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DIABETIC Medicine

REVIEW

Transitioning from basal–bolus or premix insulin therapy to a combination of basal insulin and glucagon-like peptide-1 receptor agonist in people with type 2 diabetes

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Abstract

Aims: Two fixed-ratio combinations (FRCs) of basal insulin and glucagon-like peptide-1 receptor agonist (GLP-1RA) are available for once-daily use in adults with type 2 diabetes. We aimed to review the clinical evidence for the efficacy and safety of changing treatment from a basal–bolus insulin (BBI) regimen or a premix insulin to these combination treatments (fixed-ratio or loose) and provide expert opinion on the practicalities of making such a change.

Methods: Relevant clinical and trial evidence and general review articles were identified through a literature review of ProQuest (comprising BIOSIS Previews®, Current Contents® Search, Embase® and MEDLINE®) for articles published between 2009 and 2021.

Results: We identified nine articles reporting the results of FRCs, and seven articles reporting results of loose combinations of basal insulin and GLP-1RAs, in people who transitioned treatment from BBI or premix regimens. In most trials, combination treatment led to improved or equivalent glycaemic control, and a reduction in body weight or BMI, versus the original regimens. Some trials reported a reduction in total insulin dose. A few trials reported reduced or unchanged hypoglycaemia rates, or increased patient satisfaction, with combination therapy where these endpoints were examined. We provide guidance on transitioning of treatment and the patient types most likely to benefit.

Conclusions: In people not achieving glycaemic control with BBI or premix insulin regimens, an FRC or loose combination of basal insulin and GLP-1RA may improve control, decrease the risk of body weight gain or hypoglycaemia and reduce the complexity of treatment.

KEYWORDS

diabetes mellitus type 2, glucagon-like peptide-1 receptor, IDegLira, insulin, liraglutide, lixisenatide, treatment outcomes

1 | INTRODUCTION

Type 2 diabetes is a chronic disease characterised by insulin resistance, progressive beta-cell dysfunction and hyperglucagonaemia.[1] Patients with type 2 diabetes commonly begin treatment with metformin, after which, if glycaemic targets are not met, different combinations of antihyperglycaemic agents can be considered and individualised according to current guidelines.[2] Treatment intensification to insulin therapy should be considered when other agents fail to achieve or maintain glycaemic targets.[2]

Despite treatment intensification with basal insulin, 30–64% of people with type 2 diabetes receiving basal insulin and oral antidiabetic drugs (OADs) do not reach an HbA1c target of <53 mmol/mol (<7.0%).[3] For these individuals, addition of bolus insulin (i.e. basal–bolus insulin [BBI] therapy) or a transition to premixed insulin or insulin coformulations is often considered as the next step to improve their glycaemic control.[4–6]

For many people, BBI regimens present challenges, including the burden of administering multiple daily insulin injections (MDIs), a relatively high risk of hypoglycaemia and difficulties with treatment adherence.[7] Furthermore, in the experience of the authors, BBI regimens can result in an undesired increase in body weight, which may be associated with 'preventive' snacking and the need to uptitrate insulin. These factors can deter patients and clinicians from intensifying treatment to BBI therapy, in turn resulting in therapeutic inertia despite suboptimal glycaemic control.[8]

Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) mimic naturally occurring GLP-1, a hormone secreted in response to food ingestion that enhances the release of endogenous insulin and suppresses endogenous glucagon secretion, both in a glucose-dependent manner.[9] Basal insulin and GLP-1RAs have complementary mechanisms of action: basal insulin targets fasting plasma glucose (FPG) levels and GLP-1RAs target postprandial plasma glucose (PPG) levels, or both FPG and PPG levels.[10] The benefits of the loose combination of these drugs are well established, including improved overall glycaemic control with a low risk for hypoglycaemia and often a weight-sparing or weight-neutral effect.[10–12] Furthermore, several trials have demonstrated the cardiovascular benefit of some GLP-1RAs.[13] Indeed, the combination of basal insulin and GLP-1RA is recommended in the latest American Diabetes Association (ADA) guidelines for the management of type 2 diabetes when the HbA1c target is not met when using a GLP-1RA alone.[2]

Until recently, basal insulin and GLP-1RA had to be administered separately as a loose combination. However, two injectable fixed-ratio combinations (FRCs) of basal insulin/GLP-1RA, namely insulin degludec/liraglutide (IDegLira)[14,15] and insulin glargine/lixisenatide (iGlarLixi),[16,17] have been approved by regulatory agencies, including the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), for once-daily use in adults with type 2 diabetes. These FRC regimens retain the efficacy and safety of their individual components while simplifying the treatment regimen by reducing the number of injections and treatment burden.[18]

This review article summarises the clinical evidence and provides expert opinion on the efficacy and safety of changing treatment from a BBI regimen to a loose or FRC regimen of basal insulin and GLP-1RA in people with type 2 diabetes. Transitioning from a premix insulin is also explored.

Novelty statement

- Patients with type 2 diabetes who do not achieve glycaemic control using a basal–bolus or premix insulin regimen can be treated with a basal insulin and glucagon-like peptide-1 receptor agonist (GLP-1RA), either as loose or fixed-ratio combinations.
- This work reviews the clinical evidence on the efficacy and safety of transitioning patients to combination treatment.
- In general, combination treatment improved clinical endpoints, with a good safety profile. Combinations of basal insulin and GLP-1RA are potentially helpful to avoid clinical inertia and to address adherence issues or clinical disadvantages associated with insulin intensification.

2 | METHODOLOGY

Relevant clinical and trial evidence and general review articles were identified through a literature review of ProQuest (comprising BIOSIS Previews®, Current Contents® Search, Embase® and MEDLINE®) for articles published between 2009 and 2021 (Supplementary Materials). The search terms are presented in Table S1. The search results were discussed by the author group and relevant articles were identified;[19–33] these are summarised in Tables 1 and 2.[19–33]

TABLE 1 Research articles for transitioning from BBI or premix insulin therapy to an FRC of basal insulin and GLP-1RA

Study name/ authors	Study design and patients	Baseline treatment arms	Key baseline characteristics in people receiving BBI or premix insulin therapy[a]	Key findings following transition to combination of basal insulin + GLP-1RA[a]
Transitioning from BBI therapy to IDegLira				
BEYOND[31]	Randomised, open-label trial in adults with type 2 diabetes receiving BBI ($n = 305$), randomised 1:1:1 to intensified BBI, basal insulin + GLP-1RA or basal insulin + SGLT2i	**BBI**: $n = 305$	BBI to FRC basal insulin + GLP-1RA subgroup, $n = 102$ **Age:** 62.6 years **Males:** 41% **Body weight:** 89.3 kg **BMI:** 32.6 kg/m^2 **HbA1c:** 69 mmol/mol (8.5%) **FPG:** 172.8 mg/dl **TDD:** 53.4 U	6 months **HbA1c change:** −6.6 mmol/mol (−0.6%)*** **Body weight change:** −1.9 kg** **FPG change:** −24 mg/dl*** **TDD:** −27.1 U***
Persano et al.[32]	Real-world observational, prospective single-arm cohort study in adults with type 2 diabetes receiving BBI ($n = 45$) switched to IDegLira	**BBI:** $n = 45$	BBI, $n = 45$ **Age:** 62 years **Males:** 68.9% **Body weight:** 94.1 kg **BMI:** 33 kg/m^2 **HbA1c:** 68 mmol/mol (8.4%) **FPG:** 159 mg/dl **TDD:** 42 U	6 months **HbA1c change:** −7.3 mmol/mol (−0.67%)* **Body weight change:** −2.4 kg* **BMI change:** −0.7 kg/m^2** **FPG change:** −35.3 mg/dl* **TDD:** −20 U*
EXTRA[19]	Retrospective chart review; adults ($n = 611$) with type 2 diabetes who started IDegLira ≥6 months before data collection	**Non-injectables:** $n = 118$ **GLP-1RA ± OAD:** $n = 60$ **Basal insulin ± OAD:** $n = 115$ **Loose combination of insulin (basal/BBI/premix) + GLP-1RA ± OAD:** $n = 145$ **MDI (BBI/premix/ other) ± OAD:** $n = 173$	MDI, $n = 173$ **Age:** 63.8 years **Males**: 59.5% **Body weight:** 102.3 kg **HbA1c:** 68 mmol/mol (8.4%) **TDD:** 67.7 U	6 months **HbA1c change:** −7.7 mmol/mol (−0.7%)* **Body weight change:** −2.4 kg* **TDD:** reduced from 65.7 to 45 U*
Melzer-Cohen et al.[20]	Retrospective study; adults ($n = 413$) with type 2 diabetes who started IDegLira and persisted with therapy for 180 days	**OAD:** $n = 29$ **GLP-1RA ± OAD:** $n = 31$ **Basal insulin ± OAD:** $n = 74$ **Insulin + GLP-1RA ± OAD:** $n = 247$ **MDI ± OAD:** $n = 32$	MDI, $n = 32$ N/D	180 days **HbA1c change:** −4.3 mmol/mol (95% CI: −9.2;0.7); −0.39% (95% CI: −0.84;0.06) No significant weight change

(Continues)

TABLE 1 (Continued)

Study name/ authors	Study design and patients	Baseline treatment arms	Key baseline characteristics in people receiving BBI or premix insulin therapy[a]	Key findings following transition to combination of basal insulin + GLP-1RA[a]
Taybani et al.[21]	Prospective, single-arm trial; adults ($n = 62$) with type 2 diabetes (non-fasting serum C-peptide levels ≥1.1 ng/ml and HbA1c ≤58 mmol/mol [≤7.5%]) who transitioned from MDI at a relatively low TDD	**BBI:** $n = 49$ **Premix insulin:** $n = 13$	MDI, $n = 62$ **Age:** 64.1 years **Body weight:** 93.8 kg **BMI:** 33.5 kg/m^2 **HbA1c:** 47 mmol/mol (6.4%) **TDD:** 43.3 U **Insulin dose:** 0.47 U/kg	99 days **HbA1c change:** −3.3 mmol/mol (−0.30%)* **Body weight change:** −3.1 to 90.7 kg* **BMI change:** decreased to 32.4 kg/m^2* 3 months **Insulin dose**: decreased to 0.23 U/kg **Daily number of injections:** reduced from 3.69 to 1 **Hypoglycaemia:** reduced from 45% of participants with at least one episode of documented or symptomatic hypoglycaemia in month before baseline versus 9.7% after IDegLira initiation **People with HbA1c ≤53 mmol/mol (≤7.0%) without weight gain and without hypoglycaemia:** 72.58% **People with HbA1c ≤47.5 mmol/mol (≤6.5%) without weight gain and without hypoglycaemia:** 46.77%
Egede et al.[22]	Retrospective EMR study; adults ($n = 296$), with both an HbA1c value in the 6-month period before the first prescription of IDegLira and in a window of ±45 days around the 6-month post-index time point	**Basal insulin only:** $n = 56$ **GLP-1RA only:** $n = 49$ **No injectables:** $n = 101$ **MDI:** $n = 29$ **GLP-1RA plus**: $n = 54$ **Bolus/premix insulin:** $n = 7$	MDI, $n = 29$ **Age:** 57.4 years **Males:** 51.7% **Body weight:** 98.9 kg **BMI:** 35.1 kg/m^2 **HbA1c:** 68 mmol/mol (8.4%)	6 months **HbA1c change:** −0.3 mmol/mol (−0.03%) **Body weight change**: −2.2 kg **BMI change:** reduction to 33.7 kg/m^2
Zenari et al.[30]	Retrospective study; adults ($n = 244$) with type 2 diabetes who started IDegLira from basal insulin or BBI	**Basal insulin:** $n = 186$ **BBI:** $n = 58$	BBI, $n = 58$ **Age:** 63 years **Males:** 58.6% **Body weight:** 101.1 kg **BMI:** 34.9 kg/m^2 **HbA1c:** 66 mmol/mol (8.2%) **TDD:** 55.9 U	6 months **HbA1c change:** −5.5 mmol/mol (−0.5%)** **Body weight change**: −2.8 kg** **BMI change:** −0.9 kg/m^2** **FPG change:** −10.2 mg/dl **Insulin dose change:** −27.0 U***

TABLE 1 (Continued)

Study name/ authors	Study design and patients	Baseline treatment arms	Key baseline characteristics in people receiving BBI or premix insulin therapy[a]	Key findings following transition to combination of basal insulin + GLP-1RA[a]
Drummond et al.[23]	International online survey in physicians from primary ($n = 132$) and secondary ($n = 103$) care			Greater physician satisfaction with IDegLira versus BBI for: • Reaching HbA1c targets (59%) • Number of injections (77%) • Avoiding weight gain (84%) 77% of physicians reported that IDegLira had more potential to improve patient motivation compared with BBI to reach target blood glucose levels
Transitioning from premix insulin therapy to IDegLira				
DUAL II Japan[29]	Post hoc analysis of a 26-week, randomised, trial; Japanese adults ($n = 39$) with type 2 diabetes, who transitioned from premixed insulin to IDegLira	**Premix insulin:** $n = 39$	Premix, $n = 39$ **Age:** 60.2 years **Males:** 69.2% **Body weight:** 71.9 kg **BMI:** 26.5 kg/m^2 **HbA1c:** 67 mmol/mol (8.3%) **FPG:** 171.9 mg/dl **TDD:** 14.1 U	26 weeks **HbA1c change**: −17 mmol/mol (−1.58%) **Body weight change:** −1.5 kg **Hypoglycaemia:** 2.6 episodes per patient-year of exposure

Abbreviations: BBI, basal–bolus insulin; BMI, body mass index; CI, confidence interval; EMR, electronic medical record; FPG, fasting plasma glucose; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; IDegLira, insulin degludec/liraglutide; MDI, multiple daily insulin injections; N/D, not disclosed; OAD, oral antidiabetic drug; TDD, total daily insulin dose; U, unit.

[a]Values are expressed as means unless otherwise indicated. Change values are relative to baseline.

*$p < 0.0001$.; **$p < 0.01$.; ***$p < 0.001$.

TABLE 2 Research articles for transitioning from BBI or premix insulin therapy to a loose combination of basal insulin + GLP-1RA

Study name/ authors	Study design and patients	Baseline treatment arms	Key baseline characteristics in people receiving BBI or premix insulin therapy[a]	Key findings following transition to combination of basal insulin + GLP-1RA[a]
Transitioning from BBI to a loose combination of basal insulin + GLP-1RA				
Miya et al.[24]	12-week, open-label, randomised trial; adult Japanese outpatients ($n = 31$) with type 2 diabetes receiving MDI for >3 months	**Continued MDI**: $n = 15$ **Basal insulin + lix:** $n = 11$	MDI versus basal insulin + lix **Age:** 59.6 versus 66.0 years **Males:** 60.0% versus 45.5% **Body weight**: 68.9 versus 69.0 kg **BMI:** 26.4 versus 27.2 kg/m^2 **HbA1c:** 55 versus 54 mmol/mol (7.2% versus 7.1%) **TDD:** 24.5 versus 21.6 U	12 weeks **HbA1c change:** −0.5 versus +0.4 mmol/mol (−0.05% versus +0.04% [$p = 0.36$]) **Body weight change:** +0.6 versus −2.5 kg* **BMI change**: +0.8 versus −3.7* **TDD change:** +0.7 versus −12.7 U/day* **Hypoglycaemia:** 1 patient (MDI) versus 0 patients (lix) **Overall DTSQ scores:** significantly greater with basal insulin + lix (+12.7) versus MDI (+5.7)***
Božek et al.[25]	Observational study; adults ($n = 111$) with type 2 diabetes inadequately controlled (HbA1c ≥53 mmol/mol [≥7%] and ≤97 mmol/mol [≤11%]) on different insulin regimes who started basal insulin + lix	**Premix:** $n = 50$ **Basal oral insulin:** $n = 46$ **BBI:** $n = 15$	BBI, $n = 15$ **Body weight:** 107 kg **BMI:** 36.0 kg/m^2 **HbA1c:** 81 mmol/mol (9.6%) **FPG:** 10.3 mmol/l **PPG:** 12.4 mmol/l **TDD:** 71.0 U	3–6 months **HbA1c change:** −22 mmol/mol (−2.0%)** **Body weight change:** −9 kg** **FPG change:** −2.7 mmol/l** **PPG change:** −3.2 mmol/l** **TDD change:** −21.0 U* **Decrease in both BMI and HbA1c <53 mmol/mol [<7.0%]:** 4.5% of participants
Horie et al.[26]	Open-label, prospective study; Japanese adults ($n = 41$) with type 2 diabetes who transitioned from BBI therapy of >3 years to basal insulin/lira combination therapy	**BBI:** $n = 41$	BBI, n = 41 **Age:** 62.9 years **Males:** 51.2% **Body weight:** 76.3 kg **BMI:** 29.4 kg/m^2 **HbA1c:** 60 mmol/mol (7.6%) **TDD:** 47.5 U	6 months **% of good responders (HbA1c <53 mmol/mol [<7.0%] or a decrease in HbA1c of >11 mmol/mol [>1.0%]):** 68.3% **Mean body weight:** similarly decreased in good versus poor responders **No severe hypoglycaemia**

TABLE 2 (Continued)

Study name/ authors	Study design and patients	Baseline treatment arms	Key baseline characteristics in people receiving BBI or premix insulin therapy[a]	Key findings following transition to combination of basal insulin + GLP-1RA[a]
Yamamoto et al.[27]	24-week, randomised, trial; adults ($n = 25$) with type 2 diabetes who continued BBI or transitioned to basal insulin + lira	**Continued BBI:** $n = 13$ **Basal insulin + lira:** $n = 12$	BBI versus basal insulin + lira **Age:** 61.5 versus 60.0 years **Males:** 61.5% versus 66.7% **Body weight:** 69.3 versus 74.1 kg **BMI:** 25.9 versus 27.8 kg/m^2 **HbA1c:** 52 versus 56 mmol/mol (6.9% versus 7.3%) **FPG:** 130.9 versus 126.3 mg/dl **TDD:** 25.3 versus 27.8 U	24 weeks **HbA1c change (basal insulin + lira):** −6.6 mmol/mol (−0.6%)*** **HbA1c change (BBI):** 0% (p = ns) **Body weight change:** +2.8 versus −2.5 kg** **FPG change:** −13.9 versus −3.7 mg/dl ($p = 0.55$) **TDD change:** BBI: 25.3 to 25.6 U ($p = 0.48$) Basal insulin + lira: 27.8 to 10.4 U**** **Overall DTSQ score**: −2.92 versus +6.17*** **DTSQ perceived frequency of hyperglycaemia:** 2.92 to 1.5 with basal insulin + lira*** 2.54 to 1.85 with BBI ($p = 0.18$) **DTSQ perceived frequency of hypoglycaemia:** 1.33 to 0.75 with basal insulin + lira ($p = 0.19$) 1.31 to 1.31 with BBI ($p = 1.0$)
FLAT-SUGAR[28]	26-week open-label study; adults ($n = 102$), who continued BBI or transitioned to basal insulin + ex (both with metformin)	**BBI:** $n = 50$ **Basal insulin + ex:** $n = 52$	Overall **Age:** 62 years **Males:** 63% **Previous CV event:** 32% **BMI:** 34 kg/m^2 BBI versus basal insulin (at randomisation) **HbA1c:** 57 versus 56 mmol/mol (7.4% versus 7.3% **Daily basal insulin dose:** 43.0 versus 57.0 U*	26 weeks **End-of-study HbA1c:** 55 versus 54 mmol/mol (7.2% versus 7.1%) **Body weight change:** +0.7 versus −4.8 kg** **No hypoglycaemia requiring medical assistance** **End-of-study daily basal insulin dose:** 43.0 versus 58.0 U***
Transitioning from premix insulin therapy to a loose combination of basal insulin + GLP-1RA				
Chen et al.[33]	Open-label, randomised, controlled study of adults with type 2 diabetes switching from premixed human insulin + metformin to ex + insulin glargine versus insulin aspart 70/30	**Premix:** $n = 180$	Ex + insulin glargine, $n = 90$ **Age:** 56.7 years **Males:** 48% **Male body weight:** 78.3 kg **Female body weight:** 69.3 kg **BMI:** 27.4 kg/m^2 **HbA1c:** 67.2 mmol/mol (8.3%) **FPG:** 9.1 mmol/L **TDD:** 39.3 U	24 weeks **HbA1c change:** −6 mmol/mol (−0.59%) **Body weight change:** −3.5 kg **FPG change:** −0.83 mmol/L **TDD change:** −10.7 U

(Continues)

TABLE 2 (Continued)

Study name/ authors	Study design and patients	Baseline treatment arms	Key baseline characteristics in people receiving BBI or premix insulin therapy[a]	Key findings following transition to combination of basal insulin + GLP-1RA[a]
Božek et al.[25]	As above	**Premix:** $n = 50$ **Basal oral insulin:** $n = 46$ **BBI:** $n = 15$	Premix, $n = 50$ **Body weight:** 104 kg **BMI:** 38.1 kg/m^2 **HbA1c:** 68 mmol/mol (8.4%) **FPG:** 10.1 mmol/L **PPG:** 10.8 mmol/L **TDD:** 53 U	3–6 months **HbA1c change:** −8.7 mmol/mol (−0.8%)** **Body weight change:** −5 kg* **FPG change:** −2.4 mmol/L** **PPG change:** −2.1 mmol/L** **TDD change:** −12 U** **Decrease in both BMI and HbA1c < 53 mmol/mol (<7.0%):** 13.5% of participants

Abbreviations: BBI, basal–bolus insulin; BMI, body mass index; CV, cardiovascular; DTSQ, Diabetes Treatment Satisfaction Questionnaire; ex, exenatide; FPG, fasting plasma glucose; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; lira, liraglutide; lix, lixisenatide; MDI, multiple daily insulin injections; PPG, prandial plasma glucose; TDD, total daily insulin dose; U, unit.

[a]Values are expressed as means unless otherwise indicated. Change values are relative to baseline.

*$p < 0.01$.; **$p < 0.001$.; ***$p < 0.05$.; ****$p < 0.0001$.

3 | OVERVIEW OF THE CLINICAL EVIDENCE FOR TRANSITIONING TO A COMBINATION OF BASAL INSULIN AND GLP-1RA

3.1 | Transitioning from basal–bolus insulin therapy to a fixed-ratio combination of basal insulin/GLP-1RA

The Phase 3b DUAL VII study provided initial evidence to support the rationale to use an FRC of basal insulin/GLP-1RA (in this case, IDegLira) over BBI therapy, as several clinical benefits were observed with the basal insulin/GLP-1RA intervention.[34] DUAL VII was a 32-week, randomised, multinational, treat-to-target, open-label trial in 506 people with type 2 diabetes uncontrolled on metformin and basal insulin. After 26 weeks of treatment, IDegLira was associated with HbA1c reductions comparable with BBI, but with statistically significantly lower hypoglycaemia rates and weight loss (compared with weight gain), as well as fewer injections.[34] Importantly, these findings were achieved with a significantly lower amount of insulin: 40.0 U/day with IDegLira compared with 84.0 U/day with BBI.[34]

Another FRC of basal insulin and GLP-1RA is iGlarLixi. In a post hoc propensity-score-matched analysis of two randomised clinical trials, iGlarLixi treatment was associated with statistically significant reductions in HbA1c and a significantly lower rate of hypoglycaemia, compared with BBI, together with weight loss (compared with weight gain).[35] The total mean (SD) basal insulin dose at the time of the final dose taken was 48 U (12) in the iGlarLixi arm versus 38 U (14) in the BBI arm.[35]

Below, we describe additional studies, mostly observational in design, that specifically explored the effectiveness of transitioning people from BBI to an FRC of basal insulin and a GLP-1RA.

In the 6-month, randomised, open-label BEYOND trial, 305 older adults (>35 years) with type 2 diabetes and HbA1c > 58 mmol/mol (7.5%), on BBI, were transitioned to either further intensified BBI ($n = 101$), an FRC of basal insulin plus GLP-1RA ($n = 102$) or basal insulin plus SGLT2i ($n = 102$).[31] In the subgroup switching from BBI to IDegLira or IGlarLixi, significant reductions were observed from baseline to end of study in mean HbA1c (−0.6%; $p < 0.001$), FPG (−24 mg/dl; $p < 0.001$), body weight (−1.9 kg; $p = 0.001$) and total insulin dose (−27.1 U/day; $p < 0.001$) **(**Table 1**)**.

A real-world observational, prospective, single-arm cohort study investigated switching 45 adults with type 2 diabetes from BBI to IDegLira.[32] Significant reductions were observed from baseline to 6 months in HbA1c (−0.67%; $p < 0.0001$), FPG (−35.3 mg/dl; $p < 0.0001$) and

body weight (−2.4 kg; $p < 0.0001$). A similar trend was observed in total daily insulin dose (−20 U/day; $p < 0.0001$) (Table 1).

The EXTRA study was a European, multi-centre, retrospective, real-world chart review that included 611 adults with type 2 diabetes who initiated IDegLira ≥ 6 months before data collection.[19] At baseline, a subgroup of 173 (28%) participants had previously received MDI ± OADs and had a mean HbA1c of 68 mmol/mol (8.4%), 102.3 kg body weight and 67.7 U total daily insulin dose (TDD) (Table 1). In this group, transitioning to IDegLira from BBI therapy was associated with changes from baseline at 6 months of −7.7 mmol/mol (−0.7%) in mean HbA1c, a reduction in TDD from 66 to 45 U (effectiveness analysis set; largely because prandial insulin was discontinued upon IDegLira initiation), and a reduction of −2.4 kg in body weight (all $p < 0.0001$).[19] Hypoglycaemia was not specifically reported in people transitioning from MDI; however, in the overall population, the hypoglycaemia rate was reduced from 0.28 events/patient-year (6 months before IDegLira) to 0.06 events/patient-year (6 months following IDegLira) (rate ratio 0.18; $p < 0.0001$).

A real-world, retrospective, observational analysis by Melzer-Cohen and colleagues included 413 adults with type 2 diabetes, managed by the Maccabi Healthcare Services (in Israel), who initiated IDegLira and persisted with therapy for at least 180 days.[20] At baseline, a subgroup of 32 (7.7%) participants had previously received MDIs ± OADs. In the overall cohort (details not provided for the MDI subgroup), baseline mean HbA1c was 70 mmol/mol (8.6%) and body weight was 92.4 kg (Table 1). After 180 days of IDegLira treatment, there was a non-significant reduction in HbA1c (−4.3 mmol/mol, 95% CI: −9.2;0.7 [−0.39%, 95% CI: −0.84;0.06]), with no significant body weight change (values not reported)[20] in people transitioning from MDI. The mean dose of the insulin degludec component of IDegLira over the 180 days in the entire cohort was 38.5 U (not reported for the MDI subgroup). Hypoglycaemia was not reported in this study.

Taybani and colleagues conducted a prospective, observational, single-arm clinical trial based in Hungary, in which 62 adults with relatively well-controlled type 2 diabetes (HbA1c ≤58 mmol/mol [≤7.5%]) were transitioned from MDI (79% from BBI; 21% from human/analogue premix insulin) to IDegLira.[21] At baseline, participants had a mean HbA1c of 47 mmol/mol (6.4%), 93.8 kg body weight and 43.3 U TDD (Table 1). After a mean follow-up period of 99 days, there was a significant reduction in mean HbA1c and body weight of −3.3 mmol/mol (−0.30%) and −3.1 kg, respectively (both $p < 0.0001$). After 3 months of treatment, the TDD was also significantly reduced, by 22.6 U (final TDD: 20.8 U). The proportion of people experiencing ≥1 documented (self-measured plasma glucose <3.9 mmol/L) or symptomatic hypoglycaemic episode was considerably reduced after starting treatment with IDegLira (Table 1).[21]

Egede and colleagues conducted an analysis of US electronic health records (EHRs) of 296 people with type 2 diabetes who started IDegLira treatment. Of this cohort, 29 (9.8%) had transitioned to IDegLira from MDIs. Baseline HbA1c in these patients was 68 mmol/mol (8.4%) and body weight 98.9 kg (Table 1). Six months after transitioning to IDegLira from MDIs, there was a reduction in mean adjusted HbA1c of −0.3 mmol/mol (−0.03%) and a reduction in mean adjusted body weight of −2.2 kg.[22] Hypoglycaemia and TDD were not reported.

Zenari and colleagues conducted a multi-centre, retrospective, observational analysis of 244 people with type 2 diabetes from seven Italian diabetes centres who transitioned to IDegLira from either basal insulin ±OADs or BBI therapy.[30] At baseline, a subgroup of 58 people (23.8%) transitioned from BBI therapy to IDegLira and had a mean HbA1c of 66 mmol/mol (8.2%), mean body weight of 101.1 kg and a mean TDD of 55.9 U (Table 1). After 6 months of IDegLira treatment, significant reductions in mean HbA1c (−5.5 mmol/mol [−0.5%], $p = 0.005$) and body weight (−2.8 kg, $p = 0.001$) were observed. In addition, after 12 months of treatment, reductions in both HbA1c (−2.2 mmol/mol [−0.2%], $p > 0.05$) and body weight (−6.2 kg, $p < 0.001$) were observed, albeit in fewer people. Transitioning to IDegLira from BBI therapy was also associated with a significant reduction in TDD of −27.0 and −31.6 U at 6 and 12 months, respectively.[30] Hypoglycaemia was not reported in this study.

Drummond and colleagues conducted a multi-country, European, online survey that included physicians from primary ($n = 132$) and secondary ($n = 103$) care examining real-world physicians' use, confidence and satisfaction with IDegLira. Respondents showed greater satisfaction with IDegLira than BBI therapy in terms of achieving HbA1c targets (59%), number of injections (77%) and avoiding weight gain (84%). Accordingly, most of the interviewed physicians (77%) agreed that IDegLira had more potential than BBI to improve patient motivation toward achieving blood glucose targets.[23]

3.2 | Transitioning from basal–bolus insulin therapy to a loose combination of basal insulin and GLP-1RA

Although only two GLP-1RAs are available as FRCs (IDegLira and iGlarLixi), GLP-1RAs have also been studied in loose combinations with basal insulins. In our search, we identified five studies that reported data

related to the use of the loose combination of basal insulin and GLP-1RA in people with type 2 diabetes.

Miya and colleagues conducted a 12-week, open-label, randomised, multi-centre, controlled trial in which patient satisfaction (primary endpoint) in relation to continuing an MDI regimen or transitioning to basal insulin and lixisenatide was evaluated in Japanese people with type 2 diabetes.[24] Of the 31 participants enrolled, 26 completed the study and were evaluated for the primary endpoint. Baseline characteristics were comparable between the two treatment groups (overall mean HbA1c: 55 mmol/mol [7.2%]; body weight: 68.9 kg; TDD: 23.3 U) (Table 2). After 12 weeks of treatment, mean HbA1c changed by −0.5 mmol/mol (−0.05%) in the MDI group and by +0.4 mmol/mol (+0.04%) in the basal insulin and lixisenatide group (statistical difference analysed using Mann–Whitney *U*-test: $p = 0.36$). Mean body weight changed by +0.6 kg in the MDI group and −2.5 kg in the basal insulin and lixisenatide group ($p < 0.01$).[24] Mean change in TDD with basal insulin and lixisenatide was significantly decreased compared with MDI by week 12 (−12.7 compared with +0.7 U/day, $p < 0.01$). Compared with continuing MDIs, transitioning to basal insulin and lixisenatide significantly improved Diabetes Treatment Satisfaction Questionnaire (DTSQ) scores,[36] particularly the 'current treatment', 'flexibility' and 'continue' subscores (Table 2).[24] The DTSQ perceived frequency of hyperglycaemia and hypoglycaemia increased in the MDI group (+1.5) and decreased in the basal insulin and lixisenatide group (−0.4; $p = 0.07$).

Božek and colleagues conducted a retrospective EHR analysis of the effectiveness of lixisenatide add-on to basal insulin in 111 Croatian people with type 2 diabetes previously treated with basal insulin, BBI or premix insulin therapy.[25] At baseline, 15 participants had previously received BBI and they had a mean HbA1c of 81 mmol/mol (9.6%), 107 kg body weight and 71 U TDD (Table 2). During the 3–6-month follow-up period, transitioning from BBI to basal insulin and lixisenatide significantly reduced HbA1c (−22 mmol/mol [−2%]; $p < 0.001$), body weight (from 107 to 98 kg; $p < 0.001$) and TDD (−21.0 U; $p = 0.006$) (Table 2).[25] Hypoglycaemia data were not collected in this study.

In a study by Horie and colleagues, glycaemic control was assessed in 41 people with type 2 diabetes transitioning from long-term (>3 years) BBI therapy to basal insulin and liraglutide.[26] Six months after changing treatment, 68.3% of participants had achieved a HbA1c level <53 mmol/mol (<7.0%), or a >11 mmol/mol (>1.0%) decrease in HbA1c.[26]

Yamamoto and colleagues conducted a 24-week, randomised, parallel-group, open-label trial investigating the superiority of basal insulin and liraglutide ($n = 12$) compared with continued BBI therapy ($n = 13$) in Japanese people with type 2 diabetes.[27] Baseline characteristics were generally comparable between treatment groups (HbA1c: 56 mmol/mol [7.3%] [basal insulin and liraglutide], 52 mmol/mol [6.9%] [BBI]; body weight: 74.1 kg [basal insulin and liraglutide], 69.3 kg [BBI]; TDD: 27.8 U [basal insulin and liraglutide], 25.3 U [BBI]) (Table 2). A significant reduction in HbA1c from baseline to week 24 was observed with basal insulin and liraglutide (−6.6 mmol/mol [−0.6%]; $p < 0.05$) compared with no change in the BBI group. Body weight also decreased significantly with basal insulin and liraglutide (−2.5 kg; $p < 0.05$), while BBI increased body weight (+2.8 kg; $p < 0.05$). A decrease in TDD was also observed with basal insulin and liraglutide after 26 weeks of treatment (from 27.8 to 10.4 U; $p < 0.0001$).[27] Overall patient satisfaction, based on DTSQ scores, significantly improved from baseline with basal insulin and liraglutide, while the reduction was not statistically significant with BBI (Table 2).[27] DTSQ perceived frequency of hyperglycaemia was significantly improved with basal insulin and liraglutide, while the perceived frequency of hypoglycaemia was unchanged in both treatment groups (Table 2).

The FLAT-SUGAR trial was a two-arm comparison and consisted of an 8–12-week open-label run-in period, followed by a 26-week open-label treatment period.[37] In total, 102 people completed the run-in (BBI) and were randomised to either basal insulin and exenatide (discontinuation of the bolus insulin) or BBI continuation. Baseline characteristics were balanced between the two groups.[28] Mean HbA1c was similar between treatment groups at randomisation (56 mmol/mol [7.3%] with basal insulin and exenatide compared with 57 mmol/mol [7.4%] with BBI) and remained similar after 26 weeks (54 mmol/mol [7.1%] with basal insulin and exenatide compared with 55 mmol/mol [7.2%] with BBI) (Table 2). Mean weight at randomisation was 101.3 kg in the basal insulin and exenatide group and 100.1 kg in the BBI group; this decreased by 4.8 kg and increased by 0.7 kg, respectively, after 26 weeks (between-group difference of 5.5 kg, $p < 0.0001$). Mean daily basal insulin dose was greater in the basal insulin and exenatide group (57.0 U) compared with the BBI group (43.0 U) at randomisation ($p = 0.04$) and this remained similar at 26 weeks (58.0 U compared with 43.0 U, respectively, $p = 0.02$). The daily bolus insulin dose in the BBI group, however, increased from 36.0 U at baseline to 45.0 U after 26 weeks. There were no significant differences in rates of hypoglycaemia between baseline and 26 weeks for either treatment.[28]

3.3 | Transitioning from premix insulin therapy to a fixed-ratio combination of basal insulin and GLP-1RA

Premix insulin is provided in a single-injection pen that can be administered once, twice or three times a day, and therefore aims to help reduce treatment burden compared with BBI therapy.[4] However, a limitation to premixed insulin formulations is that the individual basal–bolus components of premix cannot be individually adjusted.

A post hoc analysis of DUAL II Japan, a 26-week, randomised, two-arm, double-blind, treat-to-target trial, assessed the safety and efficacy of 39 Japanese people who were uncontrolled on premixed insulin and transitioned to IDegLira (Table 1). In these participants, mean HbA1c decreased from 67 mmol/mol (8.3%) at baseline to 50 mmol/mol (6.7%) after 26 weeks. Mean body weight was reduced from 71.9 kg at baseline to 70.4 kg after 26 weeks. Mean daily IDegLira dose after 26 weeks was 34.2 dose steps (34.2 U insulin degludec and 1.2 mg liraglutide). IDegLira was associated with 2.6 severe or blood glucose-confirmed hypoglycaemic episodes/patient-year of exposure after 26 weeks of treatment.[29]

3.4 | Transitioning from premix therapy to a loose combination of basal insulin and GLP-1RA

As described above, Božek and colleagues conducted a retrospective EHR analysis of the effectiveness of lixisenatide add-on to basal insulin in 111 Croatian people with type 2 diabetes previously treated with basal insulin, BBI or premix insulin therapy (Table 2). Of the overall cohort, 50 people had previously received premix insulin and, in this subgroup, transitioning to basal insulin and lixisenatide significantly reduced HbA1c from 68 mmol/mol (8.4%) to 60 mmol/mol (7.6%), body weight from 104 to 99 kg and TDD from 53 to 41 U after 3–6 months of follow-up (all $p \leq 0.003$).[25] Hypoglycaemia was not reported in this study.

In an open-label, randomised, controlled study, 200 adults with type 2 diabetes and inadequate glycaemic control on premixed human insulin + metformin were switched to a loose combination of GLP-1RA (exenatide) + insulin glargine or to insulin aspart 70/30.[33] In the 90 patients who were switched from premix therapy to exenatide + insulin glargine, least squares mean reductions were seen from baseline to week 24 in HbA1c (−6.5 mmol/mol [−0.59%]), body weight (−3.5 kg), FPG (−0.83 mmol/L) and total daily insulin dose (−10.7 U/day) (Table 2).

4 | RATIONALE FOR TRANSITIONING TO A FIXED-RATIO COMBINATION OF BASAL INSULIN AND GLP-1RA

In Table 3,[13,19–30,38–43] the potential benefits of transitioning from BBI or premix insulin regimens to an FRC of basal insulin + GLP-1RA based on the authors' clinical experience and literature review are summarised. The first benefits to note are clinical factors; these include potential for body weight loss,[34] lower hypoglycaemia risk,[34] reduced insulin dose[19,21,29,30] and potential cardiovascular benefit.[44] In the DUAL VII randomised controlled trial (RCT), IDegLira showed comparable reductions in HbA1c compared with BBI.[34] Statistical reductions in HbA1c were reported for IDegLira compared with BBI in observational studies,[19,21,30] and for iGlarLixi in a post hoc propensity-score-matched analysis of two RCTs.[35]

Patient- and physician-related factors are also important, and include a less complex treatment regimen with fewer injections,[21,40,41] which, in turn, can result in improved adherence/compliance compared with BBI or premix insulin regimens.[20] Patient satisfaction is important, as this might affect how motivated an individual will be to adhere to their regimen. Satisfaction with the ease and convenience of IDegLira compared with BBI has been reported (Table 3).[40] Furthermore, patient satisfaction might also be driven by the need for fewer self-measured blood glucose (SMBG) measurements with FRC compared with BBI or premix insulin regimens[40] (Table 3).

In a previous expert consensus review, with a focus on insulin glargine U100 and lixisenatide, the potential benefits of transitioning from a complex BBI to an FRC regimen included weight loss, reduced risk of hypoglycaemia, reduced therapy burden, improved compliance, improved health-related quality of life (HRQoL) and reduced treatment complexity (e.g. no need for precise carbohydrate counting).[43] Benefits in terms of reduced health resource utilisation were also cited, including reduced need for SMBG measurements, fewer emergency room visits due to hypoglycaemic events and fewer consultations with diabetes specialists.[43] Additional benefits to having a GLP-1RA as part of the treatment regimen include potential reductions in the risk of cardiovascular outcomes.[13]

5 | WHICH PEOPLE WITH TYPE 2 DIABETES ARE TYPICALLY TRANSITIONED?

People with type 2 diabetes receiving BBI regimens should generally be considered for optimised glucose-lowering therapy (e.g. sodium-glucose co-transporter-2 inhibitors

TABLE 3 Potential benefits of transitioning from BBI or premix insulin regimens to a combination of basal insulin + GLP-1RA

Benefit	Supporting information and/or references
Clinical factors	
Glycaemic control ↑	Transitioning from MDIs to a combination of basal insulin + GLP-1RA is associated with consistent or improved glycaemic control[19–22,24–30]
Potential for body weight loss ↑	Transitioning from MDIs to basal insulin + GLP-1RA is associated with neutral body weight change or weight reductions[19–22,24,25,27–30]
Potential CV/renoprotective benefit ↑	GLP-1RAs have been reported to improve composite CV outcomes and may exhibit renoprotective effects in people with type 2 diabetes[13,38]
Beta-cell function ↑	Liraglutide has been shown to preserve beta-cell function in type 2 diabetes[39]
Hypoglycaemia risk ↓	Transitioning from MDIs to a combination of basal insulin + GLP-1RA is associated with consistent or lower risk of hypoglycaemia[21,28,29]
Insulin dose/requirement ↓	Transitioning to a combination of basal insulin + GLP-1RA from MDIs is associated with a reduction in TDD or insulin requirement[19,21,25,27,29,30]
Patient- and physician-related factors	
Improved adherence/compliance ↑	• More convenient drug administration regimens are among the strategies shown to improve treatment adherence[20] • Compared with MDIs, IDegLira improved compliance with treatment[40]
Satisfaction ↑	• Reports suggest that patients are more satisfied with IDegLira than BBI therapy across all parameters assessed, including HbA1c targets, number of injections and avoiding body weight gain[23] • Compared with continuing MDIs or BBI therapy, transitioning to basal insulin + GLP-1RA significantly improves DTSQ scores[24,27]
Motivation ↑	Physicians reported that IDegLira had more potential to improve patient motivation to reach target blood glucose levels compared with BBI therapy[23]
Regimen complexity ↓	Compared with MDIs, a combination of basal insulin + GLP-1RA reduces the number of daily injections and treatment burden[21,40,41]
Burden of titration process ↓	IDegLira and iGlarLixi both necessitate fewer adjustments, and therefore dosing decisions, than BBI therapy,[40] which can be taken over by the patients
Healthcare resource utilisation	
Fewer SMBG measurements ↓	• The use of SMBG testing is associated with costs[42] • Treatment with IDegLira or iGlarLixi requires fewer SMBG measurements than with BBI therapy[21,40,43]

Abbreviations: BBI, basal–bolus insulin; CV, cardiovascular; DTSQ, Diabetes Treatment Satisfaction Questionnaire; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; IDegLira, insulin degludec/liraglutide; iGlarLixi, insulin glargine/lixisenatide; MDI, multiple daily insulin injections; SMBG, self-measured blood glucose; TDD, total daily insulin dose.

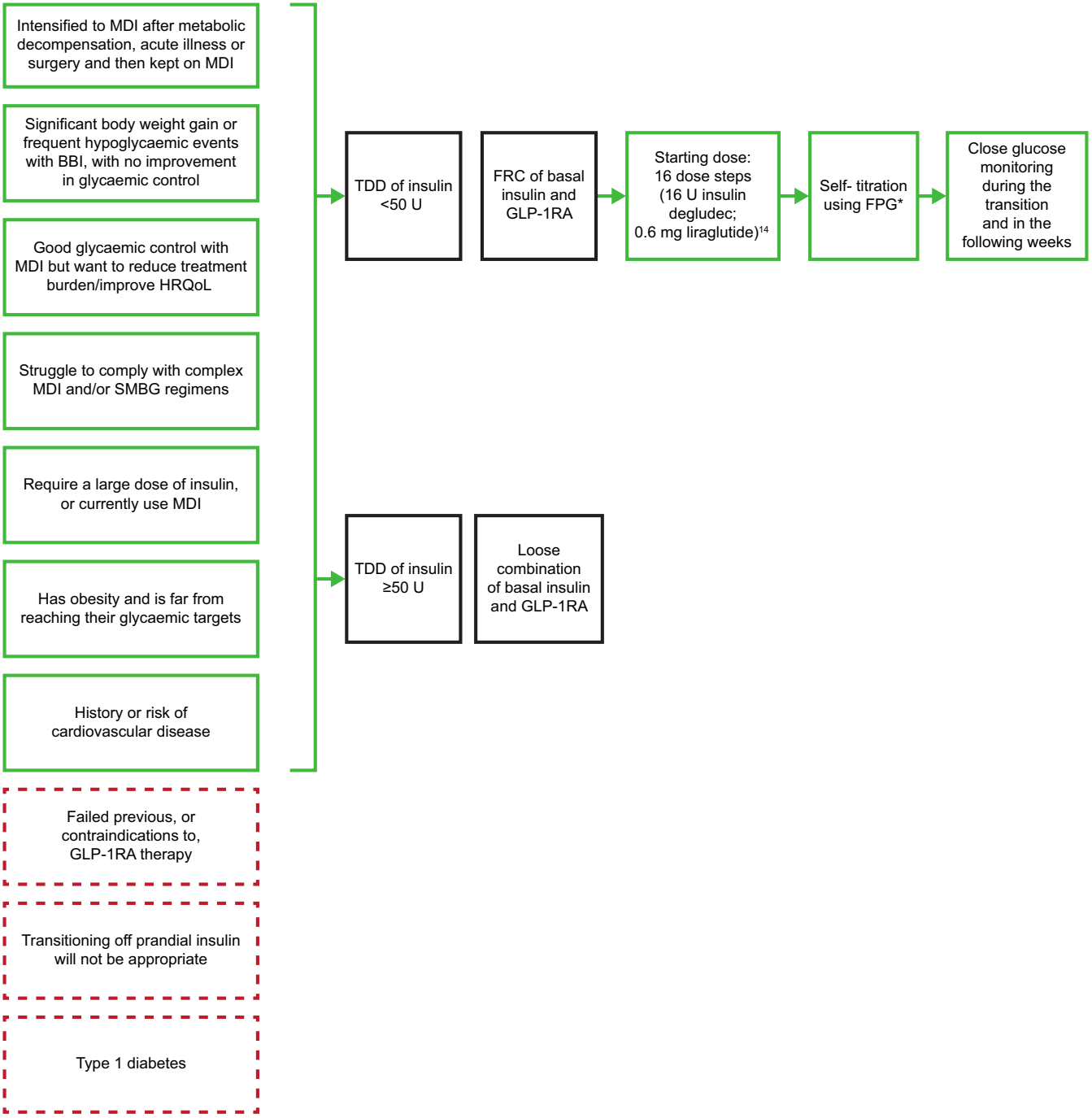

FIGURE 1 People with type 2 diabetes who are potential candidates for transition from basal–bolus or premix insulin therapy to basal insulin/GLP-1RA. *Once weekly or twice weekly using a −2/0/+2 algorithm, as described in DUAL VI;[47] maximum daily dose of IDegLira: 50 dose steps,[14] and for iGlarLixi: 60 dose steps.[16] Abbreviations: BBI, basal–bolus insulin; FPG, fasting plasma glucose; GLP-1RA, glucagon-like peptide-1 receptor agonist; HRQoL, health-related quality of life; IDegLira, insulin degludec/liraglutide; iGlarLixi, insulin glargine/lixisenatide; MDI, multiple daily insulin injections; SMBG, self-measured blood glucose; TDD, total daily insulin dose.

[SGLT-2is]) and/or transition to a combination of basal insulin and GLP-1RA, owing to the potential benefits discussed above. Figure 1 illustrates potential candidates for this transition.

In a previous expert consensus review on the use of an FRC of insulin glargine U100 and lixisenatide, potential candidates for transition from a BBI regimen to FRC included people who were intensified to a MDI regimen as a result of metabolic decompensation, acute illness or surgery and then kept on the MDI regimen.[43] Also considered suitable were those for whom the disadvantages of a MDI regimen outweighed the associated benefits and who, upon starting BBI, experienced significant body weight gain or frequent hypoglycaemic events without

any improvement in glycaemic control.[43] People who had good glycaemic control with their MDI but wanted to reduce the treatment burden and improve HRQoL were also deemed potential candidates for transitioning, as were those who struggle to comply with their MDI and/or SMBG regimens as a result of their complexity.[43]

Based on the clinical experience of the authors, candidates who also may benefit and be successful in this transition include those who have experienced limited effects with GLP-1RA (due to side effects) or insulin (due to hypoglycaemia), given that the reduced dose involved in an FRC regimen would, in turn, help reduce the number of adverse side effects. In addition, people requiring a large dose of insulin, or those who currently use multiple injections, would be appropriate targets for FRC treatment with basal insulin/GLP-1RA. There is evidence for the potential reduction in insulin dose in the EXTRA study, in which TDD was significantly reduced compared with baseline ($p < 0.0001$) in people treated with IDegLira previously receiving MDI; this was largely because 60.5% of those who were receiving a prandial insulin at baseline discontinued that insulin within 6 months of IDegLira initiation.[19] With regard to the number of injections, people with type 2 diabetes on a BBI regimen could potentially see their weekly number of total injections decrease from 28 to seven if transitioned successfully to an FRC of basal insulin/GLP-1RA.[41] Finally, people with a history or risk of cardiovascular disease (CVD) might also benefit from basal insulin/GLP-1RA, as studies of the monocomponents have shown a general improvement in CVD risk markers compared with BBI.[5]

It should be noted, however, that there may be situations in which it is not possible or appropriate to transition people to a less intensive FRC treatment regimen; for example, in people who have failed previous GLP-1RA therapy, in those with contraindications to GLP-1RA therapy, or in people with type 1 diabetes. Furthermore, in a recent 26-week, randomised, open-label study by Rosenstock and colleagues, the principle of replacing prandial insulin with a GLP-1RA (once-weekly albiglutide) in people with type 2 diabetes on MDI regimens experiencing inadequate glycaemic control (HbA1c ≥53–≤80 mmol/mol [≥7.0–≤9.5%]) was explored.[45] These participants had a mean duration of diabetes of 15 years and a mean baseline HbA1c of 60 mmol/mol (7.7%). Although the authors showed that the transition was effective in 54% of participants (with no reintroduction of prandial insulin), a large subset remained in whom prandial insulin supplementation appeared unavoidable. This is also likely to apply to some degree to people transitioning to an FRC regimen of basal insulin/GLP-1RA, and therefore there will be people for whom transitioning off prandial insulin will not be appropriate.

6 | CLINICAL GUIDANCE AND PRACTICAL ASPECTS FOR TRANSITIONING

Often, people can remain on their current regimens and continue to adapt their insulin dose without considering another treatment option. However, to healthcare providers, the combination of basal insulin and GLP-1RA is potentially helpful to avoid clinical inertia, and to address adherence issues or clinical disadvantages associated with insulin intensification.[46] Recommended practical steps for transitioning are illustrated in Figure 1.

If a patient has obesity and is far from reaching their glycaemic targets, transitioning to basal insulin and GLP-1RA may be appropriate. When switching to IDegLira from any other insulin therapy that includes a basal insulin component, the recommended starting dose is 16 dose steps (16 U insulin degludec and 0.6 mg liraglutide).[14] The dose can then be titrated using FPG. The patient can safely self-titrate the FRC dose once weekly or twice weekly by using a −2/0/+2 algorithm, as described in DUAL VI.[47] The maximum daily dose of IDegLira is 50 dose steps,[14] and for iGlarLixi is 60 dose steps.[16] Of note, based on the experience of the authors, the patient may be hyperglycaemic for a short period of time until the optimal dose is reached; close glucose monitoring is recommended during the transition and in the following weeks. Patients with TDD of insulin less than 50 U may often benefit from an FRC, while those with a greater TDD will often require a loose combination of basal insulin and GLP-1RA. For people with a high HbA1c level and TDD, transitioning to an FRC is often associated with a lower probability of success.[43]

In addition to current insulin dose, the patient's treatment compliance should also be reviewed and properly evaluated before transitioning to an FRC regimen. A detailed analysis of SMBG data by the physician is needed before and during the process.[43]

A key practical aspect to consider when deciding whether to initiate treatment with FRCs is the overall cost of the FRC and the insurance status of the patient.[41] In a US cost-effectiveness analysis, evaluation of direct medical costs suggested that the mean annual cost per patient with IDegLira was $743 lower than with BBI therapy (insulin glargine 100 U/ml plus insulin aspart).[48] The cost saving was driven predominantly by the lower annual treatment costs due to reduced needle and SMBG use for IDegLira compared with BBI therapy.[48]

7 | COMPARISON OF FIXED-RATIO COMBINATIONS COMPARED WITH LOOSE COMBINATIONS OF BASAL INSULIN AND GLP-1RA

Both FRC and loose combinations of basal insulin and GLP-1RA are effective, as evidenced in a meta-analysis of RCTs that found similar improvements in efficacy outcomes (including changes in HbA1c, hypoglycaemia and body weight) between these approaches compared with basal insulin intensification in people with type 2 diabetes.[49] Similar results have also been observed in clinical practice. Both approaches provided similar improvement in glycaemic control in a retrospective, multicentre, real-world study in people with type 2 diabetes. Greater body weight reductions were observed with the loose combination, probably attributable to the higher GLP-1 RA doses and the lower basal insulin doses than in the FRC group.[50] However, the FRC of basal insulin and GLP-1RA provides a more simplified regimen, reducing the number of injections and simplifying the titration requirements compared with the loose combination, and thereby reducing treatment burden. In a retrospective, multi-centre, real-world study, similar or greater glycaemic benefit was achieved with the FRC combination at a lower cost than with the loose combination.[50] Furthermore, although the rate of gastrointestinal adverse events associated with FRCs is greater than with basal insulin, the rate is lower compared with GLP-1RA monotherapy;[51,52] this may be as a result of a lower GLP-1RA starting dose and more gradual titration of the FRC, determined by the insulin component.

8 | CONCLUSIONS

In people receiving MDI regimens such as BBI or premix insulin regimens, an FRC or loose combination of basal insulin and GLP-1RA can be considered to reduce treatment burden/complexity of treatment and/or to decrease the risk of hypoglycaemia or body weight gain, and to improve HbA1c at the same time.

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CONFLICT OF INTEREST

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Data sharing not applicable – no new data generated.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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