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ABOUT COVER

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Fixed-ratio combinations of basal insulin and glucagon-like peptide-1 receptor agonists as a promising strategy for treating diabetes

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Abstract

The maintenance of appropriate glycemic control is important for the prevention of diabetic complications in people with type 2 diabetes (T2D). Numerous oral antidiabetic drugs are now clinically available, but in particular, the introduction of injection regimens using insulin and/or glucagon-like peptide-1 receptor agonist (GLP-1RA)s represents promising step-up options for oral antidiabetic drug treatment. The recently licensed fixed-ratio combination (FRC) products, which comprise basal insulin and a GLP-1RA, have potent anti-hyperglycemic effects and reduce the undesirable side-effects of each component, such as body weight gain, hypoglycemia, and gastrointestinal symptoms. Two FRCs-insulin degludec/Liraglutide and insulin glargine/Lixisenatide-are now clinically available and, to date, several phase II/III trials have been conducted in particular groups of subjects with T2D. However, their utility in real-world clinical settings is of interest for most clinicians. Recently reported real-world clinical trials of these two FRCs in various situations have demonstrated their efficacy regarding glycemic control and the quality of life of people with T2D. Their long-term safety and efficacy require confirmation, but a treatment strategy that includes an FRC may be compatible with the concept of "well-balanced" therapy in certain groups of patients with T2D who have inadequate glycemic control.

Key Words: Clinical trial; Diabetes mellitus, type 2; Glucagon-like peptide-1 receptor; Glycemic control; Insulin, long-acting; Quality of life

Core Tip: Fixed-ratio combination injections comprising basal insulin and glucagon-like peptide-1 receptor agonists are now available, and their efficacy for glycemic control has been demonstrated in several phase II/III trials. These injections appear to be useful based on the trial data, but real-world clinical evidence regarding the use of these compounds is limited. In this review, the clinical evidence derived from phase III and real-world clinical studies regarding the glycemic control of and other outcomes in participants with type 2 diabetes is summarized.

INTRODUCTION

The ultimate goals of the treatment of diabetes are to prevent complications and maintain the patient's quality of life (QOL). As shown by previous large-scale clinical trials of people with type 2 diabetes (T2D), the management of not only glycemic control but also of comorbidities, such as dyslipidemia, hypertension, and obesity, is critical for achieving this goal[1,2]. Of them, the maintenance of appropriate glycemic control through early diagnosis and intensive treatment has been shown to be important to prevent macro- and microvascular complications[3].

The recommended first-line treatment for diabetes is lifestyle modification, such as diet and exercise programs[4-6]. However, anti-diabetic medications are often required for people with uncontrolled T2D to achieve their glycemic targets. A number of anti-diabetic agents are now available for clinical use. Several guidelines recommend the selection of appropriate drugs based on the patient's background and complications, such as cardiovascular disease, kidney dysfunction, and/or obesity[4-6]. However, regardless of whether patients are treated with a single or multiple oral antidiabetic agents, they often require the addition of an injectable agent [insulin or a glucagon-like peptide-1 receptor agonist (GLP-1RA)].

Because an appropriate glycemic condition is associated with the best outcomes[1-3], more intensive or earlier treatment of dysglycemia using potent injectable agents may be beneficial. In addition to single-agent injectable products, fixed-ratio combination (FRC) injections, comprising basal insulin and a GLP-1RA, have recently become available. The efficacy of FRC injections for glycemic control has been demonstrated in previous phase II/III trials. Several authors have argued that these injections are useful based on the results of these clinical trials, although real-world clinical evidence regarding their utility is limited. This review discusses the utility of and clinical outcomes associated with the use of such FRCs in people with T2D, especially recently published clinical evidence derived from phase III and real-world clinical studies.

EFFECTS OF TWO INJECTABLE AGENTS: BASAL INSULIN AND GLP-1RAS

Monnier *et al*[7] reported that nocturnal-to-morning hyperglycemia is one of the characteristics of a lack of glycemic control in participants with T2D who are being treated without insulin therapy[7]. In such cases, insulin injection therapy is the most appropriate treatment option. However, insulin therapy has several disadvantages, despite its potent anti-hyperglycemic actions, such as hypoglycemia, body weight gain, and the injection frequency, especially in the case of multiple daily injection (MDI) therapy[4].

Of the existing therapeutic strategies involving insulin, regimens including basal insulin therapy are associated with a significantly lower incidence of identified hypoglycemia than MDIs, despite achieving similar glycemic control[8]. In addition, basal insulin therapy has been shown to cause less body weight gain than other insulin regimens[9,10]. The most practical protocol for a patient is a simple one of once daily injections, with easy dose adjustment, which is associated with a good QOL and appropriate fasting glucose concentrations[11,12]. However, although basal insulin is useful for managing fasting blood glucose concentrations, basal insulin does not always prevent postprandial hyperglycemia[13]. Additionally, because glucose spikes are closely associated with atherosclerotic disease[14,15], an additional therapy is often necessary in patients with such glycemic profiles.

Two types of GLP-1RAs are defined on the basis of their structural features. Some GLP-1RAs have similar structures to human endogenous GLP-1, with a few amino acid modifications to avoid cleavage by dipeptidyl peptidase (DPP)-4. However, other GLP-1RAs are derived from exendin-4, which also renders them resistant to DPP-4-mediated degradation[16,17]. GLP-1RAs act *via* the GLP-1 receptor, which is expressed on the plasma membranes of cells and activates adenylate cyclase, leading to an

increase in cAMP in pancreatic beta-cells[18,19]. This increase in cAMP increases the intracellular cAMP concentration, causing an increase in insulin secretion from vesicles in a blood glucose-dependent manner and an improvement in glycemic control[20]. The main advantage of GLP-1RAs is that they have pleotropic effects in various tissues, such as the cardiovascular system, adipose tissue, liver, and kidney[18]. Notably, several phase III trials of the safety and efficacy of high-dose GLP-1RAs have demonstrated cardioprotective effects[21-23].

Another advantage of GLP-1RAs is their effects on body weight. GLP-1RAs reduce gastric emptying and appetite, and change the eating preference *via* effects on the neural network and hypothalamus, leading to weight loss[24,25]. These actions of GLP-1RAs differ according to the duration of their activity (*i.e.*, whether they are short- or long-acting)[26]. Short-acting GLP-1RAs, such as lixisenatide and exenatide, strongly suppress gastric peristalsis, resulting in the rapid inhibition of postprandial hyperglycemia following drug administration. However, long-acting GLP-1RAs, such as liraglutide and semaglutide, have less marked effects on the gastrointestinal tract, but are more effective at increasing insulin secretion by beta-cells, and thereby have distinct anti-hyperglycemic effects[26,27]. Nevertheless, despite the clinical utility of GLP-1RAs, studies have reported that they might be less efficacious when beta-cell function is poor, thereby limiting their utility for glycemic control[28,29].

These two types of injectable agents have advantages and limitations regarding their utility for glycemic control and the correction of metabolic abnormalities. Eng *et al*[30] conducted a meta-analysis that compared the utility of a combination therapy comprising basal insulin and a GLP-1RA, along with other antihyperglycemic therapies, including MDIs[30] They found that this provided robust glycemic control, with less increase in hypoglycemia or weight gain, which represents the ideal management of diabetes. However, although this combination therapy was shown to be effective, it is relatively expensive and necessitates two injection devices, which may be associated with a deterioration in the patient's QOL.

CONCEPT AND PHASE III TRIALS OF FRCS OF BASAL INSULIN AND GLP-1RAS

Two pre-filled injectable FCR products comprising basal insulin and a relatively low-dose GLP-1RA are now clinically available. These products are insulin degludec (IDeg)/Liraglutide (IDegLira) and insulin glargine/Lixisenatide (IGlarLixi). One dose of IDegLira contains 1 unit of IDeg and 0.036 mg of liraglutide, whereas 1 dose of IGlarLixi comprises 1 unit of insulin glargine plus 0.33-to-1 μg of lixisenatide (Table 1). The use of such FCRs in the clinical setting was anticipated to be associated with a reduction in the injection frequency. This reduction aimed to maximize the efficacy, while minimizing the disadvantages of the two injectable regimens (body weight gain and hypoglycemia for basal insulin, and gastrointestinal symptoms and the inability to manage fasting plasma glucose for GLP-1RAs), and be associated with superior clinical outcomes.

The addition of an injectable therapy to the use of oral anti-diabetic agents (OADs) represents a promising step-up therapy aimed at achieving good glycemic control. Phase III trials comparing the efficacy of FRCs *vs* basal insulin and/or GLP-1RAs with that of OADs have been conducted (Table 2). The DUAL I trial compared the efficacies of IDegLira and IDeg or liraglutide in insulin-naïve patients [31]. This trial showed a reduction in glycated hemoglobin A1c (HbA1c) values in participants administered IDegLira, with non-inferiority to IDeg and superiority to liraglutide, without increasing the risk of weight gain and hypoglycemia. Similarly, the efficacy of IGlarLixi for a reduction in HbA1c values was evaluated in the LixiLan-O trial, which involved the addition of IGlarLixi, insulin glargine, or lixisenatide to the use of OADs[32]. IGlarLixi was associated with the largest reduction in HbA1c values among these arms, with no change in body weight, and a similar incidence of hypoglycemic events to insulin glargine. However, the effects on body weight clearly differed according to the GLP-1RA therapy used in these two trials. The utility of two FRCs in insulin-treated patients was also compared in the Dual V trial[33] and the LixiLan-L trial[34]. In both studies, a larger reduction in HbA1c values was achieved, along with fewer hypoglycemic events, in patients using FRCs *vs* their comparators, in the absence of body weight gain. The same trend was shown in participants with T2D and various treatment backgrounds in other trials of IDegLira[35-39] and IGlarLixi[40-43]. Therefore, these clinical trials have established these two FRCs as useful step-up therapies for particular groups of patients with T2D and poor glycemic control.

REAL-WORLD EVIDENCE FOR THE EFFICACY OF FRC THERAPIES FOR GLYCEMIC CONTROL

As described above, phase III randomized, controlled trials (RCTs) have demonstrated the efficacy and utility of the two FRCs. However, applying these results to daily clinical practice is difficult because the concomitant treatments for T2D are highly restricted, and the doses of FRCs are adjusted using tight treat-to-target strategies, resulting in the administration of relatively high doses of FRCs. Therefore, the

Table 1 Details of the fixed-ratio combinations of basal insulin and glucagon-like peptide-1 receptor agonists

	IDegLira	IGlarLixi
Combination	Insulin degludec + liraglutide	Insulin glargine + lixisenatide
Proportion (/dose)	Insulin degludec 1 unit + liraglutide 0.036 mg	(1) Glargine 1 unit + lixisenatide 0.33–0.50 µg; and (2) Glargine 1 unit + lixisenatide 1.0 µg[1]
Frequency	Once daily	Once daily
Indication	Adults with type 2 diabetes	Adults with type 2 diabetes
Dosage	Up to 50 doses/day	(1) Up to 20–60 doses/day; and (2) up to 20 doses/day
CVOT for GLP-1RA component	Liraglutide: LEADER[21]	Lixisenatide: ELIXA[62]
CVOT for insulin component	DEVOTE[63]	ORIGEN[64], DEVOTE[63]

[1]The combination of insulin glargine 1 unit + lixisenatide 1.0 µg/unit is only approved in Japan.
GLP-1RA: Glucagon-like peptide-1 receptor agonist; IDegLira: Insulin glargine/liraglutide; IGlarLixi: Insulin glargine/lixisenatide: CVOT: Cardiovascular outcome trial.

Table 2 Major phase III trials of fixed-ratio combinations of basal insulin and a glucagon-like peptide-1 receptor agonist

FRC	Name	Baseline treatment	Comparator	Duration	Relative reduction in HbA1c *vs* comparator
IDegLira	Dual I[31]	OADs	IDeg or Lira	26 wk	−0.47% *vs* IDeg ($P < 0.0001$); −0.64% *vs* Lira ($P < 0.0001$)
	Dual II[35]	Basal insulin + Met	IDeg	26 wk	−1.1% ($P < 0.0001$)
	Dual III[36]	GLP-1RA	GLP-1RA	26 wk.	−0.94% ($P < 0.001$)
	Dual IV[37]	SU or SU + Met	Placebo	26 wk	−1.02% ($P < 0.001$)
	Dual V[33]	Basal insulin	IGlar U100	26 wk	−0.59% ($P < 0.001$)
	Dual VII[38]	Basal insulin + Met	Basal-bolus therapy	26 wk	−0.02% ($P < 0.0001$)
	Dual IX[39]	SGLT2i	IGlar U100	26 wk	−0.36% ($P < 0.0001$)
IGlarLixi	LixiLan-O[32]	Met ± other OADs	IGlar or Lixi	30 wk	−0.3% *vs* IGlar ($P < 0.0001$); −0.8% *vs* Lira ($P < 0.0001$)
	LixiLan-L[34]	Basal insulin ± OADs	IGlar U100	30 wk	−0.5% ($P < 0.001$)
	LixiLan JP-O1[40]	OADs	Lixisenatide	26 wk	-1.07% ($P < 0.0001$)
	LixiLan JP-O2[41]	OADs	IGlar U100	26 wk	-0.63% ($P < 0.0001$)
	LixiLan JP-L[42]	Met + basal insulin	IGlar U100	26 wk	-0.74% ($P < 0.0001$)
	LixiLan-L-CN[43]	Basal insulin ± OADs	IGlar U100	30 wk	-0.7% ($P < 0.0001$)

FCR: Fixed-ratio combination; GLP-1RA: Glucagon-like peptide-1 receptor agonist; IDegLira: Insulin glargine/liraglutide; IGlarLixi: Insulin glargine/lixisenatide; OADs: Oral anti-diabetic agents; Met: Metformin; SU: Sulfonylurea; SGLT2i: Sodium/glucose cotransporter 2 inhibitor; IDeg: Insulin degludec; Lira: Liraglutide; IGlar: Insulin glargine.

efficacy of these new agents should be validated in real-world clinical settings.

To date, several real-world clinical trials have been conducted with various endpoints (Table 3). First, although combination therapies of basal insulin plus a GLP-1RA have several clinical advantages[30], which strategy is most appropriate for people with poorly controlled T2D who are being treated with basal insulin is unclear. Morieri *et al*[44] retrospectively analyzed the difference in efficacy between the addition of a GLP-1RA to basal insulin and switching from basal insulin to FRCs in 609 participants with T2D[44]. They found that FRC treatment resulted in a larger reduction in HbA1c values, whereas the body weight loss was larger in the GLP-1RA initiation group. Regarding the final doses of the injections, the number of units of basal insulin required was higher in the FRC group, whereas the number of units of GLP-1RA required was higher in the flexible group. The results of this study highlight the differences in the two treatment regimens. Good glycemic control can be achieved using FRCs and the extra-pancreatic effects of a GLP-1RA, such as body weight management and possibly

Table 3 Real-world evidence regarding the efficacy of fixed-ratio combinations of basal insulin and a glucagon-like peptide-1 receptor agonist for glycemic control

Ref.	Target patients	Design	Duration	Representative outcomes
Morieri et al[44], 2019	Treated w/o GLP-1RA	Retrospective, observational	5.7 mo	FRCs were associated with a larger reduction in HbA1c, whereas GLP-1RA reduced body mass
Egede et al[45], 2020	(1) OADs ± basal insulin or GLP-1RA alone; and (2) MDIs or GLP-1RA with insulin	Retrospective, observational	6 mo	(1) IDegLira use was associated with a reduction in HbA1c; and (2) Switching to IDegLira did not reduce HbA1c
Persano et al[50], 2021	MDIs	Prospective, observational	6 mo	Switching from MDIs to IDegLira improved HbA1c, body mass, and the QOL score
Kawaguchi et al[51], 2022	OADs ± basal insulin	RCT	2 wk	IDegLira resulted in a significantly longer time in the target glucose range than IDegAsp
Oe et al[52], 2022	IDeg + DPP-4i	Prospective, observational	2 wk	Switching from IDeg + DPP-4i to IDegLira significantly improved glucose fluctuations and the QOL score
Guja et al[46], 2022	GLP-1RA + OADs	RCT/prospective, observational	6 mo/26 wk	IGlarLixi significantly improved HbA1c, regardless of the use of an SGLT2i
Bala et al[47], 2022	OADs ± basal insulin	Prospective, observational	24 wk	Introduction of IGlarLixi significantly reduced HbA1c
Ramírez-Rincón et al [48], 2022	OADs and/or insulin	Retrospective, observational	3–7 mo	Introduction of IDegLira significantly reduced HbA1c and insulin requirements
Bilic-Curcic et al[49], 2022	Insulin therapy	Retrospective, observational	> 6 mo	Switching to FRCs (IDegLira and IGlarLixi) significantly reduced HbA1c and body mass

GLP-1RA: Glucagon-like peptide-1 receptor agonist; OADs: Oral anti-diabetic agents; MDIs: Multiple daily insulin injections; IDeg: Insulin degludec; DPP-4i: Dipeptidyl peptidase-4 inhibitor; RCT: Randomized, controlled trial; FRC: Fixed-ratio combination; IDegLira: Insulin glargine/liraglutide; IGlarLixi: Insulin glargine/lixisenatide; QOL: Quality of life; IDegAsp: Insulin degludec/aspart; SGLT2i: Sodium/glucose cotransporter 2 inhibitor; Lira: Liraglutide; IGlar: Insulin glargine.

cardiovascular protection, are superior to those of a GLP-1RA alone. Notably, high-dose liraglutide has been shown to reduce cardiovascular risk in high-risk patients with T2D[21]. However, to date, no prospective trials have assessed the cardiovascular outcomes of FRCs.

The efficacy of switching from basal insulin therapy to IDegLira or IGlarLixi has been confirmed in prospective and retrospective trials[45-49]. As expected, such a switch resulted in lower HbA1c values, regardless of the concomitant OADs being used. Real-world data from Egede et al[45] also showed the utility of switching from MDIs to IDegLira[45]. They found that simplification of the protocol from MDIs to FRC was not associated with a worsening of HbA1c, despite being associated with modest weight loss. However, a prospective study of a switch from MDIs to once-daily IDegLira showed a reduction in HbA1c values, the total insulin dose required, and body weight[50].

One motivation to use injections containing a GLP-1RA component is to reduce glucose fluctuations, which is difficult using basal insulin regimens. Differences in the effects of the two step-up regimens (switching from basal insulin to once-daily IDegAsp or IDegLira) on glycemic variability were confirmed in an RCT using intermittently scanned continuous glucose monitoring by Kawaguchi et al [51]. They demonstrated that a step up to IDegLira was associated with a longer period of time in the target glucose range (3.9–10.0 mmol/L) and a lower glucose variability after breakfast and lunch than the use of IDegAsp. Oe et al[52] reported that a switch from a combination therapy of a DPP-4 inhibitor plus IDeg to the same dose of IDegLira significantly ameliorated indices of glycemic variability, including the mean amplitude of glycemic excursions, even when a relatively low dose of the GLP-1RA component was administered[52]. This finding can be at least partially explained by the differences in the serum GLP-1 concentrations achieved by using DPP-4 inhibitors and GLP-1RAs. Taking into consideration that a large number of patients with T2D are treated with DPP-4 inhibitors in Asian countries [53], such a switch also represents a useful step-up treatment strategy.

Importantly, Kawaguchi et al[51] showed that endogenous insulin secretory capacity was important to maximize the efficacy of such FRCs[51]. Beta-cell function declines over time in people with T2D[54]. Therefore, early induction of FRCs might be a reasonable treatment option. However, clinical evidence assessing the efficacy of these FRCs is limited to step-up or switching therapy from other antihyperglycemic medications. In addition, these FRCs cannot be induced as a first injection regimen in certain countries. Taken together, these findings suggest that further investigation to determine whether FRCs can be a first-step treatment for T2D should be performed in the future.

Table 4 Real-world evidence regarding patients' satisfaction with fixed-ratio combinations of basal insulin and a glucagon-like peptide-1 receptor agonist

Ref.	Target patients	Design	Duration	Representative outcomes
Persano et al[50], 2021	MDIs	Prospective, observational	6 mo	Switching from MDIs to IDegLira improved HbA1c, body mass, and the QOL score
Rizza et al[55], 2021	MDIs, basal insulin + OADs, and OADs alone	Prospective, interventional	6 mo	The DTSQ score improved, but CASP-19 did not, after switching to IDegLira
Polonsky et al[56], 2022	Basal insulin + OADs	RCT	26 wk	Switching from basal insulin to IGlarLixi improved patient-reported outcomes *vs* twice daily BIAsp 30
Oe et al[57], 2023	IDeg + DPP-4i	Prospective, observational	2 wk	Switching from IDeg + DPP-4i to IDegLira improved QOL, as assessed using DTR-QOL

GLP-1: Glucagon-like peptide-1; MDIs: Multiple daily insulin injections; OADs: Oral anti-diabetic agents; IDeg: Insulin degludec; DPP-4i: Dipeptidyl peptidase-4 inhibitor; RCT: Randomized, controlled trial; IDegLira: Insulin glargine/liraglutide; QOL: Quality of life; DTSQ: Diabetes Treatment Satisfaction Questionnaire; CASP-19: 19-item Control, Autonomy, Self-realization, Pleasure scale; IGlarLixi: Insulin glargine/lixisenatide; BIAsp 30: Biphasic insulin aspart 30/70; DTR-QOL: Diabetes therapy-related QOL.

EFFECTS OF FRC THERAPIES ON PATIENT-RECORDED OUTCOMES

Another important aspect of such new injections is their effects on the QOL of the patients. Agents that not only improve glycemic control, but also avoid the worsening of or even improve QOL would be ideal. To date, the real-world evidence regarding their effects on QOL scores is limited (Table 4). A single-arm prospective trial was performed by Persano et al[50] who studied 45 participants who switched from MDIs to IDegLira[50]. The QOL was assessed in 21 participants using the Diabetes Treatment Satisfaction Questionnaire, and showed an improvement from 20.1 to 27.6. The authors considered that the reduction in the number of injections required from four to one each day might have contributed to this improvement. The same result was also obtained in older people with T2D in another prospective study conducted by Rizza et al[55]. The simplification of the treatment for diabetes using FRCs improved Diabetes Treatment Satisfaction Questionnaire scores and other indices of activities of daily living and the mental state. This was probably achieved because of greater efficiency and compliance with the therapy, and the absence of any increase in hypoglycemia or body weight gain. Another RCT showed that, even compared with twice daily biphasic insulin aspart 30/70 (BIAsp 30), IGlarLixi was associated with improvements in the management of diabetes and treatment burden[56]. Interestingly, a sub-analysis of clinical trials by Oe et al[57] showed an improvement in the QOL score after switching from insulin glargine plus a DPP-4 inhibitor to IDegLira, despite this only comparing once daily injection regimens[57]. This switch improved the Diabetes Therapy-related QOL score, and especially domain 2, which reflects anxiety and dissatisfaction with treatment. Notably, the sub-score reflecting dissatisfaction with poor blood glucose control was also significantly improved, which may be explained by the amelioration of glucose fluctuations by the FRC[57].

An economic point of view is also an important issue for such new treatment regimens. Several reports from the United Kingdom and Czech Republic compared the cost-effectiveness of IDegLira and IGlarLixi. Pöhlmann et al[58] reported that IDegLira used for treating people with T2D who were treated with basal insulin had a higher cost than IGlarLixi in the Czech Republic[58]. IDegLira was associated with a longer lifespan and quality-adjusted life-years (QALYs) than IGlarLixi[58]. However, other reports from the UK that compared the cost-effectiveness among IGlarLixi, IDegLira, and basal insulin plus dulaglutide or liraglutide showed almost similar QALYs, although IGlarLixi provided substantial cost saving owing to a lower acquisition cost[59]. The same cost-saving effect was also confirmed in an IGlarLixi add-on strategy in people with T2D treated with oral antihyperglycemic agents[60]. IGlarLixi showed slightly higher estimated QALYs at an acceptable higher cost with a reduction in the daily injection frequency compared with twice daily BIAsp 30[61]. The cost-effectiveness of these two FRCs appears to be different. However, the acquisition costs and required doses for FRCs to maintain appropriate glycemic control differ among countries and races, possibly resulting in different outcomes of patients' burden. Although large-scale, long-term RCTs of the effects of such combinations on patient-reported outcomes are required to confirm these theories, FRC therapies might represent a useful option for people with T2D who have a sub-optimal QOL.

CONCLUSION

Currently, clinicians can recommend several therapeutic approaches using injectable agents in people with T2D who have inadequate glycemic control. The purpose of such treatments differs according to

the components of each product; however, a balance of efficacy and safety is critical. FRCs comprising basal insulin and a GLP-1RA have the potential to be such a "well-balanced" therapy. However, the long-term efficacy of FRCs regarding cardiovascular outcomes and the protection of beta-cells, as well as patient-reported outcomes, should be further assessed and discussed in the future.

FOOTNOTES

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