have obesity (n = 10) had significant alterations in the release of counterregulatory hormones in response to hypoglycemia compared to older adults who did not have T2DM and obesity (n = 10) [59]. In this study, the older adults with T2DM also had decreased awareness of hypoglycemia symptoms and of alterations in cognitive function in response to low glucose values, which the authors proposed may predispose them to severe hypoglycemia [59].

Given an increased risk of hypoglycemia in older adults, agents that achieve the HbA1c target with a lower risk of hypoglycemia may be particularly advantageous in this vulnerable patient population.

Second-Generation BI Analogues in Older Adults

A number of meta-analyses [62–64], as well as one prospectively designed RCT [65], post-hoc analyses and RWE [42, 43, 66, 67], have evaluated the risk of hypoglycemia with second-generation BI analogues in older people, as summarized in Table 1.

Several meta-analyses of the EDITION and BEGIN studies have assessed the effectiveness and safety of second-generation BI analogues for the treatment of T2DM in older versus younger subjects [35, 62–64]. A patient-level meta-analysis of EDITION 1, 2 and 3 revealed
Table 1 Summary of evidence for second generation BI analogues in older adults

| Author, year of publication (study name) | Study design | Participant inclusion criteria | Interventions | Key baseline characteristics | Duration | Primary endpoint/objective |
|------------------------------------------|--------------|-------------------------------|---------------|----------------------------|----------|---------------------------|
| **Randomized Controlled Trials**         |              |                               |               |                           |          |                           |
| Ritzel et al. [32] (SENIOR)              | Multicentre, multinational, phase IIIb, open-labeled, parallel-group RCT; target FPG 5.0–7.2 mmol/L | ≥65 years (aim to include 20% ≥75 years); T2DM duration ≥1 year; HbA1c 7.5–11.0% (insulin naïve) or HbA1c 7.0–10.0% (previous basal insulin) | Gla-300 (n = 508) vs Gla-100 (n = 506) | Gla-300 vs Gla-100 (mean): Age 71 vs 71 years BMI 30.9 vs 31.2 kg/m² HbA1c 8.20 vs 8.22 % Duration of diabetes 15.29 vs 15.35 years eGFR 75.42 vs 75.42 mL/min/1.73m² Previous insulin use 67.3 vs 67.8 % | 26 weeks | HbA1c change from baseline to 26 weeks | Mean HbA1c change was –0.89% for Gla-300 and –0.91% for Gla-100 with LS mean difference of 0.02% (95% CI –0.092 to 0.129) |
| Munshi et al. [62]                       | Pooled, patient-level mITT analysis of EDITION 2 and 3 | ≥65 years: Gla-300 (n = 199) vs Gla-100 (n = 211) | Gla-300 vs Gla-100 (mean pooled data): Age 58 vs 58 years BMI 33.7 vs 34.0 kg/m² HbA1c 8.4 vs 8.4% Duration of diabetes 11.4 vs 110 years | | 6 and 12 month assessments | Efficacy and hypoglycemia at 12 months: HbA1c change from baseline was –0.90% for Gla-300 (SE 0.006) and –0.95% (SE 0.005) for Gla-100 (P= 0.255) Rate of confirmed ≤3.9 mmol/L (≤70 mg/dL) or severe hypoglycemia was lower with Gla-300 than Gla-100 (12.3 vs 14.7 events/patient/year, P= 0.005) |
| Yale et al. [64]                         | Patient-level meta-analysis of EDITION 1, 2 and 3 (≥65 years) | Gla-300 (n = 329) vs Gla-100 (n = 333) | Gla-300 vs Gla-100 (mean): Age 69 vs 70 years BMI 33.5 vs 33.9 kg/m² HbA1c 8.17 vs 8.13 % Duration of diabetes 15.8 vs 15 years eGFR 67.4 vs 68.2 mL/min/1.73m² | Variable (26–52 weeks) | 6 months | HbA1c change from baseline to month 6: L5 mean change was –1.02% for both groups with LS mean difference of 0.00% (95% CI –0.14 to 0.15) |
| Sorli et al. [63]                        | Pre-planned meta-analysis of the BEGIN program (≥65 years) | T2DM: IDeg 100 U/mL (n = 589) vs Gla-100 (n = 265) | IDeg vs Gla-100 (mean): Age 70 vs 70 years BMI 29.8 vs 29.7 kg/m² Duration of diabetes 13.8 vs 13.4 years | Variable (26–52 weeks) | | Confirmed rate of hypoglycemia < 3.1 mmol/L (< 3.1 mmol/L, [≤ 56 mg/dL]): Overall rates were lower with IDeg than Gla-100 with an estimated rate ratio 0.76 (95% CI 0.61 to 0.95) |
Table 1 continued

| Author, year of publication (study name) | Study design | Participant inclusion criteria | Interventions | Key baseline characteristics | Duration | Primary endpoint/objective |
|----------------------------------------|--------------|--------------------------------|---------------|-----------------------------|----------|---------------------------|
| **Post-hoc Trial Analyses**            |              |                                |               |                             |          |                           |
| Heller et al. [66]                     | Post-hoc analysis of SWITCH-2 (>65 years): a double-blind, two-period, crossover RCT; target FPG 3.9–<5.0 mmol/L | ≥18 years; T2DM duration ≥ 26 weeks; HbA1c ≤ 9.5%; HbA1c ≤45 kg/m²; basal insulin +/- OADs plus: ≥1 hypoglycemia risk factor (≥1 severe episode in 12 last months; eGFR 30–59 mL/min/1.73m²; hypoglycemia unawareness; insulin duration ≥ 5 years; ≥1 episode within last 12 weeks) | IDeg 100 U/mL vs Gla-100 (total analysis n = 270) | Total population >65 years (mean): Age 72 years BMI 31.2 kg/m² HbA1c 7.4% Duration of diabetes 15 years | 2 x 32 week periods | Number of overall symptomatic hypoglycemia (severe or confirmed [<3.1 mmol/L (<56 mg/dL)]) events during the maintenance period: In those >65 there were 188 events/PYE with IDeg and 269 events/PYE with Gla-100 with a treat ratio of 0.70 (95% CI 0.56 to 0.88) P = 0.0023 |
| Pratley et al. [67] (DEVOTE 7)         | Post-hoc analysis of those 50–64 years, ≥65 years or ≥75 years from DEVOTE (CVOT): a multinational, double-blind RCT; target fasting 4.0–5.0 mmol/L | T2DM treated with ≥1 oral or injectable antihyperglycemic agent; HbA1c ≥ 7.0% or HbA1c <7.0%, if treated with ≥20 units/day of basal insulin; ≥ 50 years with CVD or moderate CKD or ≥ 60 years with CVD risk factors | IDeg 100 U/mL vs Gla-100 (≥65 years n = 3136; ≥75 years n = 819) | ≥65 years population (mean): Age 69 years HbA1c 8.2% Duration of diabetes 17.8 years eGFR 63.2 mL/min/1.73m² | Until 633 adjudicated MACEs | Risk of MACEs between different age groups: No statistical difference in MACEs found for those ≥65 years (HR 1.02 [95% CI 0.86 to 1.21]) or ≥75 years (HR 1.17 [95% CI 0.91 to 1.51]) compared to those 50-64 years |
| **Real World Evidence**                |              |                                |               |                             |          |                           |
| Bailey et al. [46] (DELIVER 3)         | Retrospective, observational, propensity score-matched cohort study using EMR data from the US in patients switching to Gla-300 or Gla-100/IDet | ≥65 years; confirmed T2DM diagnosis; data ≥12 months before and ≥6 months after index date; HbA1c <15% during 6 months from baseline and 3–6 months follow up period | Gla-300 (n = 1176) vs Gla-100/IDet (n = 1176) | Gla-300 vs Gla-100/IDet (PSM mean): Age 72 years vs 72 years BMI 33.9 vs 33.8 kg/m² HbA1c 8.6 vs 8.6% eGFR 60.1 vs 59.3 mL/min/1.72m² | HbA1c during follow-up period (3–6 months post-switch) | HbA1c changes and healthcare resource utilization: Gla-300 showed similar HbA1c reductions to Gla-100/IDet with reduced rate of hypoglycemia-related inpatient visits aOR 0.27 (95% CI 0.12 to 0.58) P = <0.001 |
| Author, year of publication (study name) | Study design | Participant inclusion criteria | Interventions | Key baseline characteristics | Duration | Primary endpoint/objective |
|----------------------------------------|--------------|--------------------------------|---------------|-----------------------------|----------|----------------------------|
| Pettus et al. [43] (LIGHTNING)         | Retrospective, observational propensity score-matched cohort study and predictive modeling using machine learning using US EHR data | ≥18 years; confirmed T2DM diagnosis; insulin naive or BI switcher during a treatment period between 1 January 2007 and 31 March 2017; ≥1 HbA1c measurement at baseline | Total insulin naive population | Gla-300 insulin naive vs BI switcher (mean): Age: 60 vs 60 years BMI 34.0 vs 35.0 kg/m² HbA1c 9.5 vs 9.0 % IDeg insulin naive vs BI switcher (mean): Age: 59 vs 58 years BMI 34.6 vs 34.5 kg/m² HbA1c 9.6 vs 9.0 % Gla-100 insulin naive vs BI switcher (mean): Age: 60 vs 60 years BMI 34.2 vs 34.2 kg/m² HbA1c 9.3 vs 8.9 % IDet insulin naive vs BI switcher (mean): Age: 60 vs 60 years BMI 34.0 vs 33.8 kg/m² HbA1c 9.4 vs 9.0 % | Up to 1 year from index date (retrospective analysis) | Severe hypoglycaemia detected as reason for admission/discharge or plasma glucose <3.0 mmol/L (54 mg/dL) or IM glucagon administration or through natural language processing screening of clinical health records: ≥65 years (insulin naive) event rate PPY: Gla-300 0.09 vs (IDeg 0.12; Gla-100 0.16*; IDet 0.17*) ≥75 years insulin naive) event rate PPY: Gla-300 0.11 vs (IDeg 0.15; Gla-100 0.2*; IDet 0.2*) ≥65 years (BI switcher) event rate PPY: Gla-300 0.23 vs (IDeg 0.26; Gla-100 0.29; IDet 0.32*) ≥75 years (BI switcher) event rate PPY: Gla-300 0.27 vs (IDeg 0.32; Gla-100 0.33; IDet 0.37) |
that there was a comparable reduction in HbA1c and a lower risk of nocturnal hypoglycemia with Gla-300 versus Gla-100, which was more apparent in the subgroup of subjects aged ≥ 65 years (mean age 69.6 years) than in that aged < 65 years (mean age 54.7 years) (relative risk 0.77, 95% CI 0.68–0.87 vs. 0.70, 95% CI 0.57–0.85, respectively) [64]. The composite endpoint of the percentage of patients ≥ 65 years reaching HbA1c target (< 7.0 or < 7.5%) at 6 months without confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL] or < 3.0 mmol/L [or < 54 mg/dL]) or severe hypoglycemia at night [00:00–05:59 hours] was significantly higher for Gla-300 versus Gla-100 (all p < 0.05) [64]. The percentage of participants experiencing treatment-emergent adverse events (TEAEs) was similar for both insulins (58.4 vs. 56.0% in participants aged ≥ 65 years and 56.9 vs. 52.8% in participants aged < 65 years for Gla-300 and Gla-100, respectively). The incidence of serious TEAEs leading to death or treatment discontinuation was low (< 2%) across both treatments and age cohorts [64]. Sorli et al. undertook a prospective, preplanned meta-analysis of pooled patient-level data in older adults ≥ 65 years (n = 856/3387; mean age 70 years) from five BEGIN trials involving patients with T2DM [63]. In this meta-analysis, older adults with T2DM taking IDeg had a 24% lower estimated rate of overall confirmed hypoglycemia (< 3.1 mmol/L) versus Gla-100 (estimated rate ratio [ERR] 0.76; 95% CI 0.61–0.95) in the total treatment period. Similarly, nocturnal confirmed hypoglycemia (from 00:01 to 05:59 hours) was 36% lower in the IDeg group than in the Gla-100 group (ERR 0.64; 95% CI 0.43–0.95) in the total treatment period. TEAEs aside from hypoglycemia were not reported in the published meta-analysis of BEGIN studies [63]. The hypoglycemic benefits with IDeg relative to Gla-100 in this meta-analysis of older adults were consistent with those seen in the full adult patient population reported by Ratner et al. [29]. A post-hoc analysis of data from the 32-week, randomized, double-blind, cross-over SWITCH 2 trial assessed overall symptomatic hypoglycemia events during the maintenance period (primary endpoint) in older (> 65 years; n = 270; median age 71.5 years) and younger individuals (≤ 65 years; n = 450; median age 56.6 years) with T2DM who were randomized to either the IDeg or Gla-100 treatment arm [66]. Baseline median (range) duration of diabetes was 12 (1–40) versus 15 (1–54) years, with a mean eGFR of 87.0 versus 63.7 mL/min/1.73 m² in the younger versus older cohorts, respectively. There was no statistically significant difference in the older versus younger participants in terms of the estimate risk of overall symptomatic hypoglycemia (RR 1.05, 95% CI 0.79–1.40; p = 0.73) or nocturnal symptomatic hypoglycemia (RR 0.93, 95% CI 0.63–1.36; p = 0.70). During both maintenance periods, treatment with IDeg lowered the rates of overall severe and blood glucose-confirmed symptomatic hypoglycemia by 30 and 31% versus Gla-100 in individuals aged > 65 years and ≤ 65 years, respectively. The treatment ratio was 0.70 (95% CI 0.56–0.88; p = 0.0023) in the older group IDeg/Gla-100 and 0.69 (95% CI 0.58–0.83; p < 0.0001) in the younger group. Similarly, the reduction in the rate of nocturnal symptomatic hypoglycemia or blood glucose-confirmed symptomatic hypoglycemia with IDeg versus Gla-100 was 41 and 43%, respectively (0.59; 95% CI 0.39–0.89; p = 0.012), in the older group and 0.57 (95% CI 0.42–0.78; p < 0.0005) in the younger group. In the total population the rate of severe hypoglycemia in the IDeg and Gla-100 arms was not significantly different (1.6 vs. 2.4%; p = 0.35) [11]; however, there were very few severe hypoglycemia events overall: six and nine severe hypoglycemic events occurred in individuals aged ≥ 65 years in the IDeg and Gla-100 arms, respectively, and four and eight such events occurred in those aged > 65 years, respectively. Adverse event (AE) rates in the IDeg and Gla-100 groups were 3.2 and 3.3 events/patient per year, respectively, for individuals aged ≤ 65 years and 3.5 and 4.1 events/patient per year, respectively, for individuals aged > 65 years [66].
Pratley et al. undertook a post-hoc analysis of the DEVOTE (CV outcomes trial comparing \( \text{IDeg} \) with Gla-100) population to investigate the effect of increased age and major CV events (primary endpoint) and severe hypoglycemia (secondary endpoint) [67]. Randomized patients \((n = 7637; \text{mean age 65 years})\) on either IDeg or Gla-100 were included in this analysis and divided into three age groups: 50–64 years \((n = 3682)\); 65–74 years \((n = 3136)\) and ≥ 75 years \((n = 819)\). The investigators reported that with increasing age there was a significantly greater risk of CV death (hazard ratio [HR] 1.47, 95% CI 1.02–2.12) in participants aged ≥ 75 years compared to those aged 50–64 years. All-cause mortality was also higher in those aged ≥ 75 years versus individuals aged 50–64 years (HR 2.06, 95% CI 1.36–2.26). Patients randomized to \( \text{IDeg} \) had a lower risk of severe hypoglycemia compared to those randomized to Gla-100. The rate ratios were significantly lower for people aged 65–74 years (RR 0.65, 95% CI 0.45–0.93) and those aged 50–64 years (RR 0.55, 95% CI 0.39–0.77) in the \( \text{IDeg} \)- versus Gla-100-treated patients, but not in the patients aged ≥ 75 years (RR 0.76, 95% CI 0.39–1.49). Similarly, the risk of severe hypoglycemia was significantly less in patients aged 50–64 years (RR 0.33, 95% CI 0.17–0.63) but not in the higher aged groups. The oldest age group (≥ 75 years) had significantly higher rates of serious AEs. The most frequent serious AEs were cardiac disorders, which were reported in 19% of patients aged ≥ 75 years, 15.5% of those aged 50–64 years and 15% of subjects aged 50–64 years. The authors concluded that further data for the risk of hypoglycemia were warranted in older individuals ≥ 75 years [67].

There is one prospectively designed, open-label, RCT in older adults (≥ 65 years; mean age 71 years; \( n = 1014 \) (SENIOR study) that investigated the efficacy and safety of Gla-300 in this at-risk population [65]. Eligible patients, who were either insulin naïve or previously on BI, were randomized to Gla-300 \((n = 508)\) or Gla-100 \((n = 505)\). Overall, there were 135 participants (26.6%) in the Gla-300 group and 106 participants (20.9%) in the Gla-100 group, all aged ≥ 75 years. The BIs were self-administered once daily at the same time each day ± 3 h [65]. The fasting plasma glucose target used in this study was 5–7.2 mmol/L, which is consistent with the American Diabetes Association/European Society for the Study of Diabetes (ADA/EASD) HbA1c recommended glycemic target in older adults [1].

SENIOR investigators assessed the percentage of participants with one or more confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL] or severe hypoglycemic events occurring at any time of day [24 h] or at night [00:00–05:59 h or 22:00–08:59 hours]), the percentage of participants experiencing hypoglycemic events and annualized rates of hypoglycemia at either threshold (≤ 3.9 mmol [≤ 70 mg/dL] and < 3.0 mmol/L [< 54 mg/dL]) at any time of day [24 h] and at night [00:00–05:59 hours]) over 26 weeks of treatment with Gla-300 versus Gla-100 [65]. The authors reported a significantly lower incidence of symptomatic (< 3.0 mmol/L [< 54 mg/dL]) hypoglycemia at any time of the day (24 h) with Gla-300 in the very old subgroup of participants aged ≥ 75 years versus Gla-100-treated patients (1.5 vs. 10.4%; relative risk 0.33, 95% CI 0.12–0.88). Similarly, there was a statistically significant lower annualized rate of hypoglycemia versus Gla-100-treated patients in those aged ≥ 75 years treated with Gla-300 or symptomatic hypoglycemia (< 3.0 mmol/L [< 54 mg/dL]) (0.03 vs. 0.35 events/participant/year; RR 0.08, 95% CI 0.02–0.42) and confirmed (< 3.0 mmol/L [< 54 mg/dL] or severe hypoglycemia at any time of the day (24 h) (0.18 vs. 0.51 events/participant/year; RR 0.36, 95% CI 0.15–0.89). However, in the overall population (≥ 65 years), the incidence and rates of confirmed (< 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycemia events were low and not statistically different between treatment groups. There was no statistically significant difference in nocturnal hypoglycemia between the treatment groups [65].

In terms of overall safety, TEAEs were reported in 58.9% of those on Gla-300 and in 60.2% of those on Gla-100, with infections being the most commonly reported AE (25.8 and 29.7% for the Gla-300 and Gla-100 patients, respectively). The incidence of TEAEs among
participants aged ≥ 75 years was similar to the overall incidence in the ≥ 65-year-old population. Overall, the SENIOR study supports a comparable safety and tolerability profile of Gla-300 in the older adult population, including people ≥ 75 years of age. However, a limitation of this study was that patients with cognitive disorders or dementia (Mini-Mental State Examination score < 24) were excluded from the analysis [65].

The RWE in older adults appears to confirm the above findings. DELIVER 3, a retrospective, observational cohort study of US electronic medical records in patients aged ≥ 65 years (n = 1176; mean age 71.8 years), supports the efficacy and safety of Gla-300 in older persons in clinical practice [42]. In this study, older adults had a reduced rate of hypoglycemic events after switching from BI to Gla-300 versus switching to a first-generation BI analogue. The adjusted rate ratio of hypoglycemia (aRR) for subjects switching to Gla-300 was 0.63 (95% CI 0.53–0.75; p < 0.001), and inpatient/ED-associated hypoglycemia aRR was 0.58 (95% CI 0.37–0.90; p = 0.016). The aRR for inpatient/ED-associated hypoglycemia in subjects switching to Gla-300 was 0.43 (95% CI 0.31–0.60; p < 0.001) by variable follow-up [42].

Utilizing information from a US electronic health records database, the LIGHTNING investigators predicted the rate of severe hypoglycemia with second-generation BI analogues across various categories of patients with high hypoglycemia risk, including older adults, in both insulin-naïve patients aged ≥ 65 years (n = 20,885) and ≥ 75 years of age (n = 10,325) and in patients switching from another BI analogue who were ≥ 65 years (n = 15,837) and ≥ 75 years of age (n = 5654). In all these subanalyses there was numerically less predicted severe hypoglycemia with Gla-300 or IDeg versus either Gla-100 or IDet; however, the difference was not statistically significant in some subgroups [43]. It should be noted that in this analysis no test for heterogeneity was carried out between the subgroups and the overall population.

**Comments and Recommendations for Older Adults**

In summary, the advantages of second-generation BI analogues are maintained in the older adult population. The consequences of hypoglycemia are often more pronounced in older persons who may have coexisting morbidities. In clinical circumstances where insulin treatment is warranted in older adults, a second-generation BI analogue, which reduces the risk of hypoglycemia, may be preferable to a first-generation analogue. In addition, the greater flexibility and convenience of a once-daily injection of a second-generation BI analogue is beneficial in this population who may rely on caretakers to administer insulin. However, further data on the use of second-generation BI analogues in those aged > 75 years and in older individuals with concomitant cognitive impairment or dementia would be useful.

**Renal Insufficiency**

Renal impairment is an independent risk factor for severe hypoglycemia [12]; therefore, diabetes management in patients with renal disease warrants special consideration. For each micromole per liter increase in serum creatinine, the risk of a severe hypoglycemic event has been shown to increase by 1% [6]. Both Moen et al. [68] and Davis et al. [13] reported at least a twofold increased risk of severe hypoglycemia in patients with eGFR < 60 mL/min/1.73 m². The reasons for an increased risk of hypoglycemia include an inability to clear insulin or other renally excreted OHA and impaired gluconeogenesis. In patients with severe renal impairment, anorexia with suboptimal nutrition may lead to a reduction in glycogen stores [12].

**Second-Generation BI Analogues in Patients with Renal Insufficiency**

There are no RCTs that have specifically assessed the use of second-generation BI in people with T2DM and renal insufficiency. However, the use of these agents in this at-risk population can be gleaned from a meta-analysis of Gla-300 RCTs [69], some exploratory data from a
subgroup analysis of BRIGHT [70] and predictive modeling data based on RWE from the LIGHTNING study [43].

Javier Escalada et al. performed a patient-level, post-hoc meta-analysis of all patients enrolled in the EDITION 1, 2 and 3 studies \((n = 2,496)\) who were randomized to receive Gla-300 or Gla-100. Pooled 6-month results were assessed according to baseline renal function: eGFR \(\geq 60\) mL/min/1.73 m\(^2\) or 15 to \(< 60\) mL/min/1.73 m\(^2\). Patients with eGFR \(< 15\) mL/min/1.73 m\(^2\) were not included in this analysis as these patients were excluded from the EDITION studies. The mean baseline eGFR was 48.6 mL/min/1.73 m\(^2\) in the lower eGFR group and 85 mL/min/1.73 m\(^2\) in the higher eGFR group [69]. Overall, more patients in the lower eGFR subgroup experienced hypoglycemia compared with the higher eGFR subgroup. The authors reported a reduced risk of nocturnal confirmed \((\leq 3.9\) mmol/L \([\leq 70\) mg/dL]) or severe hypoglycemia with Gla-300 versus Gla-100 in both renal function subgroups (eGFR \(\leq 60\) mL/min/1.73 m\(^2\): RR 0.76, 95% CI 0.62–0.94; eGFR \(\geq 60\) mL/min/1.73 m\(^2\): RR 0.75, 95% CI 0.67–0.85). For confirmed \((\leq 70\) mg/dL \([\leq 3.9\) mmol/L]) or severe hypoglycemia at any time of day, the hypoglycemia risk was lower with Gla-300 than with Gla-100 in both the lower (RR 0.94, 95% CI 0.86–1.03) and higher (RR 0.90, 95% CI 0.85–0.95) eGFR cohorts [69]. The frequency of TEAEs were similar between the Gla-300- and Gla-100-treated patients, although more TEAEs were reported in participants with poorer renal sufficiency (eGFR \(< 60\) mL/min/1.73 m\(^2\)) versus the group with a higher eGFR (\(\geq 60\) mL/min/1.73 m\(^2\)). In the lower eGFR subgroup, 64.7 and 59.4% of participants in the Gla-300 and Gla-100 treatment groups, respectively, experienced TEAEs compared with 55.8 and 52.5% of participants in the Gla-300 and Gla-100 treatment groups, respectively, in the higher eGFR subgroup [69].

The SWITCH 2 cross-over study compared the efficacy and safety of IDeg \((n = 360)\) versus Gla-100 \((n = 360)\) in T2DM patients previously on prior BI who were at risk of hypoglycemia, including individuals with moderate chronic renal failure. In this study, approximately 16% of patients \((n = 159)\) had pre-existing moderate chronic renal failure (eGFR 30–59 mL/min/1.73 m\(^2\)) [11]. However, the results have not been assessed according to baseline renal function.

The BRIGHT investigators carried out a pre-specified subgroup analysis of Gla-300 versus IDeg in insulin-na"ive patients according to baseline eGFR \(\geq 90\) \((n = 467\) \([0%]\)), 60 to \(< 90\) \((n = 265\) \([0%]\)) and \(< 60\) mL/min/1.73 m\(^2\) \((n = 96\) \([0%]\)). The percentage change in Hba1c from baseline to week 24 was comparable in the renal subgroups with eGFR \(\geq 90\) and 60 to \(< 90\) mL/min/1.73 m\(^2\); however, patients with eGFR \(< 60\) mL/min/1.73 m\(^2\) randomized to Gla-300 \((n = 47)\) had a statistically greater change in Hba1c compared to IDeg patients \((n = 49)\) \((0.43; 95%\) CI \(0.74\) to \(-0.12\)). There were no differences in hypoglycemia incidence or rates over 24 weeks in the \(< 60\) mL/min1.73 m\(^2\) subgroup. Further investigation is required to determine if Gla-300 may allow more effective glycemia management in this vulnerable population [70].

The only RWE in this population comes from the LIGHTNING study investigators who utilized predictive modeling to compare hypoglycemia rates using data from a US electronic health records database. These authors analyzed subgroups of patients who were insulin-na"ive \((n = 19,205)\) or who switched from another BI analogue \((n = 15,889)\) and who had moderate/severe renal impairment, defined as compromised eGFR \(< 60\) mL/min/1.73 m\(^2\), nephropathy, proteinuria or dialysis. In the insulin-na"ive cohort, there was a statistically significant lower predicted rate of severe hypoglycemia in patients with moderate to severe renal impairment with Gla-300 versus first-generation BI analogues (Gla-100 and IDet), as well as in the BI switch cohort versus IDet (all \(p < 0.05\)) [42].

**Comments and Recommendations for Patients with Renal Insufficiency**

Reduced hypoglycemia with second-generation compared to first-generation BI analogues appears to be maintained in subjects with renal impairment. Given that this population is particularly vulnerable for hypoglycemia, especially when the eGFR falls below 45 mL/min/1.73 m\(^2\), there is an unmet need to identify safer...
treatment options for this group. The data to date support the use of second-generation BI analogues preferentially over first-generation BI analogues, given the lower risk of hypoglycemia in this population. A subanalysis of the BRIGHT study suggests that Gla-300 may provide greater HbA1c reduction in the group with eGFR < 60 mL/min/1.73m² compared to IDeg, with no increase in hypoglycemia [69], but this remains to be proven definitively. However, further data are required in patients with significantly lower eGFR (i.e. severe/end stage renal failure [eGFR < 15 mL/min/1.73 m²]) to confirm the safety of longer duration insulins in this patient population.

Prior Hypoglycemia

Retrospective studies suggest that prior severe hypoglycemia is an independent risk factor for subsequent hypoglycemia [12, 13]. Recurring hypoglycemia episodes can lead to a defective hormonal counter-regulatory response to hypoglycemia, or a failure to recognize an impending hypoglycemic event [12]. Second-generation phase III registration studies included participants with prior hypoglycemic events; however, we did not identify a randomized controlled study that evaluated participants with prior hypoglycemia.

Several RCTs and real-world analyses [11, 42, 43, 48, 71] have specifically aimed to include participants at a higher risk of hypoglycemia, such as those with a history of hypoglycemia or severe hypoglycemia. However, none of these investigations have provided further analyses to determine whether or not hypoglycemia benefits were realized in those with a documented history of hypoglycemia.

Additionally, there was a small, before/after pilot study in a single center in Columbia, involving 60 patients with either unstable type 1 diabetes mellitus (T1DM; 27.6%) or type 2 DM (T2DM; 72.4%) on basal-bolus insulin who had prior hypoglycemia, who switched from a first-generation BI to IDeg for 12 weeks [72]. Based on the results of a CGM test performed at the first study visit, participants were classified into low (n = 42) or high glycemic variability (n = 18), with a coefficient of variation threshold of 34%. In the subgroup of patients with high glycemic variability, the percentage of patients with ≥ 1 episode of hypoglycemia within 24 h (< 54 mg/dL for at least 20 min) decreased from 66.6 to 22.2% (p = 0.02); however, this decrease was not observed in the low basal glycemic variability group. The percentage of patients who had ≥ 1 episode of nocturnal hypoglycemia (< 54 mg/dL between 00:01 and 0.5:59 hours) also decreased from 37.14 to 5.71% (RR 0.154; 95% CI 0.017–0.678; p < 0.01). Changes were not significant in individuals with low glycemic variability at first visit [72].

Comments and Recommendations in Patients with Prior Hypoglycemia

Given the impact that hypoglycemia episodes can have on one’s ability to recognize future hypoglycemic symptoms, management of people with T2DM with a known history of hypoglycemia should prioritize therapies that are known to reduce the risk. However, based on the limited data available to date, it cannot be concluded that second-generation BI analogues confer less hypoglycemia than other BI. As numerous studies have included such patients, it would be prudent to carry out the appropriate subgroup analyses to determine if these insulins should also be prioritized in people with T2DM requiring insulin treatment.

Duration of Diabetes/Duration of Insulin Use

Duration of diabetes and duration on insulin treatment have both been associated with an increased risk of hypoglycemia. In the UKPDS study, rates of severe hypoglycemia rose once known diabetes duration exceeded 9 years [73]. Davis et al. reported that an increase of 1 year on insulin was independently associated with an increased risk of time to first severe hypoglycemic event during follow-up (HR 1.33, 95% CI 1.15–1.53; p < 0.001) [13].

Published studies have shown that second-generation BIs are as effective as Gla-100 at
controlling HbA1c, with a similar or lower risk of hypoglycemia in a broad range of patients, including high-risk patients with a long duration of diabetes (> 10 years) and those with a long duration on insulin treatment (> 5 years) [11, 23, 30, 35, 65, 69].

In the phase IIIa Gla-300 studies, the average duration of diabetes in the subjects enrolled in the EDITION studies was 12.7 years. In a meta-analysis of these studies, comparable glycemic control was achieved in patients on Gla-300 or Gla-100 with a diabetes duration of < 10 years (n = 970) and in patients with a diabetes duration of ≥ 10 years (n = 1496) (LS mean difference – 0.09, 95% CI – 0.21 to 0.03 and 0.05, 95% CI – 0.04 to 0.15, respectively) [35]. Similarly, there was no difference in glycemic control according to age at onset of diabetes (< 40 years, 40–50 years and ≥ 50 years) between Gla-300 and Gla-100 in the EDITION studies [35]. The mean age of onset of diabetes was 46.5 years. The lower risk of ≥ 1 nocturnal (00:00–05:59 hours) confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycemic event with Gla-300 versus Gla-100 was also unaffected by baseline duration of diabetes or age of onset [35]. It should be noted, however, that this meta-analysis did not perform a test for heterogeneity between the subgroups and the overall population, meaning that the results should not be viewed as conclusive.

Additionally, in a post-hoc, patient-level analysis of EDITION 1 and 2 studies, Bonadonna et al. assessed the impact of the duration of prior BI treatment on study outcomes in 1618 people with T2DM receiving Gla-300 or Gla-100 for 6 months. A lower risk of ≥ 1 confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycemic event, at night or any time (24 h), in patients on Gla-300 versus Gla-100 was unaffected by the duration of prior BI therapy, including those with a treatment duration > 5 years [41].

**Comments and Recommendations in Patients with Long Duration of Diabetes/Long Duration on Insulin**

Patients with a longer duration of diabetes or longer insulin use are at higher risk of developing hypoglycemia. The benefits of second-generation BI analogues over first-generation BI analogues appear to be maintained among these patients, including those who have required basal insulin for > 5 years. However, further robust analysis of people who have required insulin for longer periods (e.g. > 15 years) is warranted to gauge if this benefit persists over the longer term.

**SPECIAL POPULATIONS**

**CV Disease**

An association between severe hypoglycemia and CVD is well established [5, 6]. A systematic review and meta-analysis in over 900,000 patients with 1–5.6 years of follow-up found that severe hypoglycemia was associated with a doubling of the risk of CVD in people with T2DM (p < 0.001) [5].

A dedicated CV outcomes trial (DEVOTE) involving 7637 participants with T2DM at high CV risk demonstrated the CV safety of IDeg compared to Gla-100. Most patients (85.2%) had established CVD, CKD or both at baseline, with a mean age of 65 years and a mean duration of diabetes of 16.4 years. The authors reported a 40% statistically significant reduction in adjudicated severe hypoglycemia with IDeg versus Gla-100 (4.9 vs. 6.6%; RR 0.60; p < 0.001) at similar levels of glycemic control. The large number of patients and longer duration of a CV outcome trial compared to usual glycemic studies likely allowed for sufficient statistical power to demonstrate the difference in severe hypoglycemia that has not been shown in other studies [74].

A pre-specified secondary analysis (DEVOTE 14) investigated baseline factors and treatment differences associated with an increased risk of hospitalization for heart failure (hHF), including an association with severe hypoglycemia. Overall, the time to first hHF was not statistically significant between IDeg- and Gla-100-treated patients. Hospitalization for HF occurred in 4.6% of IDeg patients, with a rate of 3.42 events/100 patient-years of observation, and in 5.2% of Gla-100 patients, with a rate of 3.85 events/100 patient-years of observation (HR
Although this trial was not powered to compare differences in hHF or the relationship between severe hypoglycemia and the risk of hHF, the authors found that the risk of hHF (at any time to the end of the trial) more than doubled (HR 2.2, 10 vs. 18 events; \( p = 0.0002 \)) after experiencing an episode of severe hypoglycemia compared with before an episode [75].

Amod et al. undertook a secondary, pooled analysis (DEVOTE 11) of outcomes according to baseline eGFR (\( \geq 90, 60 \) to \( < 90, 30 \) to \( < 60 \) and \( < 30 \) mL/min/1.73 m\(^2\)) in 7522 patients. They found that the risks of major adverse cardiovascular events, CV death and all-cause mortality significantly increased with worsening baseline eGFR category (\( p < 0.05 \)). Numerically, there were higher rates of severe hypoglycemia with more advanced baseline eGFR category; however, this difference did not reach statistical significance [76].

The CV safety of Gla-100 was established in the Outcome Reduction with Initial Glargine Intervention (ORIGIN) study [77]. Regulatory bodies assessed that Gla-300 is sufficiently similar to Gla-100 in terms of metabolites that there was no need for another CV safety trial to be conducted with Gla-300.

**Comments and Recommendations in Patients with CVD**

The second-generation BI analogues have been shown to be safe from a CV perspective. The reduction in severe hypoglycemia with IDeg compared to Gla-100 observed in the DEVOTE trial supports the expectation of less hypoglycemia with second-generation BI analogues. Therefore, in patients with CVD the second-generation BI analogues remain a safe and effective option for glycemic control.

**Obesity**

Patients with T2DM and obesity (BMI \( \geq 30 \) kg/m\(^2\)) have greater insulin resistance [78]. These patients generally require larger insulin doses to control glucose levels. Hence, BIs with more units per volume are advantageous in this patient population, as a lower volume can be administered.

Most patients in the EDITION and BEGIN pivotal clinical trials had obesity. The mean BMI of patients in the EDITION studies was 34.8 (range 32.8–36.6) kg/m\(^2\) [35] and that of the T2DM patients in the BEGIN studies was 30.14 kg/m\(^2\) [29].

In a post-hoc, patient-level meta-analysis conducted by Twigg et al., Gla-300 and Gla-100 were comparable in terms of glycemic control in patients with BMI \( < 30 \) kg/m\(^2\) (\( n = 617 \)) and those with BMI \( \geq 30 \) kg/m\(^2\) (\( n = 1857 \)) (LS mean difference 0.03, 95% CI –0.12 to 0.17, and –0.01, 95% CI –0.10 to 0.07, respectively) [36]. The lower risk of \( \geq 1 \) nocturnal (00:00–05:59 hours) confirmed (\( \leq 3.9 \) mmol/L (\( \leq 70 \) mg/dL)) or severe hypoglycemic event with Gla-300 versus Gla-100 was unaffected by baseline BMI [35]. However, the heterogeneity testing in this analysis was not performed against the main population, thereby limiting the interpretation of these results.

Results for RWE studies also support the efficacy and safety of second-generation BIs in individuals with T2DM and obesity [42, 43, 51, 52]. For example, in the DELIVER 3 [42], DELIVER Naı̂ ve [46], DELIVER Naı̂ ve D [45], DELIVER D+, [51] CONFIRM [52] and LIGHTNING [43] studies, the mean baseline BMI of patients was approximately 33–35 kg/m\(^2\). Similarly, most patients in the SWITCH 2 double-blind, cross-over study with IDeg versus Gla-100 had obesity, with an mean BMI of 32.2 kg/m\(^2\).[11]

**Comments and Recommendations in People with Obesity**

It appears that the benefits of second-generation BI analogues compared to first-generation BI analogues are preserved in those with an elevated BMI. Dose requirements are higher in this population. In the case of Gla-300, RCTs have shown a slightly higher insulin dose requirement for this medication than for Gla-100 [1, 30, 37]. The increase in insulin dose, however, was weight neutral and did not cause further weight gain [19, 30, 37]. Among patients who require a higher dose due to body weight, a smaller volume insulin, such as Gla-300 or
IDeg-200, may be preferable for patient comfort. Further research is required for people with BMI > 35 kg/m².

Race and Ethnicity

Race and ethnicity can influence disease state factors, drug pharmacokinetics or pharmacodynamics, all of which may impact the efficacy and safety of antihyperglycemic treatments. For example, compared to Caucasians, Asian patients with T2DM tend to have more impaired insulin secretion than insulin resistance [79].

Most T2DM patients in the Gla-300 and IDeg phase III clinical trials were Caucasian. In four of the EDITION studies, 87.8% of the study population were Caucasian, 7.4% were Black, 3.9% were Asian and 0.95% were other ethnicities [35]. Additionally, there were two EDITION studies in Japanese subjects, with the findings consistent findings to those for the other EDITION study populations [34, 80]. One of the BEGIN trials included 27% Asian subjects [26]. At least 7–19% of the patients in the IDeg phase III trials were Hispanic or Latin American [23, 24, 39]. Non-Caucasian populations were also included in the real-world studies, such as DELIVER D, where 13.5% were African American, 5.8% were “other” and 5.8% were “unknown” [51].

A number of post-registration studies have assessed the safety and efficacy of second-generation BI analogues in non-Caucasian populations. In a post-hoc analysis of Hispanic (n = 262) and non-Hispanic patients (n = 458) from the SWITCH 2 study, Chaykin et al. reported lower hypoglycemia with IDeg versus Gla-100, with a similar level of glycemic control in both ethnic cohorts [81].

Multiple published studies have assessed the efficacy and safety of second-generation BI analogues in East Asian populations. A multinational, 26-week, open-label trial assessed the efficacy and safety of IDeg versus Gla-100 in 435 participants from Hong Kong, Japan, Malaysia, South Korea, Taiwan or Thailand who were inadequately controlled on OHA [28]. All participants were Asian (97.9% non-Indian; 2.1% Indian) and insulin-naïve. The mean age was 58.6 years and the mean BMI was 25 kg/m². Treatment with IDeg provided similar improvement in long-term glycemic control to Gla-100, with a significantly lower rate of overall confirmed hypoglycemia during the maintenance period (RR 0.52, 95% CI 0.27–1.00; p = 0.05). However, there was no significant difference in overall confirmed hypoglycemia during the full trial period or in nocturnal confirmed hypoglycemia. AEs were similar between the BI treatments [28].

More recently, Thewjitcharoen et al. published a prospective RWE study in 55 patients from Thailand who received IDeg over a 3- to 12-month period (mean age 57.1 years, duration of diabetes 16.7 years, BMI 27.4 kg/m²). Forty-two (76.4%) of these patients had T2DM, of which nine patients were newly initiated on insulin. The authors concluded that the effectiveness of IDeg in this Asian population was consistent with the results seen in the registration trials, with a low risk of hypoglycemia with IDeg at 12 months compared to baseline. The rate of self-reported major hypoglycemia (< 54 mg/dL or requiring assistance) in the overall T2DM and T1DM population fell from 4% at baseline to 0% at 12 months (no p value provided) [82].

Hypoalbuminemia

A small, single-center, open-label study in Japan evaluated the effect of serum albumin and the risk of hypoglycemia using CGM. A total of 30 subjects with T2DM (mean age 69.5 years, duration of diabetes 18 years) were randomized to receive Gla-300 or IDeg and then crossed-over to the other BI analogue [83]. The investigators reported a negative correlation between 24-h hypoglycemia and nocturnal hypoglycemia and serum albumin levels in patients treated with IDeg, while glycemic risk was not affected by serum albumin levels in patients treated with Gla-300 [83]. The authors then hypothesized that the higher hypoglycemia reported in their study with IDeg versus Gla-300 could be related to the high (> 99%) binding of IDeg to serum albumin in patients with
hypoalbuminemia [47]. Since free insulin binds to the insulin receptor and elicits a hypoglycemic effect, the lower the serum albumin, the higher the risk of hypoglycemia with IDeg. They postulated that Gla-300 may be less likely to cause hypoglycemia in individuals with hypoalbuminemia as it does not bind to serum albumin. Supporting this hypothesis, Kawaguchi et al. showed in patients with serum albumin levels < 3.8 g/dL (n = 15) that the mean percentage of time with hypoglycemia (< 70 mg/dL) was significantly lower in those treated with Gla-300 (1.9%) than in those treated with IDeg (11.1%) (p = 0.002). Similarly, there was a statistically lower percentage of time with clinically important hypoglycemia (< 54 mg/dL) and nocturnal hypoglycemia (< 70 mg/dL) in patients treated with Gla-300 than in those treated with IDeg (p = 0.002 and p = 0.004 respectively) [83].

Patients in Hospital

A few published studies have compared insulin initiation with a second-generation versus a first-generation BI analogue in hospitalized T2DM patients, but only limited data are available on patients with dementia or those with physical or intellectual disability living in long-term care facilities.

The largest prospective, open-label, RCT conducted to date compared second-generation versus first-generation BI analogues in 176 noncritically ill hospitalized patients with T2DM. Patients were randomized to receive either Gla-300 or Gla-100 as part of a basal-bolus regimen upon admission to hospital. Insulin doses were adjusted to achieve a target blood glucose of 70–180 mg/dL. There were no significant differences in the mean daily blood glucose levels between the Gla-300 and Gla-100 groups (186 ± 40 vs. 184 ± 46 mg/dL; p = 0.62) (primary endpoint). The percentage of readings within the target blood glucose, the length of hospital stay, the frequency of complications and the total daily insulin dose also did not differ significantly between the treatment groups. With respect to hypoglycemia endpoints, there was no statistically significant difference in the proportion of patients with a blood glucose < 70 mg/dL between the Gla-300 and Gla-100 groups (8.7 vs. 9.5%; p = 0.99); however, the Gla-300-treated group had a significantly lower rate of clinically relevant hypoglycemia (blood glucose < 54 mg/dL) (0 vs. 6.0%, respectively; p = 0.023) [84].

Additionally, Okajima et al. published a small RCT that evaluated the efficacy and safety of insulin basal-bolus therapy with Gla-300 compared with Gla-100 in well-controlled T2DM patients at the end of short-term hospitalization (n = 40; mean age 58 years, mean duration of diabetes 5 years) [85]. The duration of hospitalization was 15 days in both groups, and the required insulin doses to maintain normoglycemia were not different between the two groups. The frequency of nocturnal hypoglycemia (00:00–8:00 hours), however, was significantly lower in the Gla-300 group than in the Gla-100 group (1.2 vs. 10.7%; p = 0.039) [85].

In a small, open-labelled, randomized, controlled, 12-day study, Suzuki et al. evaluated the efficacy and safety of IDeg 100 IU/mL versus Gla-100 in combination with meal-time bolus insulin in 68 hospitalized patients with T2DM. There was no statistically significant difference in the achievement of target glycemic control during the first 12 days (primary endpoint) between the two groups. The incidence of hypoglycemia (54 to ≤ 70 mg/dL) during the introduction of insulin was low and not statistically significant between IDeg- and Gla-100-treated patients (40.6 vs. 41.7%, respectively). Similarly, there was no significant difference in the incidence of severe hypoglycemia (< 54 mg/dL) between the two groups (9.4 vs. 11.1%, respectively; p = 0.782) [86].

A small, 7-day, non-randomized, open-label pilot study compared IDeg once daily versus IDeg three times weekly in 22 older Japanese adults with T2DM who could not perform self-injection due to cognitive dysfunction, paralysis, visual impairment or other disabilities (median age 78 years) [87]. There were no symptomatic hypoglycemic events reported in either groups during the short study period, and both regimens were reported to be well tolerated [87].
Discussion

Drug-induced hypoglycemia is a major obstacle to achieving target HbA1c levels [3]. T2DM patients at risk of hypoglycemia require individualized, evidenced-based therapies to minimize hypoglycemia, prevent complications and optimize QoL [1]. Evidence to date demonstrates that second-generation BI analogues have comparable HbA1c control to first-generation BI analogues, but a lower association to hypoglycemia. This holds true across a wide range of patients: individuals with obesity, subjects with CVD and populations at risk of hypoglycemia, such as older adults, subjects with renal impairment and individuals with a long duration of diabetes or insulin use [11, 35, 42, 43, 62–67, 69]. Less hypoglycemia associated with second-generation BI analogues may be particularly meaningful in some of these vulnerable populations by removing barriers to insulin initiation, improving adherence [71], potentially improving QoL [88, 89] and reducing hypoglycemia-related healthcare resource utilization and associated costs [44]. Flexibility in the timing of injection with second-generation BIs may provide greater convenience, for example when travelling, for institutionalized patients or shift workers. Second-generation BIs may also offer an advantage to those who are undergoing prolonged fasting (e.g. Ramadan), but more evidence on this specific issue is needed although the existing single arm observational data are promising [90]. While available data support less hypoglycemia with second-generation versus first-generation BIs, there remain populations for whom more data are required. Data on the efficacy and safety of BIs in other special populations, such as patients with multiple coexisting morbidities [91], reduced hypoglycemia awareness or cognitive impairment, are limited. Patients with cognitive impairment or dementia were excluded from the SENIOR study [65]. The SWITCH 2 [11] and CONCLUDE [48] studies included some patients with hypoglycemia unawareness, but data specifically from those patients have not been published. Future studies should utilize CGM for better detection of hypoglycemia and include parameters such as time-in-range.

Studies are needed to address other important clinical questions, including the efficacy and safety of second-generation BI analogues in patients with more severe renal impairment (eGFR < 15 mL/min/1.73 m²) and those with hepatic dysfunction, alcoholism or cancer. There is also a great need to understand the use of BIs in the acute hospital setting, perioperative and long-term care environment, particularly in vulnerable individuals with cognitive, physical or intellectual disability.

Hypoglycemia results in a substantial burden on the healthcare system and can result in serious consequences. T2DM patients require individualized, evidenced-based therapies to minimize hypoglycemia, prevent complications and optimize QoL. Personalized strategies are particularly important in high-risk populations who are vulnerable to hypoglycemia, such as older adults, patients with renal impairment and/or longer duration of insulin use and those with prior episodes of hypoglycemia.

RCTs, meta-analyses and RWE demonstrate that patients taking second-generation BI analogues have less hypoglycemia than those on Gla-100 without compromising glycemic control. A reduced risk of hypoglycemia with second-generation BIs extends to special populations, such as older adults; those with renal impairment, obesity and/or CVD; and individuals with a long duration of insulin use. Less hypoglycemia associated with second-generation BIs may help reduce barriers for insulin use, improve adherence and QoL, as well as reduce hypoglycemia-related healthcare resource utilization and associated costs.

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### APPENDIX 1: REGISTRATION RANDOMIZED CONTROLLED TRIALS

| Author, year of publication (study name) | Study design | Participant inclusion criteria | Interventions | Key baseline characteristics | Duration | Primary endpoint |
|-----------------------------------------|-------------|--------------------------------|---------------|-----------------------------|----------|------------------|
| Terauchi et al. [34] (EDITION JP 2)     | Multicentre (Japan), open-label, parallel-group RCT; target FPG 4.4–5.6 mmol/L | ≥18 years; T2DM duration ≥1 year; taking basal insulin (≥6 months); HbA1c 7.0–10.0%; BMI <35 kg/m² | Gla-300 (n = 121) vs Gla-100 (n = 120) | Gla-300 vs Gla-100 (mean): Age 61 vs 61 years; BMI 25.7 vs 24.8 kg/m²; HbA1c 7.99 vs 8.06 %; Duration of diabetes 14.0 vs 13.9 years; Basal insulin dose 0.25 vs 0.24 U/kg/day | 6 months (+ 6 month extension) | HbA1c change from baseline to month 6: LS mean difference between groups was 0.10% (95% CI −0.08 to 0.27) |
| Bolli et al. [19] (EDITION 3)           | Multicentre, multinational, open-label, parallel-group RCT; target FPG 4.4–5.6 mmol/L | ≥18 years; T2DM duration ≥1 year; OAD use ≥1 year; insulin naive; HbA1c 7.0–11.0% | Gla-300 (n = 439) vs Gla-100 (n = 439) | Gla-300 vs Gla-100 (mean): Age 58 vs 57 years; BMI 32.8 vs 33.2 kg/m²; HbA1c 8.49 vs 8.58 %; Duration of diabetes 10.1 vs 9.6 years | 6 months (+ 6 month extension) | HbA1c change from baseline to month 6: LS mean change was −1.42% (SE 0.05) for Gla-300 and −1.46% (SE 0.05) (mean difference 0.04% [95% CI −0.09 to 0.17]) |
| Author, year of publication (study name) | Study design | Participant inclusion criteria | Interventions | Key baseline characteristics | Duration | Primary endpoint |
|-----------------------------------------|--------------|-------------------------------|---------------|----------------------------|----------|------------------|
| Riddle et al. [30] (EDITION 1)          | Multicentre, multinational, open-label, parallel-group RCT; target FPG 4.4–5.6 mmol/L | ≥18 years; taking basal insulin (≥42 units) and mealtime insulin therapy +/- metformin; HbA1c 7.0–10.0% | Gla-300 (n = 404) vs Gla-100 (n = 403) | Age 60 vs 60 years | 6 months (+ 6 month extension) | HbA1c change from baseline to month 6 or last visit on treatment: LS mean change was −0.83% (SE 0.06) for both groups (mean difference −0.00% [95% CI −0.11 to 0.11]) |
| Yki-Jarvinen et al. [37] (EDITION 2)    | Multicentre, multinational, open-label, parallel-group RCT; target FPG 4.4–5.6 mmol/L | ≥18 years; T2DM duration ≥1 year; taking basal insulin (≥6 months and ≥42 units) +/- metformin; HbA1c 7.0–10.0% | Gla-300 (n = 404) vs Gla-100 (n = 407) | Age 58 vs 59 years | 6 months (+ 6 month extension) | HbA1c change from baseline to month 6 or last visit on treatment: LS mean change from baseline was −0.57% (SE 0.09) for Gla-300 and −0.56% (SE 0.09) for Gla-100 (mean difference −0.01% [95% CI −0.14 to 0.12]) |
| Author, year of publication  
(study name) | Study design | Participant inclusion criteria | Interventions | Key baseline characteristics | Duration | Primary endpoint |
|----------------|------------|-------------------------------|--------------|--------------------------|----------|-----------------|
| Gough et al. [24]  
(BEGIN Low Volume) | Multicentre, multinational, open-label, parallel-group RCT; target FPG <5.0 mmol/L | Insulin naïve adults; T2DM duration ≥6 months, treated with metformin +/- other OADs (≥3 months); HbA1c 7.0–10.0%; BMI ≤45 kg/m² | IDeg 200 U/mL (n = 228) vs Gla-100 (n = 229) | IDeg 200 U/mL vs Gla-100 (mean): Age 58 vs 57 years BMI 32.2 vs 32.7 kg/m² HbA1c 8.3 vs 8.2% Duration of diabetes 8.4 vs 8.0 years | 26 weeks | HbA1c change from baseline to week 26: Mean HbA1c change was −1.3% (SD 1.01%) for both treatment with estimated mean difference of 0.04% (95% CI −0.11 to 0.19) |
| Meneghini et al. [26]  
(BEGIN Flex) | Multicentre, multinational, open-label, 3-arm, parallel group RCT; target FPG 3.9–<5.0 mmol/L | ≥18 years; T2DM duration ≥6 months, treated with OADs and HbA1c 7.0–11.0% or treated with basal insulin +/- OADs with HbA1c 1.0–10.0%; BMI ≤40 kg/m², | IDeg 100 U/mL flexible injection regimen (n = 229) vs IDeg OD (n = 228) vs Gla-100 OD (n = 230) | IDeg Flex  vs IDeg OD vs Gla-100 OD (mean): Age 56 vs 57 vs 57 years BMI 29.3 vs 29.4 vs 30.0 kg/m² HbA1c 8.5 vs 8.4 vs 8.4 % Duration of diabetes 10.8 vs 10.3 vs 10.8 years | 26 weeks | HbA1c change from baseline to week 26: Mean HbA1c change was −1.28 % for IDeg Flex, −1.07 for IDeg OD and 1.26% for Gla-100 OD with estimated mean treatment difference between IDeg Flex and Gla-100 OD was 0.04% (95% CI −0.12 to 0.20) |
| Author, year of publication (study name) | Study design | Participant inclusion criteria | Interventions | Key baseline characteristics | Duration | Primary endpoint |
|-----------------------------------------|--------------|--------------------------------|---------------|-----------------------------|----------|------------------|
| Onishi et al. [28] (BEGIN Pan-Asian)    | Multicentre, multinational, open-label, parallel-group RCT; target FPG 3.9–5.0 mmol/L | ≥18 years (≥20 years in Japan); T2DM duration ≥6 months; treated with OADs (stable dose ≥3 months); HbA1c 7.0–10.0%; BMI ≤35 kg/m² | IDeg 100 U/mL (n = 289) vs Gla-100 (n = 146) | Age 59 vs 58 years; BMI 24.6 vs 25.8 kg/m²; HbA1c 8.4 vs 8.5% Duration of diabetes 11.8 vs 11.1 years | 26 weeks | HbA1c change from baseline to week 26: Mean changes from baseline were -1.24% with IDeg and -1.35% with Gla-100 with estimated mean treatment difference of 0.11% (95% CI -0.03 to 0.24) |
| Garber et al. [23] (BEGIN Basal Bolus Type 2) | Multicentre, multinational, open-label, parallel-group RCT; target FPG 3.9–5.0 mmol/L | ≥18 years; T2DM duration ≥6 months; taking any insulin therapy (≥3 months +/- OADs; HbA1c 7.0–10.0%; BMI ≤40 kg/m² | IDeg 100 U/mL (n = 744) vs Gla-100 (n = 248) | Age 59 vs 58 years; BMI 32.3 vs 31.9 kg/m²; HbA1c 8.3 vs 8.4% Duration of diabetes 13.6 vs 13.4 years | 52 weeks (+ 26 week extension) | HbA1c change from baseline to week 52: Estimated mean change from baseline was -1.10% with IDeg and -1.18% with Gla-100; treatment difference of 0.08% (95% CI -0.05 to 0.21) |
| Zinman et al. [39] (BEGIN Once Long)   | Multicentre, multinational, open-label, parallel-group RCT; target FPG 3.9–4.9 mmol/L | ≥18 years; T2DM duration ≥6 months; OADs (stable dose ≥3 months); HbA1c 7.0–10.0%; BMI ≤40 kg/m² | IDeg 100 U/mL (n = 773) vs Gla-100 (n = 257) | Age 59 vs 59 years; BMI 30.9 vs 31.6 kg/m²; HbA1c 8.2 vs 8.2% Duration of diabetes 9.4 vs 8.6 years | 52 weeks | HbA1c change from baseline to week 52: Mean change from baseline was -1.06 with IDeg and -1.19% with Gla-100 with an estimated treatment difference of 0.09% (95% CI -0.04 to 0.22) |
## APPENDIX 2: META-ANALYSES OF SECOND GENERATION BI VS FIRST GENERATION BI ANALOGUES

| Author, year of publication | Study design | Participant inclusion criteria | Interventions | Key baseline characteristics | Duration | Primary objective/s |
|-----------------------------|-------------|--------------------------------|---------------|-----------------------------|----------|---------------------|
| Bolli et al. [20]           | Post-hoc, patient-level, pooled analysis of EDITION 2, 3 and JP2 trials | See appendix 1 for individual trial criteria | Gla-300 (n = 958) vs Gla-100 (n = 946) | Gla-300 vs Gla-100 (mean): Age 58 vs 58 years BMI 32.8 vs 32.8 kg/m² HbA1c 8.3 vs 8.4 % Duration of diabetes 11.7 vs 11.4 years | 6 months | Confirmed or severe hypoglycemia ≤3.9 mmol/L (≤70 mg/dL) examined across various nocturnal windows: The percentage of participants with at least one event was lower with Gla-300 than Gla-100 in all windows examined |
| Bonadonna et al. [21]       | Patient-level, pooled analysis of EDITION 1, 2 and 3 trials | See appendix 1 for individual trial criteria | Gla-300 (n = 1247) vs Gla-100 (n = 1249) | Gla-300 vs Gla-100 (mean): Age: 59 vs 59 years BMI 34.7 vs 34.8 kg/m² HbA1c 8.31 vs 8.32 % Duration of diabetes 12.7 vs 12.6 years | 6 months | Annualized hypoglycemia rate confirmed ≤3.9 mmol/L (≤70 mg/dL) or severe as a function of HbA1c at month 6 using a negative binomial regression model: Participants on Gla-300 had a lower rate of hypoglycemia regardless of HbA1c at month 6 |
| Author, year of publication | Study design                  | Participant inclusion criteria                                                                 | Interventions                  | Key baseline characteristics | Duration            | Primary objective/s                                                                 |
|-----------------------------|-------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------|-------------------------------|---------------------|-------------------------------------------------------------------------------------|
| Diez-Fernandez et al. [22]  | Systematic review and meta-analysis | RCTs comparing Gla-300 and Gla-100 reporting the rate ratio or number of events of nocturnal hypoglycemia and HbA1c levels in T1DM or T2DM | Gla-300 (n = 1998) vs Gla-100 (n = 1979) | Not reported—see appendix 1 for individual T2DM studies | Variable (up to 12 months) | Incidence rate ratio (RR) of nocturnal hypoglycemia: Nocturnal events ≤3.9 mmol/L (≤70 mg/dL) were lower with Gla-300 RR=0.81 (95% CI 0.69 to 0.95) and nocturnal events <3.0 mmol/L (<54 mg/dL) were lower with Gla-300 RR=0.75 (95% CI 0.63 to 0.91) |
| Zhou et al. [40]            | Systematic review and meta-analysis | RCTs in T2DM comparing IDeg with insulin glargine (Gla-300 or Gla-100) | IDeg (n = 9619) vs Gla-300 or Gla-100 (n = 7075) | Refer to publication for individual trial breakdown of baseline characteristics | Variable (24–104 weeks) | Efficacy (HbA1c change from baseline) and safety of IDeg compared with pooled insulin glargine: Insulin glargine led to a greater mean reduction in HbA1c than IDeg mean difference 0.07% (95% CI 0.01 to 0.13) P= 0.019 |
| Author, year of publication | Study design | Participant inclusion criteria | Interventions | Key baseline characteristics | Duration | Primary objective/s |
|-----------------------------|-------------|-------------------------------|---------------|-----------------------------|----------|---------------------|
| Bonadonna et al. [41]       | Post-hoc, patient-level, meta-analysis of EDITION 1 and 2 | See appendix 1 for individual trial criteria | Gla-300 (n = 808) vs Gla (n = 810) | Gla-300 vs Gla-100 (range): | 6 months | Assess the impact of duration of prior basal insulin therapy outcomes with Gla-300 vs Gla-100 for 6 months: |
|                            |             |                               |               | Age 57 to 61 years          |          | HbA1c change from baseline to month 6 was comparable groups with a lower risk of ≥1 confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycaemic events, at night or any time (24 h) with Gla-300, regardless of duration of prior basal insulin therapy |
|                            |             |                               |               | BMI 35.2 to 36.2 kg/m²      |          | |
|                            |             |                               |               | HbA1c 8.1 to 8.3 %          |          | |
|                            |             |                               |               | Duration of disease 10.6 to 17.8 years |          | |
|                            |             |                               |               | Dose of basal insulin 0.63 to 0.68 U/kg/day |          | |
| Ritzel et al. [65]          | Patient-level pooled meta-analysis of EDITION 1, 2 and 3 at 12 months | See appendix 1 for individual trial criteria | Gla-300 (n = 1247) vs Gla-100 (n = 1249) | Gla-300 vs Gla-100 (mean): | 12 months | HbA1c change from baseline to month 12: |
|                            |             |                               |               | Age 59 vs 59 years          |          | LS mean change was −0.91% (SE 0.03) for Gla-300 and −0.080 (SE 0.03) for Gla-100 with treatment difference of −0.1% (95% CI −0.18 to −0.02) |
|                            |             |                               |               | BMI 34.7 vs 34.8 kg/m²      |          | |
|                            |             |                               |               | HbA1c 8.31 vs 8.32 %        |          | |
|                            |             |                               |               | Duration of diabetes 12.7 vs 12.6 years |          | |
| Author, year of publication | Study design | Participant inclusion criteria | Interventions | Key baseline characteristics | Duration | Primary objective/s |
|-----------------------------|-------------|--------------------------------|---------------|-----------------------------|----------|---------------------|
| Twigg et al. [35]           | Post-hoc, patient-level meta-analysis of EDITION 1, 2 and 3 at 6 months | See appendix 1 for individual trial criteria | Gla-300 (n = 1247) vs Gla-100 (n = 1249) | *Gla-300 vs Gla-100 (mean)*: Age 59 vs 59 years BMI 34.7 vs 34.8 kg/m² HbA1c 8.31 vs 8.32 % Duration of diabetes 12.7 vs 12.6 years | 6 months | Association of patient baseline characteristics with glycemic control and hypoglycemia: HbA1c reductions were comparable between Gla-300 and Gla-100 regardless of patients baseline characteristics |
| Zhang et al. [38]           | Systematic review and meta-analysis | RCTs comparing IDeg with Glargine in T1DM and T2DM with at least 16 weeks follow up | 18 RCTs including 16791 participants on either IDeg or Gla-100 | Refer to publication for individual trial breakdown of baseline characteristics | Variable (16–104 weeks) | Efficacy and hypoglycemia: No significant difference in HbA1c changes with estimated treatment difference of 0.03% (95% CI −0.00 to 0.06) *P* = 0.06 IDeg showed reduced hypoglycemia vs Gla-100 across multiple measures including severe hypoglycemia in T2DM (estimated RR 0.65 (95% CI 0.52 to 0.89) *P* = 0.005 |
| Author, year of publication | Study design | Participant inclusion criteria | Interventions | Key baseline characteristics | Duration | Primary objective/s |
|-----------------------------|--------------|--------------------------------|---------------|-----------------------------|----------|---------------------|
| Ritzel et al. [31]          | Patient-level pooled meta-analysis of EDITION 1, 2 and 3 at 6 months | See appendix 1 for individual trial criteria | Gla-300 (n = 1247) vs Gla-100 (n = 1249) | Gla-300 vs Gla-100 (mean): Age 59 vs 59 years BMI 34.7 vs 34.8 kg/m² HbA1c 8.31 vs 8.32 % Duration of diabetes 12.7 vs 12.6 years | 6 months | HbA1c change from baseline to month 6: LS mean change was −1.02% (SE 0.03) for both groups with LS mean difference of 0.00% (95% CI −0.08 to 0.07) |
| Vora et al. [36]            | Meta-analysis of BEGIN phase IIIa program | 6 phase IIIa treat to target RCTs of the BEGIN program, including T1DM and T2DM | IDeg (n = 2848) vs Gla-100 (n = 1205) | See appendix 1 for individual trial baseline characteristics | Variable (26–52 weeks) | HbA1c change from baseline: IDeg non-inferior to Gla-100 in basal bolus regimens with an estimated mean difference of 0.08% (95% CI −0.05 to 0.21) and insulin naïve 0.08% (95% CI −0.01 to 0.16) |
| Author, year of publication | Study design | Participant inclusion criteria | Interventions | Key baseline characteristics | Duration | Primary objective/s |
|-----------------------------|-------------|---------------------------------|---------------|-----------------------------|----------|---------------------|
| Monami and Mannucci [27]    | Meta-analysis of IDeg | RCTs with a duration of at least 16 weeks comparing IDeg with other insulins +/− OADs and prandial insulin, including T1DM and T2DM | IDeg (n = 1517) vs comparators (Gla-100 n = 526; Biais 30 n = 62) | Range across 5 RCTs: | (16–52 weeks) | Change in HbA1c and hypoglycemia outcomes: |
|                             |             |                                 |               | Age 43–59 years |                      |       | In T2DM: mean difference in HbA1c change between IDeg and Gla-100 was 0.02% (95% CI −0.10 to 0.14) P= 0.72; confirmed hypoglycemia was lower with IDeg OR 0.95 (95% CI 0.93 to 0.97) p <0.001 and no difference in nocturnal hypoglycaemia OR 0.95 (95% CI 0.30 to 3.05) P= 0.94 |
| Ratner et al. [29]          | Pre-planned patient-level, meta-analysis of BEGIN phase IIIa program | 7 phase IIIa treat to target RCTs of the BEGIN program, including T1DM and T2DM | IDeg (n = 2899) vs Gla-100 (n = 1431) | See appendix 1 for individual trial baseline characteristics | (26–52 weeks) | Overall confirmed hypoglycaemia <3.1 mmol/L (≤54 mg/dL): |
|                             |             |                                 |               |                      |       | In T2DM: overall confirmed hypoglycaemia was lower with IDeg vs Gla-100, treatment difference ERR: 0.83 (95% CI 0.74 to 0.94) |
APPENDIX 3: STUDIES COMPARING SECOND GENERATION BI ANALOGUES (GLA-300 VS IDEG)

| Author, year of publication (study name) | Study design | Participant inclusion criteria | Interventions | Key baseline characteristics | Duration | Primary endpoint/s |
|-----------------------------------------|--------------|--------------------------------|---------------|-----------------------------|----------|-------------------|
| Randomized Controlled Trials            |              |                                |               |                             |          |                   |
| Philis-Tsimikas et al. [48] (CONCLUDE)  | Multicentre, multinational, open-label, parallel-group RCT (superiority testing of the primary endpoint); target FPG 4.0–5.0 mmol/L | ≥18 years with T2DM; previous basal insulin use +/- OADs (stable dose for ≥90 days); HbA1c ≤9.5%; BMI ≤45 kg/m² | IDEg 200 U/mL (n = 805) vs Gla-300 (n = 804) | Age 63 vs 63 years BMI 31.7 vs 31.5 kg/m² HbA1c 7.6 vs 7.6 % Duration of diabetes 15.1 vs 15.0 years Basal insulin dose 42.7 vs 42.2 U/day | Up to 94 weeks* | IDEg vs Gla-300 (mean): Rate of overall symptomatic hypoglycemic events (defined as severe or confirmed blood glucose < 3.1 mmol/L [with symptoms]) during the maintenance period of 36 weeks: No significant difference was found with IDEg (216.8 events per 100 PY) compared with Gla-300 (243.9 events per 100 PY) during the maintenance period (RR 0.88 [95% CI 0.73, 1.06]). Because there was no significant difference between treatments for the primary endpoint, the confirmatory testing procedure for superiority was stopped |
| Kawaguchi et al. [47]                   | Single-centre, open-label, parallel-group, two-period, randomized cross-over study; target FPG 5.6–7.2 mmol/L | ≥20 years; T2DM ≥1 year; OADs +/- insulin ≥6 months; HbA1c 6.5-11.0% | Gla-300 vs IDEg 100 U/mL (total population n = 30) | Age 70 years BMI 24.6 kg/m² HbA1c 8.2% Duration of diabetes 18.3 years | 2 x 5 day CGM periods (excluding titration periods) | Mean percentage of time within the target glucose range of 3.9–10 mmol/L (70–180 mg/dL) and hypoglycemia of < 3.9 mmol/L (< 70 mg/dL) measured by CGM: Similar time within target range between Gla-300 (77.8%) vs IDEg (76.9%) (P= 0.85). Gla-300 had less time in hypoglycaemia vs IDEg (1.3% vs 5.5%, respectively P=0.002) |

△ Adis
| Author, year of publication (study name) | Study design | Participant inclusion criteria | Interventions | Key baseline characteristics | Duration | Primary endpoint/s |
|-----------------------------------------|--------------|--------------------------------|---------------|----------------------------|----------|-------------------|
| Yamabe et al. [50]                     | Single-centre, open-label, parallel-group, two-period, randomized cross-over study; Target FPG 5.6–8.3 mmol/L | T2DM; previously treated on IDeg (morning dosing) with OADs ≥3 months | Gla-300 vs IDeg 100 U/mL (total population n = 24) | Total study population (mean): Age 71 years; BMI 23.1 kg/m²; HbA1c 6.8%; Duration of diabetes 14 years; Insulin dose 6 U/day | 8 weeks with 2 x 14 day FGM periods | Mean percentage of time within a glucose range of 3.9–9.9 mmol/L (70–179 mg/dL) for the seven consecutive days of each treatment period: Time in range for Gla-300 was 73.4% (SD 14.9) and 77.3% (SD 11.8) for IDeg P=0.31 |
| Rosenstock et al. [49] (BRIGHT)        | Multicentre, multinational, open-label, parallel-group, non-inferiority RCT; target FPG 4.4–5.6 mmol/L | ≥18 years; T2DM duration ≥1 year; OADs +/- GLP-1 RA (stable dose ≥3 months; insulin naïve; HbA1c 7.5–10.5%; BMI 25–40 kg/m² | Gla-300 (n = 462) vs IDeg 100 U/mL (n = 462) | Gla-300 vs IDeg (mean): Age 61 vs 61 years; BMI 31.7 vs 31.3 kg/m²; HbA1c 8.7 vs 8.6% | 24 weeks | HbA1c change from baseline to week 26: LS mean change was -1.64% (SE 0.04) for Gla-300 and -1.59% (SE 0.04) with a LS mean difference of -0.05% (95% CI -0.15 to 0.05) P<0.0001 demonstrating non-inferiority of Gla-300 vs IDeg |
| Sullivan et al. [45] (DELIVER Naïve D) | Retrospective, observational, propensity score-matched cohort study using EMR data from the US | ≥18 years; confirmed T2DM on OADs +/- GLP-1 RA commenced on Gla-300 or IDeg commenced on 1 March 2015 and 30 September 2017 | Gla-300 (n = 638) vs IDeg (n = 638) | Gla-300 vs IDeg (mean): Age 59 vs 59 years; BMI 33.5 vs 33.3 kg/m²; HbA1c 9.7 vs 9.6% | Change in HbA1c from 6 month baseline period to the latest value in 3–6 months follow-up period: HbA1c decreased significantly from baseline to follow-up in both groups; and these reductions were comparable in the Gla-300 and IDeg cohorts -1.67% (SD 2.22) vs. -1.58% (SD 2.20) respectively; P= 0.51 |
| Author, year of publication (study name) | Study design | Participant inclusion criteria | Interventions | Key baseline characteristics | Duration | Primary endpoint/s |
|------------------------------------------|--------------|--------------------------------|---------------|-----------------------------|----------|--------------------|
| Sullivan et al. [51] (DELIVER D+)        | Retrospective, observational, propensity score-matched cohort study using EMR data from the US in patients switching to Gla-300 or IDeg | ≥18 years; confirmed T2DM who switched from Gla-100 or IDet to either Gla-300 or IDeg during 1 March 2015 to 31 January 2017; ≥12 month baseline period in EMR | Gla-300 (n = 1592) vs IDeg (n = 1592) | Gla-300 vs IDeg (mean); Age 59 vs 59 years, BMI 34.8 vs 34.7 kg/m², HbA1c 9.1 vs 9.1 %, Hypoglycaemia incidence in previous 6 months 15.6 vs 14.3 % | HbA1c during follow-up period (3-6 months from index date) | Change in HbA1c from 6 month baseline period to the latest value in 3–6 months follow-up period: HbA1c decreased significantly from baseline in both groups without any difference the groups (Gla-300 −0.63% [SD 1.7] vs IDeg −0.58% [SD 1.6], P=0.49) |
| Tibaldi et al. [52] (CONFIRM)            | Retrospective, observational, propensity score-matched cohort study using EMR data from the US | ≥18 years; confirmed T2DM on OADs +/- GLP-1 RA commenced on Gla-300 or IDeg commenced on March 2015 and January 2018 with 360 days of data prior to insulin initiation and ≥1 HbA1c measure at baseline | PSM cohort: IDeg (n = 2028) vs Gla-300 (n = 2028) | IDeg vs Gla-300 (mean PSM cohort); Age 58 years, BMI 34.0 vs 34.7 kg/m², HbA1c 9.6 vs 9.5 %, Duration of diabetes 4.8 vs 4.8 years, Hypoglycaemia incidence in 180 days prior 6.7 vs 5.6 % | Up to 180 days follow-up | Change in baseline HbA1c from initiation of basal insulin (−90 days to +7 days) until 180 days of follow-up: Change of −1.48% for IDeg and −1.22% for Gla-300 with estimated treatment difference of −0.27% (95% CI −0.51 to −0.03) P=0.03 |
REFERENCES

1. Davies MJ, D’Alessio DA, Fradkin J, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2018;61(12):2461–98.

2. Blonde L, Meneghini L, Peng XV, et al. Probability of achieving glycemic control with basal insulin in patients with type 2 diabetes in real-world practice in the USA. Diabetes Ther. 2018;9(3):1347–58.

3. Russell-Jones D, Pouwer F, Khunti K. Identification of barriers to insulin therapy and approaches to overcoming them. Diabetes Obes Metab. 2018;20(3):488–96.

4. Geller AI, Shehab N, Lovgrove MC, et al. National estimates of insulin-related hypoglycemia and errors leading to emergency department visits and hospitalizations. JAMA Intern Med. 2014;174(5):678–86.

5. Goto A, Arah OA, Goto M, et al. Severe hypoglycemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. BMJ. 2013;347:f4533.

6. Zoungas S, Patel A, Chalmers J, et al. Severe hypoglycemia and risks of vascular events and death. N Engl J Med. 2010;363(15):1410–8.

7. Amiel SA, Dixon T, Mann R, Jameson K. Hypoglycemia in type 2 diabetes. Diabet Med. 2008;25(3):245–54.

8. Huang ES, Laiteerapong N, Liu JY, et al. Rates of complications and mortality in older patients with diabetes mellitus: the diabetes and aging study. JAMA Intern Med. 2014;174(2):251–8.

9. Miller ME, Bonds DE, Gerstein HC, et al. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. BMJ. 2010;340:b5444.

10. Shafiee G, Mohajeri-Tehrani M, Pajouhi M, Larijani B. The importance of hypoglycemia in diabetic patients. J Diabetes Metab Disord. 2012;11(1):17.

11. Wysham C, Bhargava A, Chaykinet L, et al. Effect of insulin degludec vs insulin glargine u100 on hypoglycemia in patients with type 2 diabetes: the SWITCH 2 randomized clinical trial. JAMA. 2017;318(1):45–56.

12. Yun JS, Ko SH. Risk factors and adverse outcomes of severe hypoglycemia in type 2 diabetes mellitus. Diabetes Metab J. 2016;40(6):423–32.

13. Davis TM, Brown SGA, Jacobs IG, et al. Determinants of severe hypoglycemia complicating type 2 diabetes: the Fremantle diabetes study. J Clin Endocrinol Metab. 2010;95(5):2240–7.

14. Becker RH, Nowotny I, Teichert L, et al. Low within- and between-day variability in exposure to new insulin glargine 300 U/ml. Diabetes Obes Metab. 2015;17(3):261–7.

15. Bergenstal RM, Bailey TS, Rodbard D, et al. Comparison of insulin glargine 300 units/mL and 100 units/mL in adults with type 1 diabetes: continuous glucose monitoring profiles and variability using morning or evening injections. Diabetes Care. 2017;40(4):554–60.

16. Haahr H, Heise T. A review of the pharmacological properties of insulin degludec and their clinical relevance. Clin Pharmacokinet. 2014;53(9):787–800.

17. Heise T, Nosek L, Bettcher SG, Hastrup H, Haahr J. Ultra-long-acting insulin degludec has a flat and stable glucose-lowering effect in type 2 diabetes. Diabetes Obes Metab. 2012;14(10):944–50.

18. Schilsky RL. Finding the evidence in real-world evidence: moving from data to information to knowledge. J Am Coll Surg. 2017;224(1):1–7.

19. Bolli GB, Riddle MC, Bergenstal RM, et al. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naive people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). Diabetes Obes Metab. 2015;17(4):386–94.

20. Bolli GB, Wysham C, Fisher M, et al. A post-hoc pooled analysis to evaluate the risk of hypoglycaemia with insulin glargine 300 U/mL (Gla-300) versus 100 U/mL (Gla-100) over wider nocturnal windows in individuals with type 2 diabetes on a basal-only insulin regimen. Diabetes Obes Metab. 2019;21(2):402–7.

21. Bonadonna RC, Yale JF, Brulle-Wohlueter C, et al. Hypoglycaemia as a function of HbA1c in type 2 diabetes: insulin glargine 300 U/mL in a patient-level pooled analysis of edition 1, 2 and 3. Diabetes Obes Metab. 2019;21(3):715–9.

22. Diez-Fernandez A, Cavero-Redondo I, Moreno-Fernández J, et al. Effectiveness of insulin glargine U-300 versus insulin glargine U-100 on nocturnal hypoglycemia and glycemic control in type 1 and type 2 diabetes: a systematic review and meta-analysis. Acta Diabetol. 2019;56(3):355–64.
23. Garber AJ, King AB, Del Prato S, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet. 2012;379(9825):1498–507.

24. Gough SC, Bhargava A, Jain R, et al. Low-volume insulin degludec 200 units/ml once daily improves glycemic control similarly to insulin glargine with a low risk of hypoglycemia in insulin-naive patients with type 2 diabetes: a 26-week, randomized, controlled, multinational, treat-to-target trial: the BEGIN LOW VOLUME trial. Diabetes Care. 2013;36(9):2536–42.

25. Hollander P, King AB, Del Prato S, et al. Insulin degludec improves long-term glycaemic control similarly to insulin glargine but with fewer hypoglycaemic episodes in patients with advanced type 2 diabetes on basal-bolus insulin therapy. Diabetes Obes Metab. 2015;17(2):202–6.

26. Meneghini L, Atkin SL, Gough SCL, et al. The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily: a 26-week, randomized, open-label, parallel-group, treat-to-target trial in individuals with type 2 diabetes. Diabetes Care. 2013;36(4):858–64.

27. Monami M, Mannucci E. Efficacy and safety of degludec insulin: a meta-analysis of randomised trials. Curr Med Res Opin. 2013;29(4):339–42.

28. Onishi Y, Iwamoto Y, Yoo SJ, et al. Insulin degludec compared with insulin glargine in insulin-naive patients with type 2 diabetes: a 26-week, randomized, controlled, Pan-Asian, treat-to-target trial. J Diabetes Investig. 2013;4(6):605–12.

29. Ratner RE, Gough SCL, Mathieu C, et al. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. Diabetes Obes Metab. 2013;15(2):175–84.

30. Riddle MC, Bolli GB, Ziemen M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 1). Diabetes Care. 2014;37(10):2755–62.

31. Ritzel R, Roussel R, Bolli GB, et al. Patient-level meta-analysis of the EDITION 1, 2 and 3 studies: glycemic control and hypoglycaemia with new insulin glargine 300 U/ml versus glargine 100 U/ml in people with type 2 diabetes. Diabetes Obes Metab. 2015;17(9):859–67.

32. Ritzel R, Bolli GB, Giacciari A, et al. Better glycaemic control and less hypoglycaemia with insulin glargine 300 U/mL vs glargine 100 U/mL: 1-year patient-level meta-analysis of the EDITION clinical studies in people with type 2 diabetes. Diabetes Obes Metab. 2018;20(3):541–8.

33. Terauchi Y, Koyama M, Cheng X, et al. Glycaemic control and hypoglycaemia with insulin glargine 300 U/mL compared with glargine 100 U/mL in Japanese adults with type 2 diabetes using basal insulin plus oral anti-hyperglycaemic drugs (EDITION JP 2 randomised 12-month trial including 6-month extension). Diabetes Metab. 2017;43(5):446–52.

34. Terauchi Y, Koyama M, Cheng X, et al. New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 2). Diabetes Obes Metab. 2016;18(4):366–74.

35. Twigg SM, Escalada J, Stella P, et al. Association of patient profile with glycemic control and hypoglycemia with insulin glargine 300 U/mL in type 2 diabetes: a post hoc patient-level meta-analysis. Diabetes Ther. 2018;9(5):2043–53.

36. Vora J, Christensen T, Rana A, et al. Insulin degludec versus insulin glargine in type 1 and type 2 diabetes mellitus: a meta-analysis of endpoints in phase 3a trials. Diabetes Ther. 2014;5(2):435–46.

37. Yki-Jarvinen H, Bergenstal R, Ziemen M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycaemia in a 6-month randomized controlled trial (EDITION 2). Diabetes Care. 2014;37(12):3235–43.

38. Zhang XW, Zhang XL, Xu B, et al. Comparative safety and efficacy of insulin degludec with insulin glargine in type 2 and type 1 diabetes: a meta-analysis of randomized controlled trials. Acta Diabetol. 2018;55(5):429–41.

39. Zinman B, Philis-Tsimikas A, Cariou B, et al. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). Diabetes Care. 2012;35(12):2464–71.

40. Zhou W, Tao J, Zhou X, Chen H. Insulin degludec, a novel ultra-long-acting basal insulin versus insulin glargine for the management of type 2 diabetes: a systematic review and meta-analysis. Diabetes Ther. 2019;10(3):835–52.
41. Bonadonna RC, Renard E, Cheng A, et al. Switching to insulin glargine 300 U/ml: is duration of prior basal insulin therapy important? Diabetes Res Clin Pract. 2018;142:19–25.

42. Bailey TS, Wu J, Zhou FL, et al. Switching to insulin glargine 300 units/ml in real-world older patients with type 2 diabetes (DELIVER 3). Diabetes Obes Metab. 2019;21(11):2384–93.

43. Pettus J, Roussel R, Zhou FL, et al. Rates of hypoglycemia predicted in patients with type 2 diabetes on insulin glargine 300 U/ml versus first- and second-generation basal insulin analogs: the real-world LIGHTNING study. Diabetes Ther. 2019;10(2):617–33.

44. Zhou FL, Ye F, Berhanu P, et al. Real-world evidence concerning clinical and economic outcomes of switching to insulin glargine 300 units/ml vs other basal insulins in patients with type 2 diabetes using basal insulin. Diabetes Obes Metab. 2018;20(5):1293–7.

45. Sullivan SD, Nicholls CJ, Gupta RA, et al. Comparable glycaemic control and hypoglycaemia in adults with type 2 diabetes after initiating insulin glargine 300 units/ml or insulin degludec: the DELIVER Naive D real-world study. Diabetes Obes Metab. 2019;21(9):2123–32.

46. Bailey TS, Zhou FL, Gupta RA, et al. 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 Naive cohort study. Diabetes Obes Metab. 2019;21(7):1596–605.

47. Kawaguchi Y, Sawa J, Sakuma N, Kumeda Y. Efficacy and safety of insulin glargine 300 U/ml vs insulin degludec in patients with type 2 diabetes: a randomized, open-label, cross-over study using continuous glucose monitoring profiles. J Diabetes Investig. 2019;10(2):343–51.

48. Philis-Tsimikas A, Klonoff DC, Khunti K, et al. Risk of hypoglycaemia with insulin degludec versus insulin glargine U300 in insulin-treated patients with type 2 diabetes: the randomised, head-to-head CONCLUDE trial. Diabetologia. 2020;63(4):698–710.

49. Rosenstock J, Cheng A, Ritzel R, et al. More similarities than differences testing insulin glargine 300 units/ml versus insulin degludec 100 units/ml in insulin-naïve type 2 diabetes: the randomized head-to-head BRIGHT trial. Diabetes Care. 2018;41(10):2147–54.

50. Yamabe M, Kuroda M, Hirosawa Y, et al. Comparison of insulin glargine 300 U/ml and insulin degludec using flash glucose monitoring: a randomized cross-over study. J Diabetes Investig. 2019;10(2):352–7.

51. Sullivan SD, Bailey TS, Roussel R, et al. Clinical outcomes in real-world patients with type 2 diabetes switching from first- to second-generation basal insulin analogues: comparative effectiveness of insulin glargine 300 units/ml and insulin degludec in the DELIVER D+ cohort study. Diabetes Obes Metab. 2018;20(9):2148–58.

52. Tibaldi J, Hadley-Brown M, Lieble A, et al. A comparative effectiveness study of degludec and insulin glargine 300 U/ml in insulin-naïve patients with type 2 diabetes. Diabetes Obes Metab. 2019;21(4):1001–9.

53. Centers for Disease Control and Prevention (CDC). National diabetes statistics report, 2017. Estimates of Diabetes and Its Burden in the United States. 2017. https://dev.diabetes.org/sites/default/files/2019-06/cdc-statistics-report-2017.pdf. Accessed on June 1, 2020.

54. Whitmer RA, Karter AJ, Yaffe K, Quesenberry Jr CP, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA. 2009;301(15):1565–72.

55. Freeman J. Management of hypoglycemia in older adults with type 2 diabetes. Postgrad Med. 2019;131(4):241–50.

56. Majumdar SR, Hemmelgarn BR, Lin M, McBrien K, Manns BJ, Tonelli M. Hypoglycaemia associated with hospitalization and adverse events in older people: population-based cohort study. Diabetes Care. 2013;36(11):3585–90.

57. Lipska KJ, Ross JS, Wang J, et al. National trends in US hospital admissions for hyperglycemia and hypoglycemia among Medicare beneficiaries, 1999 to 2011. JAMA Intern Med. 2014;174(7):1116–24.

58. Greco D, Angileri G. Drug-induced severe hypoglycaemia in Type 2 diabetic patients aged 80 years or older. Diabetes Nutr Metab. 2004;17(1):23–6.

59. Meneilly GS, Cheung E, Tuokko H. Counterregulatory hormone responses to hypoglycemia in the elderly patient with diabetes. Diabetes Care. 1994;17(3):403–10.

60. Jaap AJ, Jones GC, McCrimmon RJ, Deary IJ, Frier BM. Perceived symptoms of hypoglycaemia in elderly type 2 diabetic patients treated with insulin. Diabet Med. 1998;15(5):398–401.

61. Matyka K, Evans M, Lomas J, Cranston I, MacDonald I, Amiel SA. Altered hierarchy of protective responses against severe hypoglycaemia in normal
aging in healthy men. Diabetes Care. 1997;20(2):135–41.

62. Munshi MN, Gill J, Chao J, Nikonova EV, Patel M. Insulin Glargine 300 U/mL is associated with less weight gain while maintaining glycemic control and low risk of hypoglycemia compared with insulin glargine 100 U/mL in an aging population with type 2 diabetes. Endocr Pract. 2018;24(2):143–9.

63. Sorli C, Warren M, Oyer D, Mersebach H, Johansen T, Gough SCL. Elderly patients with diabetes experience a lower rate of nocturnal hypoglycaemia with insulin degludec than with insulin glargine: a meta-analysis of phase IIIa trials. Drugs Aging. 2013;30(12):1009–18.

64. Yale JF, Yale J-F, Aroda VR, et al. Glycaemic control and hypoglycaemia risk with insulin glargine 300 U/mL versus glargine 100 U/mL: a patient-level meta-analysis examining older and younger adults with type 2 diabetes. Diabetes Metab. 2020;46(2):110–8.

65. Ritzel R, Harris SB, Baron H, et al. A randomized controlled trial comparing efficacy and safety of insulin glargine 300 units/mL versus 100 units/mL in older people with type 2 diabetes: results from the SENIOR study. Diabetes Care. 2018;41(8):1672–80.

66. Heller SR, Devries JH, Wysham C, et al. Lower rates of hypoglycaemia in older individuals with type 2 diabetes using insulin degludec versus insulin glargine U100: results from SWITCH 2. Diabetes Obes Metab. 2019;21(7):1625–33.

67. Pratley RE, Emerson SS, Franek E, et al. Cardiovascular safety and lower severe hypoglycaemia of insulin degludec versus insulin glargine U100 in patients with type 2 diabetes aged 65 years or older: results from DEVOTE (DEVOTE 7). Diabetes Obes Metab. 2019;21(7):1625–33.

68. Moen MF, Zhan M, Zhu VD, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. Clin J Am Soc Nephrol. 2009;4(6):1121–7.

69. Javier Escalada F, Halimi S, Senior PA, et al. Glycaemic control and hypoglycaemia benefits with insulin glargine 300 U/mL extend to people with type 2 diabetes and mild-to-moderate renal impairment. Diabetes Obes Metab. 2018;20(12):2860–8.

70. Haluzik M, Cheng A, Müller-Wieland D, et al. Differential glycaemic control with basal insulin glargine 300 U/mL versus degludec 100 U/mL according to kidney function in type 2 diabetes—a subanalysis from the BRIGHT trial. Diabetes Obes Metab. 2020;22(8):1369–37.

71. Zhou FL, Nichols C, Lin X, et al. Hypoglycaemia and treatment patterns among insulin-treated patients with type 2 diabetes who switched to insulin glargine 300 units/mL versus other basal insulin in a real-world setting. Endocrinol Diabetes Metab. 2019;2(3):e00073.

72. Henao-Carrillo DC, Muñoz OM, Gómez AM, et al. Reduction of glycemic variability with Degludec insulin in patients with unstable diabetes. J Clin Transl Endocrinol. 2018;12:8–12.

73. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837–53.

74. Marso SP, McGuire DK, Zinman B, et al. Efficacy and safety of degludec versus glargine in type 2 diabetes. N Engl J Med. 2017;377(7):723–32.

75. Pratley RE, Husain M, Lingvay I, et al. Heart failure with insulin degludec versus glargine U100 in patients with type 2 diabetes at high risk of cardiovascular disease: DEVOTE 14. Cardiovasc Diabetol. 2019;18(1):156.

76. Amod A, Buse BJ, McGuire DK, et al. Glomerular filtration rate and associated risks of cardiovascular events, mortality, and severe hypoglycemia in patients with type 2 diabetes: secondary analysis (DEVOTE 11). Diabetes Ther. 2020;11(1):53–70.

77. Gerstein HC, Bosch J, Dagenais GR, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med. 2012;367(4):319–28.

78. Czech MP. Insulin action and resistance in obesity and type 2 diabetes. Nat Med. 2017;23(7):804–14.

79. Chen KW, Boyko EJ, Bergstrom RW, et al. Earlier appearance of impaired insulin secretion than of visceral adiposity in the pathogenesis of NIDDM. 5-year follow-up of initially nondiabetic Japanese-American men. Diabetes Care. 1995;18(6):747–53.

80. Matsuhashi M, Koyama M, Cheng X, et al. New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese adults with type 1 diabetes using basal and mealtime insulin: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 1). Diabetes Obes Metab. 2016;18(4):375–83.

81. Chaykin L, Bhargava A, de la Rosa R, et al. Effect of insulin degludec versus insulin glargine U100 on hypoglycemia in Hispanic patients with type 2
diabetes: results from the SWITCH 2 trial. Clin Diabetes. 2019;37(1):73–81.

82. Thewjitcharoen Y, Yenseung N, Malidaeng A, et al. Effectiveness of insulin degludec in Thai patients with diabetes mellitus: real-world evidence from a Specialized Diabetes Center. Exp Clin Endocrinol Diabetes. 2019. https://doi.org/10.1055/a-0899-5118.

83. Kawaguchi Y, Sawa J, Hamai C, et al. Differential effect of hypoalbuminemia on hypoglycemia on type 2 diabetes patients treated with insulin glargine 300 U/ml and insulin degludec. Diabetes Ther. 2019;10(4):1535–41.

84. Pasquel FJ, Lansang MC, Khowaja A, et al. A randomized controlled trial comparing glargine U300 and glargine U100 for the inpatient management of medicine and surgery patients with type 2 diabetes: glargine U300 hospital trial. Diabetes Care. 2020;43(6):1242–8.

85. Okajima F, Nakamura Y, Yamaguchi Y, et al. Basal-bolus insulin therapy with Gla-300 during hospitalization reduces nocturnal hypoglycemia in patients with type 2 diabetes mellitus: a randomized controlled study. Diabetes Ther. 2018;9(3):1049–59.

86. Suzuki J, Yamakawa T, Oba M, et al. Efficacy and safety of insulin degludec U100 and insulin glargine U100 in combination with meal-time bolus insulin in hospitalized patients with type 2 diabetes: an open-label, randomized controlled study. Endocr J. 2019;66(11):971–82.

87. Nagai Y, Murakami M, Igarashi K, et al. Efficacy and safety of thrice-weekly insulin degludec in elderly patients with type 2 diabetes assessed by continuous glucose monitoring. Endocr J. 2016;63(12):1099–106.

88. Weatherall J, Polonsky WH, Lanar S, et al. When insulin degludec enhances quality of life in patients with type 2 diabetes: a qualitative investigation. Health Qual Life Outcomes. 2018;16(1):87.

89. Wieringa TH, de Wit M, Twisk JW, et al. Improved diabetes medication convenience and satisfaction in persons with type 2 diabetes after switching to insulin glargine 300 U/mL: results of the observational OPTIN-D study. BMJ Open Diabetes Res Care. 2018;6(1):e000548.

90. Hassanein M, Buyukbese MA, Malek R, et al. Real-world safety and effectiveness of insulin glargine 300 U/mL in participants with type 2 diabetes who fast during Ramadan: the observational ORION study. Diabetes Res Clin Pract. 2020;166:108189.

91. Lingvay I, Chao J, Dalal MR, et al. Efficacy and safety of insulin glargine 300 U/mL versus insulin glargine 100 U/mL in high-risk and low-risk patients with type 2 diabetes stratified using common clinical performance measures. Diabetes Technol Ther. 2017;19(5):315–22.
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