Type 2 diabetes is a chronic, progressive disease that remains difficult to control despite a growing armamentarium of treatment options. National data show that only 52.5% of people with diabetes achieved a goal A1C <7% in the 2007–2010 period, indicating the continued need for effective and durable treatment approaches (1). The typical clinical course of type 2 diabetes involves periods ...
of adequate glycemic control followed by glycemic deterioration and the need for additional treatment. Ideally, add-on therapies should provide significant glucose reduction with a complementary mechanism of action, without adding significant side effects. Basal insulin (e.g., detemir, glargine, or degludec) is a recommended option at many stages of type 2 diabetes and is often added to oral antidiabetic agents (OADs) to achieve target fasting plasma glucose (FPG) levels. However, it increases the risk of hypoglycemia and weight gain, and its dosage must be titrated effectively to achieve glycemic targets (2,3). Glucagon-like peptide 1 (GLP-1) receptor agonists are also reasonable options at many stages of type 2 diabetes. These agents effectively lower A1C, show favorable effects on weight, and have a low risk of hypoglycemia (4). Their use may be limited by gastrointestinal (GI) adverse effects (AEs), administration requirements, and cost. The combination of basal insulin and a GLP-1 receptor agonist offers several potential benefits to patients with type 2 diabetes. This review focuses on the rationale for, clinical evidence on, and implications of the combination of basal insulin and GLP-1 receptor agonists in the treatment of type 2 diabetes.

### Rationale for Combining Basal Insulin with GLP-1 Receptor Agonists

Several considerations make the combination of basal insulin and a GLP-1 receptor agonist appealing (Table 1). First, the combination provides complementary effects on the glucose profile. Basal insulin delivers sustained insulin throughout the day, and therapy can be individualized by titrating the dose to the patient’s target FPG levels. However, barriers such as fear of hypoglycemia and weight gain may limit the initiation and adequate titration of basal insulin (5,6). In addition, basal insulin does not target postprandial glucose (PPG); thus, more than half of patients treated with basal insulin do not achieve A1C targets (7–9). GLP-1 receptor agonists stimulate glucose-dependent insulin secretion, inhibit glucose-dependent glucagon secretion, slow gastric emptying, and increase satiety. Some evidence also suggests that GLP-1 receptor agonists may preserve β-cell function (10,11). Through these mechanisms, GLP-1 receptor agonists provide improvements in both PPG and FPG levels, complementing the effects of basal insulin.

There are currently six GLP-1 receptor agonists approved for use in either the United States or Europe (Table 2). The pharmacokinetics, pharmacodynamics, dosing, and clinical effects differ among these agents. The shorter-acting agents (exenatide and lixisenatide) are associated with more significant delays in gastric emptying and more targeted reductions in PPG. Compared to short-acting GLP-1 receptor agonists, the longer-acting agents (albiglutide, dulaglutide, exenatide XR, and lixiluglutide) have less of an effect on gastric emptying and rely more on the insulin secretion mechanism, which leads to reductions in both FPG and PPG (4,12). Of note, although lixiluglutide and lixisenatide are both dosed once daily, lixisenatide has a shorter half-life and primarily lowers PPG, whereas lixiluglutide has a longer half-life, thus lowering both PPG and FPG (13). These distinctions should be considered when selecting a specific GLP-1 receptor agonist to use in combination with basal insulin.

Combining therapy may also potentially lower the risk of AEs. Basal insulin may cause weight gain and hypoglycemia. GLP-1 receptor agonists usually cause weight loss and have a low risk of hypoglycemia but do cause GI AEs. Combining the two classes may allow patients to achieve glycemic control with lower doses, which could potentially result in

### Table 1. Complementary Characteristics of Basal Insulin and GLP-1 Receptor Agonists

| Mechanism of action | Basal Insulin | GLP-1 Receptor Agonists |
|---------------------|--------------|------------------------|
| Augments basal insulin | Increases glucose-dependent insulin secretion from the pancreas |
| Increases glucose disposal | Decreases glucose-dependent secretion of glucagon |
| Decreases hepatic glucose production | Slows gastric emptying |
| Increased satiety |

| Glucose profile effects | Primarily lowers FPG | Short-acting agents primarily lower PPG excursions |
|-------------------------|----------------------|-----------------------------------------------|
|                         |                      | Longer-acting agents lower PPG and FPG |

| Effect on weight | Increases weight | Decreases weight |
|------------------|------------------|------------------|

| Main adverse effect | Hypoglycemia | GI issues (nausea, vomiting, diarrhea) |
|--------------------|--------------|-------------------------------------|
|                    |              | Low risk of hypoglycemia |

| Administration requirements | Subcutaneous injection once or twice daily | Subcutaneous injection once or twice daily or once weekly |
|----------------------------|------------------------------------------|-----------------------------------------------|
fewer AEs than when the individual drugs are used independently.

Finally, adding a GLP-1 receptor agonist to basal insulin offers a potentially safer and easier approach to achieving glycemic control compared to prandial insulin. Initiation of prandial insulin increases treatment burden for patients and management burden for providers. It requires one to three injections per day in addition to the basal insulin injection, significant patient education, dose titration, and increased monitoring and increases the risk of hypoglycemia and weight gain. Alternatively, adding a GLP-1 receptor agonist involves fewer injections, simplified dose titration, less education, reduced weight, and a lower risk of hypoglycemia.

**Clinical Evidence**

Evidence supporting the use of GLP-1 receptor agonists in combination with basal insulin is growing. A meta-analysis from 2014 described 15 studies (n = 4,348) in which GLP-1 receptor agonists were added to basal insulin therapy or vice versa in type 2 diabetes patients (14). The authors determined that combination therapy yielded a mean reduction in A1C of 0.44% (95% CI –0.60 to –0.29, \( P < 0.0001 \)) and weight of 3.22 kg (95% CI –4.90 to –1.54, \( P < 0.0001 \)). Combination therapy did not increase the relative risk of hypoglycemia (relative risk 0.99, 95% CI 0.76–1.29, \( P < 0.0001 \)). Although these findings were favorable, only 4 of the 15 studies in the meta-analysis used an active comparator.

The four active comparator studies, plus a fifth study published after the meta-analysis was completed, compared the addition of a GLP-1 receptor agonist or prandial insulin to basal insulin therapy (15–19). Of these, two evaluated twice-daily exenatide (15,16); two evaluated once-daily liraglutide and lixisenatide, respectively (17,18); and one evaluated once-weekly albiglutide (19). Overall, these studies demonstrated efficacy with regard to A1C and body weight reductions of basal insulin plus a GLP-1 receptor agonist compared to basal insulin plus prandial insulin (Table 3). There was minimal hypoglycemia in the GLP-1 receptor agonist–treated patients; the most common AEs were predictably GI related.

Diamant et al. randomized 627 patients with insufficient glycemic control despite 12 weeks of intensive protocol-driven glargine titration to add twice-daily exenatide or thrice-daily lispro to their regimen (15). Patients receiving exenatide reduced their glargine dose by 10% (or more if their A1C was ≤ 8%), and patients receiving lispro reduced their glargine dose by 33–50%. Exenatide was initiated at 5 \( \mu g \) twice daily for 4 weeks and then up-titrated to 10 \( \mu g \) initiated at a dose to replace the reduced dose of glargine, divided across three meals. After exenatide or lispro initiation, glargine was titrated based on premeal glucose values. After 30 weeks of therapy after the optimization phase, patients in each treatment arm experienced similar reductions in A1C based on the initial A1C at the end of the optimization phase (exenatide –1.13%, 95% CI –1.24 to –1.03; lispro –1.10%, 95% CI –1.20 to –1.0).

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**TABLE 2. GLP-1 Receptor Agonists Approved for Use in the United States or Europe**

| Generic name (trade name) | Short-Acting | Long-Acting |
|---------------------------|--------------|-------------|
| Exenatide (Byetta)        |              |             |
| Lixisenatide (Lyxumia)    |              |             |
| Liraglutide (Victoza)     |              |             |
| Exenatide XR (Bydureon)   |              |             |
| Albiglutide (Tanzeum, Eperzan) |         |             |
| Dulaglutide (Trulicity)   |              |             |
| **Year of FDA approval**  | 2005         | 2014        |
| **Year of EMA approval**  | 2006         | 2014        |
| **Dose**                  | 5–10 \( \mu g \) | 10–20 \( \mu g \) | 0.6–1.8 mg | 2 mg | 30–50 mg | 0.75–1.5 mg |
| **Administration**        | Twice daily  | Once daily  | Once daily | Once weekly | Once weekly | Once weekly |
| **Delivery**              | Multi-use pen | Multi-use pen | Multi-use pen | Single-use pen# | Single-use pen# | Single-use pen# |
| **Renal dosing**          | Not recommened if CrCl is <30 mL/min; use caution if CrCl is 30–50 mL/min | None | None | Not recommened if CrCl is <30 mL/min; use caution if CrCl is 30–50 mL/min | None | None |

*Delivered via subcutaneous injection.

#Requires reconstitution.

**CrCl**, creatinine clearance; **EMA**, European Medicines Agency; **FDA**, U.S. Food and Drug Administration.
| Clinical Trial | (Duration) | Background | Therapy | Comparator Arms | Baseline A1C (% | Baseline FPG (mg/dL | Baseline Basal Insulin Dose (units/day) | Δ A1C (%) | Final Basal Insulin Dose (units/day) | Δ Weight (kg) | Hypoglycemia* (% | Nausea (%) | Vomiting (%) | Diarrhea (%) | Definition of hypoglycemia |
|----------------|------------|------------|---------|-----------------|-----------------|-----------------|--------------------------|-------------|--------------------------|---------------|-----------------|-------------|--------------|-------------|------------------|
| Diamant et al. (15) | (30 weeks) | Glargine (+ metformin) | 627 | 11.5 | Exenatide | 8.3 | 120 | 97 | 0.8 | 0 | 0 | 0 | <54 mg/dL |
| Shao et al. (16) | (12 weeks) | None | 60 | Newly diagnosed | Exenatide (+ glargine) | 7.6 | 81 | 68 | 3.3 | 0 | 0 | 0 | <70 mg/dL |
| Mathieu et al. (17) | (28 weeks) | Degludec (+ metformin) | 177 | 11.8 | Liraglutide | 7.7 | 112 | 85 | 0.7 | 0 | 0 | 0 | <56 mg/dL |
| Roy-Duval et al. (18) | § (26 weeks) | Glargine (+ metformin) | 890 | Unknown | Exenatide | 7.7 | 112 | 80 | 0.4 | 0 | 0 | 0 | <61 mg/dL |
| Rosenstock et al. (19) | (26 weeks) | Glargine (+ metformin, pioglitazone, or both) | 566 | 11 | Albiglutide | 8.4 | 132 | 107 | 0.7 | 0 | 0 | 0 | <70 mg/dL |

* Definition of hypoglycemia was unique to each study: Diamant et al., blood glucose <54 mg/dL; Shao et al., blood glucose <70 mg/dL; Mathieu et al., blood glucose <56 mg/dL; Roy-Duval et al., blood glucose <60 mg/dL; and Rosenstock et al., blood glucose <70 mg/dL. ** Episodes per patient-year of exposure. NA, not applicable; NR, not reported. # P < 0.05 versus baseline. ¶ P < 0.05 versus comparator group. ‡ Met noninferiority criteria. $ Definition of hypoglycemia was unique. ** Episodes per patient-year of exposure. NA, not applicable; NR, not reported.
The difference in A1C between exenatide and lispro was −0.04% (95% CI −0.18 to 0.11) in the per-protocol population and −0.03% (95% CI −0.16 to 0.11) in the intent-to-treat population, which met noninferiority criteria. The glargine dose decreased from a mean of 61.5 to 56.8 units in the exenatide group and from 61.1 to 51.5 units in the lispro group (P < 0.001 for between-group difference). Patients receiving exenatide lost weight, whereas those receiving lispro gained weight. The incidences of minor and non-noc- turnal hypoglycemia were lower in the exenatide group compared to the lispro group (30 vs. 41%, P = 0.004, and 15 vs. 34%, P < 0.001, respectively). However, the incidence of nocturnal hypoglycemia was similar between groups (25 vs. 27%, P not reported). GI AEs were more prevalent in the exenatide group, but no cases of pancreatitis were observed in either group. The authors concluded that twice-daily exenatide was a reasonable alternative to prandial insulin for type 2 diabetes patients with sub- optimal glycemic control despite glargine therapy (15).

Shao et al. also studied the addition of twice-daily exenatide or prandial insulin to glargine (16). This study enrolled 60 patients with newly diagnosed type 2 diabetes, obesity (BMI ≥28 kg/m²), and non-alcoholic fatty liver disease (NAFLD) with elevated liver enzymes. Thirty patients were randomized to twice-daily exenatide plus glargine, and 30 patients were randomized to thrice-daily aspart plus glargine. Exenatide was initiated at 5 μg twice daily for 4 weeks and up-titrated to 10 μg twice daily for 8 weeks. Insulin dosing algorithms and mean daily doses of insulin were not reported. At the end of 12 weeks, A1C had decreased by 1.42% in the exenatide group and 1.31% in the aspart group (both P < 0.001 vs. baseline A1C at diagnosis). Patients in the exenatide group lost weight (−7.77 kg, P < 0.001), whereas those in the aspart group gained weight (+3.27 kg, P < 0.001). Patients in the exenatide group experienced decreases in liver enzymes compared to the aspart group (P < 0.001). One-third of patients in the exenatide group reported a mild to moderate GI AE, and 10% of patients in the aspart group reported an episode of symptomatic hypoglycemia. The authors concluded that exenatide was effective at decreasing A1C, weight, and elevated liver enzymes in newly diagnosed type 2 diabetes patients with obesity and NAFLD (16).

BEGIN: VICTOZA ADD-ON was a 26-week study by Mathieu et al. that evaluated the addition of once-daily liraglutide or aspart with the largest meal in 177 patients with type 2 diabetes receiving degludec with or without metformin who had completed the 52-week BEGIN ONCE-LONG trial plus a 52-week extension and had an A1C ≥7% (17). These 177 patients had a mean A1C of 7.7% at the end of the 104 total weeks from previous study enrollment. Patients receiving liraglutide had their degludec dose decreased by 20% at study initiation, and the dose could not be increased until week 6. Liraglutide was initiated at 0.6 mg daily for 1 week and increased to 1.2 mg daily for 5 weeks. At week 5, if the mean prebreakfast FPG value was ≥90 mg/dL, liraglutide was increased to 1.8 mg daily. From week 6 onward, if the mean prebreakfast FPG value was ≥90 mg/dL, liraglutide was increased to 1.8 mg daily, or the degludec dose could be increased per the study-specified titration schedule. Patients receiving aspart started on a dose of 4 units before their largest meal of the day. Aspart was titrated weekly based on the mean of three premeal or bedtime blood glucose values. At 26 weeks, A1C decreased more in the liraglutide group than in the aspart group (−0.74 vs. −0.39%, P = 0.0024). The mean degludec dose in the liraglutide group was 0.70 units/kg/day at study initiation and 0.65 units/kg/day at 26 weeks, and the mean degludec dose in the aspart group was 0.66 units/kg/day at study initiation and 0.64 units/kg/day at week 26 (P not reported). The mean aspart dose at week 26 was 0.21 units/kg/day. Patients receiving lira- glutide lost weight, whereas patients receiving aspart gained weight (−2.8 vs. +0.9 kg, P < 0.0001 for the comparison). Patients randomized to liraglutide were less likely to experience hypoglycemia than those in the aspart group (estimated rate ratio 0.13, 95% CI 0.08–0.21, P < 0.0001). The most common AEs in the lira- glutide group were GI-related. The authors concluded that the addition of liraglutide was more effective at reducing A1C than aspart; however, aspart was only given once daily. Liraglutide had positive effects on weight and was associated with a low risk of hypoglycemia (17).

Roy-Duval et al. evaluated the addition of the GLP-1 receptor agonist lixisenatide 20 μg daily versus daily glulisine or thrice-daily glulisine in 890 patients with type 2 diabetes poorly controlled on glargine ± metformin after a 12-week optimization phase (18). Data are currently published only in abstract form. At the end of a 12-week run-in period, the mean daily doses of glargine were similar between the lixisenatide, daily glulisine, and thrice-daily glulisine groups (67 ± 32 units, 65 ± 32 units, and 65 ± 27 units, respectively). Lixisenatide was deemed noninferior to either once- or thrice-daily glulisine with respect to A1C change from the end of the 12-week optimization phase to the end of the 26-week study period (−0.59 vs. −0.52 vs. −0.83%) and was superior in terms of weight loss, as patients lost weight with lixisenatide and gained with glulisine (P < 0.0001 for lixisenatide vs. each glulisine arm). The mean daily dose of glargine in the lixisenatide, daily glulisine, and thrice-daily glulisine groups remained the same or decreased (67 ± 36 units, 64 ± 36 units, and 61 ± 29 units, respectively; the treatment difference
between the lixisenatide and thrice-daily glulisine groups was statistically significant. The patients receiving lixisenatide experienced significantly less hypoglycemia than those receiving thrice-daily glulisine \((P < 0.0001)\); however, patients in the lixisenatide group experienced more GI AEs compared to either glulisine group. The authors concluded that once-daily lixisenatide may be a preferred add-on therapy to glargine for improving glycemic control while minimizing hypoglycemia and promoting weight loss \((18)\).

Finally, the Harmony 6 study by Rosenstock et al. evaluated once-weekly albiglutide versus thrice-daily lispro as add-on therapy in 566 patients with uncontrolled type 2 diabetes despite therapy with glargine \pm OADs \((19)\). Patients receiving albiglutide initiated at 30 mg weekly and up-titrated to 50 mg weekly if their A1C was >8% between weeks 8 and 12. Patients receiving thrice-daily lispro had their dose initiated based on self-monitoring of blood glucose data and were titrated to a preplanned goal of 80–130 mg/dL. Patients in each group had their glargine titrated in increments of 2–8 units to a FBG goal of 100 mg/dL. The mean daily glargine dose increase was similar between groups over the 26-week study period \((16, 18)\); however, patients in the degludec group, and 1.21% in the degludec group, and 1.21% in the degludec group \((P < 0.0001)\) for IDegLira plus either degludec or liraglutide. The daily degludec dose was 37% lower in the IDegLira group \((39 \text{ units})\) versus the degludec group \((62 \text{ units})\); estimated treatment difference –23.4 units, 95% CI –26.4 to –20.3, \(P < 0.0001\). The rate of confirmed hypoglycemia was significantly lower in the IDegLira group compared to the degludec group \((\text{rate ratio} 0.63, 95\% \text{CI} 0.50–0.79, P < 0.0001)\) \((25)\).

**Fixed-Ratio Combinations**

Two fixed-ratio combinations (FRCs) containing a GLP-1 receptor agonist and a basal insulin in a single injection are in the development pipeline. Novo Nordisk has submitted materials for U.S. Food and Drug Administration (FDA) approval of an FRC containing degludec and liraglutide \((\text{IDegLira})\) \((21)\). The combination product has been approved in Europe under the trade name Xultophy and is supplied as a 3-mL pen device containing 100 units/mL degludec and 3.6 mg/mL liraglutide \((22)\). Sanofi submitted materials for FDA approval of an FRC containing glargine and lixisenatide \((\text{LixiLan} \text{ or } \text{iGlarLixi})\) in December 2015 and redeemed a priority review voucher to shorten the review time to 6 months \((23)\).

The DUAL I study evaluated IDegLira versus each of its individual components in insulin-naïve patients taking metformin with or without pioglitazone with a baseline A1C of 7–10% \((24)\). At the end of 26 weeks, patients receiving IDegLira experienced an A1C reduction of 1.9% compared to a 1.4% reduction with degludec \((\text{IDegLira noninferior}; \text{treatment difference } –0.47\%, 95\% \text{CI } –0.58 \text{ to } –0.36, P < 0.0001)\) and a 1.3% reduction with liraglutide \((\text{IDegLira superior}; \text{treatment difference } –0.64\%, 95\% \text{CI } –0.75 \text{ to } –0.53, P < 0.0001)\) \((24)\). A 26-week extension to this study confirmed sustained efficacy and safety in 78% \((n = 1,311/1,663)\) of the patients enrolled in the original DUAL I study \((25)\). At the end of 52 weeks, mean A1C had decreased by 1.84% in the IDegLira group, 1.4% in the degludec group, and 1.21% in the liraglutide group \((P < 0.0001)\) for IDegLira vs. either degludec or liraglutide. The daily degludec dose was 37% lower in the IDegLira group \((39 \text{ units})\) versus the degludec group \((62 \text{ units})\); estimated treatment difference –23.4 units, 95% CI –26.4 to –20.3, \(P < 0.0001\). The rate of confirmed hypoglycemia was significantly lower in the IDegLira group compared to the degludec group \((\text{rate ratio} 0.63, 95\% \text{CI} 0.50–0.79, P < 0.0001)\) \((25)\).

The DUAL II study evaluated the safety and efficacy of degludec versus IDegLira, each in combination with metformin in 413 patients with a mean baseline A1C of 8.7–8.8 ± 0.7% already receiving basal insulin and OADs \((26)\). Patients were randomized to receive IDegLira plus metformin or degludec plus metformin for 26 weeks, with titration aimed to achieve an FPG of 72–90 mg/dL. The maximum doses allowed were 50 units for degludec and 50 units for degludec plus 1.8 mg of liraglutide for IDegLira. At equivalent degludec doses \((\text{mean dose of 45 units in each group})\), IDegLira decreased A1C by more than twice that of degludec \((–1.9 \text{ vs. } –0.9\%); \text{estimated treatment difference } –1.1\%, 95\% \text{CI } –1.3 \text{ to } –0.8\%, P < 0.0001)\). Patients randomized to IDegLira lost weight \((–2.7 \text{ kg})\), whereas patients on degludec maintained their weight \((P < 0.0001)\), and the incidence of hypoglycemia between groups was similar \((24 \text{ vs. } 25\%\). The most common AEs of IDegLira were GI-related, but the incidence was much less than that observed in other liraglutide studies; incremental titration allowed for improved GI tolerability. The authors concluded that the FRC IDegLira was superior to degludec for optimizing glycemic control in patients inadequately controlled on OADs and basal insulin \((26)\).

Post-hoc analyses of the DUAL I extension and DUAL II studies determined that IDegLira is efficacious irrespective of baseline A1C, duration of diabetes, and diabetes treatment...
at screening. In the DUAL I study, IDegLira significantly reduced A1C irrespective of baseline A1C; this trend held true for the DUAL II study in all baseline A1C categories except for those with an A1C <7.5%. The dose of insulin and rates of hypoglycemia were lower for the IDegLira versus the degludec group, and as expected, the rate of hypoglycemia was higher in the IDegLira versus the liraglutide group in DUAL I. In DUAL II, insulin doses and rates of hypoglycemia were similar between groups. In both studies, reduction in A1C with IDegLira was independent of type 2 diabetes duration and baseline insulin dose but varied based on baseline OAD use (27).

The DUAL V study evaluated the safety and efficacy of IDegLira compared to continued titration of insulin glargine in type 2 diabetes patients not controlled on metformin and insulin glargine (28). A1C reduction was greater in patients taking IDegLira compared to patients continuing with glargine (–1.81 vs. –1.13%; estimated treatment difference –0.59%, 95% CI –0.74 to –0.45%, meeting criteria for noninferiority and superiority, \( P < 0.001 \)). Treatment with IDegLira was associated with weight loss compared to weight gain with glargine (–1.4 vs. +1.8 kg, \( P < 0.001 \)). IDegLira had lower rates of hypoglycemia but higher rates of GI AEs compared to insulin glargine (28).

The completed but not yet published LixiLan-O \( (n = 1,170) \) and LixiLan-L \( (n = 736) \) phase III 30-week clinical studies evaluated the efficacy and safety of LixiLan. LixiLan-O evaluated LixiLan versus each of its individual components in insulin-naive type 2 diabetes patients not controlled on metformin (29). LixiLan-L evaluated LixiLan compared to glargine in type 2 diabetes patients not controlled on basal insulin plus one or two OADs (30). Patients in each study continued on metformin throughout. Both studies have been reported to have met their primary endpoints showing superior A1C reduction by LixiLan versus the comparator arms (29,30). A phase IIIB study evaluated LixiLan versus glargine (each in combination with metformin) in 323 type 2 diabetes patients with a mean baseline A1C of 8%. The results of this study, currently reported in abstract form, demonstrated superior glycemic efficacy with LixiLan versus glargine without increased risk of hypoglycemia. Patients receiving LixiLan experienced a decrease in A1C from a mean of 8.1 to 6.3% after 24 weeks. Nearly two-thirds of patients achieved an A1C <7% with no documented hypoglycemia (31).

**Clinical Implications**

Treatment guidelines from the American Diabetes Association indicate that either basal insulin or GLP-1 receptor agonists are reasonable agents to add on as second- or third-line options (2). In 2015, these recommendations were updated to include GLP-1 receptor agonists as alternatives to prandial insulin to treat PPG excursions in patients with uncontrolled A1C despite reaching FPG goals with basal insulin (3). These recommendations are well supported by clinical evidence and offer several advantages, making the use of this combination in clinical practice increasingly more common. There likely will be several clinical scenarios in which the combination may be used. Each scenario requires unique considerations to ensure safe and effective use. In most of these situations, patients likely also would be taking one or more additional OADs such as metformin.

**Adding a GLP-1 Receptor Agonist to Basal Insulin**

This scenario is well supported by clinical evidence showing decreased A1C and weight compared to placebo and similar efficacy with less hypoglycemia compared to prandial insulin. This option would be a reasonable treatment option in patients with controlled FPG levels but elevated PPG and A1C levels. This may also be a reasonable option for patients on a large dose of basal insulin or those who are not willing or able to optimize their basal insulin dose. A GLP-1 receptor agonist would be a more straightforward approach to glycemic control with less treatment burden and less training, monitoring, and dose titration necessary than with prandial insulin. In most case scenarios, it would increase the injection burden only modestly.

Clinicians should consider patients’ primary glucose profile defect to determine whether a short- or long-acting GLP-1 receptor agonist would be preferred. Adherence to administration requirements, patients’ preferences, and insurance coverage also will help to determine which GLP-1 receptor agonist would be most appropriate.

When initiating a GLP-1 receptor agonist, the basal insulin dose may need to be decreased as the GLP-1 receptor agonist starts to take effect. Across clinical studies, there were varying approaches to adjusting basal insulin doses, with some empirically decreasing the dose by 10–20% when the GLP-1 receptor agonist was initiated. This basal dose adjustment should depend on baseline glucose and A1C levels, as well as the onset of action, dose titration schedule, and expected impact on glucose profile of the specific GLP-1 receptor agonist. Patients should be educated about the potential for GI AEs, which likely will be transient in nature, and close follow-up is warranted.

**Adding Basal Insulin to a GLP-1 Receptor Agonist**

The addition of basal insulin to a GLP-1 receptor agonist is also well supported by clinical evidence. This is a reasonable option to consider for patients with uncontrolled FPG and A1C levels despite treatment with one or more OADs and a GLP-1 receptor agonist. Clinicians should educate patients about how to titrate their dose to a target FPG range and, for pa-
patients taking a sulfonylurea, should evaluate the additive risk of hypoglycemia and consider discontinuation of the sulfonylurea.

Adding Basal Insulin Plus a GLP-1 Receptor Agonist Simultaneously

Adding basal insulin plus a GLP-1 receptor agonist simultaneously has been shown to be safe and effective in insulin-naïve patients (16,24,25,29). In DUAL-1, adding both simultaneously (IDegLira) allowed patients to use lower doses of each component to achieve the same glycemic control as with the basal insulin degludec and glycemic control superior to that with liraglutide (24,25). Adding the combination also negated some of the side effects of each component, particularly the GI AEs of the GLP-1 receptor agonist, likely because of the slower titration. This may be a reasonable option for a wide range of patients; post-hoc analysis of the DUAL studies demonstrated efficacy independent of duration of disease, background therapies, and baseline A1C levels (except for patients with A1C levels <7.5%) (27).

FRCs offer the advantage of fewer injections and possibly improved adherence and less transient GI AEs resulting from the slower titration of the GLP-1 receptor agonist component. Challenges are similar to those with many combination products. Patients’ AEs related to one component may limit their ability to titrate the dose or their persistence with both components. Patients also may reach the maximum dose of the combination but still require more basal insulin to reach FPG goals. Prescribing information for IDegLira indicates that the FRC pen is recommended for patients with basal insulin needs of 20–50 units (22). The recommended starting dose of IDegLira is 10 dose steps (10 units insulin degludec and 0.36 mg liraglutide). The dose can be titrated by 2 dose steps every 3 days until an FPG target of <90 mg/dL is reached. The maximum dose is 50 units of insulin degludec and 1.8 mg of liraglutide (22). When added to a sulfonylurea, a reduction of the dose of the sulfonylurea should be considered.

Switching to an FRC Product

It may be appropriate for patients to switch from basal insulin alone or a GLP-1 receptor agonist alone to an FRC product. In either scenario, the prescribing information for IDegLira recommends a starting dose of 16 units of insulin degludec and 0.6 units of liraglutide (22). This regimen could lead to challenges in short-term glycemic control for patients who were already taking higher doses of either component individually. To date, transitioning from patients taking <20 units or >50 units of basal insulin per day has not been studied. For patients who are switching from a long-acting GLP-1 receptor agonist, there may be overlapping effects during the transition because of its longer duration of action. Either scenario necessitates close follow-up and education during the transition.

Conclusion

Clinical studies have demonstrated improved glycemic control and low risk of hypoglycemia and weight gain with the combination of basal insulin and a GLP-1 receptor agonist. This approach provides a safe and effective alternative to basal-bolus insulin with less treatment burden. FRC products are in the pipeline and will offer additional options for clinicians and patients.

Duality of Interest

Dr. Trujillo is an advisory board consultant for Sanofi. No other potential conflicts of interest relevant to this article were reported.

References

1. Stark Casagrande S, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988–2010. Diabetes Care 2013;36:2271–2279
2. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364–1379
3. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140–149
4. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol 2012;8:728–742
5. Cryer PE. Hypoglycemia: the limiting factor in glycemic management of type 1 and type II diabetes. Diabetologia 2002;45:937–948
6. Peyrot M, Rubin RR, Lauritzen T, et al. Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. Diabetes Care 2005;28:2673–2679
7. Blak BT, Smith HT, Hards M, Maguire A, Gimeno V. A retrospective database study of insulin initiation in patients with type 2 diabetes in UK primary care. Diabet Med 2012;29:e191–198
8. Giugliano D, Maiorino MI, Bellastella G, Chiordini P, Ceriello A, Esposito K. Efficacy of insulin analogs in achieving the hemoglobin A1C target of <7% in type 2 diabetes: meta-analysis of randomized controlled trials. Diabetes Care 2011;34:510–517
9. Raccah D, Bretzel RG, Owens D, Riddle M. When basal insulin therapy in type 2 diabetes mellitus is not enough—what next? Diabetes Metab Res Rev 2007;23:257–264
10. Bunck MC, Diamant M, Corner A, et al. One-year treatment with exenatide improves beta-cell function, compared to insulin glargine, in metformin treated type 2 diabetes patients: a randomized, controlled trial. Diabetes Care 2009;32:762–768
11. Bunck MC, Corner A, Eliasson B, et al. Effects of exenatide on measures of beta-cell function after 3 years in metformin-treated patients with type 2 diabetes. Diabetes Care 2011;34:2041–2047
12. Meier JJ, Rosenstock J, Hincelin-Mery A, et al. Contrasting effects of lixisenatide and liraglutide on postprandial glycemic control, gastric emptying, and safety parameters in patients with type 2 diabetes on optimized insulin glargine with or without metformin: a randomized, open-label trial. Diabetes Care 2015;38:1263–1273
13. Kapitza C, Forst T, Coester HV, Poitiers F, Ruus P, Hincelin-Mery A. Pharmacodynamic characteristics of lixisenatide once daily versus liraglutide once daily in patients with type 2 diabetes insufficiently controlled on metformin. Diabetes Obes Metab 2013;15:642–649
14. Eng C, Kramer CK, Zinnman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combina-
tion treatment for the management of type 2 diabetes: a systematic review and meta-analysis. Lancet 2014;384:2228–2234
15. Diamant M, Nauck MA, Shaginian R, et al. Glucagon-like peptide-1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. Diabetes Care 2014;37:2763–2773
16. Shao N, Kuang HY, Hao M, Gao XY, Lin WJ, Zou W. Effects of exenatide on obesity and NAFLD with elevated liver enzymes in patients with type 2 diabetes. Diabetes Metab Res Rev 2014;30:521–529
17. Mathieu C, Rodbard HW, Cariou B, et al. A comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with type 2 diabetes (BEGIN: VICTOZA ADD-ON). Diabetes Obes Metab 2014;16:636–644
18. Roy-Duval C, Hanefeld M, Gentile S, et al. Advancing basal insulin glarginie with prandial lixisenatide QD vs insulin glulisine QD or TID in type 2 diabetes: the GetGoal-Duo2 evidence-based trial (Abstract #78). Diabetologia 2015;58(Suppl. 1):S39
19. Rosenstock J, Fonseca VA, Gross JL, et al. Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist versus thrice-daily prandial insulin lispro. Diabetes Care 2014;37:2317–2325
20. Fonseca VL, Ahren B, Chow F, et al. Once weekly GLP-1 receptor agonist albiglutide vs prandial lispro added to basal glargine in type 2 diabetes: similar glycaemic control with weight loss and less hypoglycaemia [Abstract]. Available from http://www.absconline.com/plan/ViewAbstract.aspx?mID=2978&sKey=880b06e6-7bc0-41d3-8a60-ceca06f88cd&cKey=a4a9d018-2d00-4efe-a431-b3e439d6635c&mKey=2dbfca7-1539-42d5-8dda-0a94abb089e8. Accessed 5 April 2016
21. Novo Nordisk. Xultophy (NN9068) type 2 diabetes: filed for registration. Available from http://www.novonordisk.com/rnd/pipelinedetails.l42830648863_2.html. Accessed 23 February 2016
22. Novo Nordisk. Xultophy®. Annex I: Summary of product characteristics. Available from http://ec.europa.eu/health/documents/community-register/2014/2014091829550/anx_129550_en.pdf. Accessed 20 February 2016
23. Zealand Pharmaceuticals. Zealand announces that Sanofi has submitted LixiLan for regulatory review in the US, triggering a USD 20 million milestone payment [Press Release]. Available from https://newsclient.omxgroup.com/cdsPublic/viewDisclosure.action?disclosureId=690565&lang=en. Accessed 20 February 2016
24. Gough SC, Bode B, Woo V, et al. Efficacy and safety of a fixed-ratio combination of insulin degludec and lixisenatide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes. Lancet Diabetes Endocrinol 2014;2:885–893
25. Gough SC, Bode BW, Woo VC, et al. One-year efficacy and safety of a fixed combination of insulin degludec and lixisenatide in patients with type 2 diabetes: results of a 26-week extension to a 26 week main trial. Diabetes Obes Metab 2015;17:965–973
26. Buse JB, Viscillo T, Thurman J, et al. Contribution of lixisenatide in the fixed-ratio combination of insulin degludec and lixisenatide (IDegLira). Diabetes Care 2014;37:2926–2933
27. Rodbard HW, Buse JB, Woo V, et al. Benefits of combination of insulin degludec and lixisenatide are independent of baseline glycated hemoglobin level and duration of type 2 diabetes. Diabetes Obes Metab 2016;18:40–48
28. Lingvay I, Manghi FP, Garcia-Hernandez P, et al. Effect of insulin glargine up-titration vs insulin degludec/lixisenatide on glycated hemoglobin levels in patients with uncontrolled type 2 diabetes: the DUAL V randomized controlled trial. JAMA 2016;315:898–907
29. Sanofi-Aventis. Sanofi announces that first LixiLan phase III study met primary endpoint [Press Release]. Available from http://www.news.sanofi.us/2015-07-29-Sanofi-Announces-that-First-LixiLan-Phase-III-Study-Met-Primary-Endpoint. Accessed 20 February 2016
30. Sanofi-Aventis. Sanofi reports positive top-line results in second pivotal LixiLan phase III study [Press Release]. Available from http://www.news.sanofi.us/2015-09-14-Sanofi-Reports-Positive-Top-Line-Results-in-Second-Pivotal-LixiLan-Phase-III-Study. Accessed 20 February 2016
31. Rosenstock J, Guerci B, Paranjape S, Berria R, Souhami E, Aroda VR. Improved glucose control without increased hypoglycaemia risk at any level of HbA1c reduction with insulin glargine/lixisenatide fixed-ratio combination (LixiLan) vs. insulin glargine alone both added on to metformin in type 2 diabetes (T2DM) [Abstract 169-OR]. Presented at the American Diabetes Association’s 75th Scientific Sessions, 5–9 June 2015, Boston. Mass.