# Clinical Use of IDegLira: Initiation to Titration After Basal Insulin

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Delayed treatment intensification is common in U.S. patients with type 2 diabetes uncontrolled on basal insulin. Concerns about weight gain, hypoglycemia, increased regimen complexity, and additional copayments may lead to reluctance to initiate prandial insulin. IDegLira is a titratable, fixed-ratio coformulation that combines the advantages of insulin degludec and the glucagon-like peptide 1 receptor agonist liraglutide in a single once-daily injection and mitigates the side effects associated with each component. Clinical trials have demonstrated that IDegLira improves glycemic control without the increased risk of hypoglycemia and weight gain observed with basal insulin up-titration and the addition of prandial insulin, and this is achieved using twice-weekly titration. Clinical trials and real-world studies have also shown that IDegLira has the potential to reduce therapeutic and titration inertia. However, better outcomes could be achieved with IDegLira initiation in suitable patients with timely titration and by providers sharing their experience with this combination product. This review describes considerations for initiation, titration, and intensification of IDegLira in patients previously receiving basal insulin.

In the United States, many patients with type 2 diabetes do not attain an A1C <7.0% with basal insulin (1,2), and this is often due to insufficient titration and delays in treatment intensification (3–5). The reasons for this therapeutic inertia include concerns about weight gain, hypoglycemia, and increased regimen complexity/treatment burden (6,7) and have been reviewed in detail elsewhere (8).

A possibly lesser-known form of therapeutic inertia is "over-basalization," or, the continued up-titration of basal insulin despite a lack of improvement in glycemic control with this regimen (9–11). As type 2 diabetes progresses, some patients will become so insulin resistant that continued up-titration of basal insulin is not matched by a proportional improvement in fasting plasma glucose (FPG) or A1C. American Diabetes Association (ADA) guidelines suggest that, if insulin is appropriately titrated and doses reach >0.5 units/kg/day without achieving glycemic targets, an additional strategy for intensifying treatment should be considered rather than continuing to up-titrate basal insulin (12). Patients experiencing recurrent hypoglycemia on basal insulin are often over-basalized or are using a secretagogue in conjunction with basal insulin. Discontinuation of secretagogue therapy on initiation of insulin therapy is recommended to avoid the increased risk of hypoglycemia associated with concomitant use (12), but that does not address the problems arising from excess basal insulin.

The optimal time for adding a mealtime insulin rather than up-titrating the basal dose for such patients is unknown. However, it has been suggested that a large decrease in glucose values between bedtime and morning (sometimes called the "BeAm value") may be an indicator of insufficient postprandial control and over-basalization (13).

There is a clinical need for alternative treatment options for patients whose diabetes is uncontrolled on basal insulin. In this review, we introduce IDegLira, a fixed-ratio combination (FRC) of insulin degludec and the glucagon-like peptide 1 (GLP-1) receptor agonist liraglutide; consider whether it would be an appropriate treatment option for patients whose diabetes is uncontrolled on basal insulin; and discuss the practicalities of initiating and titrating IDegLira in clinical practice.

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## What Is IDegLira?

IDegLira is a titratable FRC of insulin degludec and liraglutide (14). The benefits of combining basal insulin with GLP-1 receptor agonist therapy have been reviewed in detail elsewhere (15–17). In particular, this combination affords good control of postprandial glucose and FPG, predominantly provided by the GLP-1 receptor agonist and the basal insulin component, respectively (15). In addition, the joint use of these two agents has a dose-sparing effect, thereby minimizing unwanted side effects such as gastrointestinal (GI) adverse events with GLP-1 receptor agonists and weight gain with insulin (18,19). The lower rate of GI adverse events observed with IDegLira compared with liraglutide can also be explained by the more gradual titration of liraglutide as part of the IDegLira FRC (14,20,21). Furthermore, the favorable effect of IDegLira on weight compared with other insulin regimens is likely to be related to the effects of liraglutide on satiety (22).

## What Have Trial Data Shown Us?

The safety and efficacy of IDegLira have been studied in the phase 3 Dual Action of Liraglutide and Insulin Degludec in Type 2 Diabetes (DUAL) clinical trial program. Here, we will focus on the trials involving patients whose diabetes was uncontrolled on basal insulin. These trials compared IDegLira to ≤50 units degludec (DUAL II) (23), continued up-titration of insulin glargine 100 units/mL (IGlar U100) (DUAL V) (24), and basal-bolus therapy (IGlar U100 and insulin aspart) (DUAL VII) (25).

Key results from these trials are summarized in Figure 1. A1C reductions with IDegLira were greater than with basal insulin and similar to basal-bolus therapy (Figure 1*A*), and a high percentage of patients using IDegLira achieved an A1C <7% (Figure 1*B*). The rate of confirmed hypoglycemia was 57% lower with IDegLira than with continued up-titration with IGlar U100 and 89% lower with IDegLira than with basal-bolus therapy (Figure 1*C*). Hypoglycemia rates were similar for IDegLira and degludec (DUAL II), probably because the dose of degludec was capped at 50 units (because this trial assessed the contribution of the liraglutide component of IDegLira) (23), whereas in the two trials using IGlar U100, the basal insulin dose was not capped, and hypoglycemia rates were lower with IDegLira (24,25). Mean change in body weight is shown in Figure 1*D*. In all three trials, patients randomized to IDegLira achieved weight loss after 26 weeks, whereas degludec resulted in no change of weight; IGlar U100 resulted in weight gain (1.8 kg), as did basal-bolus therapy (2.6 kg).

In a post hoc analysis, the odds of achieving a clinically relevant triple composite end point of A1C <7% without hypoglycemia and without weight gain were significantly higher with IDegLira in all three trials (at least 38% of patients using IDegLira achieved this composite, compared with no more than 12.2% of patients who up-titrated basal insulin or who used basal-bolus therapy) (23–25). More IDegLira-treated patients in DUAL trials V and VII also achieved the triple composite end point when incorporating higher A1C targets (<7.5%, <8%, ≤9%) that might be used either in some clinical practice settings in which more stringent targets are not suitable or by quality metrics such as the Healthcare Effectiveness Data and Information Set (26). Specifically, in DUAL VII, the odds of achieving an A1C <7.5% or <8% with no weight gain and without hypoglycemia were 10 times higher for IDegLira compared with basal-bolus therapy (27).

In a DUAL V post hoc analysis, Lingvay et al. (28) demonstrated that, across different categories of baseline A1C, FPG, and BMI levels, estimated treatment differences for change in A1C and body weight all significantly favored IDegLira over IGlar U100 up-titration (Table 1); the clinical benefits of IDegLira were achieved in patients with different degrees of glycemic and metabolic control.

The benefit of a simple, once-daily IDegLira regimen is reflected in the greater improvements observed in patient-reported outcomes with IDegLira versus comparators in DUAL V and DUAL VII (24,29). Improvements in scores on the Treatment-Related Impact Measure for Diabetes were significantly greater with IDegLira than with IGlar U100 (24) or basal-bolus therapy (29) for all domains and total scores. The greatest improvements were in the diabetes management and treatment burden domains (24,29). The patient-reported outcomes results from DUAL V are partly attributable to the reduced treatment complexity of IDegLira versus basal-bolus therapy in terms of the number of daily injections and the number of dose adjustments (30). Despite IDegLira being initiated at 16 units compared with continued titration of IGlar U100 from pre-trial doses (mean 33 units), the mean number of basal insulin dose adjustments was similar in the IDegLira (16.6) and basal-bolus (17.1) groups during 26 weeks of treatment. Furthermore, in the basal-bolus treatment arm, 153 patients (66.5%) required three or more daily bolus insulin injections, and the mean number of bolus insulin

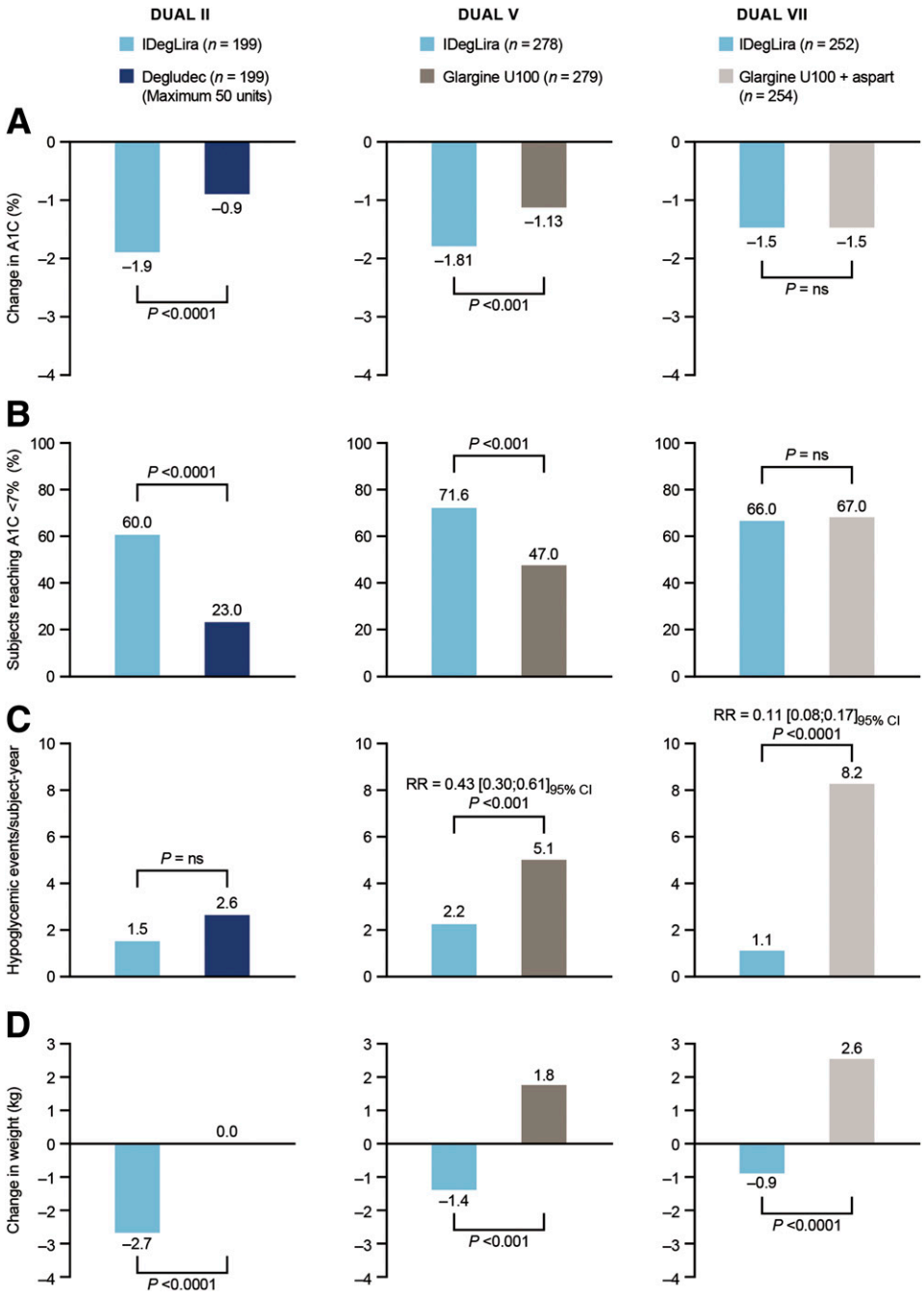


FIGURE 1 Key results from the DUAL research program trials comparing IDegLira to basal insulin (23–25). For DUAL II, hypoglycemia was defined as episodes confirmed by a plasma glucose value <56 mg/dL (regardless of symptoms) and severe episodes (requiring assistance of another person); for DUAL V, confirmed hypoglycemic episodes were defined as episodes in which plasma glucose was biochemically confirmed as <56 mg/dL, with or without symptoms or for which the patient required assistance; and for DUAL VII, hypoglycemic events were defined as either severe, according to the ADA classification (requiring assistance of another person to take corrective actions), or symptomatic (blood glucose–confirmed <56 mg/dL accompanied by glycopenic symptoms). ns, nonsignificant; RR, rate ratio.

adjustments required during 26 weeks of treatment was 200.1 (30).

Adherence to trial protocols and titration algorithms is closely monitored in clinical trials, and the above-described results are unlikely to be replicated in clinical practice. However, greater satisfaction with IDegLira compared with basal-bolus therapy is consistent with physicians' experience of real-world IDegLira use in Europe, according to the results of a multicenter survey (31); the authors observed greater patient adherence with IDegLira compared with other intensification strategies involving multiple daily injections.

## Safety Areas of Interest

GLP-1 receptor agonist therapy is associated with GI side effects at initiation (12). Overall, the incidences of GI adverse events, including nausea, vomiting, and diarrhea, were generally low across the DUAL trials and largely restricted to the first few weeks of treatment (14). GI adverse events were reported

**TABLE 1** Estimated Treatment Differences Over 26 weeks in A1C and Body Weight Across Baseline Categories of A1C, FPG, and BMI in Patients Intensifying Treatment With IDegLira Versus Up-Titration of Insulin Glargine in the DUAL V Trial

| | End Point Measured | |
|---|---|---|
| Patient Characteristic at Baseline | A1C, % | Change in Body Weight, kg |
| A1C category | | |
| ≤7.5% | -0.48 (-0.73 to -0.23), $P = 0.0002$ | -2.26 (-3.35 to -1.17), $P < 0.0001$ |
| >7.5 to ≤8.5% | -0.55 (-0.80 to -0.31), $P < 0.0001$ | -2.84 (-3.68 to -2.01), $P < 0.0001$ |
| >8.5–10% | -0.68 (-0.93 to -0.42), $P < 0.0001$ | -4.21 (-5.17 to -3.24), $P < 0.0001$ |
| FPG category (mg/dL) | | |
| <129.7 | -0.75 (-0.99 to -0.51), $P < 0.0001$ | -3.08 (-4.10 to -2.06), $P < 0.0001$ |
| ≥129.7 | -0.52 (-0.70 to -0.34), $P < 0.0001$ | -3.32 (-4.00 to -2.64), $P < 0.0001$ |
| BMI category (kg/m$^2$) | | |
| <30 | -0.68 (-0.94 to -0.42), $P < 0.0001$ | -3.40 (-4.32 to -2.49), $P < 0.0001$ |
| ≥30 to <35 | -0.52 (-0.76 to -0.28), $P < 0.0001$ | -2.75 (-3.63 to -1.87), $P < 0.0001$ |
| ≥35–40 | -0.59 (-0.83 to -0.34), $P < 0.0001$ | -3.65 (-4.91 to -2.39), $P < 0.0001$ |

Adapted from ref. 28. Values are estimated treatment difference (95% CI) between IDegLira and IGlar U100.

in fewer insulin degludec–treated patients but more liraglutide-treated patients compared with patients treated with IDegLira (20). This observation is likely related to the slower and more gradual liraglutide titration as a constituent of IDegLira treatment (32).

The U.S. Food and Drug Administration requires an assessment of cardiovascular (CV) safety for all new diabetes drugs (33). Although a CV outcomes trial has not been conducted for IDegLira, such trials have been carried out on its individual components of degludec (34) and liraglutide (35). The DEVOTE (Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events) trial demonstrated insulin degludec's noninferiority to IGlar U100 for the primary composite outcome of first occurrence of CV death, nonfatal myocardial infarction (MI), or nonfatal stroke (34). Additionally, a post hoc analysis demonstrated that patients treated with degludec or IGlar U100 plus liraglutide had significantly fewer major adverse CV events compared with patients who did not receive liraglutide (36). Using the same primary composite outcome, the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial confirmed superiority of liraglutide versus placebo in terms of incidence of major adverse CV events, with fewer deaths from CV or any cause and numerically lower rates of nonfatal MI, nonfatal stroke, and hospitalization for heart failure (35). Post hoc analyses of the LEADER trial suggested that participants also using basal insulin benefitted from the relative cardioprotection of liraglutide versus placebo (37). Meanwhile, post hoc analyses of the DUAL II, V, and VII trials found that, compared with basal insulin treatment, patients treated with IDegLira demonstrated a general improvement in CV risk markers, including systolic blood pressure, LDL cholesterol levels, and brain natriuretic peptide (38). It should be noted that these positive CV outcome data have been observed with the liraglutide 1.8-mg dose (35); patients receiving IDegLira would need to be receiving the maximum dose to achieve this dose of liraglutide (14).

## What Can We Learn From Real-World Evidence?

Real-world evidence on IDegLira use in U.S. patients has not yet been published, but two studies from Europe have provided some insight (39,40). The larger of the studies was a retrospective chart review of 611 patients from 61 centers in five countries (40). Before switching to IDegLira, patients were on a variety of injectable and oral medications, used alone or in combination. Most patients (71.8%) switched to IDegLira because of a lack of efficacy of their previous regimen, whereas 26.5% switched because of concerns about weight gain on their previous regimen. After 6 months, significant A1C reductions were observed regardless of the baseline regimen, and rates of hypoglycemia were low. Mean changes in body weight were generally small, and the only statistically significant

change was a 2.4-kg decrease in weight for patients changing from multiple daily insulin injections. At 6 months, 45 patients (7.4%) had discontinued IDegLira, but 69% of those discontinuations were because of changes in reimbursement that occurred in Germany. In the second study, which was conducted at a single center in Switzerland, 61 patients switching to IDegLira (mostly from regimens of insulin plus oral antidiabetic drugs) experienced a decrease of 1.7% in A1C (39). After 6 months, there was a mean loss of 1.9 kg body weight, and there were no episodes of severe hypoglycemia. Six patients (9.8%) discontinued IDegLira because of GI side effects.

Finally, research has consistently linked cost with medication nonadherence (41). In terms of out-of-pocket costs for patients, IDegLira has the advantage of providing two branded drugs for just one copayment, rather than the two separate copayments that would be required if degludec and liraglutide were initiated sequentially, for example. It is important to note that IDegLira is more expensive than other antidiabetic drug classes, which means that insurance coverage can be a practical barrier for providers and patients, but short- and long-term cost-effectiveness analyses demonstrate that its higher cost is offset by its greater efficacy (42–49). Short-term analyses in the United States have reported lower or equivalent annual costs of achieving A1C targets or the composite end point of A1C targets without weight gain and/or hypoglycemia with IDegLira versus basal insulin (IGlar U100) or basal-bolus therapy (IGlar U100 plus insulin aspart four or more times per day) (42,46). Greater differences in favor of IDegLira were observed when the avoidance of weight gain/hypoglycemia was factored in (42,46). Moreover, long-term cost-effectiveness analyses using models that account for insulin dosing, hypoglycemia rates, and the development of diabetes-related complications have reported that IDegLira is cost-effective compared with IGlar U100, the combination of basal insulin and liraglutide administered separately, or basal-bolus therapy (43,47–49).

## Practicalities of Using IDegLira in a Clinical Setting

### *Administration*

The IDegLira 100/3.6 pen provides 100 units/mL degludec and 3.6 mg/mL liraglutide. Each unit of IDegLira contains 1 unit degludec and 0.036 mg liraglutide, and the pen can deliver doses from 10 to 50 units with each injection (14).

IDegLira should be administered once daily subcutaneously into the thigh, upper arm, or abdomen and at the same time each day, with or without food. IDegLira can be given at any time of the day, and the choice of dose timing can be individualized for each patient. Basal insulin is traditionally dosed in the evening (50), so patients switching from basal insulin may prefer to continue with that routine. In our experience, administration in the evening may be preferable for patients who have previously experienced GI side effects with initiation of GLP-1 receptor agonist therapy, but not for patients who usually have good blood glucose readings at bedtime (and thus may be more likely to omit or underestimate the dose required if IDegLira is given at bedtime). Treatment should be discussed with patients, and dose timing should be individualized to their needs and preferences (51,52).

### *Starting Dose*

The IDegLira label states that it should be initiated at 10 units (10 units degludec plus 0.36 mg liraglutide) in patients transferring from oral antidiabetic drugs and at 16 units (16 units degludec plus 0.58 mg liraglutide) in patients transferring from basal insulin or a GLP-1 receptor agonist (14). This review is focused on patients who are transferring from basal insulin therapy.

Initially, such patients may be skeptical that 16 units of IDegLira will be sufficient to maintain or improve glycemic control. In such cases, it is important to refer patients to findings from clinical trials. For example, a post hoc analysis of the DUAL V trial demonstrated that, compared with IGlar U100 up-titration, IDegLira resulted in significantly greater reductions in A1C and body weight and lower hypoglycemia rates at a lower end-of-trial insulin dose, regardless of pre-trial IGlar U100 dose. Importantly, across all pretrial insulin dose groups (20 to <30, ≥30 to <40, and ≥40 to ≤50 units/day), there were no clinically relevant increases in self-monitoring of blood glucose (SMBG) levels and no withdrawals due to hyperglycemia with IDegLira during the first 8 weeks (53). Although not recommended nor studied, we have had success with patients coming from >50 units basal insulin, with some achieving glycemic targets soon after switching to IDegLira.

### *Titration*

The outcomes observed in DUAL V and VII trials were achieved using twice-weekly titration of IDegLira, based on the mean of three consecutive daily fasting SMBG values, to a fasting glucose target of 72–90 mg/dL

(24,25). We have found that pointing out that the mean insulin dose in these trials approached 40 units by week 12 can be a helpful frame of reference for patients. To achieve the best outcomes, IDegLira should be adjusted every 3–4 days by 2 units upward or downward as required, based on metabolic needs, SMBG measurements, and glycemic targets, until the desired FPG is achieved. To minimize the risk of hypo- or hyperglycemia, additional titration may be needed with changes in physical activity, meal patterns, renal or hepatic function, or during acute illness. It is often difficult for patients to exactly adhere to regimens used in clinical trials (8). In a prospective, observational, single-center, Swiss study investigating the effectiveness of IDegLira initiation in 61 patients, titrating IDegLira by 4 units once weekly, according to individualized fasting blood glucose targets, resulted in favorable outcomes (39).

If patients miss a dose, they should resume, as prescribed, with the next scheduled dose. However, if >3 days have elapsed since the previous dose, it is recommended to revert to the initial starting dose to mitigate any GI symptoms. Several resources are available for patients on the Novo Nordisk IDegLira website, such as a video showing how to use the IDegLira pen and adjust the dose. Patients may find these resources helpful in mitigating confusion about dosing and refreshing their knowledge (54). We have also found it beneficial to ensure prompt follow-up after IDegLira initiation (e.g., ask patients to contact the clinic after 2–3 weeks if they are struggling to control their blood glucose and routinely have patients return to the clinic 6 weeks after initiating IDegLira). This level of support for patients can overcome barriers to treatment intensification and improve their glycemic control.

### *What to Do If Patients Need Further Intensification?*

When the addition of an oral antidiabetic drug to IDegLira therapy fails to improve glycemic control, we recommend considering a prandial insulin regimen. Patients may need to discontinue IDegLira and switch to multiple daily injections of basal and prandial insulin with or without a GLP-1 receptor agonist. The safety and efficacy of IDegLira in combination with prandial insulin has not been studied (14). Patients who continue to experience postprandial glucose excursions while taking the maximum dose of IDegLira may benefit from the addition of prandial insulin.

## *Titration in Clinical Practice*

Compared with other insulin regimens, IDegLira provides improved glycemic control without increased risk of hypoglycemia and weight gain in a simple, once-daily regimen. By combining degludec and liraglutide in a single pen, it also allows two branded drugs to be initiated with a single copayment. Therefore, IDegLira is an attractive alternative to other intensification strategies for patients who are reluctant to take more than one injection per day or are concerned about additional costs, weight gain, or hypoglycemia.

The titration schedule relies on frequent self-titration at home, which may be a barrier to achieving good glycemic control, particularly for patients with low health literacy. These patients may need assistance and education to understand effective titration of the medication. Good communication between health care professionals and patients is crucial to alleviate patient concerns and offer potential solutions (8). Pharmacists and specialist nurses are well positioned to assist patients with titration.

An example from our clinical practice in which IDegLira initiation and titration, as recommended, was successful is a 56-year-old man with diabetes inadequately controlled on IGlar U100 and metformin. His A1C was 8.2%, and he was administering 45 units of IGlar U100 at bedtime but would frequently omit or adjust the IGlar U100 dose when his bedtime blood glucose reading was <100 mg/dL due to fear of nocturnal hypoglycemia. When considering intensification options, he had concerns about taking multiple daily injections and about the cost of additional medications; he was therefore pleased to learn that IDegLira required only one copayment and could be administered once daily. Three months after switching to 16 units of IDegLira (dosed in the morning) and increasing the dose by 2 units every 3 days until his fasting blood glucose readings were consistently <130 mg/dL, his IDegLira dose was 32 units, and his A1C had improved to 6.9%.

It is crucial to emphasize the importance of timely titration to patients so they achieve the best outcomes with treatment, and the above-mentioned case exemplifies success with this approach. However, our experience with patients in regular clinical practice has also demonstrated the virtues of tailoring the approach to IDegLira initiation and titration to individual patients. For example, patients with a recurrent history of hypoglycemia start on 16 units of IDegLira as recommended, but some patients may benefit from titrating once weekly, initially in increments of 1 unit. Fear of hypoglycemia could also be allayed in these patients with education about the lower rates of hypoglycemia observed with IDegLira

compared with up-titration of basal insulin in clinical trials (24).

Some patients may be wary of decreasing their dose of insulin when starting IDegLira if they have previously experienced persistent hyperglycemia on a much higher dose of insulin. An example from our clinical practice is a 49-year-old woman who was receiving 45 units/day of IGlar U100 in combination with 2 g/day of metformin but had poor glycemic control with an A1C of 8.3% and fasting blood glucose levels between 130 and 150 mg/dL. Stressing the importance of twice-weekly titration and reassuring her that most patients had an IDegLira dose approaching 40 units after 3 months empowered her to titrate effectively, and she was encouraged by experiencing an improvement in her fasting blood glucose levels after 2 weeks. She ultimately required 38 units, demonstrating the insulin dose–sparing properties of IDegLira.

Taken together, these examples demonstrate the importance of having an initial discussion with patients regarding what they can expect and the important points to bear in mind when switching to IDegLira.

## Conclusion

In our experience, IDegLira is an effective choice for patients languishing in poor glycemic control with basal insulin because it provides the benefits of good glycemic control with a low risk of weight gain and hypoglycemia at a lower basal insulin dose than with other insulin regimens. Additionally, its once-daily administration and simple titration algorithm are conducive to medication adherence and use in primary care settings. Real-world experience of IDegLira use demonstrates the importance of both reassuring patients so they are empowered to titrate IDegLira as required to achieve optimal outcomes and of tailoring initiation and titration of IDegLira to individual patient circumstances. By sharing our experience, we hope to have outlined important considerations when using IDegLira in clinical practice.

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### AUTHOR CONTRIBUTIONS

Both authors made substantial contributions to the design and interpretation of data and the drafting of the manuscript and approved the final version. M.W. is the guarantor of this work and, as such, takes responsibility for the integrity and accuracy of this review.

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