Fixed-Ratio Combinations
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Introduction
Combination treatment with basal insulin and a glucagon-like peptide-1 (GLP-1) receptor agonist targets different aspects of the pathophysiology of type 2 diabetes to achieve glycemic control. In November 2016, the U.S. Food and Drug Administration approved two titratable fixed-ratio combinations (FRCs) of basal insulin and a GLP-1 receptor agonist: insulin glargine/lixisenatide 3:1 ratio (iGlarLixi [Soliqua]) and insulin degludec/liraglutide 1:0.036 ratio (IDegLira [Xultophy]) (1,2).

Indications
Both agents are indicated to improve glycemic control in adults with type 2 diabetes inadequately controlled on basal insulin or the respective GLP-1 receptor agonist along with diet and exercise (1,2). Use of these agents is not recommended for patients with type 1 diabetes, diabetic ketoacidosis, gastroparesis, or a history of pancreatitis. Additionally, these agents should be avoided in patients using another GLP-1 receptor agonist or prandial insulin (1,2).

Mechanisms of Action
Insulin glargine and insulin degludec improve glycemic control through stimulation of glucose uptake in the body and inhibition of glucose production in the liver (1,2). Lixisenatide and liraglutide mimic the action of GLP-1 through stimulation of glucose-dependent insulin release, suppression of glucagon production, and slowing of gastric emptying (1,2).

Potential Advantages
A main advantage of FRCs, as single daily injections of two glycemic control medications, is regimen simplification to promote treatment adherence with less potential for clinical inertia. Greater efficacy in glycemic control is achieved with FRCs compared to each of their component agents alone (Table 1) (3–9). Furthermore, the principal side effects of each component agent when used alone are mitigated when used in combination. Less weight gain and hypoglycemia occurred in patients on FRCs compared to those taking basal insulin alone, and fewer gastrointestinal (GI) adverse effects were observed in patients on FRCs compared to those taking a GLP-1 receptor agonist alone (Table 1) (3–9).

Potential Disadvantages
FRCs are injectable products. Although these agents are titratable based on the basal insulin component, patients requiring less than the minimum starting doses (iGlarLixi, 15 units; IDegLira, 16 units) or more than the maximum doses (iGlarLixi, 60 units; IDegLira, 50 units) may not be good candidates for these agents (1,2). At the end of the study periods, mean daily doses of iGlarLixi were -40–50 units (3,4) and mean daily doses of IDegLira were -30–45 units (5–9). For patients who struggle with compliance, reinitiating at the starting dose is recommended for IDegLira after missing 3 days, whereas no guidance has been pro-
| Table 1. Summary of Clinical Trials of FRCs in Patients With Type 2 Diabetes (3–9) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Population Characteristics** | **A1C Change From Baseline (%)** | **Patients Achieving A1C <7.0% (%)** | **Body Weight Change From Baseline (kg)** | **Patients With Hypoglycemia* (%)** | **Patients With GI Side Effects† (%)** |
| iGlarLixi                       | iGlarLixi: –1.6  | iGlarLixi: 73.7 | iGlarLixi: –0.3  | iGlarLixi: 25.6 | iGlarLixi: 21.7 |
| LixiLan-O                       | iGlar: –1.3‡    | iGlar: 59.4‡   | iGlar: +1.1‡    | iGlar: 23.6§   | iGlar: 12.6§    |
| n = 1,170                       | Lixi: –0.9‡     | Lixi: 33.0‡    | Lixi: –2.3      | Lixi: 6.4§     | Lixi: 36.9§     |
| Duration: 30 weeks              |                 |                 |                 |                 |                 |
| Inadequately controlled on metformin ± a second oral antidiabetic agent |                 |                 |                 |                 |                 |
| Mean age: 58.4 years            |                 |                 |                 |                 |                 |
| Mean BMI: 31.7 kg/m²            |                 |                 |                 |                 |                 |
| Mean duration of diabetes: 8.8 years |                 |                 |                 |                 |                 |
| Mean A1C at baseline: 8.1%      |                 |                 |                 |                 |                 |
| iGlarLixi                       | iGlarLixi: –1.1  | iGlarLixi: 54.9 | iGlarLixi: –0.7  | iGlarLixi: 40.0 | iGlarLixi: 17.0 |
| LixiLan-L                       | iGlar: –0.6‡    | iGlar: 29.6‡   | iGlar: +0.7‡    | iGlar: 42.5§   | iGlar: 7.9§     |
| n = 736                         |                 |                 |                 |                 |                 |
| Duration: 30 weeks              |                 |                 |                 |                 |                 |
| Inadequately controlled on basal insulin ± 1–2 OADs |                 |                 |                 |                 |                 |
| Median age: 60.0 years          |                 |                 |                 |                 |                 |
| Mean BMI: 31.2 kg/m²            |                 |                 |                 |                 |                 |
| Mean duration of diabetes: 12.1 years |                 |                 |                 |                 |                 |
| Mean A1C at baseline: 8.1%      |                 |                 |                 |                 |                 |
| IDegLira                        | IDegLira: –1.9  | IDegLira: 80.6 | IDegLira: –0.5  | IDegLira: 31.9 | IDegLira: 39–8.8 |
| DUAL I                          | IDeg: –1.4¶     | IDeg: 65.1‡   | IDeg: +1.6‡    | IDeg: 38.6§   | IDeg: 1.5–4.6§  |
| n = 1,663                       | Lira: –1.3‡     | Lira: 60.4‡   | Lira: –3.0‡    | Lira: 6.8§    | Lira: 8.5–19.7§ |
| Duration: 26 weeks              |                 |                 |                 |                 |                 |
| Previously treated with metformin ± pioglitazone |                 |                 |                 |                 |                 |
| Mean age: 55.0 years            |                 |                 |                 |                 |                 |
| Mean BMI: 31.2 kg/m²            |                 |                 |                 |                 |                 |
| Mean duration of diabetes: 6.9 years |                 |                 |                 |                 |                 |
| Mean A1C at baseline: 8.3%      |                 |                 |                 |                 |                 |
| IDegLira                        | IDegLira: –1.9  | IDegLira: 60.3 | IDegLira: –2.7  | IDegLira: 24.1 | IDegLira: <2–6.5 |
| DUAL II                         | IDeg: –0.9‡     | IDeg: 23.1‡   | IDeg: 0‡       | IDeg: 24.6    | IDeg: 0–3.5§    |
| n = 413                         |                 |                 |                 |                 |                 |
| Duration: 26 weeks              |                 |                 |                 |                 |                 |
| Inadequately controlled on basal insulin + metformin ± sulfonylurea or glinides |                 |                 |                 |                 |                 |
| Mean age: 57.5 years            |                 |                 |                 |                 |                 |
| Mean BMI: 33.7 kg/m²            |                 |                 |                 |                 |                 |
| Mean duration of diabetes: 10.5 years |                 |                 |                 |                 |                 |
| Mean A1C at baseline: 8.8%      |                 |                 |                 |                 |                 |

TABLE CONTINUED ON P. 244
| TABLE 1. Summary of Clinical Trials of FRCs in Patients With Type 2 Diabetes (3–9), continued from p. 243 |
|---------------------------------------------------------------|
| Population Characteristics | A1C Change From Baseline (%) | Patients Achieving A1C <7.0% (%) | Body Weight Change From Baseline (kg) | Patients With Hypoglycemia* (%) | Patients With GI Side Effects† (%) |
|----------------------------|-----------------------------|---------------------------------|-------------------------------------|---------------------------------|-----------------------------------|
| **DUAL III**               |                             |                                 |                                     |                                 |                                   |
| n = 438                    |                             |                                 |                                     |                                 |                                   |
| Duration: 26 weeks         |                             |                                 |                                     |                                 |                                   |
| Inadequately controlled with a GLP-1RA and OADs (metformin ± pioglitazone ± sulfonylurea) | | | | | |
| Mean age: 58.4 years       |                             |                                 |                                     |                                 |                                   |
| Mean BMI: 33.0 kg/m²       |                             |                                 |                                     |                                 |                                   |
| Mean duration of diabetes: 10.4 years | | | | | |
| Mean A1C at baseline: 7.8% | | | | | |
| IDegLira: –1.3 U GLP-1RA: –0.3‡ | | | | | |
| IDegLira: 75 U GLP-1RA: 36‡ | | | | | |
| IDegLira: +2.0 U GLP-1RA: –0.8‡ | | | | | |
| IDegLira: 32.0 U GLP-1RA: 2.8‡ | | | | | |
| IDegLira: 3.1 U GLP-1RA: 4.1§ | | | | | |
| **DUAL IV**                |                             |                                 |                                     |                                 |                                   |
| n = 435                    |                             |                                 |                                     |                                 |                                   |
| Duration: 26 weeks         |                             |                                 |                                     |                                 |                                   |
| Inadequately controlled on metformin ± sulfonylurea | | | | | |
| Mean age: 59.7 years       |                             |                                 |                                     |                                 |                                   |
| Mean BMI: 31.6 kg/m²       |                             |                                 |                                     |                                 |                                   |
| Mean duration of diabetes: 9.2 years | | | | | |
| Mean A1C at baseline: 7.9% | | | | | |
| IDegLira: –1.5 Placebo: –0.5‡ | | | | | |
| IDegLira: 79.2 Placebo: 28.8‡ | | | | | |
| IDegLira: +0.5 Placebo: –1.0‡ | | | | | |
| IDegLira: 41.7 Placebo: 17.1‡ | | | | | |
| Not reported as one of the most frequently occurring adverse events | | | | | |
| **DUAL V**                 |                             |                                 |                                     |                                 |                                   |
| n = 557                    |                             |                                 |                                     |                                 |                                   |
| Duration: 26 weeks         |                             |                                 |                                     |                                 |                                   |
| Inadequately controlled on insulin glargine and metformin | | | | | |
| Mean age: 58.8 years       |                             |                                 |                                     |                                 |                                   |
| Mean BMI: 31.7 kg/m²       |                             |                                 |                                     |                                 |                                   |
| Mean duration of diabetes: 11.5 years | | | | | |
| Mean A1C at baseline: 8.3% | | | | | |
| IDegLira: –1.8 iGlar: –1.1‡ | | | | | |
| IDegLira: 71.6 iGlar: 47.0‡ | | | | | |
| IDegLira: –1.4 iGlar: +1.8‡ | | | | | |
| IDegLira: 28.4 iGlar: 49.1‡ | | | | | |
| IDegLira: 9.4 iGlar: 1.1§ | | | | | |

* LixiLan trials, symptomatic and blood glucose ≤70 mg/dL; DUAL trials, requiring assistance or blood glucose <56 mg/dL.
† GI side effects include nausea, vomiting, and/or diarrhea; not defined or reported similarly in each study.
‡ Statistically significant with comparator(s).
§ Did not report or unknown whether statistical significant was determined.
‖ Met noninferiority.
GLP-1RA, GLP-1 receptor agonist; IDeg, insulin degludec; iGlar, insulin glargine; Lira, liraglutide; Lixi, lixisenatide; U, unchanged.
vided for iGlarLixi (1,2). Antibody development has been noted for the individual components in both FRCs; clinical significance is unknown at this time (1,2). Attenuated glycemic response and a higher incidence of allergic reactions were seen in patients on lixisenatide with elevated antibody concentrations (1). Cost may also be a hindrance (10).

**Cost**

Both FRCs are supplied as 3-mL prefilled pens. The wholesale acquisition cost for five pens of iGlarLixi is $635 and for IDegLira is $953 (10). Using a mid-dose range of 35 units for a 30-day supply, the FRCs cost less than the combined costs of their component agents at the corresponding available doses (Table 2) (10). However, it is difficult to make direct comparisons because the individual GLP-1 receptor agonist products are supplied as fixed amounts per dose.

**Commentary**

LixiLan-O and LixiLan-L examined the effects of iGlarLixi over 30 weeks (Table 1) (3,4). Patients were insulin-naive in LixiLan-O and insulin-experienced in LixiLan-L. A run-in period was conducted in both trials, during which all oral antidiabetic agents (OADs) except metformin were discontinued. Patients receiving iGlarLixi achieved a statistically significant greater reduction in mean A1C from baseline compared to each individual agent. Additionally, a larger proportion of patients achieved an A1C <7.0%. Similar proportions of serious adverse effects were observed between comparison groups (~4–5%). Weight loss was achieved in patients on iGlarLixi. Conversely, weight gain was seen in patients on insulin glargine. Rates of hypoglycemia were comparable between patients on iGlarLixi and insulin glargine. GI adverse effects were greater in patients on iGlarLixi compared to those on insulin glargine but less compared to those taking lixisenatide alone (3,4).

IDegLira has been examined in five pivotal clinical trials (5–9). Patients taking IDegLira alone experienced fewer than patients on liraglutide (5–9). Novo Nordisk, November 2016. [Insulin glargine (Xultophy®) injection, for subcutaneous use [product information]. Plainsboro, N.J., Sanofi-Aventis, November 2016. [Insulin degludec and liraglutide (SoliquaTM) injection, for subcutaneous use [product information]. Bridgewater, N.J., Sanofi-Aventis, November 2016. [Insulin glargine and lixisenatide (SoliquaTM) injection, for subcutaneous use [product information]. Bridgewater, N.J., Sanofi-Aventis, November 2016.

**Bottom Line**

These agents are approved for patients not meeting target A1C goals on basal insulin or the respective GLP-1 receptor agonist alone. FRCs offer another option to patients with type 2 diabetes with inadequate glycemic control, especially for those desiring a simplified method of treatment intensification to improve adherence. FRCs are titratable based on the basal insulin dose. Previous basal insulin therapy should be discontinued before initiation of an FRC (1,2). Prandial insulin has not been studied with these agents. The use of FRCs provides the benefits of greater efficacy with blood glucose control and weight loss while decreasing the risk of principal side effects associated with each individual agent (i.e., hypoglycemia with insulin therapy and GI adverse effects with GLP-1 receptor agonists).

**Duality of Interest**

No potential conflicts of interest relevant to this article were reported.

**References**

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GOOD TO KNOW

Information from the American Diabetes Association for people with diabetes
Preventing or Delaying Kidney Disease

If you have diabetes, you’re at risk for kidney disease, also called diabetic nephropathy. In fact, diabetes is the leading cause of kidney failure. But there are things you can do to prevent, delay, or treat kidney disease, including keeping blood glucose (sugar) and blood pressure on target.

What do my kidneys do?
Your kidneys clean your blood by constantly filtering it through millions of tiny blood vessels. They remove unwanted substances from your blood, such as extra fluid and the waste products made by normal processes within the body. Your kidneys perform other functions as well, such as helping to regulate blood pressure, stimulating your bone marrow to produce red blood cells, and helping your bones and your blood absorb calcium.

How can diabetes hurt my kidneys?
Frequent high blood glucose levels over the years can lead to changes in how the kidneys function. High blood glucose causes extra blood to flow through the filters, making the kidneys work harder than usual. Many people with diabetes have high blood pressure. High blood pressure in the kidneys’ tiny blood vessels also puts added strain on the kidneys. High blood glucose and blood pressure levels can lead to scarring inside the filters so they don’t work as they should.

Who gets kidney disease?
Not everyone with diabetes develops kidney disease. Factors that can influence kidney disease development include genetics, blood glucose control, and blood pressure. The better a person keeps diabetes and blood pressure under control, the lower the chance of getting kidney disease.

YOU CAN PREVENT OR DELAY KIDNEY DISEASE BY:
- keeping your blood pressure and blood glucose levels in the target range
- taking medications for diabetes and high blood pressure as prescribed
- having regular checkups and getting a kidney function check once a year
- losing just 10 to 15 pounds, if you are overweight, which can help you reach your blood glucose and blood pressure targets