ABSTRACT

Treatment of type 2 diabetes (T2D) requires progressive therapy intensification to reach and maintain individualized glycemic targets. iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL (iGlar) and lixisenatide (Lixi), has been shown to provide robust HbA1c reductions allowing more people to reach HbA1c targets compared with separate administration of iGlar or Lixi. The purpose of this review is to help clinicians understand treatment intensification using iGlarLixi by presenting typical clinical scenarios supported by research evidence. These cases will focus on individuals with T2D inadequately controlled by oral antihyperglycemic drugs, basal insulin, or glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and take into consideration T2D duration, body mass index, incidence of adverse events, and regimen simplicity. Clinical evidence on the efficacy, effectiveness, and safety of iGlarLixi from randomized controlled trials and real-world studies will be discussed in the context of these cases.

Keywords: Fixed-ratio combination; GLP-1 RA; Glycemic control; Insulin therapy; Type 2 diabetes
Due to the progressive nature of type 2 diabetes (T2D), many people eventually require therapy advancement with either a basal insulin or a glucagon-like peptide-1 receptor agonist (GLP-1 RA), with further advancement requiring combination therapy with these two injectables [1, 2].

Because T2D has a multifaceted pathophysiology, combination therapy is likely to be more effective than therapy with a single agent [3].

Fixed-ratio combinations (FRCs) of basal insulin and GLP-1 RAs can provide a simplified combination therapy regimen.

iGlarLixi, an FRC of the basal insulin glargine 100 U/mL and the GLP-1 RA, lixisenatide, is approved for use in people with T2D, and has been shown to help more people reach glycemic targets compared with its individual components, while providing similar hypoglycemia risk to basal insulin and fewer gastrointestinal adverse events compared with lixisenatide [4–6].

This review discusses clinical evidence and real-world data for efficacy/effectiveness and safety of iGlarLixi applied in the management of typical case studies.

INTRODUCTION

Near normoglycemic control with individualized targets is a primary therapeutic goal for reducing the risk of micro- and macrovascular complications associated with type 2 diabetes (T2D) [1, 2]. Current consensus from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend a glucagon-like peptide-1 receptor agonist (GLP-1 RA) as the first injectable therapy in people with T2D inadequately controlled on combination oral agents, with the addition of basal insulin therapy as needed [3, 4]. Indeed, given the progressive nature of T2D, intensification to injectable therapies such as GLP-1 RAs and basal insulin is often required over time to maintain or improve glycemic control, with further intensification involving basal insulin and GLP-1 RA combination therapy [3, 4]. However, real-world evidence (RWE) suggests that less than 60% of individuals with T2D reach an HbA1c target of <7% within 12 months of initiating either GLP-1 RA or basal insulin [5].

T2D has a complex clinical presentation that requires individualized, patient-specific treatment. The multifaceted pathophysiology of T2D means that, in some individuals, combining the complementary actions of each individual therapy to simultaneously target distinct physiological pathways could potentially be more effective than therapy with a single agent. Basal insulin primarily reduces fasting plasma glucose (FPG) through inhibition of overnight hepatic glucose production [6]. GLP-1 RAs improve glycemic control by glucose-dependent stimulation of insulin release, suppression of glucagon secretion, and, in the case of short-acting GLP-1 RAs, delaying gastric emptying which has a pronounced postprandial glucose (PPG)-lowering effect following administration [7]. GLP-1 RAs also prevent or reduce weight gain while having a low risk of hypoglycemia [8].
Using a fixed-ratio combination (FRC) of basal insulin and GLP-1 RA may provide a simplified, more acceptable approach than separate administration of either component [9]. Currently, two FRCs have been approved for treatment of T2D: iGlarLixi, a once-daily titratable FRC of basal insulin glargine 100 U/mL (iGlar) plus lixisenatide (Lixi) [9–11]; and IDegLira, a once-daily titratable FRC of insulin degludec (IDeg) plus liraglutide (Lira) [12, 13]. The safety and efficacy of iGlarLixi and IDegLira were assessed in the LixiLan and DUAL randomized controlled trial programs. Briefly, both iGlarLixi and IDegLira demonstrated greater glycemic control compared with their individual components alone, while demonstrating good safety and tolerability profiles [14–18]. Details of the LixiLan trials are provided in Table 1 [14, 15, 18]. iGlarLixi is available in the US as the Soliqua® 100/33 pen (Sanofi, Paris), in which each unit of iGlar is given with 0.33 µg of Lixi and that delivers iGlar doses ranging from 15 to 60 U in combination with Lixi from 5 to 20 µg [10]. In Europe, iGlarLixi is available as two pens: the first pen (Suliqua® 10–40 [Sanofi]), contains 0.50 µg of Lixi per unit of iGlar and delivers doses between 10 and 40 dose steps (10–40 U iGlar in combination with 5–20 µg Lixi); the second pen (Suliqua® 30–60 [Sanofi]), contains 0.33 µg of Lixi per unit of iGlar and delivers doses between 30 and 60 dose steps (30–60 U iGlar in combination with 10–20 µg Lixi) (Tables 2, 3) [11].

The aim of this review is to examine iGlarLixi efficacy and safety in clinical scenarios based on typical profiles of people with T2D to help inform treatment decisions in various situations. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

**Case 1: Inadequately controlled (HbA1c > 8–< 9%) on OAD therapy**

**Clinical profile**

Name: Michael  
Age: 60 years  
Diabetes duration: 12 years  
BMI*: 32 kg/m²  
Laboratory results: HbA1c: 8.5%; Creatinine: 1.2 mg/dL; eGFRb: 65 mL/min/1.73 m²  
Previous medical history: hypertension, dyslipidemia controlled with therapy  
Current medication: metformin + empagliflozin/linagliptin fixed-dose combination + hydrochlorothiazide + lisinopril + atorvastatin

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**Case History**

Michael has an HbA1c of 8.5%, despite losing 3 kg through diet and appropriately prescribed physical activity in the last 6 months. Michael’s clinician had previously intensified his therapy by adding a GLP-1 RA to his background of metformin and sulfonylurea (glipizide); however, GLP-1 RA therapy was stopped after experiencing GI AEs. At his most recent appointment, Michael’s sulfonylurea was stopped and replaced with a fixed-dose combination of a sodium-glucose co-transporter-2 inhibitor (SGLT2i) (empagliflozin) and a dipeptidyl peptidase-4 inhibitor (DPP-4i) (linagliptin) to simplify his treatment, while improving the likelihood of continued weight loss, decreasing the risk of hypoglycemia, and providing additional renal protection [3]. Michael’s HbA1c subsequently dropped to 7.6% but did not reach his target of <7%, fluctuating between 7.6% and 7.9%. He recognizes that his HbA1c is greater than it should be but is reluctant to initiate basal insulin due to concerns about potential weight gain, despite his clinician recommending this...
**Table 1** Summary of the trials in the LixiLan program [14, 15, 18]

| Study     | Eligibility criteria                                                                 | Run-in                                                                 | Randomization                          | Key results                                                                 | Main outcome                                                                 |
|-----------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------|----------------------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| LixiLan-O [18] | Insulin-naı ¨ve adults (≥ 18 years) with T2D diagnosed ≥ 1 year prior to screening | The second OAD was discontinued at the start of the 4-week run-in period, during which met dose was optimized (≥ 1500 mg/day) | Those with an HbA1c ≥ 7.0% to ≤ 10.0% and FPG ≤ 250 mg/dL at the end of the run-in period were randomized 2:2:1 to receive iGlarLixi, iGlar, or Lixi for 30 weeks | HbA1c change was greater with iGlarLixi (−1.6%) compared with iGlar (−1.3%) or Lixi (−0.9%; both p < 0.0001); with final LS mean HbA1c values of 6.5%, 6.8%, and 7.3%, respectively | Participants with T2D inadequately controlled on OADs demonstrated meaningful HbA1c reductions without increases in hypoglycemia compared with iGlar and had low GI AEs compared with Lixi. Additionally, combined iGlar and Lixi treatment prevented the weight gain previously observed with basal insulin therapy alone |
|           | Inadequate glycemic control despite treatment with met ± another OAD for ≥ 3 months |                                                                      |                                        | A greater proportion of participants reached HbA1c < 7% (< 53 mmol/mol) with iGlarLixi (7%) versus iGlar (5.9%) or Lixi (3.3%; p < 0.0001 for all) |                                                                                           |
|           | HbA1c ≥ 7.5% to ≤ 10.0% for participants on met alone                                |                                                                      |                                        | Mean body weight change was − 0.3 kg with iGlarLixi, − 2.3 kg with Lixi, and + 1.1 kg with iGlar (between-treatment difference for iGlarLixi vs iGlar, p < 0.0001) |                                                                                           |
|           | HbA1c ≥ 7.0% to < 9.0% for participants treated with met and a second OAD          |                                                                      |                                        | Incidence of documented symptomatic hypoglycemia (≤ 70 mg/dL [3.9 mmol/L]) was similar between iGlarLixi and iGlar (2.6%) and 24.0%, respectively, but lower with Lixi (6.0%) |                                                                                           |
|           |                                                                      |                                                                      |                                        | Fewer participants reported GI AEs with iGlarLixi (nausea, 9.6%; vomiting, 3.2%; diarrhea, 9.0%) versus Lixi (nausea, 24.0%; vomiting, 6.4%; diarrhea, 9.0%) |                                                                                           |
| Study    | Eligibility criteria                                                                                                                                                                                                 | Run-in                                                                                                                                                                                                                     | Randomization                                                                                                                                                                                                 | Dose titration                                                                                                                                                                                                 | Key results                                                                                                                                                                                                                      | Main outcome                                                                                                                                                                                                                     |
|----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| LixiLan-L [14] | Adults (≥ 18 years) with T2D diagnosed ≥ 1 year prior to screening Treated with basal insulin for ≥ 6 months prior to screening, stable regimen for ≥ 3 months, plus up to two OADs (met, SU, glinide, SGLT2i, or DPP-4i) FPG ≤ 180 mg/dL for participants on basal insulin + 2 OADs or one OAD other than met FPG ≤ 200 mg/dL for participants on basal insulin ± met | OADs except met were discontinued during a 6-week run-in period, during which time participants were switched to iGlar (if they had previously received a different BI), and the daily dose was optimized | Those with HbA1c of 7–10%, mean fasting SMPG ≤ 140 mg/dL, daily iGlar dose 20–50 U, calcitonin ≤ 20 pg/mL, amylase/lipase levels < 3 × upper limit of normal at the end of the run-in period were randomized 1:1 to receive iGlar/Lixi or iGlar for 30 weeks | In all studies, the titration target was an SMPG of 80–100 mg/dL, while avoiding hypoglycemia. The maximum daily dose was 60 U iGlar/20 μg Lixi | HbA1c change was greater with iGlar/Lixi (−1.1%) compared with iGlar (−0.6%), with final LS mean HbA1c values reaching 6.9% and 7.5% (p < 0.0001) | Participants with T2D inadequately controlled on basal insulin demonstrated improved glycemic control with a beneficial effect on body weight, no additional risk of hypoglycemia, and low levels of GI AEs |

- **ΔAIs**

- **Adv Ther (2021) 38:1715–1731**
| Study         | Eligibility criteria                                                                 | Run-in                                      | Randomization                                    | Dose titration                     | Key results                                                                 | Main outcome                                                                 |
|--------------|---------------------------------------------------------------------------------------|---------------------------------------------|--------------------------------------------------|------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| LixiLan-G[15]| Adults (≥ 18 years) with T2D diagnosed ≥ 1 year prior to screening<br>Insufficient glycemic control (HbA1c ≥ 7.0% to ≤ 9.0%)<br>Despite treatment with a GLP-1 RA for ≥ 4 or ≥ 6 monthsa<br>prior to screening plus<br>met ± pioglitazone, ± SGLT2i | None                                        | Randomized 1:1 to continue current GLP-1 RA treatment or switch to iGlarLixi for 26 weeks | In all studies, the titration target was an SMPG of 80–100 mg/dL, while avoiding hypoglycemia. The maximum daily dose was 60 U iGlar/20 μg Lixi | HbA1c change was greater with iGlarLixi (−1.0%) compared with GLP-1 RA (−0.4%), with final LS mean HbA1c values of 6.7% and 7.4% (p < 0.001) | Participants with T2D inadequately controlled on a maximum tolerated dose of a GLP-1 RA plus OADs demonstrated improved glycemic control with iGlarLixi |

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DPP-4: dipeptidyl peptide-4 inhibitor; FPG: fasting plasma glucose; GI: gastrointestinal adverse event; GLP-1: glucagon-like peptide-1 receptor agonist; HbA1c: glycated hemoglobin; iGlar: insulin glargine 100 units/mL; iGlarLixi: once-daily titratable fixed-ratio combination of basal insulin glargine 100 units/mL and the GLP-1 RA, Lixi; Lixi: lixisenatide; met: metformin; OAD: oral antihyperglycemic drug; PPY: per patient year; SGLT2: sodium–glucose cotransporter-2 inhibitor; SMPG: self-measured plasma glucose; SU: sulfonylurea; T2D: type 2 diabetes; U: units

a: ≥ 4 months for liraglutide or exenatide; ≥ 6 months for exenatide extended-release, dulaglutide, or albiglutide
treatment strategy on several occasions. He is also hesitant to reinitiate GLP-1 RA therapy alone due to his previous experience of GI AEs.

Research Evidence

In the LixiLan-O trial, greater reductions in HbA1c from baseline were achieved with iGlarLixi compared with iGlar (−1.6% vs. −1.3%, respectively; \( p < 0.0001 \)) or Lixi (−1.6% vs. −0.9%, respectively; \( p < 0.0001 \)) [18]. Additionally, iGlarLixi treatment enabled more participants to reach a target HbA1c < 7% than iGlar (74% vs. 59%, respectively; \( p < 0.0001 \)) or Lixi (74% vs. 33%, respectively; \( p < 0.0001 \)), while providing a more favorable weight change profile than iGlar (iGlarLixi, −0.3 kg; iGlar, +1.1 kg) but not Lixi (−2.3 kg), over 30 weeks of therapy [18]. A post hoc analysis of the LixiLan-O study comparing glycemic outcomes and weight gain in subgroups of participants with HbA1c < 8.0% and BMI < 30 kg/m², showed that iGlarLixi provided greater HbA1c reductions and higher glycemic target achievement compared with iGlar or Lixi alone, without weight gain or increasing documented symptomatic hypoglycemia (≤ 70 mg/dL) [19].

Michael’s current medication includes the SGLT2i empagliflozin. SGLT2i have been shown to provide a cardio- and reno-protective benefit

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### Table 2 iGlarLixi ratios and recommended starting doses in the US [10]

| Dose ratio in pen \(^a\) | Previous therapy \(^b\) | 30–60 U of basal insulin |
|-------------------------|------------------------|-------------------------|
| 100 U iGlar + 33 μg Lixi | 15 U (15 U iGlar + 5 μg Lixi) | 30 U (30 U iGlar + 10 μg Lixi) |

\( GLP-1 \) RA glucagon-like peptide-1 receptor agonist; \( iGlar \) insulin glargine 100 U/mL; \( Lixi \) lixisenatide; \( U \) units

\( ^a \) Maximum daily dose of iGlarLixi is 60 U (60 U iGlar + 20 μg Lixi)

\( ^b \) Prior GLP-1 RA and basal insulin use must be discontinued before initiating iGlarLixi therapy

\( ^c \) Patients may or may not also have been using a GLP-1 RA

### Table 3 iGlarLixi ratios and recommended starting doses in Europe [11]

| Dose ratio in pen \(^a\) | Previous therapy \(^b\) |
|-------------------------|-----------------------|
| 100 U iGlar + 50 μg Lixi | Insulin-naïve |
| 10 dose steps (10 U iGlar + 5 μg Lixi) | iGlar ≥ 20– < 30 U \(^c\) |
| 20 dose steps (20 U iGlar + 10 μg Lixi) | iGlar ≥ 30– ≤ 60 U \(^c\) |

\( GLP-1 \) RA glucagon-like peptide-1 receptor agonist; \( iGlar \) insulin glargine 100 U/mL; \( Lixi \) lixisenatide; \( U \) units

\( ^a \) Maximum daily dose of iGlarLixi is 60 U (60 U iGlar + 20 μg Lixi)

\( ^b \) Therapy with basal insulin, GLP-1 RA or OAD other than metformin or SGLT2i should be discontinued prior to initiating therapy with iGlar/Lixi

\( ^c \) If switching from twice-daily basal insulin or insulin glargine 300 U/mL, the total daily dose previously used should be reduced by 20% to choose the appropriate starting dose of iGlarLixi. For any other basal insulin, the starting dose recommendations made for iGlar also apply.
in people with T2D and are recommended for use in people with cardiovascular risk factors and renal impairment [3, 4]. It also contains linagliptin, a DPP-4i shown to have a good cardiovascular and renal safety profile [20]. A study which combined a post hoc analysis of the LixiLan-G trial and RWE from electronic healthcare records of people with T2D treated with OADs ± GLP-1 RAs showed similar glycemc control and comparable low hypoglycemia risk between subgroups of people who did or did not use SGLT2i [21]. Additionally, the iGlarLixi safety profile reflected the established safety profiles of iGlar and Lixi, but with fewer events of nausea and vomiting than Lixi alone, leading to fewer study discontinuations [18]. iGlarLixi, being an FRC, enables the Lixi dose to be gradually increased as the iGlar component is titrated, thus increasing gastrointestinal (GI) tolerance [18]. iGlarLixi is approved for use in the US for people with T2D inadequately controlled on basal insulin, GLP-1 RAs, and OADs [10]. In Europe, iGlarLixi is approved for use in people with T2D in addition to metformin with or without SGLT2i [11].

**Case Summary**

Recognizing his elevated cardiovascular risk and moderate renal impairment, Michael’s clinician initiated therapy with an SGLT2i and a DPP-4i using a fixed-dose combination of these two therapies. Michael’s glycemic control can be improved by initiating an FRC of basal insulin and GLP-1 RA. To continue his cardiovascular and renal protection, Michael’s fixed-dose combination of SGLT2i and DPP-4i should be replaced with a fixed-dose combination of metformin plus SGLT2i. Given that Michael has no history of insulin therapy, he should be initiated on the recommended starting dose for insulin-naïve individuals (Tables 2 and 3) with doses titrated weekly to reach and maintain his individualized fasting self-monitored plasma glucose (SMPG) target while avoiding hypoglycemia (see Table 4 for a recommended titration algorithm). iGlarLixi may provide a suitable intensification option for Michael as it can improve glycemic control compared with initiation of basal insulin alone [19, 22], and has been shown to provide comparable safety and efficacy regardless of SGLT2i use [21]. The gradual increase in GLP-1 RA dose as the basal insulin component is titrated should help to reduce the risk of renewed GI AEs [18]. Finally, iGlarLixi also decreases the likelihood of further weight gain compared with basal insulin therapy; this could address Michael’s fears of undoing the weight loss progress he has achieved through diet and exercise. Recognizing Michael’s concerns about weight gain and GI events, his clinician can use shared decision-making to reinforce the need for therapy intensification, while explaining the reduced risk of weight gain and GI events associated with iGlarLixi compared with basal insulin alone or GLP-1 RA alone.

**Table 4** Weekly recommended dose titration algorithm [10]

| Fasting SMPG          | Weekly dose titration algorithm [10]                      |
|----------------------|----------------------------------------------------------|
| Above target range   | + 2 U (2 U iGlar + 0.66 μg Lixi) to + 4 U (4 U iGlar + 1.32 μg Lixi) |
| Within target range  | 0 U                                                      |
| Below target range   | − 2 U (2 U iGlar + 0.66 μg Lixi) to − 4 U (4 U iGlar + 1.32 μg Lixi) |

*Doses should be titrated every week based on the individuals fasting SMPG and individualized glycemic control goal until the desired FPG is achieved. To minimize the risk of hypoglycemia or hyperglycemia, additional titration may be needed with changes in physical activity; meal patterns; renal or hepatic function; during acute illness; or when used with other medications.
*SMPG self-measured plasma glucose; U units
Case 2: Inadequately controlled (HbA1c > 9%) on OAD therapy

Clinical profile

Name: Thomas
Age: 54 years
Diabetes duration: 3 years
BMI: 32 kg/m²
Laboratory results: HbA1c: 9.6%; Creatinine: 1.1 mg/dL; eGFR: 88 mL/min/1.73 m²
Previous medical history: Hypertension
Current medication:
  Metformin + empagliflozin + glimepiride

Case History

Thomas had been unable to achieve his individualized target HbA1c (<7%) with OADs alone, with his current medication consisting of metformin with an SGLT2i (empagliflozin) and a sulfonylurea (glimepiride). He has not been consistent with his medications and has a sedentary life. Thomas is aware that his HbA1c is >2% above target and will require treatment intensification.

Research Evidence

The recommended treatment for people with T2D inadequately controlled on OADs with no established atherosclerotic cardiovascular disease, renal disease, or heart failure is sequential intensification to injectable therapy with GLP-1 RAs or basal insulin when HbA1c is >9% or >10%, with the ADA currently recommending a GLP-1 RA as the first injectable for most individuals [3, 4]. However, this alone may be insufficient for reaching glycemic goals in people with high initial HbA1c levels. A pooled analysis of 16 RCTs indicated that 53.6% of people failing on OADs were unable to reach glycemic control (HbA1c < 7%) when initiated with basal insulin, even in controlled trial settings [23]. An RWE study showed that, among individuals with an HbA1c ≥ 9%, <25% obtained HbA1c < 7% within 12 months upon intensification with basal insulin or GLP-1 RA [5]. Conversely, another RWE study found that a larger proportion of participants reached glycemic control following initiation of GLP-1 RAs and basal insulin within 90 days of each other, compared with those who delayed initiation of the second injectable by >90 days [24]. Furthermore, RWE suggests that simultaneous initiation (within <30 days of one another) of GLP-1 RA and basal insulin increased the likelihood of reaching glycemic control compared with separate initiation [24].

The LixiLan-O trial noted a significantly greater proportion of participants reaching HbA1c < 7% following therapy with iGlarLixi (74%) compared with iGlar (59%) or Lixi (33%) alone (p < 0.0001 for both comparisons) [18]. iGlarLixi facilitated greater FPG reductions versus Lixi at week 30 with least squares (LS) mean (standard error [SE]) changes from baseline of −63 (2) mg/dL (−3.5 [0.1] mmol/L) vs. −27 (2) mg/dL (−1.5 [0.1] mmol/L). PPG reductions were also more substantial compared with iGlar, with LS mean (SE) changes from baseline of −103 (4) mg/dL (−5.7 [0.2] mmol/L) vs. −59 (4) mg/dL (−3.3 [0.2] mmol/L) [18]. In a post hoc analysis of the LixiLan-O trial in participants with HbA1c >9% and no history of injectable therapy, 74% of participants reached HbA1c < 7% with iGlarLixi, compared with 47% with iGlar, and 0% with Lixi, over the 30-week study period [25]. In participants with baseline HbA1c of ≥ 9%, HbA1c reductions were greater with iGlarLixi (2.9%) versus iGlar or Lixi (2.5% and 1.7%, respectively) [25].

Case Summary

For Thomas, immediate adoption of iGlarLixi may be a more efficacious treatment option than sequential addition of either GLP-1 RAs or
basal insulin. Given that Thomas has no history of insulin therapy, he should initiate iGlarLixi on the recommended starting dose for insulin-naive individuals (Tables 2, 3) with weekly dose titration (see Table 4 for a recommended titration algorithm) to reach and maintain his individualized fasting SMPG target while avoiding hypoglycemia. When initiating iGlarLixi therapy, Thomas’ physician should continue his metformin in addition to maintaining his SGLT2i therapy for cardiovascular and renal protection, but sulfonylurea treatment should be discontinued. With no history of injectable therapy and T2D inadequately controlled on OADs alone, FRC therapy could help Thomas reach his HbA1c target as early as possible. In turn, this would help to reduce cumulative glycemic exposure and potentially reduce cardiovascular disease complications [26].

Case 3: Intensification in people inadequately controlled (HbA1c > 7%) on basal insulin

### Clinical profile

Name: Jane

Age: 58 years

Diabetes duration: 10 years

BMI: 29 kg/m²

Laboratory results: HbA1c: 7.9%; Creatinine: 0.8 mg/dL; eGFR: 91/mL/min/1.73 m²

Previous medical history: Hypertension, hypothyroidism, depression currently well controlled on medications, infrequent non-severe hypoglycemia (< 70 mg/dL) in previous year

Current medication: Metformin + iGlar 38 U/day + lisinopril + atorvastatin + levothyroxine + escitalopram + dapagliflozin

Case History

Jane has been on basal insulin for 2.5 years and is still not reaching her HbA1c target (< 7%). She checks her blood glucose infrequently, and her FPG is typically 100–130 mg/dL; however, her PPG is usually greater than 200 mg/dL. Jane presents with no atherosclerotic cardiovascular or renal conditions other than hypertension, and has been started on an SGLT2i (dapagliflozin) to continue cardiovascular and renal protection. She claims to be under stress as a result of looking after her two young grandchildren, and considers her diabetes as an additional burden. She was advised to start prandial insulin, but she wishes to avoid the increased self-monitoring and injection requirements of basal bolus therapy and avoid further hypoglycemia and weight gain.

Research Evidence

Guidelines recommend intensification of basal insulin therapy in people unable to reach HbA1c targets, with addition of GLP-1 RA as the preferred therapy option [3, 4]. An RWE study indicated that if an individual has not reached HbA1c < 7% within 6–12 months despite basal insulin therapy, they are unlikely to do so without further intensification [5]. Furthermore, in a study of individuals with a mean baseline HbA1c of 9.1%, only 25% reached HbA1c < 7% by 6 months, a further 13% by 12 months (38% total), and 8% more by 2 years after basal insulin initiation (46% total), indicating a decreasing likelihood of reaching glycemic control over time if only basal insulin is used [27]. In the LixiLan-L trial, more participants in the iGlarLixi than the iGlar group reached HbA1c < 7% (55% vs. 30%, respectively; p < 0.0001) with no increase in body weight or hypoglycemia [14].

An exploratory analysis using propensity score matching (PSM) indirectly compared outcomes for people switching to iGlarLixi (simultaneous intensification) versus those who received sequential intensification with iGlar first followed by Lixi after either short-term basal insulin therapy (LixiLan-O [18] vs.
GetGoal Duo-1 in which participants had 12 weeks of iGlar therapy before intensification with Lixi [28]) or long-term basal insulin therapy (LixiLan-L [14] vs. GetGoal Duo-2 in which participants had received basal insulin therapy for ≥6 months before intensification with Lixi [29]) [22]. Results showed that iGlarLixi was associated with greater reductions in mean HbA1c after 24 weeks for both populations (p < 0.0001 for both). Specifically, for individuals with prior short-term therapy, mean HbA1c at week 24 was 7.0% following addition of Lixi only compared with 6.4% after switching to iGlarLixi. For individuals with long-term prior basal insulin therapy, mean HbA1c at week 24 was 7.3% following addition of Lixi and 6.8% with iGlarLixi. Furthermore, significantly greater proportions of participants reached HbA1c < 7% at week 24 (p < 0.0001 for both comparisons). For individuals intensified with Lixi following short-term basal insulin therapy, 51% reached target following addition of Lixi compared with 79% with iGlarLixi, while for those with long-term prior basal insulin therapy, 33% reached target following addition of Lixi versus 62% with iGlarLixi therapy. Furthermore, no increase of confirmed symptomatic hypoglycemia, defined as typical symptoms of hypoglycemia accompanied by an SMPG value of ≤ 70 mg/dL (≤ 3.9 mmol/L) was seen in those treated with iGlarLixi versus those with basal insulin therapy intensified with Lixi [short term: iGlarLixi, 0.38 events per patient-year (PPY) vs. iGlar + Lixi, 0.56 events PPY; long term: iGlarLixi, 0.66 events PPY vs. iGlar + Lixi, 0.74 events PPY], and lower incidence of GI AEs were seen with iGlarLixi versus addition of Lixi to basal insulin [22].

Post hoc analyses of the LixiLan-L study showed that the improved HbA1c target attainment seen with iGlarLixi versus iGlar was maintained regardless of baseline HbA1c at week 30 (≤ 8%: 74% vs. 37%; 8.0–< 9.0%: 55% vs. 32%; > 9.0%: 52% vs. 24%; p < 0.0001 for all) [30], T2D duration (< 10 years: 56% vs. 35%; ≥ 10 years: 54% vs. 26%; p < 0.0001 for both), and BMI (< 30 kg/m²: 58% vs. 28%; ≥ 30 kg/m²: 52% vs. 31%; p < 0.0001 for both) [31]. A further LixiLan-L post hoc analysis demonstrated that iGlarLixi provided significantly greater HbA1c reductions versus iGlar after 30 weeks of treatment across a spectrum of people with different durations of T2D, even in people with T2D with diabetes duration > 15.7 years [32]. Moreover, in these individuals who are at greater risk of hypoglycemia [33], results suggested that the event rate was lower with iGlarLixi compared with iGlar (3.3 vs. 6.9 events PPY; p < 0.0001); although the post hoc nature of this analysis means this finding should be interpreted with caution [32].

A post hoc PSM analysis of the LixiLan-L [14] and GetGoal Duo-2 [29] studies suggested that, compared with a basal bolus regimen, more participants reached HbA1c targets with iGlarLixi (24 weeks for iGlarLixi, 26 weeks for basal bolus; 55% vs. 37%, respectively; p = 0.0002) [34]. Body weight decreased with iGlarLixi treatment and increased with basal bolus treatment [LS mean (SE) – 0.62 kg (0.24) vs. +0.70 kg (0.24), respectively; p < 0.0001] [34]. Additionally, iGlarLixi was associated with lower rates of symptomatic documented hypoglycemia [≤ 54 mg/dL (< 3.0 mmol/L)] than basal bolus (0.68 vs. 1.94 events PPY, respectively; p < 0.0001); although this post hoc analysis was not sufficiently powered to test for these differences [34].

Residual hyperglycemia, defined as a HbA1c above target despite FPG at or near target, is a pattern associated with failure to reach glycemic targets in 24–54% of individuals with T2D, indicating a need for postprandial glycemic control [35]. iGlarLixi combination therapy facilitates PPG control through the action of Lixi in slowing gastric emptying [8], and FPG control through stimulation of glucose-lowering activity by iGlar [36]. In participants with HbA1c > 7% and FPG ≤ 130 mg/dL, iGlarLixi reduced the proportion of people with residual hyperglycemia more than iGlar alone after 30 weeks (24% of participants with residual hyperglycemia at week 30 with iGlarLixi vs. 47% with iGlar; p < 0.0001) [37].

Case Summary

iGlarLixi may be a suitable therapy option for Jane as it can improve HbA1c target...
achievement in people inadequately controlled on basal insulin therapy for more than 6 months. FPG levels of 100–130 mg/dL, despite HbA1c of 7.9%, demonstrate that HbA1c excursions may be being driven by post-meal elevations of blood glucose, which could be documented using glucose profiles in practice. As Jane is already not maintaining regular blood glucose measurements and expressed a desire not to increase self-monitoring and insulin injections, adding prandial rapid-acting insulin would be a choice that would not be consistent with her concerns. By switching Jane’s therapy to iGlarLixi, she can maintain a simple once-daily injection while potentially avoiding the increased risk of hypoglycemia or weight gain associated with advancing insulin therapy to a basal-bolus regimen. As Jane is currently receiving 38 U of iGlar daily, she should be initiated on 30 U of iGlarLixi using a pen containing 100 U iGlar and 33 μg Lixi to allow dose titration (see Tables 2, 3, 4 for recommended starting doses and titration) to reach and maintain her individualized fasting SMPG target while avoiding hypoglycemia and her current basal insulin therapy should be stopped. In addition, Jane’s SGLT2i therapy will be maintained to continue cardiovascular and renal protection.

### Case 4: Inadequately controlled (HbA1c > 7%) on GLP-1 RA therapy

#### Clinical profile

**Name:** Betty  
**Age:** 58 years  
**Diabetes duration:** 18.2 years  
**BMI:** 29.1 kg/m²  
**Laboratory results:** HbA1c: 7.9%; Creatinine: 0.95 mg/dL; eGFR: 66 mL/min/1.73 m²  
**Previous medical history:** Hypertension  
**Current medication:** Metformin + canagliflozin + GLP-1 RA (liraglutide)

### Case History

Previously, Betty had inadequate HbA1c control on OADs alone despite good treatment adherence. In response to an HbA1c of 9.2% 6 months ago, daily GLP-1 RA (liraglutide) was added, which is consistent with guideline recommendations for the first injectable agent to be a GLP-1 RA for most individuals. Despite intensification, Betty has been unable reach HbA1c < 7%, remaining at an HbA1c of 7.9%. Given her moderately impaired renal function, Betty has also been started on an SGLT2i (canagliflozin) for cardiovascular and renal protection.

### Research Evidence

GLP-1 RAs are recommended as the first injectable therapy for individuals with inadequate control on dual/triple OAD therapy [3, 4]. However, <25% of individuals on GLP-1 RAs with an HbA1c ≥ 9% reach an HbA1c of < 7%, indicating a need for further treatment intensification [5]. One possible reason for not reaching glycemic control could be due to insufficient β-cell function. Long-acting GLP-1 RAs primarily act through insulinotropic effects of GLP-1 receptors on β-cells (relying on adequate β-cell function) and reduction of glucagon secretion. However, Lixi primarily functions through inhibition of gastric emptying, which is independent of β-cell function [7]. A pooled analysis of phase 3 trials showed that Lixi effectively reduced HbA1c compared with placebo in older people (≥ 65 years and ≥ 75 years) who typically have a longer duration of T2D, suggesting efficacy in people with significant β-cell dysfunction [38].

The LixiLan-G study demonstrated that switching to iGlarLixi more effectively improved glycemic control than continued adherence to GLP-1 RA; 62% of participants reached their HbA1c target of < 7% with iGlarLixi, compared with 26% with GLP-1 RA (p < 0.0001) [15]. Additionally, 57% of the iGlarLixi group reached HbA1c < 7% without documented symptomatic hypoglycemia, compared with 25% of the GLP-1 RA group [15]. The incidence and rates of symptomatic
documented hypoglycemia (≤ 70 or < 54 mg/dL) were low with iGlarLixi (28% and 9%, respectively), but higher than in people continuing GLP-1 RA therapy (2% and < 1%, respectively), as expected when comparing an insulin-based therapy with a GLP-1 RA [15]. Additionally, iGlarLixi treatment significantly reduced FPG, PPG, and PPG excursions versus continuing GLP-1 RA therapy [15]. Fewer AEs were observed with GLP-1 RAs versus iGlarLixi, although the incidence of AEs with iGlarLixi was low. This was attributed to the initiation of a different GLP-1 RA versus continuation of an already stable GLP-1 RA regimen [15].

Subanalyses of the LixiLan-G study demonstrated that, compared with continued GLP-1 RA with adherence being actively monitored, iGlarLixi therapy consistently resulted in more individuals reaching HbA1c < 7% across groups with different T2D duration [39]. Furthermore, regardless of baseline HbA1c or previous GLP-1 RA administration (once- or twice-daily; once-weekly), iGlarLixi was associated with a mean HbA1c < 7% by the end of the 26-week study, whereas average HbA1c levels remained > 7% with GLP-1 RA [40].

Case Summary

iGlarLixi may provide a more suitable therapy option for Betty than adding basal insulin separately, as switching to iGlarLixi from GLP-1 RA therapy can provide significant improvements in glycemic control, regardless of baseline HbA1c, T2D duration, or type of previous GLP-1 RA therapy. As Betty also has no history of insulin therapy, she should be initiated on the dose recommended for insulin-naïve individuals (Tables 2, 3), while stopping her current GLP-1 RA therapy, and her dose titrated weekly to reach and maintain her individualized fasting SMPG while avoiding hypoglycemia (Table 4). As with any therapy containing insulin, care should be taken to ensure that Betty is properly educated on the risks of hypoglycemia and how to avoid this. Additionally, canagliflozin use should be maintained for continued cardiovascular and renal protection.

CONCLUSIONS

Due to its progressive nature, most people with T2D will eventually require treatment intensification with injectable therapies, specifically GLP-1 RAs and basal insulin [3, 4]. FRCs consisting of both basal insulin and GLP-1 RA can address the unmet medical need for targeting both FPG and PPG in a simplified regimen [36]. Two such FRCs are approved by the Food and Drug Administration and European Medicines Agency for the treatment of T2D, iGlarLixi and IDegLira [10–13]. The LixiLan clinical trials demonstrated robust glycemic benefits with iGlarLixi versus basal insulin or GLP-1 RA alone in individuals with or without a history of injectable therapy [14, 15, 18, 41]. Additionally, iGlarLixi mitigated the level of weight gain associated with initiation and titration of basal insulin and provided comparable risk of hypoglycemia compared with iGlar. Incidence of GI AEs were also lower with iGlarLixi compared with Lixi alone. iGlarLixi provided a good option for intensification of GLP-1 RA therapy [15], even in people with long-standing diabetes [32], who may have decreased β-cell function [42]. This may be due to the use of a short-acting GLP-1 RA (Lixi), whose primary mechanism of action is slowing of post-prandial gastric emptying rather than insulinotropic effects on β-cells (as is the case for long-acting GLP-1 RAs) [7, 43]. Recent evidence suggests that avoiding hyperglycemia improves cardiovascular outcomes in people with T2D [44]. Intensifying therapy in individuals inadequately controlled on their previous therapeutic regimens with iGlarLixi can provide robust glycemic reductions, including PPG reductions, while providing a similar hypoglycemia risk profile to that of basal insulin, and may potentially help improve cardiovascular outcomes in patients with T2D. In conclusion, the FRC of iGlar and Lixi provides a patient-centric, easy-to-use, treatment approach with robust glucose-lowering efficacy, a low incidence of hypoglycemia, and mitigation of weight gain and nausea compared with separate initiation of basal insulin or GLP-1 RA, respectively [9].
ACKNOWLEDGEMENTS

**Funding.** Funding for this study and the journal’s rapid service and open access fees was provided by Sanofi.

**Authorship.** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. Editorial assistance was provided by Cameron Hubert, PhD, of Fishawack Communications Ltd, and was funded by Sanofi. We thank Ana Merino-Trigo, PhD, (Sanofi) for coordinating the development, facilitating author discussions, and critical review of this manuscript.

**Disclosures.** Neil Skolnik reports receiving non-financial support from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Sanofi; and receiving personal fees and serving on advisory boards of AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Intarcia, Janssen Pharmaceuticals, Merck, Mylan, Sanofi, and Teva Pharmaceutical. Stefano Del Prato has been a consultant for AstraZeneca, Boehringer Ingelheim, Eli Lilly and Co, GlaxoSmithKline, Merck & Co, Novartis Pharmaceuticals, Novo Nordisk. Sanofi, Laboratoires Servier, and Takeda Pharmaceuticals; has received grant/research support from AstraZeneca, Boehringer Ingelheim, and Novartis Pharmaceuticals; and has been speaker for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novartis Pharmaceuticals, Novo Nordisk, Sanofi, and Takeda. Lawrence Blonde has been a consultant for AstraZeneca, Gilead Sciences, Janssen, Merck, Novo Nordisk, and Sanofi; has received grant/research support (including to his institution) from Janssen, Lexicon, Merck, Novo Nordisk, and Sanofi; and has been a speaker for Janssen, Novo Nordisk, and Sanofi. Gagik Galstyan has served on advisory boards for MSD, AstraZeneca, Novo Nordisk, Sanofi, Abbott, and Pfizer; and has been a speaker for Eli Lilly, Novo Nordisk, Sanofi, Novartis, Berlin Chemie, MSD, Boehringer Ingelheim, AstraZeneca, Amgen, LifeScan, Servier, and Takeda. Julio Rosenstock has been a consultant for Applied Therapeutics, Boehringer Ingelheim, Eli Lilly, Intarcia, Janssen, Novo Nordisk, Oramed, and Sanofi; and has received grant/research support from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Genentech, GlaxoSmithKline, Intarcia, Janssen, Lexicon, Merck, Novartis, Novo Nordisk, Oramed, Pfizer, and Sanofi.

**Compliance with Ethics Guidelines.** This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

**Data Availability.** Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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**REFERENCES**

1. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577–89.
2. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321:405–12.

3. American Diabetes Association. Standards of Medical Care in Diabetes—2020. Diabetes Care. 2020;43:S1-212.

4. Davies MJ, D’Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018;2018(41):2669–701.

5. Peng XV, McCrimmon RJ, Shepherd L, et al. Glycemic control following GLP-1 RA or basal insulin initiation in real-world practice: a retrospective, observational, longitudinal cohort study. Diabetes Ther. 2020. https://doi.org/10.1007/s13300-020-00905-y.

6. Sharabi K, Tavares CD, Rines AK, Puigserver P. Molecular pathophysiology of hepatic glucose production. Mol Aspects Med. 2015;46:21–33.

7. Meier JJ. GLP-1 receptor agonists for individualised treatment of type 2 diabetes mellitus. Nat Rev Endocrinol. 2012;8:728–42.

8. Christensen M, Miossec P, Larsen BD, Werner U, Knop FK. The design and discovery of lixisenatide for the treatment of type 2 diabetes mellitus. Expert Opin Drug Discov. 2014;9:1223–51.

9. Hinnen D, Strong J. iGlarLixi: A new once-daily fixed-ratio combination of basal insulin glargine and lixisenatide for the management of type 2 diabetes. Diabetes Spectr. 2018;31:145–54.

10. Soliqua US Prescribing Information. 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208673s000lbl.pdf. Accessed 26 Nov 2020.

11. Suliqua Summary of Product Characteristics. 2020. https://www.ema.europa.eu/en/medicines/human/EPAR/suliqua. Accessed 26 Nov 2020.

12. Xultophy Summary of Product Characteristics. 2020. https://www.ema.europa.eu/en/documents/product-information/xultophy-epar-product-information_en.pdf. Accessed 26 Nov 2020.

13. Xultophy US prescribing Information. 2020. https://www.novo-pi.com/xultophy10036.pdf. Accessed 26 Nov 2020.

14. Aroda VR, Rosenstock J, Wysham C, et al. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of insulin glarginie plus lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: the Lixilan-L randomized insulin trial. Diabetes Care. 2016;39:1972–80.

15. Blonde L, Rosenstock J, Del Prato S, et al. Switching to iGlarLixi versus continuing daily or weekly GLP-1 RA in type 2 diabetes inadequately controlled by GLP-1 RA and oral antihyperglycemic therapy: The LixiLan-G randomized clinical trial. Diabetes Care. 2019;42:2108–16.

16. Buse JB, Vilsbøll T, Thurman J, et al. Contribution of Liraglutide in the Fixed-Ratio Combination of Insulin Degludec and Liraglutide (IDegLira). Diabetes Care. 2014;37:2926–33.

17. 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;2:885–93.

18. Rosenstock J, Aronson R, Grunberger G, et al. Benefits of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide, versus insulin glargine and lixisenatide monocomponents in type 2 diabetes inadequately controlled on oral agents: the LixiLan-O randomized trial. Diabetes Care. 2016;39:2026–35.

19. Davies MJ, Leiter LA, Guerci B, et al. Impact of baseline glycated haemoglobin, diabetes duration and body mass index on clinical outcomes in the LixiLan-O trial testing a titratable fixed-ratio combination of insulin glargine/lixisenatide (iGlarLixi) vs insulin glargine and lixisenatide monocomponents. Diabetes Obes Metab. 2017;19:1798–804.

20. Rosenstock J, Perkovic V, Johansen OE, et al. Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. JAMA. 2019;321:69–79.

21. Rosenstock J, Ali A, Meier J, et al. Similar efficacy and safety of iGlarLixi when initiated in patients with type 2 diabetes (T2D) with or without concomitant sodium-glucose cotransporter-2 inhibitor (SGLT2i) use in a randomized controlled trial (RCT) and real-world setting. Diabetes. 2020;69:88-LB.

22. Rosenstock J, Handelsman Y, Vidal J, et al. Propensity-score-matched comparative analyses of simultaneously administered fixed-ratio insulin glargine 100 U and lixisenatide (iGlarLixi) vs sequential administration of insulin glargine and lixisenatide in uncontrolled type 2 diabetes. Diabetes Obes Metab. 2018;20:2821–9.
23. Owens DR, Landgraf W, Frier BM, et al. Commencing insulin glargine 100 U/mL therapy in individuals with type 2 diabetes: Determinants of achievement of HbA1c goal less than 7.0%. Diabetes Obes Metab. 2019;21:321–9.

24. Rosenstock J, Ampudia-Blasco FJ, Lubwama R, et al. Real-world evidence of the effectiveness on glycaemic control of early simultaneous versus later sequential initiation of basal insulin and glucagon-like peptide-1 receptor agonists. Diabetes Obes Metab. 2020;22:2295–304.

25. Davies MJ, Russell-Jones D, Barber TM, et al. Glycaemic benefit of iGlarLixi in insulin-naive type 2 diabetes patients with high HbA1c or those with inadequate glycaemic control on two oral antihyperglycaemic drugs in the LixiLan-O randomized trial. Diabetes Obes Metab. 2019;21:1967–72.

26. van Wijngaarden RPT, Overbeek JA, Heintjes EM, et al. Relation Between Different Measures of Glycemic Exposure and Microvascular and Macrovascular Complications in Patients with Type 2 Diabetes Mellitus: An Observational Cohort Study. Diabetes Ther. 2017;8:1097–109.

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

28. Riddle MC, Forst T, Aronson R, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: a 24-week, randomized, placebo-controlled study (GetGoal-Duo 1). Diabetes Care. 2013;36:2497–503.

29. Rosenstock J, Guerci B, Hanefeld M, et al. Prandial options to advance basal insulin glargine therapy: testing lixisenatide plus basal insulin versus insulin glulisine either as basal-plus or basal-bolus in type 2 diabetes: The GetGoal Duo-2 trial. Diabetes Care. 2016;39:1318–28.

30. Niemoeller E, Souhami E, Wu Y, Jensen K. iGlarLixi reduces glycated hemoglobin to a greater extent than basal insulin regardless of levels at screening: Post hoc analysis of LixiLan-L. Diabetes Ther. 2018;9:373–82.

31. Wysham C, Bonadonna RC, Aroda VR, et al. Consistent findings in glycaemic control, body weight and hypoglycaemia with iGlarLixi (insulin glargine/lixisenatide titratable fixed-ratio combination) vs insulin glargine across baseline HbA1c, BMI and diabetes duration categories in the LixiLan-L trial. Diabetes Obes Metab. 2017;19:1408–15.

32. Blonde L, Berard L, Saremi A, Huang Y, Aroda VR, Raccah D. Fixed-ratio combination of insulin and GLP-1 RA in patients with longstanding type 2 diabetes: a subanalysis of LixiLan-L. Diabetes Ther. 2020;11:1007–15.

33. Akram K, Pedersen-Bjergaard U, Carstensen B, Borch-Johnsen K, Thorsteinsson B. Frequency and risk factors of severe hypoglycaemia in insulin-treated Type 2 diabetes: a cross-sectional survey. Diabetes Med. 2006;23:750–6.

34. Tahák AG, Anderson J, Aschner P, et al. Efficacy and safety of iGlarLixi, fixed-ratio combination of insulin glarginle and lixisenatide, compared with basal-bolus regimen in patients with type 2 diabetes: Propensity score matched analysis. Diabetes Ther. 2020;11:305–18.

35. Raccah D, Chou E, Colagiuri S, et al. A global study of the unmet need for glycemic control and predictor factors among patients with type 2 diabetes mellitus who have achieved optimal fasting plasma glucose control on basal insulin. Diabetes Metab Res Rev. 2017;33:e2858.

36. Skolnik N, Hinnten D, Klatkov Y, Magwire ML, White JR Jr. Initiating titratable fixed-ratio combinations of basal insulin analogs and glucagon-like peptide-1 receptor agonists: what you need to know. Clin Diabetes. 2018;36:174–82.

37. Morea N, Retnakaran R, Vidal J, et al. iGlarLixi effectively reduces residual hyperglycaemia in patients with type 2 diabetes on basal insulin: a post hoc analysis from the LixiLan-L study. Diabetes Obes Metab. 2020;22:1683–9.

38. Raccah D, Miossec P, Esposito V, Niemoeller E, Cho M, Gerich J. Efficacy and safety of lixisenatide in elderly (≥65 years old) and very elderly (≥75 years old) patients with type 2 diabetes: an analysis from the GetGoal phase III programme. Diabetes Metab Res Rev. 2015;31:204–11.

39. Del Prato S, Frias J, Blonde L, et al. Abstract 876. Impact of disease duration and beta cell reserve on the efficacy of iGlarLixi in patients with type 2 diabetes: the LixiLan-G trial. Diabetologia. 2019;62:1–600.

40. Del Prato S, Frias J, Henry RR, et al. Influence of screening HbA1c levels on glucose control achieved when switching to iGlarLixi in T2D inadequately controlled on GLP-1RA and OAD(s). Diabetes Care. 2019;68:1139-P.

41. Frias J, Puig Domingo M, Meneghini L, et al. More patients reach glycaemic control with a fixed-ratio combination of insulin glargine and lixisenatide (iGlarLixi) than with basal insulin at 12 weeks of treatment: a post hoc time-to-control analysis of LixiLan-O and LixiLan-L. Diabetes Obes Metab. 2018;20:2314–8.
42. Bagust A, Beale S. Deteriorating beta-cell function in type 2 diabetes: a long-term model. QJM. 2003;96:281–8.

43. Kalra S, Das AK, Sahay RK, et al. Consensus recommendations on GLP-1 RA use in the management of type 2 diabetes mellitus: South Asian task force. Diabetes Ther. 2019;10:1645–717.

44. Rawshani A, Rawshani A, Franzén S, et al. Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2018;379:633–44.