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# FIXED-RATIO COMBINATIONS: A RELATIVELY NOVEL, ALBEIT SIMPLE APPROACH TO INTENSIFYING BASAL INSULIN

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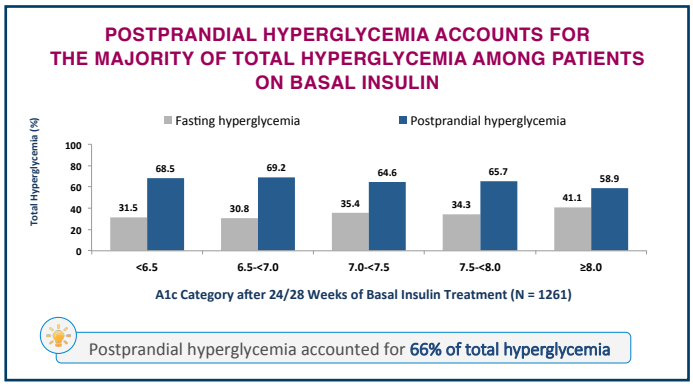
Type 2 diabetes is a progressive condition. Due to a decline in beta cell function over time, many patients will eventually require insulin therapy to maintain adequate glycemic control. Insulin is often initiated in a stepwise approach, starting with long-acting basal insulin, and short-acting mealtime insulin is added subsequently. Although basal insulin is fairly effective in controlling fasting glucose levels, many patients will remain – or eventually become – suboptimally controlled due to postprandial glucose excursions. In fact, a pooled analysis of six studies by Riddle et al. revealed that among patients treated with basal insulin, postprandial hyperglycemia accounted for 66% of total hyperglycemia[1].




## Intensification Beyond Basal Insulin: Paradigm Change

Traditionally, postprandial hyperglycemia was treated by adding prandial insulin injections to either one meal ("basal-plus") or to 2-3 meals ("basal-bolus"). There are several disadvantages to this approach, including increasing the risk for hypoglycemia and weight gain, increasing the injection burden, and increasing the complexity of their diabetes management. These can all have deleterious effects on treatment adherence and quality of life. One potential strategy to mitigate these undesirable effects is to add a glucagon-like 1 receptor agonist (GLP-1 RA) instead of prandial insulin. These agents increase insulin secretion and inhibit glucagon secretion in a glucose-dependent manner, in addition to delaying gastric emptying and increasing satiety. The 2018 Diabetes Canada Guidelines mention that a GLP-1 RA should be considered before initiating or intensifying bolus insulin for patients inadequately controlled on basal insulin (Grade A recommendation)[2]. The rationale for prioritizing GLP-1 RAs over prandial insulin is the favourable effects of GLP-1 RA's on reducing body weight and lowering the risk of hypoglycemia. Basal insulin and

> **"among patients treated with basal insulin, postprandial hyperglycemia accounted for 66% of hyperglycemia"**

GLP-1 RAs have complementary modes of action, and can therefore address many of the pathophysiologic defects of type 2 diabetes. There are a number of GLP-1 RAs available, including two co-formulations with basal insulin in a fixed-ratio combination (FRC) approved by Health Canada: iDegLira (Xultophy®) and iGlarLixi (Soliqua®).

## Fixed-Ratio Combinations (FRCs)

There are several advantages to using a FRC as opposed to administering basal insulin and a GLP-1 RA separately. These include a convenient and simplified therapy (administered as a single daily injection using a single pen), a lower incidence of GI adverse effects, and a reduced cost.

iGlarLixi is a combination of insulin glargine 100 U/mL (Lantus®) and the GLP-1 RA lixisenatide (Adlyxine®) 33 µg/mL. iDegLira is a combination of insulin degludec 100 U/mL (Tresiba®) and the GLP-1 RA liraglutide (Victoza®) 3.6 mg/mL. At the present time, these FRCs are approved as an add-on for patients on basal insulin with inadequate glycemic control.

> **"iDegLira was found to have similar A1C reduction compared to basal-bolus therapy"**

## Studies on FRCs

In the LixiLan and DUAL clinical trial programs, FRCs have demonstrated improved glycemic efficacy compared to their individual components alone, similar risk of hypoglycemia compared to basal insulin alone, and superior tolerability compared with the standalone GLP-1 RA[3–7]. As well, iDegLira was found to have similar A1C reduction compared to basal-bolus therapy[8]. In all studies, a greater proportion of patients treated with FRC achieved target A1C of <7.0% compared with basal insulin or GLP-1 RA alone. Modest weight loss was observed with the FRCs in the majority of trials. The data for these studies are summarized in Table 1. No head-to-head studies have been conducted comparing the two approved FRCs. Therefore, we cannot make direct comparisons of these two agents due to different patient populations and study designs of the individual trials.

GLP-1 RAs are most commonly discontinued due to GI adverse events (AEs), namely nausea, vomiting and diarrhea[9]. The rate of GI AEs with FRCs is considerably lower than standalone GLP-1 RAs since the dose of FRC is titrated slower. Even patients with prior GLP-1 RA intolerance may tolerate FRC better than GLP-1 RAs alone.

> **"Even patients with prior GLP-1 RA intolerance may tolerate FRC better than GLP-1 RAs alone"**

## Who Should Avoid FRCs

It should be noted that FRCs are not appropriate for all patients. For instance, patients with a daily basal insulin dose >60 units would not be candidates for iGlarLixi since the pen administers insulin dosages of up to 60 units. Similarly, patients with a daily basal insulin dose >50 units would not be appropriate candidates for iDegLira since the pen administers insulin dosages up to 50 units. If such patients would benefit from basal insulin and GLP-1 RA combination therapy, they should take these agents as separate injections. Approximately 80% of patients on basal insulin take doses that fall within the range offered by FRC[14]. Like GLP-1 RA, FRCs are contraindicated for patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN 2). FRCs have not been studied in patients with a history of pancreatitis, so alternative agents should be considered[15,16].

**TABLE 1. SUMMARY OF KEY FIXED-RATIO COMBINATION TRIALS**

| Study | Treatment arm | MeanA1C reduction | Weight change (kg) | Incidence of hypoglycemia (% of patients) | Rate of Nausea (%) |
|---|---|---|---|---|---|
| Lixi-Lan-O[4] | iGlarLixi | 1.6 | -0.3 | 26 | 9.6 |
| | iGlar | 1.3 | +1.1 | 24 | 3.6 |
| | Lixi | 0.9 | -2.3 | 6 | 24 |
| Lixi-Lan-L[3] | iGlarLixi | 1.1 | -0.7 | 40 | 10.4 |
| | iGlar | 0.6 | +0.7 | 42.5 | 0.5 |
| Lixi-Lan-G | iGlarLixi | 1.0 | +1.9 | 24 | 8.6 |
| | GLP-1 RA | 0.4 | -1.1 | 1 | 2.3 |
| Dual-I[6] | iDegLira | 1.9 | -0.5 | 32 | 9 |
| | iDeg | 1.4 | +1.6 | 39 | 4 |
| | Lira | 1.3 | -3.0 | 7 | 20 |
| Dual II[5] | iDegLira | 1.9 | -2.7 | 24 | 6.5 |
| | iDeg | 0.9 | 0 | 25 | 3.5 |
| Dual III[10] | iDegLira | 1.3 | +2.0 | n/a | 3.1 |
| | GLP-1 RA | 0.3 | -0.8 | n/a | 4.1 |
| Dual VII[8] | iDegLira | 1.5 | -0.9 | 19.8* | 11.1 |
| | IGlar U100 + iAsp | 1.5 | +2.6 | 52.6* | 1.6 |

*severe of BG-confirmed symptomatic hypo

## Cardiovascular Safety

FRCs have not been subjected to cardiovascular (CV) outcomes trials; however, their individual components have. Glargine was found to have a neutral effects on CV outcomes in the ORIGIN trial, while degludec was found to be noninferior to glargine in the DEVOTE trial[17,18]. For the GLP-1 RA components, lixisenatide was found to be neutral in the ELIXA trial, while liraglutide demonstrated CV superiority in the LEADER trial[19,20].

## A TYPICAL PATIENT

**Charles: T2DM for 10 years**

- **Age: 52**
- **BMI:** 26 Kg/m$^2$
- **Current A1C:** 9.1%
- **Recent FBGs:** 7-9 mmol/L
- **Recent PPGs:** 11-17 mmol/L
- **Diabetes-related comorbidities:**
  - UACR 6.8 mg/mmol
  - eGFR 82 ml/min/1,73 m$^2$
- **BP:** 128/80 mmHg
- **LDL-C:** 1.8 mmol/L

**Oral Medications**:
- Metformin 1000 mg BID
- Gliclazide MR 120 mg
- Empagliflozin 25 mg
- On statin therapy and ACEi

**Injectables:**
- Gla-100 32 U daily

**Additional details:**

- **No CVD**
- Privately **insured**
- **Steadily gaining weight** since initiating basal insulin (about 3.5 Kg)
- Reluctant to up-titrate basal insulin due to **concerns over weight gain and hypoglycemia**
- Overwhelmed by **polypharmacy** and increasing **regimen complexity. Very discouraged**
- Not keen on **more injections**
- **Prior intolerance** to once-daily GLP-1 RA

**What is your next step?**

A. **Titrate up his basal insulin**

B. **Change Metformin to a DPP-4i/ Metformin fixed-dose combination**

C. **Add prandial insulin**

D. **Initiate a once-weekly GLP-1 RA**

E. **Initiate a Fixed ratio combination of Basal insulin/GLP-1RA**

## Simultaneously Dosing Insulin and a GLP-1 RA in One Pen

With respect to dose escalation of FRCs, the dosing is based on the insulin (and not the GLP-1 RA) component, and similarly the dosing window on the pen corresponds to the insulin dose. Therefore, it is important to explain to patients that when dosing their FRC, they only need to focus on the insulin dose being administered, with the GLP-1 RA "coming along for the ride". The ratio of GLP-1 RA to basal insulin is fixed, and therefore the insulin and GLP-1 RA component will increase or decrease in a proportional manner when titrating.

## Initiating FRCs

Once a patient initiates a FRC, they should discontinue their basal insulin (and GLP-1 RA if they are already taking one). If a patient is taking a DPP-4 inhibitor, this agent should also be discontinued since they will now be taking a much more potent incretin in the GLP-1 RA.

For patients taking <30 units of basal insulin, the starting dose of iGlarLixi should be 15 units[15]. If taking ≥30 units, then the starting dose of iGlarLixi should be 30 units. Administration of iGlarLixi should be within 1 hour prior to the first meal of the day . A short half-life of lixisenatide (2-4 hours) has a predominant effect on postprandial glucose. The dose of iGlarLixi should be titrated upwards or downwards by 2-4 units every week if the fasting glucose is above or below the desired target, respectively[15].

The starting dose of iDegLira is 16 units, regardless of the patient's prior dose of basal insulin[16]. Titration (upwards or downwards) should occur in 2 unit increments every 3-4 days based on target fasting glucose[16]. iDegLira may be administered at any time of day (since liraglutide has a longer half-life of 13 hours and exerts effects on both the postprandial and fasting glucose values), though it is recommended to administer it consistently each day[16].

## Deciding Between Basal Insulin + Once Weekly GLP-1 RA vs. a FRC

Today, there are more patients treated with basal insulin plus a once-weekly GLP-1 RA, such as dulaglutide (Trulicity®) or semaglutide (Ozempic®) compared to FRCs. The injection burden of a basal insulin plus once-weekly GLP-1 RA is still comparable, with one daily injection on six days of the week, and two injections only once weekly. In Ontario and Alberta at the time of this Clinical Practice Update publication,the once-weekly GLP-1 RA, semaglutide, is covered under the respective provincial formulary. From a practical standpoint, there are two key situations where I favour a FRC. The first is if the patient's BMI is not particularly elevated (e.g. <27 kg/m2) and robust weight loss is not being sought. Although the vast majority of patients with type 2 diabetes are overweight or obese,13% of patients with type 2 diabetes are lean (BMI <25 kg/m2)[21]. The second scenario where I would favour a FRC is if my patient has a predilection for GI AEs, given the superior tolerability of FRCs.

## Summary

Although there several approaches to intensifying basal insulin, using a basal insulin/GLP-1 RA FRC is a relatively simple and effective way to achieve target A1C levels in the appropriate patient. By making use of a single daily injection, patients can conveniently intensify their treatment by focusing on only their fasting glucose levels. FRCs offer the distinct advantage of improving A1C without the increased risk of hypoglycemia and weight gain associated with basal-bolus therapy, and with fewer GI AEs compared with a stand-alone GLP-1 RA. Given these favourable attributes, patients are likely to remain adherent with their therapy, thereby achieving better long-term glycemic control.

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# MAKING SENSE OF WEIGHT MANAGEMENT – UNDERUTILIZED TREATMENT OPTIONS

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## WHY IS THIS IMPORTANT FOR MY PRACTICE?

Obesity is a chronic progressive disease that affects one in three of your patients in Canada. It is a complex and multifactorial condition that is often related to multiple risk factors, including genetics, environmental, socioeconomic, biological and behavioural factors.

Obesity is the leading cause of type 2 diabetes, hypertension, and fatty liver disease, in addition to being associated with certain cancers, mental illness, and infertility that impact mortality, morbidity and quality of life. A modest weight loss of about 5-10% is effective in reducing many health related consequences of obesity. However, due to adaptive changes in both central appetite control centers and adaptations in response to weight loss, behavioural modification alone is often not enough to maintain long-term weight reduction.

There are three modalities of treatment for obesity including behavioural and psychological management, pharmacotherapy, and bariatric surgery. Bariatric surgery remains the gold standard treatment for long-term success with weight management, and has even demonstrated a mortality benefit. Pharmacotherapy is an effective tool to help more of our patients achieve and maintain clinically significant weight reduction long-term.

## WHAT ARE THE DIFFERENT PHARMACOTHERAPY OPTIONS AVAILABLE IN CANADA?

| MEDICATION | MECHANISM OF ACTION | DOSE | EFFICACY | TOLERABILITY | CONTRAINDICATIONS |
|---|---|---|---|---|---|
| **Orlistat** (Xenical®) | Gastrointestinal Lipase Inhibitor (decreases fat absorption) | 120mg po TID with meals | ~3% | Fecal urgency, stool incontinence, oily spotting, reduced absorption of fat soluble vitamins | Chronic malabsorption, cholestasis, hypersensitivity |
| **Liraglutide** (Saxenda®) | GLP1 recent agonist (increases satiety, delays gastric emptying) | 0.6mg SC daily, increase by 0.6mg per week until target 3.0 SC daily is reached | 4-5.4% | Nausea, vomiting, diarrhea, constipation, dyspepsia, headache, hypoglycemia (with use of concomitant medicaitons that cause hypoglycemia (ex. SU) | Personal/Family history of MEN2, medullary thyroid cancer, pregnancy, hypersensitivity |
| **Naltrexone HCl/Buproprion HCl (Contrave®)** | Opiod receptor antagoinist/ Aminoketone antidepressant (decreases cravings from the mesolimbic reward system, decreases hunger | 8/90mg (1 tablet) po daily, increase by 1 tablet per week until target dodse of 2 tab po BID is reached | 3.3-4.8% | Nausea, vomiting, diarrhea, dry mouth, insomnia | Uncontrolled hypertension, seizures, bulimia/anorexia nervosa, concomitant use of bupropion, opioids, MAOI, abrupt discontinuation of alcohol/sedatives/ anti epileptics, severe hepatic/renal impairment, pregnancy, hypersensitivity |

Consider pharmacotherapy (Table) for patients with a BMI≥ 30 or a BMI≥ 27 with an obesity-related comorbidity when behavioural modification has been unsuccessful.

## WHEN SHOULD I REFER MY PATIENT?

Management of obesity is complex and should ideally be in a multidisciplinary care setting. A referral can be considered for patients that have multiple comorbidities or complications, patients who remain refractory to treatment, in the case of unfamiliarity with available treatment options, or due to inadequate time/resources for behavioural or nutritional counselling.



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