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Comparative efficacy and safety of two fixed ratio combinations in type 2 diabetes mellitus patients previously poorly controlled on different insulin regimens: a multi-centric observational study

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Abstract. – OBJECTIVE: To evaluate the efficacy and safety profile of fixed ratio combinations (FRC) in patients with type 2 diabetes mellitus (DMT2) poorly controlled on different insulin regimens.

PATIENTS AND METHODS: This multicentric observational study included 376 patients (157 males, 219 female), with longstanding DMT2 inadequately controlled (HbA1c >7%) on different insulin regimens; premix insulin analogs (MIX) (23.2%), basal-bolus regimen (BB) (30.9%) or basal oral therapy (BOT) (37.1%) to whom FRC was introduced at least 6 months prior to data collection.

RESULTS: Median age of patients was 67 years, with the duration of diabetes for 14 years, median HbA1c of 8.4% and BMI of 34.35 kg/m^2. The proportion of patients treated with IDegLira and IGlarLixi was similar (48.4% *vs.* 51.6%). There was a borderline difference regarding regimen groups ($p = 0.059$) implying the greatest improvement of HbA1c in the MIX group. The significant interaction between BOT and BB/MIX regimens ($p = 0.011$) was noted indicating the largest reduction of BMI in BB and MIX groups. After the FRC administration, there was no significant difference in gastrointestinal (GIT) side-effects. The number of patients with hypoglycemic episodes decreased from 24% to 7% after FRC initiation ($p < .001$). The group using IGlarLixi required a significantly higher average dose steps compared to IDegLira ($p < .001$ for all) to achieve glycemic goals, while a larger proportion of patients using IDegLira lost more than 5 kg, compared to IGlarLixi ($p < .001$). Significant improvement was observed in all glycemic parameters in all insulin treated patients after replacement of insulin therapy with FRC ($p < .001$ for all). Composite outcome defined as any weight loss and HbA1c below 7% was accomplished in 20.3% of patients.

CONCLUSIONS: In real life setting switching to both FRC options in people with longstanding inadequately controlled DMT2 treated with different insulin regimens could offer an effective therapeutic choice for achieving glycemic goals, with an improved safety profile.

Key Words:
Type 2 diabetes, Fixed ratio combination, Insulin therapy, Observational study, Glycemic control.

Introduction

Fixed-ratio combinations (FRC) of basal insulin and GLP-1 receptor agonist (GLP-1RA) have recently been introduced as a treatment option for patients with type 2 diabetes (DMT2). Mentioned combination exerts potential benefits when compared to insulin alone due to the complementary effects of GLP-1RA on both fasting and postprandial glycaemia. Besides, added value of FRC is in the simplicity of use (once a day injection), beneficial effects on body weight, and no additional risk of hypoglycemia, which might secure long term adherence and persistence of patients to mentioned treatment[1].

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Furthermore, the prescription of GLP-1RA depends on the health reimbursement policy of a specific country and quite often there are limitations. In Croatia, the prerequisite for the introduction of GLP-1RA until recently was the failure of dual oral therapy (HbA1c < 7%) and body mass index (BMI) over 35 kg/m^2, but in July 2020 BMI cut off was reduced to 30 kg/m^2 which significantly influenced the increased proportion of GLP-1Ras' use in the treatment of DMT2 patients. Nonetheless, a problem reaching from the past remains, since a large proportion of patients did not meet the previous criteria for GLP-1RA therapy and were consequently treated with different insulin regimens.

Given the complexity and all the adverse effects of insulin therapy such as weight gain and hypoglycemia as well as a large number of injections per day, a fixed combination of basal insulin and GLP-1RA seems to be the ideal therapy choice in these obese, poorly regulated patients with long-standing diabetes who failed to achieve glycemic targets with previous insulin therapy.

FRC might be especially effective for patients with very high HbA1c [> 86 mmol/mol (10.0%) and/or 22 mmol/mol (2.0%) above target] in whom further intensification would previously be based on the addition of prandial insulin and/or up-titration of basal insulin, which is commonly followed by increased risk for hypoglycemia development[2]. In the mentioned subset of patients, FRC led to improvement of glycemic control, a significant reduction in HbA1c and to some degree potential to lose weight[3,4].

Today, two FRC options are available: IDegLira (Xultophy) a combination of insulin degludec and liraglutide and IGlarLixi (Suliqua) combining insulin glargine U100 and lixisenatide. The IGlarLixi is applied within an hour before a big meal once a day and targets postprandial hyperglycemia, and IDegLira, a long acting FRC, usually before bedtime, and application is not related to the meal[5]. Moreover, the IDegLira, due to the proven cardiovascular benefits of liraglutide, might be more suitable for patients with established cardiovascular disease[6-11]. In addition, differences between the two FRCs are in the basal insulin component, where degludec, compared to glargine U100, might be a better option in terms of hypoglycemia, especially with a lower risk of nocturnal episodes [12].

The aim of this retrospective multicenter analysis was to assess and compare the efficacy and safety of two FRCs administered once a day to patients with longstanding type 2 diabetes previously not reaching glycemic targets on different insulin regimens (basal supported oral therapy-BOT, basal bolus-BB, premix insulin analogues-MIX) in the real-life setting.

Patients and Methods

This was a multicentric observational study conducted in tertiary hospital centers in Croatia (Zagreb, Osijek, Rijeka). Patients were recruited from diabetes outpatient clinics and data from electronic medical records (EMRs) was collected retrospectively and analyzed starting from July 2018 until July 2021. The study included 376 patients (157 males, 219 female), diagnosed with type 2 diabetes aged 20–80 (77.9% older than 60 years), the majority with long diabetes duration (over 10 years), inadequately controlled (HbA1c > 7%) on different insulin regimens; premix insulin analogs (23.2%), basal-bolus regimen (30.9%) or basal supported oral therapy (37.1%). The following patients were excluded: those with incomplete EMRs who did not have the follow-up visit, or the follow-up visit was not within the 6-month window interval. Due to some missing data, the number of subjects analyzed varied at study entry; however, only the subjects with all available data were included in the statistical analysis (N 345). This study complied with the Declaration of Helsinki and was approved by the Local Ethics Committees of University Hospital Centre Osijek, University Hospital Centre Rijeka and Clinical Hospital Merkur. Due to the retrospective nature of the study, informed consent was waived.

Study Protocol

The following data at baseline and follow-up visits (after 6 months) was collected; age, duration of diabetes, sex, diabetic medications, HbA1c, weight, height, BMI, fasting and postprandial blood glucose levels (FPG and PPG respectively). Changes in HbA1c, fasting blood glucose (FPG), postprandial blood glucose (PPG), weight, BMI, were assessed and analyzed. The primary study endpoint was the proportion of participants achieving HbA1c < 7.0% (53 mmol/mol) and/or any bodyweight reduction. The secondary endpoint included changes in insulin doses, FPG and PPG. Data on the safety of FRC was also collected and recorded (primarily on gastrointestinal side-effects and hypoglycemia). Endpoints were analyzed and compared for both FRC together, between 2 FRCs separately (IDegLira vs IGlarLixi) and with regards to initial insulin regimen (basal-bolus, basal supported oral therapy, premix insulin analogs).

Table I. Baseline characteristics of subjects.

	Mean	SD	Median	Min.	Max.	N
Diabetes duration (years)	15.32	7.24	14.00	0.50	44.00	364
Age (years)	66.85	8.80	67.00	40.00	89.00	376
BMI (kg/m^2)	34.75	4.39	34.35	26.60	53.30	368
Insulin daily dosage (IU)	43.00	31.18	40.00	0.00	224.00	376
HbA1c (%)	8.63	1.41	8.40	5.90	14.00	361
FPG mmol/l	8.71	3.07	8.10	3.30	24.80	374
PPG mmol/l	11.72	2.82	11.70	5.70	23.00	345
FRC daily dosage (U)	24.76	9.84	24.00	10.00	60.00	376

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; FRC, fixed ratio combination.

Statistical Analysis

Descriptive statistics were used to describe baseline characteristics of the study sample (proportions for categorical data, mean±standard deviation for normally distributed continuous variables, and median+interquartile range for continuous variables deviating from normal distribution). Differences in baseline characteristics of patients according to different insulin regimens were calculated using one-way ANOVA or Kruskal-Wallis when the non-parametric substitute was required. Categorical variables of composite outcomes (reduction in weight gain and HbA1c) between three groups according to regimen were analyzed with Chi square test (with Fisher's exact p for 2x2 tables). Two-way repeated-measures ANOVA and ANCOVA (with the duration of insulin therapy and age as covariates for adjustment in baseline differences) were used to determine the change in given parameters over the follow-up period, regarding three groups of patients (with Scheffe's post hoc test, and Bonferroni correction for multiple comparisons). Independent samples Student's t-test od Mann-Whitney U were used for calculating the statistical significance of differences in HbA1c, PPG and BMI between IdegLira and IglarLixi. All statistical comparisons are two-tailed, and they were considered significant at the $p < 0.05$.

Results

Patients' Characteristics

Our study included 376 subjects treated with different insulin regimes who were switched to FRC therapy. The median age of patients was 67 years, with the duration of diabetes for 14 years, median HbA1c of 8.4% and BMI of 34.35 kg/m^2. Total insulin daily dose was 40 IU, whereas FRC daily dose at the initiation was 24 units (Table I).

31.9% of patients were treated with basal bolus regimen (BB), 38.2% with basal oral therapy (BOT), and 23.9% used premixed insulin analogs (MIX). 6% were insulin naïve and GLP-1RA therapy was used by 27.9% of patients before FRC initiation. Most patients (88.2%) received metformin, followed by DPP4i in 29.1% and SGLT2i in 25.4%, while SU was used by 2.4% of the patients. After FRC initiation DPP4i therapy was excluded (29.1% *vs.* 0%) whereas a slight increase in SGLT2i therapy was observed (25.4% *vs.* 34%). There was a modest increase in usage of metformin and SU (88.2 *vs.* 98.2% and 2.4 *vs.* 4.1% respectively) (Table II).

Table II. Non-injectable concomitant therapy prior and after FRC initiation.

Prior FRC initiation	n	(%)	After FRC initiation	n	(%)
No concomitant therapy	34	(9.1)	no concomitant therapy	5	(1.5)
Metformin	330	(88.2)	metformin	333	(98.2)
DPP4i	109	(29.1)	DPP4i	0	(0)
SGLT2i	95	(25.4)	SGLT-2	115	(34.0)
SU	9	(2.4)	SU	14	(4.1)
Other	10	(2.7)	other	5	(1.5)
Total	374	(100.0)	total	338	(100.0)

Abbreviations: DPP4i, dipeptidyl peptidase IV inhibitors; SGLT2i, sodium-glucose cotransporter 2 inhibitors; SU, sulphonylurea; FRC, fixed-ratio combination.

Table III. Presence of chronic complications.

Chronic complication	N	%
Retinopathy	144	(46.5%)
Polyneuropathy	153	(49.4%)
Nephropathy	55	(17.7%)
CVD	80	(25.8%)
PAD	15	(4.8%)

Abbreviations: Cardiovascular disease (CVD); peripheral arterial disease (PAD).

The most frequent chronic complications of diabetes were retinopathy and polyneuropathy (46.5 and 49.4%), followed by cardiovascular disease in 25.8% and nephropathy in 17.7 % of patients (Table III). There was no difference in the proportion of micro- or macrovascular complications according to the insulin regimen. The groups differed in some initial parameters. Patients in MIX group were older compared to the BB ($p < .001$) and BOT group ($p < .001$; Scheffe post hoc test). Total insulin daily dose was lowest in BOT group, while the highest doses of insulin and FRC were recorded in the BB group ($p < .001$ for all, Kruskall-Wallis test) (Table IV).

The proportion of patients treated with IDegLira and IGlarLixi was similar, 48.4% of patients were treated with IDegLira while 51.6% received IGlarLixi. Both were administered most frequently in the morning before breakfast (82.5%).

The Difference in FRC Efficacy According to Different Insulin Regimen Groups

After adjustment for the duration of insulin therapy and age, there was no significant decrease in HbA1c over a follow-up period according to ANCOVA. The interaction of the regimen and HbA1c overtime was not significant [F (2,240) = 2,044, $p = 0.132$], however there was a borderline difference regarding regimen group comparing MIX to BB and BOT [F (2,240) = 2,870, $p = 0.059$] implying greatest improvement of HbA1c in the MIX group (Figure 1a).

No statistically significant differences in BMI were found between the two time points [F (1,249) = 2,588, $p = 0.109$], and BMI was similar in all three groups [F (2,249) = 1,385, $p = 0.252$], but there was a significant interaction between BOT and BB/MIX regimens [F (2,249) = 4,600, $p = 0.011$], indicating the largest reduction of BMI in BB and MIX groups, Figure 1b.

ANCOVA analysis showed a significant reduction in FPG from baseline to control time point [F (1,292) = 4,161, $p = 0,042$], but there was no significant difference between the three groups [F (2,292) = 0.266, $p = 0.767$]. The interaction of the regimen group and FPG over time was statistically significant [F (2,292) = 3,086, $p = 0.047$] because in the BOT group a smaller decrease in FPG was registered compared to the other two groups (Figure 1c).

No differences were found in postprandial glucose over a follow up period [F (1,264) = 1,189, $p = 0.276$)], and there were no differences between groups [F (2,264) = 0.416, $p = 0.660$)].

Side Effects

Regarding side effects, in the group that had GLP-1RA therapy before FRC initiation, more GIT side effects were observed compared to patients without previous GLP-1RA ($p < .001$, Fisher's exact). In the control time point, after the FRC administration, there was no significant difference in GIT side effects between the GLP-1 RA treated and non-GLP-1 RA treated group ($p = 0.734$, Fisher's exact).

Table IV. Baseline characteristics of patients according to different insulin regimens.

Variable	BB (N 116)		BOT (N 139)		MIX (N 87)		F ratio/Kruskal-Wallis	p
	Mean	SD	Mean	SD	Mean	SD		
Diabetes duration	15.88	7.50	14.50	7.01	16.46	7.38	2.145	0.119
Age	65.67	8.42	65.68	8.81	70.48	7.99	10.437	<.001
BMI	34.78	4.08	34.65	4.65	34.35	4.12	0.256	0.775
Total insulin daily dosage	69.41	33.05	29.59	17.53	45.72	18.24	--	<.001
HbA1c1	8.58	1.38	8.66	1.45	8.56	1.33	0.141	0.869
FPG	8.83	3.36	8.35	2.86	8.88	2.74	1.158	0.315
PPG	11.65	2.91	11.77	2.82	11.51	2.88	0.212	0.809
Total FRC daily dosage	27.61	9.97	24.82	10.92	22.06	8.09	--	<.001

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; FRC, fixed-ratio combination.

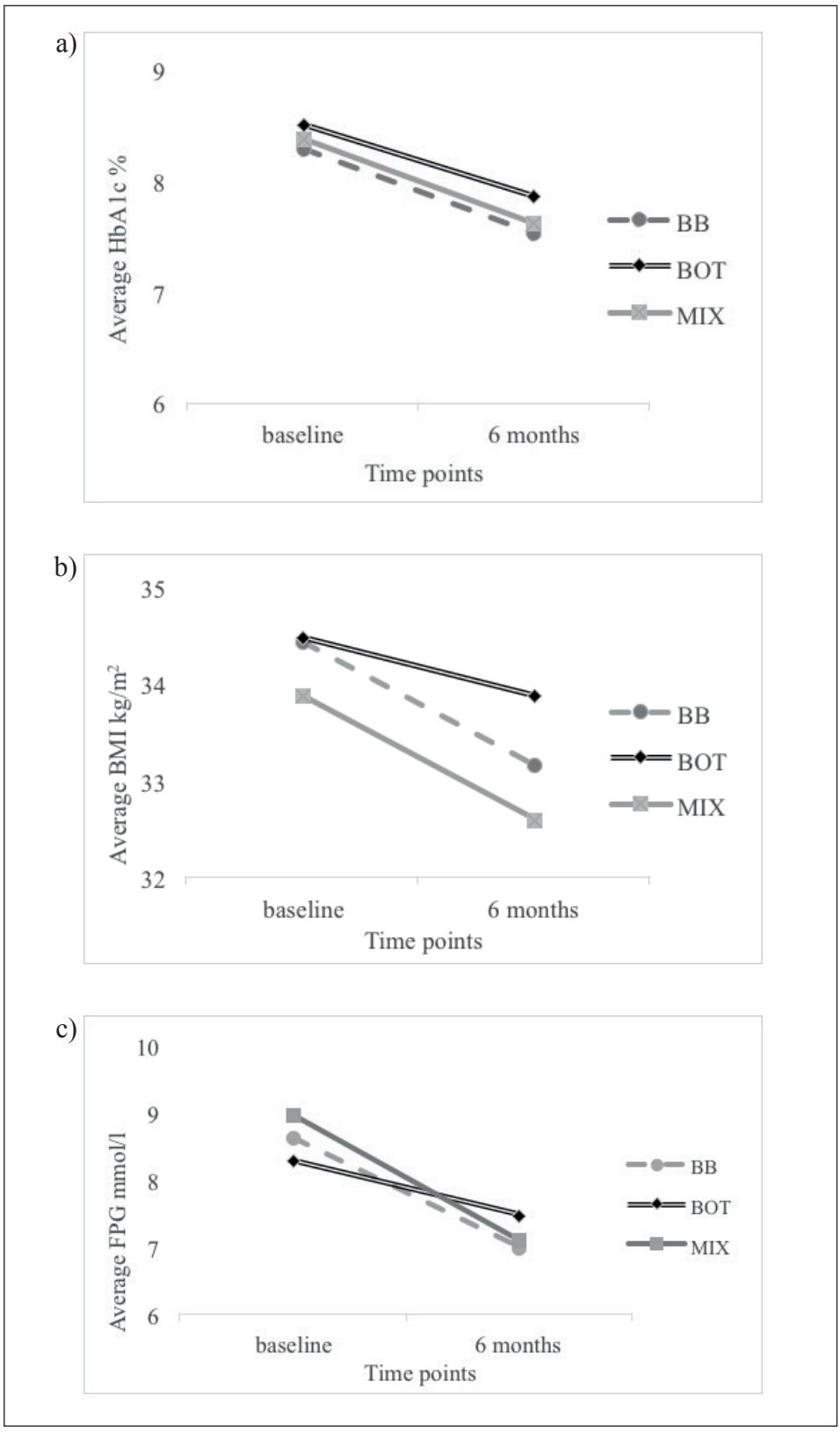

Figure 1. Change in HbA1c, BMI and FPG over a follow up period of 6 months.
Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; MIX, premix insulin analogues; BB, basal-bolus regimen; BOT, basal oral therapy.

Table V. Average doses of FRC required to achieve glycemic targets.

Variable	Level	Dose of IdeglLira		Dose of IglarLixi		p
		Median	SD	Median	SD	
HbA1c1	≤7%	20.27	5.08	29.83	8.75	<.001
	>7%	19.79	7.06	31.26	10.14	<.001
HbA1c2	≤7%	29.56	9.90	34.83	11.38	<.001
	>7%	31.75	11.81	39.69	12.37	<.001

HbA1c1, HbA1c at first time point; HbA1c2, HbA1c at control time point; FRC, fixed-ratio combination.

The number of patients with hypoglycemic episodes decreased from 24% to 7% after FRC initiation (p <.001, McNemar's test).

Comparative Assessment of FRC Efficacy

There were no differences between HbA1c, FPG and BMI between IDegLira and IGlarLixi. However, to achieve the target glycemic values, the group using IGlarLixi required significantly higher average doses compared to IDegLira (p < 0.001 for all) (Table V). In the IdegLira group 10,4% (N=19) patients achieved a maximum of 50 dose steps, while in the IglarLixi 8,8% (N=17) accomplished maximum of 60 dose steps.

In the ANCOVA analysis, a significant increase in the average dose of FRC after the follow-up period (F (1,336) = 366,902, p < .001) was observed. Moreover, there was a significant effect of FRC (F (1,336) = 107,919, p < .001) suggesting patients differed in the average dose depending on which FRC was used. The baseline average dose of IGlarLixi was higher as well as the dose at the end of the follow-up treatment compared to IDegLira. The interaction of FRC and daily dose was also significant (F (1,336) = 9,494, p = 0.002) indicating that the average dose did not increase equally for both FRCs and the increase was greater for IDegLira. A significant effect of the regimen was registered (F (2,336) = 9,972, p < .001) and the Scheffe post hoc test showed that in the BB group the average dose of FRC was higher than in BOT (p = 0.008) and MIX (p < .001) groups, while patients in MIX and BOT groups did not differ (p = 0.263). The interaction of daily dose and group per regimen was also significant (F (1,336) = 3,854, p = 0.022) suggesting that changes in daily dose were greatest in BB regimen (Figure 2). The proportion of patients experiencing weight loss was equal in both FRC options. Still, a larger proportion of patients using IDegLira lost more than 5 kg, compared to those treated with IGlarLixi (p < .001) (Figure 3).

Assessment of FRC Efficacy in All Insulin-Treated Patients

A significant reduction was observed in glycemic parameters in all insulin-treated patients after replacement of insulin therapy with FRC (p < .001 for all) (Table VI).

Most patients experienced some weight loss after the introduction of FRC while a smaller number of subjects achieved target HbA1c values below 7%. Composite outcome defined as any weight loss and HbA1c below 7% was accomplished in 20.3% of patients (Table VII).

Discussion

Historically, insulin therapy has played a significant role in the treatment of DMT2 patients and was the first choice of injectable therapy (usually basal insulin) until the appearance of GLP-1RA on the market. However, with the arrival of GLP-1RA on the diabetology scene, treatment of DMT2 changed significantly, marginalizing insulin therapy, especially after positioning GLP-1RA as the first choice of the injectable agent by the current guidelines[13]. Still, a need for a combination of basal insulin and GLP-1RA for their complementary action is frequently necessary to achieve therapeutic goals[3,5,14]. The complexity of the regimen involving two or more injectable preparations in case of different insulin regimens continues to be a significant barrier to patients' adherence and persistence, ultimately preventing treatment success. Therefore, FRC initiation in patients previously treated with insulin therapy might improve glucose regulation and possibly long-term outcomes[11,15,16].

In our study, the majority of patients were treated with BOT (38.2%), followed by BB regi-

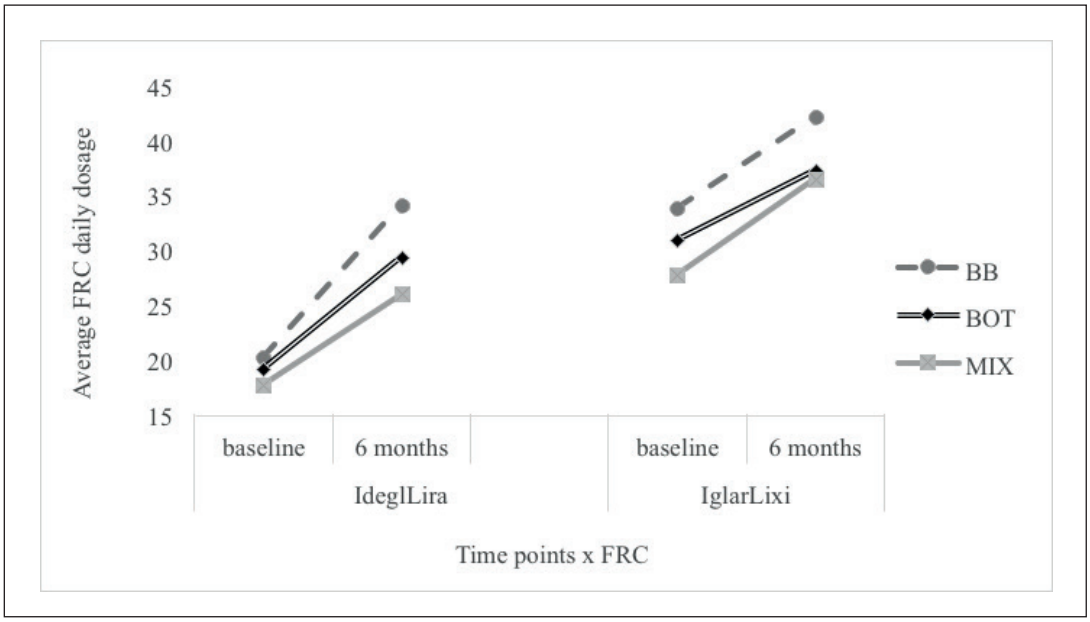

Figure 2. Average daily dose of FRC at baseline and follow-up, according to FRC treatment and regime.
Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; MIX, premix insulin analogues; BB, basal-bolus regimen; BOT, basal oral therapy.

men (31.9%) reflecting a need for therapy intensification with prandial insulin due to insulin resistance and/or progressive nature of diabetes itself. Those problems are most likely solvable with the addition of GLP-1RA to therapy[3,17-19]. Still, until recently prescription of GLP-1RA in Croatia was restricted by a cut-off BMI value of 35 kg/m^2 consequently promoting intensification with insulin therapy in patients with BMI < 35 kg/m^2. The premixed insulin analogs were used in a small proportion of older patients (23.9%) supporting the use of this therapeutic regimen in elderly patients

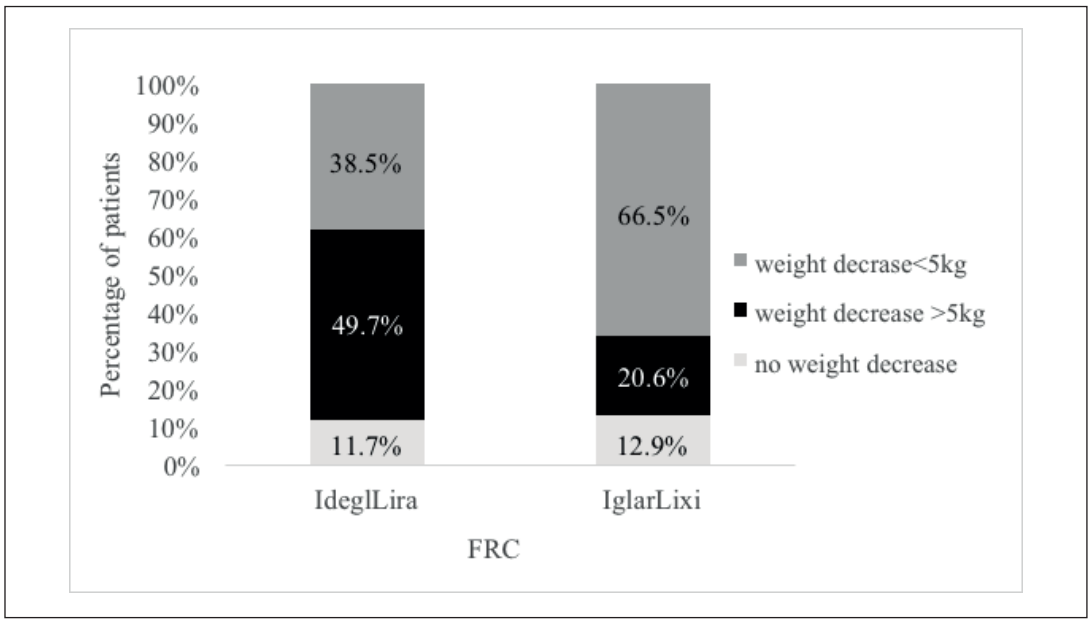

Figure 3. Percentage of patients with weight loss according to FRC therapy.

Table VI. Assessment of glycemic parameters after FRC initiation in all insulin-treated patients.

Variable	Baseline		Follow-up				Wilcoxon
	Mean	SD	Mean	SD	Mean	SD	p
BMI	34.75	4.39	34.35	33.73	4.50	33.02	<.001
HbA1c	8.63	1.41	8.40	7.70	1.36	7.50	<.001
FPG	8.71	3.07	8.10	7.23	2.25	6.90	<.00
PPG	11.72	2.82	11.70	9.77	2.14	9.40	<.001

Abbreviations: BMI; body mass index; FPG; fasting plasma glucose; PPG; prandial plasma glucose.

with a sedentary lifestyle[13]. Furthermore, implementation of current guidelines[20] into everyday clinical practice was reflected through concomitant therapy. Before the introduction of FRC the most prevalent oral agents after metformin were DPP4i, followed by SGLT2i. After the FRC initiation, the proportion of patients treated with metformin and SGLT2i increased. The smaller share of SGLT2i in relation to DPP4i could be attributed to the fact that they are available in Croatia with a co-payment as opposed to DPP4i. The use of sulfonylureas was negligible, but this could reflect the characteristics of the study population, as the use of SU is neither justified nor common with insulin therapy due to the high rate of hypoglycemic incidents[21].

Most participants had chronic complications of diabetes, retinopathy and neuropathy were present in almost half of the patients, while as many as a third of the study population had both, CV disease and renal impairment, emphasizing their extreme vulnerability. Thus, the use of new therapeutic agents such as SGLT2i and GLP-1RA with proven CV and renal benefits is imperative to provide cardiorenal protection and improve treatment outcomes[22,23].

As expected, the insulin dose was the highest in the BB group, followed by the MIX, and BOT groups. However, the total insulin dose in the BOT group was 30 IU which is consistent with published observational studies[24,25], yet significantly lower than in the RCTs[12,26,27], emphasizing the problem of clinical inertia (both physicians' and patients' related) when it comes to adequate basal insulin titration, despite relatively simple titration algorithms and the improved safety profile of new generations of basal insulin analogues[28]. A similar problem with patient adherence and persistence exists with GLP-1RA therapy, which is associated with GIT side effects[29]. Therapy with FRC offers potential solutions to both problems leading to improved treatment outcomes.

Regarding the efficacy of FRC therapy according to different insulin regimens, there was no significant difference in the decrease of HbA1c over time, although there was a borderline difference comparing MIX to BB and BOT implying the most prominent HbA1c reduction in the MIX group. After FRC introduction, there was a tendency of lowering BMI without reaching statistical significance, while significant interaction between BOT and BB/MIX regimens was observed indicating the largest decrease of BMI in the BB and MIX groups. In addition, there was a statistically significant reduction in FPG which was more pronounced in the BB and MIX group. Furthermore, hypoglycemic episodes were significantly reduced after FRC initiation, with no significant difference in GIT side effects. Based on our data analysis, we can conclude that in patients treated with BB and MIX regimen, FRC therapy demonstrated the greatest efficacy due to a significant reduction in required insulin doses, introduction of GLP-1RA, although in submaximal therapeutic range, and improvement in adherence due to the simplicity of the new therapeutic regimen with fewer side effects. RCTs investigating efficacy and safety of both FRC preparations demonstrated greater HbA1c reductions in DMT2 patients inadequately treated with or without insulin therapy, when compared with the insulin and GLP-1RA component alone without an increase in the risk of hypoglycemia[30-33], while IDegLira demonstrated equal effectiveness as a basal-bolus

Table VII. Assessment of outcomes after FRC initiation in all insulin-treated patients.

Outcome	n	%
Any decrease in body weight and HbA1c < 7%	60	20.3
Any decrease in body weight	236	63.3
Decrease in HbA1c < 7%	104	32.7

regimen but with less weight gain and hypoglycemic episodes[15]. *Post hoc* analysis of DUAL II Japan in 39 unregulated DMT2 patients has shown improvement in HbA1c and weight loss after switching from premixed insulin to IDegLira in patients with uncontrolled T2DM[34]. In addition, in a real-life study investigating the efficacy of switching predominantly BOT treated patients to IDegLira, a significant improvement in glycemic control was noted with no gain in body weight[35]. In our BOT group, 27% of patients were treated with GLP-1RA in combination with basal insulin before the introduction of FRC, therefore merging these two components into one could not accomplish such a pronounced effect as in GLP-1RA naive patients explaining the lack of significant HbA1c reduction.

In the EXTRA trial, IDegLira after 6 months of treatment and at a moderate dose led to an HbA1c reduction, improvement in body weight and a decrease of hypoglycemia in a real-world population with type 2 diabetes treated with or without insulin[36].

In a recently published systematic review and Bayesian network meta-analysis, IGlarLixi was equally effective or even superior compared to intensification with premix insulins or addition of prandial insulin in patients previously uncontrolled with basal insulin[37]. The same was shown in the observational study switching diabetic type 2 patients previously treated with different insulin regimes to a combination of lixisenatide and basal insulin[38].

Our results are in accordance with the result of the aforementioned trials since a comprehensive analysis of all patients included in this study clearly demonstrated the benefits of FRC therapy over insulin treatment with respect to all glycemic parameters. However, while most patients experienced some weight loss after the introduction of FRC, a smaller number of subjects achieved target HbA1c values below 7% (60.3% *vs.* 32.7%) and composite outcome defined as any weight loss and HbA1c below 7% was accomplished in only 20.3% of patients. Therefore, FRC therapy along with GLP-1RA should be given priority when intensifying basal insulin therapy or be the first choice with patients who are poorly regulated on oral agents with HbA1c over 9% to avoid problems of clinical inertia and improve cardiometabolic outcomes.

A comparative analysis of IglarLixi *vs.* IDegLira showed that there was no significant difference in the effect on glycemic parameters, except that lower doses of IDegLira were required to achieve the target FPG values with slightly faster titration than IglarLixi. The proportion of patients who lost more than 5 kg was also greater in the IDegLira treated group due to the more pronounced weight loss effect attained with long-acting agents[39]. In addition, at the end of the study, the average dose of iDegLira in well-regulated and unregulated patients was 29.5 *vs*. 31.75 dose steps and 34.8 *vs.* 39.69 dose steps for IGlarLixi, with the slower titration in the IglarLixi group. Similarly, In the EXTRA study including insulin naïve and insulin-treated patients, the mean dose of IDegLira was 30.2 dose steps at 6 months (the change was 8.5 dose steps). In our study, only 10.4% in the IDegLira and 8.8% in the IGlarLixi group achieved maximum dose steps, although HbA1c < 7% was achieved by only 32.7% of patients. The question imposes whether the average dose steps achieved were insufficient considering the long duration of diabetes, high HbA1c and high doses of insulin (average 43 IU) of our study cohort. Obviously, adequate titration remains an unattainable goal.

Study limitations are typical of real-life observational trials including possible missing data due to extraction from medical records, lack of active comparator or control group and possible beneficial effect of introducing a new therapeutic agent into treatment. Therefore, further studies, like RCTs comparing the efficacy and safety of those two FRC agents in insulin-treated patients would be desirable.

Conclusions

In general, poorly controlled insulin treated DMT2 patients switched to either one of the available FRC options benefited from a change in therapy in terms of HbA1c improvement, loss of body weight and reduction of hypoglycemia regardless of the insulin regimen, while BB and MIX treated patients seemed to accomplish the greatest benefit. Although a statistically significant reduction of HbA1c was achieved, only a small proportion of patients managed to attain HbA1c below 7%, pointing out the unmet need for timely intensification with the optimal choice of injectable agent. Still, in most patients, the change in therapy resulted in weight loss, with a slightly better effect of IDegLira compared to IGlarLixi. According to the results of the RCTs, the full potential of the FRCs is expected to be greater if introduced in a timely manner and in proper doses, but our results

demonstrate that even delayed FRC introduction could improve glycemic regulation and consequently, cardiometabolic outcomes.

Authors' Contribution

Ines Bilic Curcic - conceptualization; Ana Simel, Tomislav Bozek, Sanja Klobucar Majanovic - Data curation; Ines Bilic Curcic - Funding acquisition; Silvija Canecki Varzic - Supervision; Ines Bilic Curcic, Maja Cigrovski Berkovic - original draft; Ines Bilic Curcic, Maja Cigrovski Berkovic - review & editing.

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Conflict of Interest

The Authors declare no conflict of interest

Ethical Approval

This study complied with the Declaration of Helsinki and was approved by the local Ethics Committees.

Informed Consent

Due to the retrospective nature of the study, informed consent was waived.

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